ORAL PRESENTATIONS

S1 – TREATMENT OF METASTATIC HORMONE SENSITIVE PROSTATE CANCER

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With the emergence of recent trials, the treatment for castration sensitive metastatic prostate cancer (mCSPC) is changing from ADT alone to combination therapy – chemotherapy or/and novel androgen receptor targeted agents.

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 at that time, had 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 CSPC 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 placebo (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).

Enzalutamide has been studied in treatment of mCSPC in ENZAMET clinical trial comparing ADT and enzalutamide versus ADT and non-steroidal antiandrogen. Results have shown the 3-year overall survival rates were 80% and 72% in the enzalutamide and NSAA arms, respectively, and at 5 years the rates were 67% and 57%. Median OS was not reached in the enzalutamide arm and was 73.2 months in the control arm. The enzalutamide group were treated for a median 57.8 months while those in the NSAA group were treated for a median 22.6 months.

Apalutamide use in mCSPC has been studied within TITAN clincial trial. Results have shown overall survival (OS) and radiographic progression-free survival improvement in patients with metastatic castration-sensitive prostate cancer (mCSPC) receiving ADT. Compared with placebo, apalutamide plus ADT significantly reduced the risk of death by 35% (median OS not reached v 52.2 months; hazard ratio, 0.65; 95% CI, 0.53 to 0.79; P < .0001) and by 48% after adjustment for crossover (hazard ratio, 0.52; 95% CI, 0.42 to 0.64; P < .0001).

Addtion of abiraterone acetate plus prednisone on top of androgen-deprivation therapy plus docetaxel improved survival in patients with de novo metastatic castration-sensitive prostate cancer vs androgen-deprivation therapy plus docetaxel alone. (PEACE-1 clinical trial).

In patients who received the triplet combination, radiographic progression-free survival had a median of 4.5 years vs 2 years without abiraterone acetate plus prednisone. The addition of abiraterone acetate plus prednisone to androgen-deprivation therapy plus docetaxel improved overall survival by 25% vs androgen-deprivation therapy plus docetaxel alone. Both radiographic progression-free survival and overall survival periods were prolonged in men receiving abiraterone.

Darolutamid is an agent that has been used in conjunction with ADT, docetaxel and evaluated in ARASENSE clinical trial. Results have shown increased overall survival (OS), independent of risk or

volume stratification. In ARASENS, the treatment effect of darolutamide on OS was favorable in patients with de novo (HR 0.71; 95% CI 0.59 to 0.85) and recurrent (HR 0.61; 95% CI 0.35 to 1.05) metastatic hormone-sensitive prostate cancer.

Looking at all the data exposed in randomised clinical trials it is completely clearly visible evolvement of therapeutic landscape in the treatment of metastatic hormone sensitive prostate carcinoma. Triplet therapies might be more potent then doublet therapies and further development of novel therapy agents and strategies is awaited.

Keywords: prostate cancer; metastatic hormone sensitive; treatment

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S2 – ADJUVANT THERAPY FOR HIGH-RISK LOCALIZED RENAL CELL CARCINOMA

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Renal cell carcinoma (RCC) represents around 3% of all cancers. For patients who are fit for surgery, the standard of care for localized RCC is radical nephrectomy (RN) or partial nephrectomy (PN). Despite the definitive surgical treatment, the recurrence rate of RCC at 5-years is significant, varying from 2.2% to 58.1% depending on risk factors such as tumor size, histology, and other clinical features. Therefore, perioperative treatment to reduce the risk of recurrence and improve survival remains an area of unmet clinical need.

Currently, the standard of care in metastatic RCC involves a combination of two immune-checkpoint inhibitors (ICIs), or one ICI combined with a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI). The success of ICIs in the metastatic setting has generated immense interest in their perioperative application to reduce disease recurrence.

Since 2016, a number of large, phase III randomized controlled trials have been published exploring the role of adjuvant agents in patients with high-risk RCC but no therapy to date has demonstrated an overall survival benefit.

Sunitinib (based on data from S-TRAC) and pembrolizumab (based on data from KEYNOTE-564) are the only systemic agents that are currently approved for adjuvant use in RCC with data demonstrating a disease-free survival (DFS) benefit. In Europe, only adjuvant pembrolizumab should be considered optional for patients with intermediate- or high-risk operable ccRCC.

As data regarding the benefit of perioperative targeted and immune-based systemic therapies emerges, accurate and applicable prognostic models will become crucial tools in selecting patients who would benefit from perioperative strategies. Despite the availability of several prognostic models, there is a lack of consensus on the optimal stratification approach for localized RCC. Several molecular and genomic factors have been identified as having prognostic value in localized RCC and might be incorporated to clinicopathologic factors in novel prognostic models. The use of genomic expression profiles (GEPs) in predicting recurrence after nephrectomy is an active area of research. ClearCode34 is a validated prognostic tool for clear cell RCC, which stratifies patients into low-risk (ccA) and high-risk (ccB) categories based on the expression of 34 genes. It has been demonstrated in retrospective datasets to be superior to the UISS and SSIGN clinical models at assessing risk of death from RCC.

RCC can pose a risk of both local and systemic recurrence following local surgical resection. The rate of local recurrence compared to systemic is comparatively low from 2% to 6% but those with locoregional recurrence have poor overall survival. Therefore, adjuvant radiation therapy has been explored in many trials. Although, meta-analysis of 12 clinical studies showed some evidence thatadjuvant radiation c ould reduce locoregional recurrence, there was no overal survival (OS) or progression free survival (PFS) benefit.

Only further research into new systemic therapies and combinations or prognostic models may contribute to patient selection for peri-operative therapy and survival benefit in localized RCC.

Keywords: localized renal cell carcinoma, adjuvant therapy, sunitinib, pembrolizumab, prognostic models

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S3 – ARTIFICIAL INTELLIGENCE, ACTIVE SURVEILLANCE AND TREATMENT OF LOCALIZED PROSTATE CANCER

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Treatment landscape of localized prostate cancer is rapidly changing. Both radical prostatectomy and radiotherapy as two main treatment modalities in this setting have adopted new technologies that optimally would translate into more precise treatment with better cure rates and less side-effects. Robot-assisted radical prostatectomy, patient-friendly alternative to open retropubic prostatectomy, is gaining momentum worldwide for prostate and lymph nodes removal and has become standard-of-care. Radiotherapy is nowadays coupled with unprecedented imaging and computing capabilities allowing millimeter-level accuracy and safe delivery of larger doses per fraction, enabling shorter courses of previously weeks-long treatment schedules for localized prostate cancer. There is still ongoing competition between radiotherapy and prostatectomy in localized prostate cancer. As previously discussed, both treatments changed and improved over the last decade. To complicate things further, active surveillance emerged as increasingly utilized third option in localized disease management. In this context the only randomized trial that assessed long-term efficacy and side-effects profile of these treatment options for localized prostate cancer is The Prostate Testing for Cancer and Treatment (ProtecT) randomized clinical trial. ProtecT trial recruited 1643 men aged 50–69 years with clinically localized prostate cancer and randomized them to active monitoring, radical prostatectomy and radical radiotherapy. The primary intention-to-treat analysis at a median follow-up of 10 years showed that the rate of overall mortality was ~1%, irrespective of treatment assigned. However, radical treatment was associated with ~50% reduced disease progression/metastasis compared with active monitoring (active monitoring 6.3, radiotherapy 3.0 and radical prostatectomy 2.4 events per 1000 person-years; $p = 0.004$).

With the progression of prostate cancer radiotherapy the idea was born that hypofractionation can bring clinical benefit based on the assumptions of low alpha/beta ratio for prostate cancer, which was con-

sidered to be in the range of 1.5 Gy. However, mature trial results widely refuted theoretically anticipated hypofractionation advantage (i.e. superiority). Actually, what was largely observed at best is the non-inferiority of hypofractionation compared to standard fractionation. Furthermore, analysis showed that there might be dose-threshold effect on dose-response curve. With radiotherapy equivalent doses (EQD2) going beyond 80 Gy it seems the gain associated with further dose escalation would be marginal at best, suggesting plateau of the dose-response curve for doses ≥80 Gy While there is limit of safe whole prostate dose escalation with external beam radiotherapy, there is potentially a therapeutic gain if we specifically target and boost portion of the prostate containing the bulk of the tumor, are called dominant intraprostatic lesion (DIL). Wide use of MRI allowed to dissect prostate anatomy and to clearly visualize intraprostatic tumors which enabled their targeting with radiotherapy. Authors performed stereotactic boost to DIL using volumetric modulated arc therapy and reported early efficacy and toxicity endpoints in the recent JCO publication. In the FLAME trial the authors hypothesized that focal boosting of the macroscopic visible tumor with external beam radiotherapy would increase biochemical control in patients with localized prostate cancer. They recruited 571 patients with intermediate- and high-risk prostate cancer and randomized them to either standard treatment (77 Gy in 2.2 Gy daily fractions) or to the addition of integrated simultaneous tumor boosting to 95 Gy (2.7 Gy fractions, EQD2=115.8 Gy). Majority of patients received long-term ADT. Reported 5-year biochemical control was 92% in focal boost arm and 85% in the standard arm ($p<0.001$) without additional toxicity associated with focal dose escalation.

Altogether, horizons of radiation therapy in localized disease are changing adopting multimodal treatment such as focal mpMRI guided radiotherapy boosts, external beam radiotherapy with brachytherapy boosts, extreme hypofractionation for appropriately selected patients, consideration for pelvic lymph node irradiation in men at high risk for nodal involvement. Radiotherapy is becoming more precise and personalized.

Active surveillance (AS) is nowadays viable option for patients with low-risk localized prostate cancer. It emerged because of the clear and obvious fact that today more patients are diagnosed with prostate cancer than ever before and many of them are over-diagnosed and overtreated. More than 6 times of the patients are diagnosed with prostate cancer, then the number of patients who dies from it at the end. AS consists of periodical MRI scans, prostate biopsies and biochemical surveillance (PSA blood test) to catch ''upgrade'' of the prostate cancer in due time. The pros for this kind of watchful waiting is evading potential short and long-term side effects that can emerge after radical prostatectomy or during and after prostate cancer radiotherapy and prevention of overtreatment in patients who will, maybe, never need active treatment. The cons for this kind of prostate cancer management are that there is still no consensus on optimal AS protocol and inclusion criteria for appropriate low-risk patients.

Unfortunately, today there is still no effective predictive biomarker who can select appropriate patients with local prostate cancer that can benefit from specific kind of available treatment options. This is especially seeable when trying to decide which patients with intermediate or high risk localized prostate cancer will benefit from radiotherapy alone or radiotherapy + ADT combined. Dan Spratt published very interesting results where his team trained and validate first ever predictive biomarker that can help assess patients with prostate cancer who can clearly benefit from ADT use. They used pretreatment biopsy slides from multiple phase III NRG Oncology randomized trials of men receiving RT or RT+ADT. At the end they have managed to train artificial intelligence (AI) to derive predictive biomarker from screening pretreatment biopsy slides and was trained to predict distant metastases. The results showed that 15-year distant metastases rate difference between RT versus RT+ADT in the biomarker negative group was 0.3%, vs biomarker positive group 9.4%. This clearly shows the potential benefit of using AI in patient treatment deci-

sion making, which can lead to prevention of overtreatment and lower the overall cost of potentially not needed therapy.

Keywords: prostate cancer, personalized radiotherapy, focal boost, active surveillance, artificial intelligence, androgen-deprivation therapy, hypofractionation

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S4 – ADVANCED UROTHELIAL CANCER, NEW TREATMENT OPTIONS

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Bladder cancer is the most common malignancy involving the urinary system. 90 percent of bladder malignancies in the United States and Europe are of the histologic type known as urothelial (transitional cell) carcinoma. Approximately 25 percent of patients will have muscle-invasive disease and either present with or later develop metastases. Systemic chemotherapy is the standard approach for the initial treatment of patients with inoperable locally advanced or metastatic urothelial malignancies. Although initial response rates are high, the median survival with multiagent chemotherapy is approximately 15 months. Second-line chemotherapy has had only a limited role, but checkpoint inhibitor immunotherapy offers an additional option for patients progressing after their initial systemic therapy.

First line therapy for metastatic or inoperable locally advanced urothelial cancer is cisplatin-based combination chemotherapy regimen for patients who are cisplatin-eligible. For patients who are cisplatin-ineligible due to medical frailty or comorbidities, options include a carboplatin-based regimen or immunotherapy with pembrolizumab based on the results of the Keynote-052 study. At a median follow-up of

almost five years (56 months), the ORR, the primary endpoint of this study, was 29 percent for the entire cohort, including complete and partial response rates of 9 and 20 percent. The median duration of response was 33 months. The second approved agent was atezolizumab for patients with

PD-L1 positive cancers. But recently FDA withdrew regulatory approval of atezolizumab for this indication based on the data from a randomized phase III trial (IMvigor130) in which atezolizumab failed to improve overall survival.

There are several other immunotherapy-based regimens which remain investigational in patients with metastatic urothelial carcinoma in this setting and further randomized studies are necessary (pembrolizumab plus enfortumab vedotin, nivolumab plus ipilimumab and avelumab).

A major advancement in first-line therapy has been achieved by maintenance therapy with avelumab. In the JAVELIN Bladder 100 study, avelumab plus best supportive care (BSC) significantly prolonged OS (overall survival) compared with BSC alone in the two primary populations – overall study population and population of pateints whith PD-L1 positive tumors, establishing the new first-line standard of care.

Recently published long-term follow up data from the JAVELIN Bladder 100 study (more than 38 month) demonstrated longer OS and PFS (progression-free survival) in the avelumab+BSC arm compared to the BSC arm alone with similar benefits in patients who recived cisplatin- or carboplatin-based chemotherapy.

Although a significant number of patients have an objective response to first-line therapy, most patients, eventually, have disease progression and require subsequent-line therapy. Subsequent management is based on multiple clinical factors including prior therapies received, specific tumor molecular alterations (FGFR status), as well as patient comorbidities, preferences, and treatment goals. For patients with the disease progression on first-line therapy and who have not recived immunotherapy, pembrolizumab, nivolumab or avelumab are treatments of choice in subsequent-line. For patients who have relapsed following treatment with a platinum-based regimen and immunotherapy, targeted agents are available.

For patients with FGFR mutation negative cancers, the treatment of choice is antibody-drug conjugate enfortumab vedotin which improved both OS and PFS compared to chemotherapy in a randomized phase III trial EV-301.

Another drug, sacituzumab govitecan, is an antibody-drug conjugate that targets Trop-2 and it showed effectiveness in phase II trial TROPHY-U-01. Recently published results of primary analysis of TROPHY-U-01 Cohort 2, a phase 2 study of 38 patients with metastatic bladder cancer who were platinum-ineligible and progressed after prior ICI therapy showed encouraging results regarding the safety and efficacy of sacituzumab govitecan in this population of patients.

For FGFR 3 or 2 genetic alteration the treatment option include either the fibroblast growth factor receptor (FGFR) inhibitor erdafitinib or the antibody-drug conjugate enfortumab vedotin. Erdafitinib demonstrated efficacy in an open-label, nonrandomized phase II trial (BLC2001), ORR was 40 percent, PFS was 6 and OS 11 months.

Various agents remain under investigation (especially those targeting HER 2) for the treatment of patients with treatment-refractory metastatic urothelial cancer whose results are expected. However, we can unequivocally say that immunotherapy and targeted therapies have revolutionized the treatment paradigm in metastatic urothelial cancer, with more advances to come on the horizon.

Keywords: advenced urothelial cancer, immunotherapy, targeted therapy

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S5 – DUAL IMMUNOTHERAPY FOR THE TREATMENT OF METASTATIC KIDNEY CANCER IN A PATIENT UNDERGOING HEMODIALYSIS

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In the first-line management of metastatic renal cell carcinoma (mRCC), immunotherapy-based combinations, particularly dual immunotherapy, have made significant success. Based on clinical trials, dual immune checkpoint blockade using the drugs nivolumab and ipilimumab has become the standard therapy for the treatment of patients with previously untreated advanced RCC who are at intermediate or high risk. Unfortunately, because patients undergoing hemodialysis were excluded from clinical studies, information on the security and effectiveness of immunotherapy in hemodialysis patients is limited. Nivolumab and ipilimumab's pharmacokinetics and clearance are unaffected by renal function, which is known to have no clinically meaningful impact. Furthermore, it is believed that the majority of immune-related side effects in hemodialysis patients can be treated using the same methods as in people with normal kidney function.

This case report describes a patient who underwent a nephrectomy on the right side in February 2017 and had a clear cell carcinoma of the kidney pathohistologically confirmed. Three months later, the patient

underwent a nephroureterectomy on the left side due to transitional carcinoma of the pyelon. Since then, he was regularly monitored and undergone hemodialysis. A suspected local recurrence in the adrenal glands on both sides is shown by a follow-up positron emission tomography and computed tomography (PET-CT) in August 2020. The presence of metastases is confirmed by magnetic resonance imaging (MRI) of the adrenal glands. It was determined via a CT-controlled biopsy that the left and right lesions are kidney clear cell carcinoma metastases. He was moved to the Department of Abdominal Surgery where, on November 28, 2020, he underwent surgery due to the emergence of post-interventional intra-abdominal hemorrhage. The left adrenal gland was removed during an exploratory laparotomy. Clear cell kidney cancer metastasis is confirmed by pathohistological findings. In February 2021, a PET CT is done, which displays the progression of the right adrenal gland's nodular alteration with metastatic morphological characteristics. The right adrenal gland lesion was then treated with stereotaxic ablative radiation (SABR) at a tumor dosage (TD) of 31.25 Gy. On March 19, 2021, the patient underwent a control CT scan of the abdomen and pelvis, which revealed a volume reduction of the right adrenal gland metastatic lesion by 37% with central necrosis. Then, in October 2021, a control PET CT was performed. It reveals the condition following bilateral nephrectomy and adrenalectomy on the left, without local recurrence, and partial metabolic and morphological regression following radiosurgical treatment of the right adrenal gland, but also an osteolytic lesion of the left iliac bone and a lesion of the sternum with metastatic characteristics. According to International mRCC Database Consortium (IMDC) criteria, the patient was at intermediate risk because his hemoglobin levels were below the lower limit. In the November of 2021, the patient is presented to the multidisciplinary team for urogenital tumors, who recommend starting treatment with dual immunotherapy nivolumab/ipilimumab for the first line of treatment for metastatic clear cell kidney cancer of intermediate risk with denosumab. Also, radiotherapy (RT) is administered to the area of the iliac bone's osteolytic lesion at a dose of 24 Gy over the course of four fractions. The patient will undergo five cycles of dual immunotherapy with denosumab up until March 2022. Due to high creatinine values and the fact that the CT scan performed in the month of April was stationary, additional treatment with nivolumab and denosumab was maintained. The patient receives 3 further cycles of nivolumab in addition to denosumab until July 7, 2022, and a control CT scan of the thorax, abdomen, and pelvis is done; this scan reveals stable disease by iRECIST criteria. Until October 2022, the patient receives 3 more cycles of nivolumab in addition to denosumab, and a control CT scan reveals that the disease is once more stable. After that, he received an additional 3 cycles, and at the end of January, he underwent a control CT scan of his thorax, abdomen, and pelvis. CT revealed the progression of the osteolytic lesion of the sternum, and the patient now reports an increasing amount of pain around the sternum. A palliative RT of the sternum up to a TD of 24 Gy in 4 fractions is administered. Denosumab and nivolumab therapy will continue to be administered to the patient through March 2023. A control CT scan of the thorax, abdomen, and pelvis is anticipated.

In this case report, it is important to emphasize that the patient is receiving hemodialysis, that his creatinine levels are consistently high, that he is being monitored closely by an endocrinologist and a nephrologist, and that he received the full doses of nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) without any dose adjustments. No adverse events (AEs) occurred, and the creatinine levels did not worsen while receiving the medication (meaning the ipilimumab dose did not affect the deterioration of creatinine-related laboratory parameters). In this dialysis patient, dual immune checkpoint inhibition with nivolumab and ipilimumab was safe and effective. Given our understanding of the pharmacokinetics and pharmacodynamics of dual immunotherapy, we chose not to reduce this patient's dose of nivolumab and ipilimumab. We anticipate that in the future a significant number of case studies of comparable patients

will be combined in order to appropriately discuss the risks and advantages of immunotherapy in patients with advanced malignancies who are receiving hemodialysis.

Keywords: immunotherapy, renal cell carcinoma, kidney neoplasms, hemodialysis

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S6 – TARGETED TERAPY FOR HEPATOBILIARY TRACT CANCER

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Hepatocellular carcinoma (HCC) occurs most often in people with chronic liver desease. It is sixth most commonly diagnosed cancer and fourth leading cause of cancer-related death worldwide. Stage of the desease and liver function are the most important for treatment decision. In early stages, potentially curative treatments as liver transplantation and resection are the most commonly used. Other options are MWA, chemoembolisation, radioembolisation.

First step forward in systemic treatment was in 2008 with the results of SHARP trial. In that trial sorafenib added benefit of 2.8 months compared to placebo. Before and after that no other drug achieved better result, except lenvantinib as a non inferiority treatment approved in August 2018.

In May2020 IMbrave trial results were published. Combination of atezolizumab and bevacizumab achieved statistically significant improvement of OS (67.2%) compared to sorafenib (54.6%). Also mPFS in sorafenib group was 4.3 months and atezolizumab/bevacizumab combination group was 6.8 months. Less than two years later we had HIMALAYA trial results, where the durvalumab/tremelimumab combination reduced risk of death by 22% in patients with stage III or IV unresectable HCC compared to patients who received sorafenib alone. mOS in combination group was 16.43 months compared to 13.77 months in sorafenib group. Considering this results this combinations became golden standard for treatment stage III and IV unresectable HCC.

In second-line treatment of HCC we can use regorafenib, cabozantinib, and in patients with high levels of AFP and ascites ramucirumab. Checkpoint inhibitors (nivolumab, pembrolizumab, ipilimumab) also demonstrate effectiveness in second-line treatment.

Tials combining systemic treatment and locoregional tretment are ongoing.

Billiary tract cancers (BTC) are rare tumors with high mortality rate (5-year survival rate is less than20%). BTC include cholangiocarcinoma (intrahepatic and extrahepatic), gallbladder cancer and ampullary tumours .

Curative management relies on surgical resection followed by adjuvant capecitabine for chollangiocarcinoma and gallbladder cancers, and gemcitabine in ampullary cancer. Unfortunately relapse rate remains high, so we need better adjuvant strategies.

Current first-line standard of care in advanced disease is Combination of cisplatin/gemcitabine chemotherapy was first-line standard of care in advanced disease for over 10 years. ABC-02 trial showed better OS and PFS for this combination compared to gemcitabine alone. In 2022 TOPAZ-1 trial results were published. Gem/cis chemotherapy in combination with durvalumab achieved statistically significant OS and PFS compared to gem/cis/placebo combination. This benefit is achieved in all subgroup of patients , no matter of localisation and gene alterations.

Until 2019 we had no second-line standard of care. In 2019 ABC-06 trial established FOLFOX protocol as a second-line standard of care in advanced BTC. Two years after that we have results of NIFTY trial. Combination of liposomal irinotecan and 5FU showed better OS and PFS compared to 5FU alone.

Targeted treatments following precision medicine approach offered new possibilities in treatment of BTC. The most common alterations are IDH1 mutation, FGFR2 fusion, NTRK fusion and ERBB2 amplification. All of them are targetabele, so performing molecular profiling for patients diagnosed with CCA (especially intrahepatalCCA) is considered standard of care. Pemigatinib and infigratinib are approved for FGFR-2 fusion, and ivosidenib is approved for IDH-1 mutant CCA refractory to one or 2 lines of chemotherapy. MyPathway study explored pertuzumab/trastuzumab combination in chemorefractory BTC with HER-2 amplification or overexpression, and ORR was23% Pembrolizumab is indicated for patients with dMMR or MSI-h BTC.

Management of HCC and especially BTC is rapidly changing. Standard for curative treatment is still surgery, but precision medicine is offering new possibilities for treatment advanced tumors. Using this opportunities correctly is a big challenge. OS and PFS shouldn't be our only aim, we have to think about quality of life in our patients

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S7 – NEOADJUVANT THERAPY OF COLORECTAL CANCER

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Colorectal cancer remains a deadly disease with 2320 deaths and 3706 new cases in Croatia in 2020. Neoadjuvant therapy is more established in rectal than in colon cancer.

Today, the standard treatment is neoadjuvant chemotherapy with radiotherapy and subsequent total mesorectal excision for locally advanced rectal cancer (LARC). Although this type of treatment has improved survival, in recent years a slower decrease in mortality has been recorded due to the high rate of distant metastases (29-39%).

Neoadjuvant chemoradiotherapy (nCRT) has primarily been proven to be effective in local disease control but does not improve the overall survival (OS). Total neoadjuvant therapy (TNT) is a strategy that includes chemotherapy with chemoradiotherapy before the surgery, the advantages of which are better patient compliance, tumor downstaging, and exposure to chemotherapy earlier in the course of the disease that targets occult micrometastases and can help assess chemosensitivity.

Meta-analysis of Kasi et al showed a significantly higher chance of achieving a pathological complete response (pCR) as well as improved disease-free survival with the TNT versus nCRT. But, sphincter-preserving surgery and ileostomy rates did not significantly differ among these two approaches. Patients with pCR had better DFS compared with patients without pCR at 5 years (88.8% vs 74.9%). Similarly, 5-year overall survival was 87.6% vs 76.4% for those with and without pCR.

Given that the chances of local recurrence are significantly reduced after pCR, the added value of surgery is questionable. The treatment paradigm for LARC is shifting toward methods that increase the oncologic outcomes and organ preservation rate. Preliminary results from the OPRA (Organ Preservation of Rectal Adenocarcinoma) trial showed a significantly higher rate of organ preservation in the consolidative TNT arm compared with the induction TNT arm but without significant difference between 3-year disease-free or distant metastasis–free survival.

One of the organ preservation strategy is watch and wait approach. However, the appropriate patient selection remains a challenge, because MRI-based evaluation of response at restaging is insufficiently accurate and has substantial variability of interpretation. FDG-PET/MRI assessments is better in T and N restaging compared to MRI alone, and selecting patients for rectum-sparing approaches.

Radiation has immunomodulatory effects on the host immune system in addition to the direct tumor cell killing effect. Now we have several studies (VOLTAGE-A phase I/II trial; R-IMMUNE phase Ib/II trial; AVERECTAL trial) that evaluated tumor response to nCRT combined with concurrent and/or consolidation immune checkpoint inhibitors.

Most recently, neoadjuvant dostarlimab monotherapy for nonoperative management of MMR-D/MSI-H rectal cancer and neoadjuvant NICHE trial with nivolumab and ipilimumab for MMR-D/MSI-H colon cancer resulted in groundbreaking results.

In colon cancer, neoadjuvant chemotherapy use has increased too, more so in patients with clinical node-positive disease. Six weeks of preoperative oxaliplatin-fluoropyrimidine chemotherapy for operable colon cancer showed better 2-year disease control, fewer incomplete resections. Patients with node-positive colon cancer treated with neoadjuvant chemotherapy had higher overall-survival compared to upfront surgery (57% vs.43%).

However, despite identical tumor histology, individual patient response to nCRT can range from complete remission to disease progression. It has been reported that, in the radio-resistant rectal cancer cells, most of the differently expressed genes were associated with cell-cell adhesion and regulation of epithelial cell differentiation. Chen et al identified that the dehydrogenase/reductase 9 (DHRS9) gene level was the most considerably upregulated among CCRT nonresponders in rectal cancer.

Given that patients respond differently to neoadjuvant therapy, more research is needed to identify the most effective treatments.

Keywords: neoadjuvant chemoradiotherapy, watch and wait, total neoadjuvant therapy

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S8 – TARGETED THERAPY OF METASTATIC COLORECTAL CANCER

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Considering the global incidence and mortality of colorectal cancer (CRC), it represents an important public health problem. It is the second most common cause of cancer related death in the world, and its incidence is continuously increasing, especially in younger population. About half of patients with localized disease develop metastases in the later course of treatment and follow-up, whereas about 20 percent of patients initially present with metastatic disease. In recent decades, significant progress has been made not only in the treatment but also in the diagnostics of CRC. However, despite progress, metastatic colorectal cancer (mCRC) still represents a challenge, mainly due to great genetic heterogeneity, the intertwining of different intracellular signaling pathways, a small number of defined therapeutic targets and insufficient knowledge about the influence of tumor microenvironment, immune reactions, gut microbiota, and other factors. With the introduction of multidisciplinary teams and careful planning of the treatment strategy, especially in metastatic disease, a significant step forward in treatment outcomes was achieved. Nevertheless, most patients have an incurable disease. With the implementation of new surgical techniques, local ablative methods, new chemotherapeutics, targeted therapy and the introduction of personalized medicine based on established biomarkers, we have stepped into a new era, the era of precision oncology. In mCRC, only a few clinical and molecular biomarkers have been established for routine testing, and are recommended by international guidelines, whether they are predictive and/or prognostic (primary tumor site, RAS, BRAF, HER2, MSI/dMMR, NTRK). The choice of therapy is based on patient characteristics and needs, as well as the resectability of the disease, molecular biomarkers and the location of the primary tumor. The use of chemotherapy in addition to surgery and/or the use of local ablative methods can lead to the cure of up to a third of patients with limited and resectable metastatic disease. For most patients with unresectable mCRC, the standard of treatment is still the combination of chemotherapy protocols based on 5-fluorouracil with targeted therapy for vascular endothelial growth factor (VEGF) or epidermal growth factor (EGFR), depending on established biomarkers. For the 3 to 5 percent of mCRC patients with microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) tumors, the use of immune checkpoint inhibitors (ICIs) is the standard first-line therapy. Clinical trials have shown a clinically significant and durable response to ICIs in the majority of these patients, with approximately 30 percent of patients exhibiting a complete response. The use of BRAF and anti-EGFR inhibitors has been shown to be clinically and statistically significantly effective compared to standard therapy, in overall response rate (ORR), overall survival (OS) and progression-free survival (PFS), in patients with $BRAF^{V600E}$ mutation who were previously treated with systemic therapy. Promising results were also demonstrated by the use of this combination of drugs with nivolumab, after progression to earlier standard lines of treatment. Considering that BRAF inhibitor monotherapy proved to be ineffective in first-line treatment, the use of a combination of BRAF and anti-EGFR drugs with or without chemotherapy versus doublet or triplet chemotherapy with or without an anti-VEGF antibody in first-line treatment is being investigated. HER2 amplification is a negative predictive marker of response to anti-EGFR therapy. Clinical studies have shown the effectiveness of the use of combined anti-HER2 therapy after progression on earlier standard systemic therapy, and trastuzumab-deruxtecan is effective after progression on earlier anti-HER2 therapy. The most common mutation in most solid malignant tumors, including mCRC, is that of the KRAS and

NRAS genes, and till recently it was considered *undruggable*. RAS mutation are negative prognostic factors in particular in MSS mCRC and are negative predictive factors for a response to anti-EGFR therapy. In the last few years, the development of targeted therapy for the $KRAS^{G12C}$ mutation has demonstrated the efficacy of these inhibitors in solid tumors, and mCRC, either alone or in combination with cetuximab.

Comprehensive research is underway, not only on the genetic profile, but also on the influence of the tumor microenvironment, gut microbiota, proteomics, epigenomics, transcriptomics, etc., which can help to better define tumor biology and contribute to the further definition of predictive and prognostic biomarkers that are necessary for the development of precision therapy in the treatment of patients with mCRC.

Keywords: metastatic colorectal cancer, standard treatment, precision medicine, targeted therapy

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S9 – STATE OF THE ART: DIAGNOSTICS AND TREATMENT OF GEP-NET

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The treatment options for advanced and metastatic GEP-NENs have significantly expanded during the past two decades. Some important clinical studies, including the PROMID and CLARINET trials, have demonstrated a significant efficacy of somatostatin analogues (SSA) in the control of tumor growth in patients with metastatic GEP-NETs. A recent CLARINET FORTE phase 2 clinical trial further supports the clinical benefit of the SSA lanreotide autogel (LAN), which led to significantly improved progression-free survival (PFS) and disease control rate in patients with GEN-NETs, especially in cases with a Ki67 index ≤ 10%. In addition to SSA, novel therapeutic approaches, including PRRT, targeted therapy, and immunotherapy, have demonstrated promising clinical benefits. PRRT is a type of systemic radiotherapy specifically targeting tumor cells expressing somatostatin receptors (SSTR). In the phase 3 NETTER-1 trial, for

patients with metastatic well-differentiated midgut NETs, treatment with ^{177}Lu-dotatate led to a significantly improved PFS (median PFS not reached vs 8.4 mo in the control group with high-dose octreotide alone) and an improved radiographic response rate (18% vs 3% in the control group) The most common adverse effects for ^{177}Lu-dotatate are nausea and vomiting. Based on this trial, PRRT with ^{177}Lu-dotatate has been approved for patients with advanced GEP-NETs and SSTR expression on imaging. Due to its hypervascularity, GEP-NETs were investigated for therapy against vascular endothelial growht factor (VEGF). In a phase 3 trial, patients with low- to intermediate-grade P-NETs received placebo vs sunitinib, a tyrosine kinase inhibitor targeting multiple receptors, including VEGF receptors-1, 2, and 3. Sunitinib led to a significantly longer median PFS [11.4 mo vs 5.5 mo in the control group; hazard ratio (HR) for progression or death, 0.42; $P < 0.001$]. Sunitinib has been approved for patients with advanced P-NETs. mTOR is a multifunctional serine/threonine kinase related to NET growth. mTOR pathway genes, including PTEN, TSC2, and PIK3CA, are also frequently mutated in NETs. Multiple clinical trials have been conducted to test the treatment effect of the mTOR inhibitor everolimus in GEP-NETs. In the RADIANT-3 trial, for patients with advanced P-NETs, everolimus treatment led to a significantly longer median PFS (11 mo vs 4.6 mo in the control group; HR: 0.35). In the RADIANT-4 trial, patients with advanced nonfunctioning GI and lung NETs had a longer median PFS in the everolimus arm (11 mo vs 3.9 mo in the control group; HR: 0.48). Everolimus is approved for patients with advanced P-NETs and nonfunctioning GI NETs. Immune checkpoint inhibitors and antibodies targeting programmed cell death protein-1 (PD-1), programmed cell death protein ligand-1 (PD-L1), or cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), have demonstrated promising therapeutic responses in various types of cancers. The majority of GEP-NETs are not suitable for immunotherapy but some of them are. For example, in Merkel-cell carcinoma, a high-grade cutaneous NEC or tumors with MSI, high tumor burden, and/or mutational load. Multiple clinical trials have been conducted to test the efficacy of immunotherapy in GEP-NENs. Currently, these studies only showed very limited therapeutic effects for GEP-NENs. Interestingly, in a phase 1b trial on toripalimab (an anti-PD-1 antibody) for patients with high-grade NENs, patients with PD-L1 expression greater than 10% and/or high tumor mutational burden (TMB) had a better objective response rate (ORR) than low PD-L1 (< 10%) (50.0% vs 10.7%, $P = 0.019$) and low TMB patients (75.0% vs 16.1%, $P = 0.03$). Therefore, PD-L1 expression is a potential therapeutic and prognostic biomarker for GEP-NENs. Due to its complexity, a multidisciplinary approach is mandatory in order to achieve optimal clinical outcome for patients with GEP-NENs.

Keywords: GEP-NET, somatotastin analogues, PRRT, immunotherapy

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S10 – THE IMPORTANCE OF MULTIMODALITY TREATMENT FOR PANCREATIC CANCER: A CASE REPORT

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Introduction: Pancreatic cancer is the fourth most common cause of cancer death among men and women in Europe. In recent years, the adoption of minimally invasive surgical techniques has improved the quality and safety of pancreatic cancer surgery. Moving chemotherapy to earlier stages of treatment also contributed to better outcomes, and it is now increasingly being utilized in the neoadjuvant setting, often with concomitant radiotherapy. Targeted therapies as well as immunotherapy are the subject of numerous current studies. But despite advances in therapy, mortality rates have remained largely unchanged. Almost 50-60% of patients at diagnosis have distant metastatic disease, 25-30% have regional disease and only 10-15% of patients have local disease. The only hope for curing pancreatic cancer involves a combination of complete resection and systemic polychemotherapy. Median 5-year survival after surgery according to modern reports is about 20%. The overall recurrence rate, however, remains high at 70-80%. In this paper, through a case report, we will try to demonstrate the importance of a multidisciplinary approach in achieving better outcomes in the treatment of patients with pancreatic cancer.

Case report: We present a case of a 57-year-old patient who was initially admitted to the Clinic for Internal Medicine due to acute pancreatitis at the beginning of January 2018. The radiological examination revealed a neoplasm within the head of the pancreas up to 2 cm in diameter without signs of local invasion or regional lymphadenopathy. Carbohydrate antigen 19-9 (CA19-9) serum level was elevated preoperatively at 68.4 kU/L. In accordance with the decision of the multidisciplinary team, a pancreatoduodenectomy was performed at the end of January 2018, which confirmed adenocarcinoma of the pancreatic head. Postoperatively, the tumor marker values normalized, and the patient received adjuvant chemotherapy with gemcitabine for 6 months until the summer of 2018. He was monitored clinically and radiologically at regular intervals for 3 years without signs of disease progression. In the summer of 2021, an increase in tumor marker (CA19-9 1346.0 kU/L) was recorded, and PET-CT revealed metabolically active secondary lesions in the lungs and pleura with minimal pleural effusion. In the first-line metastatic setting treatment, he received 6 cycles of polychemotherapy with nab-paclitaxel and gemcitabine until March 2022. Treatment was complicated by the development of bacteremia and epileptic seizures without an organic substrate. Unfortunately, in April 2022, the disease progressed in the form of new pleural deposits and dissemination of disease in the bones of the spine, sacrum, and ribs. The treatment was continued with polychemotherapy (FOLFOX protocol) followed by capecitabine as maintenance therapy until January 2023. Due to further disease progression, but now with the worsening of the patient's performance status (ECOG 2), treatment with oxaliplatin was reintroduced, but as monotherapy. The last work-up was done in March of this year after 4 cycles of oxaliplatin treatment. It verified the progression of secondary lesions of the skeleton, so the patient is currently undergoing chemotherapy with monoirinotecan along with regular zolendronic acid applications and palliative radiotherapy for painful bone lesions of the ribs.

Conclusion: In conclusion, pancreatic cancer remains a disease with a poor outcome, and the benefit of new therapies is still modest despite a growing body of research. Consequently, it is critical that deci-

sions about diagnostic procedures, assessment of resectability, and systemic therapeutic options are made within a multidisciplinary team to maximize survival and optimize outcomes for these patients.

Keywords: pancreatic cancer, multimodality treatment, pancreatic cancer resectability

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S11 – METASTATIC GASTRIC CARCINOMA - A CASE REPORT

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Introduction: Gastric cancer is one of the most common cancers worldwide. It presents a major global health problem with large geographical variations in incidence, with the highest rates in North-East Asia, South and Central America and Eastern Europe, and the lowest rates in Western Europe, Sub-Saharan Africa, Australia and North America. Most patients with gastric cancer already have advanced, incurable disease at the time of presentation. Gastric adenocarcinoma often develops as a consequence of chronic atrophic gastritis or intestinal metaplasia and is strongly associated with Helicobacter pylori infection. Most gastric cancers are sporadic, while familial gastric cancer accounts for 1-3% of gastric cancer cases. Hereditary gastric cancer includes three main syndromes: hereditary diffuse gastric cancer (HDGC; this is the only one that has been genetically elucidated), gastric adenocarcinoma and proximal gastric polyposis (GAPPS) and familial intestinal gastric cancer (FIGC). In addition to genetic factors, a number of environmental factors, such as Helicobacter pylori infection and consumption of high-salt foods, may contribute to carcinogenesis in gastric cancer. Unhealthy lifestyle, alcohol consumption and smoking are additional risk factors for gastric cancer.

Case report: In this report, we describe the case of a 50-year-old man who presented with dyspepsia in May 2020. An esophagogastroduodenoscopy was performed, and a tumor of the distal esophagus and cardia was found. A biopsy was taken and pathological examination revealed human epidermal growth factor receptor 2 (HER-2) positive adenocarcinoma. A computed tomography (CT) scan was done and it

showed metastases in the liver and suspicious nodules in the lungs. In June 2020, first-line treatment of the metastatic disease was started: chemotherapy with cisplatin and capecitabine, with the addition of HER-2 blockade with trastuzumab. After 4 cycles of treatment, our patient was hospitalized due to worsening general condition, vomiting, weight loss and inability to eat solid food. A thorough diagnostic workup was performed and a CT scan showed right-sided pneumonia and disease progression: enlargement of the primary tumor, increased number of liver metastases and increase in the size of pre-existing metastases. He was treated with antibiotics for pneumonia and underwent a percutaneous endoscopic gastrostomy (PEG). In December 2020, a second line of treatment was started: chemotherapy with paclitaxel and ramucirumab. Our patient tolerated the therapy very well and radiological follow-up after the first three cycles showed an excellent response to therapy. We continued with the therapy and over time, our patient's condition improved. He also gained weight: he started treatment at 70 kilograms and after 9 treatment cycles weighed 108 kilograms. In addition, in October 2021, at his request, his PEG was removed.

To date, we have continued with the same treatment and our patient's disease is still stable.

Keywords: gastric cancer, chemotherapy, liver metastases, PEG

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S12 – CHOICE OF OPTIMAL ABLATIVE METHOD IN THE TREATMENT OF OLIGOMETASTATIC DISEASE

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Percutaneous ablation methods present a significant outreach in the individualized therapy of oncologic patients. The development of image guided procedures started 30 years ago with radiofrequency ablation in the therapy of liver and kidney tumors. As a result most studies published about ablation and its efficacy include RF ablation. This method has certain limits and specific aspects such as heat-sink effect, smaller and irregular ablation zones which led to possible inferior oncologic outcomes compared to standard surgical resection as gold standard. All this led to clinical society guidelines, in which percutaneous ablation methods are classified as an alternative option only in certain patients with severe comorbidities and contraindication for surgery.

Development of microwave ablation surpassed certain limits of RF ablation with a more predictable and larger ablation zone, without heat-sink effect and with a faster procedure. All this led to possible superior oncologic outcomes in T1a renal carcinoma, HCC, hepatic, bone and lung oligometastatic disease, comparable with surgery.

Lack of larger long-term prospective studies is the reason why this method still has an experimental status in some guidelines, despite its superior characteristics.

Percutaneous cryoablation creates an oncological effect through an ice-ball formation. Controlled deposition of argon gas through cryoprobes makes this possible and one of the main advantages of this method is the clear visualization of the ablation zone. This allows for better confirmation of the ablation outcome and also for creation of customized ablation zones with multiple cryoprobes in irregular shaped lesions. This method has presented as a much safer option then other ablative techniques in kidney lesion close to the collecting system with less risk of damage and complications. In the lungs cryoablation has excellent results with minimal lung parenchyma injury which can be significant in COPD or operated patients. Another advantage of cryoablation is the analgesic effect of low temperatures which allows for the procedure to be performed in local anesthesia in patients with a contraindication for general anesthesia. Cryoablation has a higher risk of postprocedural bleeding compared to other ablative methods due to multiple probe insertion which also makes the method more time consuming and complex and requires more experience.

In the last few years a new ablation method has been invented not based on thermal effect but electric impulses causing apoptosis called IRE-irreversible electroporation. Multiple probes are positioned parallel around the tumor with impulses creating a zone within which there is apoptosis of the tissue cells but without thermal scarring. This allows for treatment of lesions close to thermo-sensitive tissues such as biliary ducts, bowels of collecting system without the risk of complications. The indications primarily include central liver lesions, but studies are also conducted for pancreatic cancer, lung tumors and prostate cancer.

All these minimally invasive treatment options allow for a customized and individualized approach to oligometastatic disease therapy. Due to the known benefits of causing less morbidity for the patients, allowing for faster recovery with less complications and less damage to the organs in question, ablative techniques have positioned themselves as a valuable tool in the oncologic treatment algorithm, with outcomes comparable to surgery.

Keywords: microwave ablation, Radiofrequency ablation, Cryoablation, Irreversible electroporation

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S13 – NOVELTIES IN THE TREATMENT OF HEAD AND NECK CANCER

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In the last year, important advances have been made in the treatment of head and neck squamous cell carcinoma (HNSCC). In particular, techniques for de-escalation of treatment of human papillomavirus (HPV)-associated oropharyngeal carcinoma (OPC) in order to reduce treatment-related toxicity and adding immunotherapy as part of first-line treatment for recurrent and/or metastatic (R/M) nasopharyngeal cancer (NPC). Results from combined therapy with PD-1 and CTLA-4 inhibitors in R/M SCCHN have also been reported.

To reduce chronic toxicity associated with radiation and/or chemotherapy, treatment deintensification approaches are of particular of interest in HPV-positive oropharyngeal cancer (OPC) patients with excellent prognosis. As transoral surgery (TOS) is resulting in more favorable functional outcomes it has been increasingly used and the first results of prospective studies are available. ECOG-ACRIN Cancer Research Group Trial (E3311) investigated transoral surgery (TOS) followed by adjuvant treatment based on pathological risk assessment in patients with HPV + OPC. The primary outcome of 2-year progression-free survival (PFS) was 94.9% in intermediate-risk patients treated with a reduced radiation dose of 50 Gy and 96.0% for intermediate-risk patients treated with a standard dose of 60 Gy. The results confirmed favourable outcomes with de-intensified postoperative therapy in intermediate-risk patients, superior to those when compared with standard chemoradiation.

Immunotherapy is now part of the standard of care in first and second-line treatment of R/M SCCHN. The phase III CheckMate 651 study evaluated dual immune checkpoint inhibitor therapy with nivolumab plus ipilimumab versus the EXTREME regimen (cetuximab plus cisplatin/carboplatin plus fluorouracil chemotherapy £ six cycles, followed by maintenance cetuximab) as first-line treatment for patients with platinum-eligible R/M SCCHN. Median OS was 13.9 months with nivolumab and ipilimumab compared with 13.5 months in patients receiving EXTREME. In patients who had higher PD-1 expression (combined positive score [CPS] ≥ 20), OS increased from 14.6 months to 17.6 months, but was not statistically significant. Interestingly, the 32.6-month duration of response is the longest ever reported in this population. Median PFS was shorter with nivolumab plus ipilimumab versus EXTREME in all populations. Nivolumab plus ipilimumab in the first-line setting did not result in a statistically significant improvement in survival compared with EXTREME in platinum-eligible SCCHN in all randomized or CPS ^{3}20 populations. The safety of nivolumab and ipilimumab compared favorably with EXTREME.

Immunotherapy has also been shown to play an important role in the first-line treatment of recurrent/metastatic nasopharyngeal cancer. In the phase 3 JUPITER-02 trial 289 patients with R/M NPC without prior chemotherapy for recurrent or metastatic disease were randomized (1/1) to receive toripalimab, a monoclonal PD-1 antibody, or placebo in combination with standard gemcitabine/cisplatin (GP) chemotherapy every 3 weeks for up to six cycles, followed by toripalimab monotherapy or placebo. In the interim analysis, toripalimab treatment provided a significant benefit, with median PFS improving from 8.0 to 11.7 months (HR, 0.52) and a 40% reduction in risk of death compared with placebo. Immature survival data suggest that overall survival is also likely to be affected. Treatment with toripalimab plus standard first-

line chemotherapy therefore resulted in improved PFS and ORR and longer duration of response (DoR) than treatment with chemotherapy alone, and without additional significant adverse effects.

Keywords: HPV-associated oropharyngeal carcinoma; de-escalation; immunotherapy; nasopharyngeal carcinoma; toripalimab

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S14 – ANTIBODY- DRUG CONJUGATES IN TREATMENT OF NON-SMALL CELL LUNG CANCER

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Even though both targeted and immunotherapy-based therapies have been established as frontline standard-of- care for patients with advanced non- small cell lung cancer (NSCLC), adverse events, resistance, and disease progression remain unavoidable in most cases. In this scenario, chemotherapy is a remaining salvage option, but it has a narrow therapeutic index. By harnessing the powers of both cytotoxic chemotherapy and targeted therapy, antibody- drug conjugates (ADCs) are unique in offering the potential to deliver highly potent cytotoxic agents to cancer cells which express a pre-defined cell surface target. These drugs have shown promising efficacy with limited toxicities compared to conventional treatment in many advanced solid tumors and have become a viable treatment option in NSCLC as well.

Structure and mechanism of action of ADCs

The basic components of an ADC are an antigen-specific monoclonal antibody (MoA) and a potent cytotoxic drug (the payload) connected via a chemical linker. Monoclonal antibody is targeted against a specific unique antigen with minimal cross reactivity and immunogenicity with normal tissue, and strong antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Cytotoxic drug is DNA damaging or microtubule disturbing agent. Antibody- drug conjugates with low drug to antibody ratio (DAR) may not offer the desired clinical effect while ADCs with high DAR can result in increased plasma concentration and off-target toxicity. The linker links the MoA with the payload. Ideally, the linker must be stable in the systemic circulation and efficiently cleaved inside the tumor cell to release the payload. The action of ADCs with cleavable linkers starts with circulating ADCs binding to the target antigen, internalization of ADC-antigen complex, then lysosomal fusion with the endosome resulting in the cytotoxic drug release. In addition to ADCs direct anti-tumor effects on antigen-positive tumor cells, the ADCs with cleavable linker also have the capacity to kill adjacent antigen-negative tumor cells, *(bystander effect)*.

Antigenic targets and ADC pharmacologic agents in NSCLC

Human epidermal growth factor receptor 2 (HER2) is coded by ERBB2 gene whose alterations (gene mutations, amplifications and HER2 protein overexpression) have been identified as oncogenic drivers and potential therapeutic targets in 2-4% of NSCLC.

Ado-trastuzumab ematansine (T-DM1) is a novel ADC that consists of anti-HER2 MoA trastuzumab linked to the microtubule inhibitor ematansine (DM1) via non-cleavable linker with DAR of 3.5. In the study of Li et al. T-DM1 showed an objective response rate (ORR) of 51% with a median PFS of 5 months in 49 patients with HER2-amplified or mutant metastatic NSCLC. Consistent responses were observed across HER2 status, with ORR of approximately 50%. Treatment was well tolerated.

Trastuzumab Deruxtecan (T-DXd) is a novel ADC that consists of trastuzumab conjugated to topoisomerase I inhibitor deruxtecan via a cleavable linker with DAR of 8. These characteristics allow for greater bystander effect and more anti-tumor activity despite low HER2 antigen density. A phase II trial (DESTINY-Lung01) evaluated the efficacy of T-DXd in advanced NSCLC in HER2 mutated and HER2 overexpressed cohort. Out of 91 patients in HER2 mutated cohort, the ORR was 54.9%, and median PFS and OS were 8.2 and 17.8 months, respectively. There were 46% patients with adverse events grade ≥ 3, and 26.4% cases of any- grade interstitional lung disease (ILD). In HER2-overexpressed cohort, out of 49 patients 24.5% had ORR, which did not differ in various HER2 expression status. The median PFS was 5.4 months. Grade ≥ 3 AEs were reported in 73.5% patients, and 16.3% developed drug related ILD. There are multiple ongoing clinical trials on T-DXd in advanced NSCLC.

Human epidermal growth factor receptor 3 (HER3) or ERBB3, a member of HER receptor family, is expressed in various cancers. Moreover, resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in lung cancer can be induced via MET amplification via HER3 activation of downstream signaling pathway.

Patritumab Deruxtecan (HER3-DXd) is a novel ADC that consists of anti-HER3 MoA patritumab linked to the topoisomerase I inhibitor DXd via a cleavable linker with DAR of 8. Tumors with EGFR-mutation are associated with higher expression of HER3 compared with EGFR wild-type NSCLC. Results of a phase I trial with HER3-DXd in patients with EGFR TKI- resistant NSCLC showed 39% ORR and 72% DCR and the activity of HER3-DXd across the spectrum of EGFR TKI resistance mechanisms including EGFR C797S, MET or HER2 amplification, and BRAF fusion. Grade ≥ 3 treatment related AEs occurred in

64% of patients; the rate of ILD was acceptable. Based on these promising results, FDA has given HER3-DXd breakthrough therapy designation and there are multiple ongoing clinical trials on HER3-DXd use especially in EGFR-mutant NSCLC.

Trophoblast cell-surface antigen (Trop-2) is a cell surface glycoprotein expressed in many epithelial cancer cells including lung cancer.

Sacituzumab govitecan (SG) is a novel ADC that consists of anti-Trop-2 MoA sacituzumab linked to the topoisomerase I inhibitor SN-38 via a cleavable linker with DAR of 7.6. In a phase I trial, 44 patients with refractory Trop-2 positive NSCLC achieved the ORR of 16.7%. The median DOR, PFS and OS were 6, 4.4 and 7.3 months, respectively. The most common reported grade ≥ 3 AEs was neutropenia (42.4%), and it is considered dose- limiting.

Datopotamab Deruxtecan (Dato-DXd)) is a novel ADC composed of anti-Trop-2 MoA datopotamab linked to topoisomerase I inhibitor deruxtecan via cleavable linker with DAR of 4. TROPION-PanTumor01 is an ongoing trial enrolling patients with Trop-2-expressing, advanced or refractory solid tumors. Data of 175 patients with NSCLC who received Dato-DXd showed ORR of 21-25%, depending on dose. The toxicity, including ILD, was dose- limiting, so dato-DXd at a dose of 6 mg/kg was selected in ongoing clinical trials.

Mesenchymal-to-epithelial transition (MET) receptor, or hepatocyte growth factor (HGF) receptor, is a transmembrane tyrosine kinase receptor encoded by MET proto-oncogene. In NSCLC, activating mutations in MET, including MET exon-14 skipping mutations, occur in about 3%. Amplification of MET occurs in 3% to 4% of treatment- naive NSCLC patients and in up to 20% in patients with acquired resistance to EGFR TKI. Due to increased prevalence of MET alterations and being involved in treatment resistance in NSCLC, MET represents a promising target for ADCs in NSCLC.

Telisotuzumab vedotin (Teliso-V) is a novel ADC that consists of anti-MET MoA ABT-700 linked to the microtubule inhibitor monomethyl auristatin E via a cleavable linker with DAR of 3.1. A phase II trial with Teliso-V was discontinued owing to toxicity and lack of efficacy. Teliso-V has been studied in patients with EGFR-mutant TKI-refractory NSCLC. In a phase Ib trial, 29 patients with MET-positive EGFR-mutant TKI- refractory NSCLC were enrolled. Patients were treated with oral erlotinib and intravenous teliso-V. Results were promising with an ORR of 34.5% and acceptable toxicity.

Future perspectives of ADCs in NSCLC

Antibody- drug conjugates are among the fastest growing drug classes in NSCLC. The development of next-generation ADCs with site-specific linker technology, enhanced mAb selectivity, and more effective cytotoxic payloads is presently underway, as are clinical trials with promising combinations of ADCs with agents such as tyrosine- kinase inhibitors or immune- checkpoint inhibitors as a strategy to overcome mechanisms of resistance to ADC treatment.

Keywords: non-small cell lung cancer; antibody-drug conjugates; targeted therapy; immunotherapy; chemotherapy

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S15 – PERIOPERATIVE IMMUNOTHERAPY FOR NSCLC

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Neoadjuvant immunotherapy provides an early opportunity to treat micrometastatic disease and enhances the immune response when bulk tumor and tumor antigens are still present during the treatment. The major pathologic response (MPR) of neoadjuvant immunotherapy ranged up to 45% when used alone, and up to 83–86% when used in combination with chemotherapy.

CheckMate816 is a phase III randomized trial designed to evaluate 3 cycles of neoadjuvant nivolumab plus platinum-doublet chemotherapy in patients with stage IB to IIIA resectable NSCLC. The primary end points were event-free survival (EFS) and pathological complete response (pCR). Nivolumab plus chemotherapy significantly improved the pCR compared with chemotherapy alone [24% vs. 2.2%; odds ratio (OR) = 13.94; P<0.0001]. The median EFS was 31.6 months in the nivolumab plus chemotherapy group and 20.8 months in the chemotherapy alone group [hazard ratio (HR): 0.63; P<0.005]. The percentage of patients with a MPR was higher with nivolumab plus chemotherapy (36.9% vs. 8.9%; OR: 5.70). At the first pre-specified interim analysis, the HR for death was 0.57 and did not meet the criterion for significance. Grade 3 or 4 treatment-related adverse events occurred in 33.5% of the patients in the nivolumab plus chemotherapy group and in 36.9% of those in the chemotherapy alone group.

In the adjuvant setting, two phase III studies announced positive results. IMpower010 randomized, open-label, phase III study included patients with stage IB to IIIA NSCLC (as per the 7th edition of the UICC/AJCC staging system). Patients were randomly assigned to receive atezolizumab (up to 16 cycles) or best supportive care (BSC) after complete resection and adjuvant chemotherapy. Atezolizumab significantly improved disease-free survival (DFS) in stage II–IIIA patients with programmed death-ligand 1 (PD-L1) was expressed on 1% or more of tumor cells (HR: 0.66; P=0·0039) with 3-year DFS rate of 60% in the treatment arm compared with 48.2% in the BSC arm, meeting one of its endpoints of this study. At 5 years the overall survival rate was 84,8% for stage II-IIIA and PD-L1 expression of at least 50% versus 67,5% in control arm.

The randomized, triple-blind phase III study KEYNOTE-091 evaluated the efficacy of adjuvant pembrolizumab (18 cycles) versus placebo after R0 resection (adjuvant chemotherapy was not mandatory) in treating stage IB to IIIA NSCLC (as per the 7th edition of the UICC/AJCC staging system). The dual primary endpoints were DFS in overall population and that of patients with high PD-L1 expression [tumor proportion score (TPS) ≥50%]. Pembrolizumab was found to significantly improve DFS in the overall population, with a median DFS of 53.6 months, which was significantly superior to that in the placebo group (median DFS 42.0 months; HR 0.76; P=0.0014). For patients with high PD-L1 expression pembrolizumab showed a favorable trend, but the pre-specified statistical difference was not reached. Safety profiles are as expected with no new safety signals. The OS data is not yet mature.

Keywords: neoadjuvant immunotherapy, adjuvant immunotherapy, NSCLC, PD-L1 expression

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S16 – IMPLEMENTATION OF IMMUNOTHERAPY IN PATIENTS WITH *CONTRAINDICATIONS* FOR THE SAME

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Immunotherapy has become the standard of care in the treatment of numerous solid tumors by providing the significant improvement in cancer patient survival. We can state unequivocally that it altered the game rules in cancer therapy. Unique population of cancer patients are patients with autoimmune disease, solid organ transplants, human immunodeficiency virus (HIV) infection, hepatitis B (HBV) and C (HCV) virus infection and patients receiving corticosteroid therapy. Due to concerns about potential toxicities, these patients were excluded from prospective clinical trials thus there are limited data on the effects, benefits and complications of immune checkpoint inhibitor (ICI) therapy in this population of patients. However, retrospective researches suggest that implementation of ICI therapy in this population of patients is safe and effective. Approximately 14%–25% of patients with lung cancer have autoimmune disease, with higher incidences in women, older patients and in patients with early stages of the cancer. Observational studies suggest that 24%-41% of these patients experienced immune-related adverse events, 22%-54% experienced a flare of the preexisting autoimmune disease and the response rates to ICI therapy in these patients were 22%-54%. Retrospective analysis suggest that the implementation of ICI therapy in patients with HIV, hepatitis B and C infection is safe. Approximately 50%-70% of patients with HIV infection experienced immune-related adverse events (mainly grade 1 or 2) and the response rate to ICI therapy in these patients were 17%-25%. Implementation of ICI therapy in patients with HIV infection is safe and effective as in general cancer patients. Regarding the patients with hepatitis B and C infection, implementation of ICI therapy in these patients confers the higher risk of viral reactivaction with the reactivation rate of 17%. There is a high incidence of de novo malignancies in organ transplant recipients. Implementation of ICI therapy in these patients confers the risk of graft rejection and is observed in 37%–41% of these

patients, resulting in graft loss in 80% of the cases and death in 38%–45% of the cases. In the cases of graft rejection, recommended therapy is high-dose corticosteroid or other immunosuppressive therapy and, in the cases of renal graft rejection, dialysis is often required. Real world data analysis of pembrolizumab monotherapy in patients with advanced, non-small cell lung cancer and the programmed cell death ligand-1 expression higher than 50%, suggest that the use of steroids, before or during the therapy with pembrolizumab, was associated with an 86% increase in the risk of progression and a 2.3-fold increase in the risk of death, even if the palliative use of steroid was taken into consideration (central nervous system metastasis etc.).

The approach to the implementation of ICI therapy in this unique population of patients should be individual considering the severity of the underlying disease (autoimmune disease, HIV etc.), severity of the cancer burden and potential therapeutic alternatives, other comorbidities and patients preferences. In conclussion, the key to the implementation of ICI therapy in these patients is close collaboration between different specialists (multidsciplinary specialist team) balancing the potential benefits and toxicity risks of ICI therapy.

Keywords: immunotherapy, autoimmune diseases, corticosteroids, solid organ transplants, infections, immune-related adverse events

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S17 – CASE REPORT OF SUCCESFUL MULTIDISIPLINARY TREATMENT FOR PATIENT WITH METASTATIC LUNG CANCER AND RELAPSED/REFRACTORY CHRONIC LYMPHATIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

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Introduction: Croatian National Cancer Registry of Croatian Institute for Public Health reported that in year 2020 lung cancer was the second most common cancer site diagnosed in men with 16% and the third most common in women with 10% incidence among all cancer sites. Unfortunatelly lung cancer has the highest mortality in both men and women. Haematological malignancies had 7% share in all malignancies in both male and female cances cases. In 2020 190 newly diagnosed cases of lymphatic leukemia in men and 128 cases in women were reporeted, meaning 1.5 and 1.2% of all malignancies, respectively. Chronic lymphatic leukemia (CLL) is an advanced age disease and incidence increases with age. Impaired immunity, T and B cell dysfunction in CLL, chromosomal aberations, long-term immunosuppressive therapy and genetic factors can all cause secondary malignancies. Co- occurence of solid tumors and CLL is very rare. Although patiens with CLL have an increased risk of developing second primary malignancies including lung carcinoma, the data about their clinical outcomes are lacking. Parekh et al. retrospectively analyzed patients with simultaneous CLL and lung carcinoma over a 20-year period, and they found that ~2% of patients with CLL actually developed lung carcinoma. The authors claimed that up to 38% of patients will also develop a third neoplasm more likely of the skin (melanoma and basal cell carcinoma), larynx (laryngeal carcinoma) or colon. Currently there are no specific guidelines for concurrent CLL and non-small cell lung carcinoma (NSCLC) treatment. Usually, when the tumors are diagnosed simultaneously, treatment is based to target the most aggressive malignancy, as the clinical outcomes depend on the response of the tumor with the poorest prognosis. For this reason, a multidisciplinary approach is mandatory.

Case report: A patient with history of coronary heart disease, myocardial infarction and paroxysmal atrial fibrillation was diagnosed in 2019 (at the age of 71) with B chronic lymphocytic leukemia with bulky tumor (inguinal lymph nodes 8x5 cm), stage B according to Binet, intermediate risk. He was treated with 6 cycles of chemoimmunotherapy (rituximab/cyclofosfamid/fludarabine). In 10/2019 remission was confirmed, but MSCT described tumor in the posterior segment of upper right lung lobe measuring 20x17 mm and bilateral metastases up to 11 mm. Bronchoscopy and biopsy were performed, and EGFR neg, ALK neg, ROS 1 neg, PD-L1>50% adenocarcinoma was confirmed. He was referred to Clinical Hospital Center Osijek where monotherapy with pembrolizumab in a standard dose of 200 mg intravenously was started in 01/2020. Partial remission was confirmed in October 2020. Immunotherapy was discontinued due to development of pneumonitis, dysphagia and severe weight loss (20kg), but without radiologically confirmed disease progression. At that time he was referred to our hospital for further treatment. Gastroscopy has shown erosive gastritis with active duodenal ulcus, Forrest III. Supportive therapy and proton pump inhibitor were introduced. After complete regression of pneumonitis, improvement of general condition and resolution of dysphagia, no signs of lung cancer progression were found and pembrolizumab was reintroduced in 12/2021. Hypothyroidism was diagnosed in 01/2021 and levothyroxine replacement ther-

apy was started. In 03/2021 he underwent surgical removal of basal cell carcinoma of skin on the right temporal region with lobe reconstruction. From 02/2021, when pembrolizumab was reintroduced, regression in tumor size was continously confirmed with complete recovery of general condition. He was hospitalized for COVID 19 infection in 09/2021, and due to complications pembrolizumab was discontinued till 11/2021. Lung cancer immunotherapy proceeded till 11/2022, when Multidisciplinary team decided to finish pembrolizumab because of CLL relapse. CLL was in remission till August 2022 when due to B symptoms, lymphcytosis, anemia and generalized lymphadenopathy, hematological workup including biopsy of cervical lymph node was performed and CLL/SLL relapse was confirmed. Initially chlorambucil was introduced, but disease was refractory. Based on cytogenetic test results (IGHV unmutated, negative TP53) and due to cardiovascular comorbidity (contraindication for BTK inhibitors) venetoclax and rituximab were started in 01/2023. After just 1 cycle of treatment normal blood count as well as regression of B symptoms and peripheral lymphadenopathy occured, indicating the probability of complete disease remission. In our patient with metastatic lung adenocarcinoma excellent disease control is achieved during 41 month of treatment in first line setting. Furthermore, relapsed/refractory CLL/SLL is currently in confirmed remission.

Conclusion: Successful treatment of patients with multiple primary malignancies is based on multidisciplinarity, early recognition and management of side effects, treatment of comorbidities with the aim of prolonging life, controlling symptoms of disease and preserving quality of life.

Keywords: multidisciplinary treatment, metastatic lung cancer, chronic lymphatic leukemia, small lymphocytic lymphoma

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S18 – IS THERE ANY NOVELTIES IN TREATING MELANOMA?

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Since 2011. new era in treating melanoma patients started with use of immunotherapy for all melanomas and targeted therapy for BRAF mutated melanomas.

Now we have published results of 5 years follow up in treating metastatic melanoma patients with ICI (immune checkpoint inhibitors). The combination immunotherapy (anti PD1 - nivolumab and anti CTLA4 - ipilimumab) versus mono therapy resulted in overall survival of 52% in the nivolumab-plus-ipilimumab group and 44% in the nivolumab group, as compared with 26% in the ipilimumab group. No new late toxic effects were noted.

The optimal sequencing treatment in metastatic melanoma with BRAF V600-mutation was evaluated in two prospective trials (SECOMBIT and DREAMseq) and updated results of these two studies shoved benefit of the use of combination ICI over targeted therapies in the first line setting. The SECOMBIT trial has observed that patients treated with ICI (immune checkpoint inhibitors) combination (ipilimumab plus nivolumab) before BRAF and MEK inhibition (encorafenib plus binimetinib) exhibited 3-year PFS (53% v 41%) and OS (62% v 54%) benefits when compared with the reverse sequence of those regimens.

The DREAMseq study compared the sequence of initial combination ICI versus targeted therapies and shoved 20% OS benefit at the 2-year for the first line therapy in BRAFV600-mutant metastatic melanoma if initially treated with combination ICI ipilimumab plus nivolumab (72%OS; 95%CI, 62 to 81) compared with initial treatment with BRAF and MEK inhibitors dabrafenib plus trametinib (52% OS; 95% CI, 42 to 62). These studies suggested the use of dual ICI therapy as first-line treatment in melanoma patients with BRAF mutations.

After ICI and BRAF-MEK combination therapy showed a significant effect in the treatment of metastatic disease, adjuvant trials were settled. The result of adjuvant combination targeted therapy trial (COMBI -AD) with dabrafenib et trametinib for stage III melanoma patients with BRAF V600E or V600K showed after the 5 years, that 52% of patients were alive and without relapse with dabrafenib plus trametinib and 36% with placebo. The percentage of patients who were alive without distant metastasis was 65% with dabrafenib plus trametinib and 54% with placebo with no manifest long-term toxic effects.

The results from adjuvant trial comparation nivolumab versus ipilimumab for patients stage IV melanoma with no evidence of disease after resection or radiotherapy, are available after 4 years. The 4-year recurrence-free survival in the nivolumab group shoved 51,7% and 41.2% in the ipilimumab group, and the 4-year overall survival of 77.9% with nivolumab and 76.6% with ipilimumab. Nivolumab remains an efficacious adjuvant treatment for patients with resected high-risk melanoma, with a safety profile that is more tolerable than that of ipilimumab.

The trials of adjuvant treatment have also started for stage II. Adjuvant pembrolizumab showed after a median follow-up of 20,9 months that 15% of patients in the pembrolizumab group and 24% in the pla-

cebo group had a first recurrence or died. According to these results pembrolizumab as adjuvant therapy for stage IIB or IIC melanoma resulted in a significant reduction in the risk of disease recurrence or death versus placebo, with a manageable safety profile.

Anti PD-1 and BRAF-MEK targeted therapy shoved excellent results in treating melanoma patients, but still there are need for choosing the right timing and finding predictable biomarkers for best response for each individual patient.

Keywords: melanoma, targeted therapy, immunotherapy

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S19 – THE OPTIMAL TREATMENT OF CUTANEOUS NON-MELANOMA SKIN CANCERS

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Within the wide range of non-melanoma skin cancer (NMSC), the most common are basal cell carcinoma (BCC), and, less frequently, cutaneous squamous cell carcinoma (CSCC).

NMSC is usually cured by surgical resection. However, in rare cases, it can progress to locally advanced and/or metastatic disease.

Risk factors for the advanced disease include comorbidities, ignoring the disease until the advanced stage, and immunosuppression.

If surgical or radiation therapies are not feasible, advanced NMSC may require systemic treatment. Chemotherapy and, later on, epidermal growth factor receptor (EGFR) inhibitors in CSCC, and hedgehog inhibitors in BCC, have been used but are generally of limited benefit, with responses often short-lived and with toxicity issues.

Due to the high mutational burden of NMSC, the use of immunotherapy has been investigated. Nowadays, two anti-PD-1 antibodies, cemiplimab and pembrolizumab, are approved for the treatment of advanced CSCC that is not curable by surgery or radiation. Both have shown durable responses with good tolerability in patients in phase II trials.

Anti-PD-1 therapy is now the standard of care for locally advanced and metastatic CSCC. PD-1 blockade is also approved as second-line therapy in advanced BCC, with frequent and durable responses after failure on hedgehog inhibitor therapy. PD-1 checkpoint inhibition is being assessed for NMSC in combination with other modalities, including oncolytic viruses and EGFR inhibitors.

Adjuvant and neoadjuvant use of cemiplimab and pembrolizumab is also being investigated in several ongoing trials. Further clinical trials of immunotherapy must be prioritized in NMSC for further improvement in outcomes.

Keywords: non-melanoma skin cancer, basal cell carcinoma, cutaneous squamous cell carcinoma, Hedgehog-inhibitors, immunotherapy, anti-PD-1 therapy

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S20 – IMMUNOTHERAPY IN THE TREATMENT OF GYNECOLOGIC TUMORS

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Organ-classified gynecologic cancers (ovarian/tubal/peritoneal, endometrial, cervical, vaginal, vulvar) have different characteristics, biology, therapies and outcomes. During the past decade, attempts have been made to subclassify them as to their heterogeneity based on next-generation profiling.

The cornerstone of the treatment for gynecologic cancers is surgical resection followed by chemotherapy, radiotherapy, targeted therapy and increasingly immunotherapy. Immunotherapy is expected to mediate tumor destruction and drive local inflammation in the tumor microinvironment but also trigger coordinated induction of multiple counter-regulatory and supressive pathways. Observations in patients with gynecologic malignancies emphasize that favorable impact of tumor-driven immune responses is associated with improved survival in patients with ovarian, endometrial and cervical cancer.

Immunotherapeutic strategies seek to induce tumor-directed immune responses through tumor antigen selection in vaccine-based approaches, reinvigorate antitumor responses using immune checkpoint inhibitors and expand T-cell populations using adoptive cellular therapy.

One of the first evidence that immune therapy might be beneficial in ovarian cancer patients was the recognition that tumor-infiltrating lymphocytes (TILs) play an important role in the tumor rejection and prognosis.

For advanced and relapsed endometrial cancer, new treatment options are urgently needed bacause standard first line chemotherapy with carboplatin and paclitaxel and subsequent therapies with agents like doxorubicin or topotecan have low/minimal activity. Beside targeted therapy, including combinations with endocrine therapy and CDK4/6 inhibitors or VEGF/R inhibitors or FGFR inhibitors, application of immunotherapy might have strong impact in these stages of disease. There are limited data available for a specific immunotherapeutic approach in endometrial cancer despite the knowledge that high mutational load tumors are expected to respond well.

Although the incidence of cervical cancer has significantly decreased in developed countries due to increased screening and HPV vaccination, limited therapeutic options contribute to poor prognosis in advanced disease. In cervical cancer, T cell cytotoxic responses are impared which was concluded from presence of CD4+ lymphocytes in precursor lesions and CD8+ lymphocytes in malignant tumors, in the absence of an effective immune response. Natural killer and cytotoxic T cells, which have a key role in the elimination of virus-infected and tumor cells, are present at reduced levels in both patients with cervical cancer and cervical intraepithelial neoplasia.

Immunotherapy as monotherapy has shown to be successfull in certain tumor types like melanoma and lung cancer while the situation is less clear in gynecologic cancers. The modest responses with immune checkpoint blockade monotherapy underscore the general principle that immunogenicity and anti-tumor responses may be largely driven by neoantigens as opposed to PD positivity and strategies to alter the

immunological response with combination therapies are needed. Current trials aim to examine the combination between immune checkpoint inhibitors and VEGF inhibitors or PARP inhibitors in patients with gynecologic cancers.

Key words: immunotherapy, immune checkpoint inhibitors, cytotoxic T cells

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S21 – NEWS IN MOLECULAR DIAGNOSTICS AND TREATMENT OF METASTATIC ENDOMETRIAL CANCER

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Endometrial cancer (EC) is the most common gynecological cancer. The incidence is rising due to increased obesity and aging of the population. In Croatia, it is the fourth most common cancer in women with 688 new cases and 185 deaths in 2020. Traditionally, EC has long been divided into two subtypes: type I (associated with estrogen stimulation) and type II (estrogen independent). However, in recent years, there is a new classification system based on molecular phenotype which are proposed by The Cancer Genome Atlas (TCGA). It is based upon the combination of somatic mutation burden and somatic copy number alterations and four different molecular subclasses have been identified: POLE- mutant, microsatellite-unstable (MSI), copy-number high (p53 positive) and copy-number low (no specific molecular profile or NSMR). Several studies have reported the strong prognostic value of molecular subgroups, and the PORTEC 3 trial also reported their predictive value. Patients in the POLE-mutant subgroup have an excellent prognosis with only occasional relapse, regardless of receiving adjuvant treatment. Copy-number high patients have the worst prognosis and generally benefit from adjuvant chemotherapy. Patients in MSI or NSMR subgroups have intermediate prognosis and little benefit from adjuvant chemotherapy. The new ESMO-ESGO ESTRO guidelines have included molecular classification as a factor in determining adjuvant therapy in early stage disease.

The ongoing PORTEC4a, TAPER and the TransPORTEC RAINBO trials will determine the value of integrating molecular parameters in adjuvant treatment.

Currently, the standard chemotherapy regimen for advanced, metastatic or recurrent disease is paclitaxel/carboplatin, but there is no standard second line therapy. New therapies have been investigated, and molecular profiling of the tumor is being used to try to find new predictive biomarkers for targeted therapy.

For patient with serous EC overexpressing human epidermal growth factor receptor 2 (HER2), addition of trastuzumab to front line chemotherapy and continuing it as maintenance therapy is an option.

For some patients with metastatic or recurrent disease, endocrine therapy is a reasonable alternative to chemotherapy, especially for low-grade tumors that are positive for estrogen and progesterone receptors. The PI3K/AKT/mTOR pathway is the most frequently altered pathway in EC tumors and patients with this dysregulation may be candidates for mTOR inhibitors. In hormone receptor positive tumors, the combination of endocrine therapy and mTOR inhibitor has been shown to be effective, especially in chemotherapy-naive patients. Another novel combination with hormone therapy that has made recent advances is the cyclin dependent kinase (CDK) 4/6 inhibitors. Tumors in copy number low group have a high proportion of hormone receptor positivity.

Bevacizumab (an antiangiogenic therapy) did not improve the outcome in EC patients but a subsequent subanalysis showed that it was beneficial in those with poor risk factors. Patients with CTTNB1 mutated tumors benefited most from bevacizumab but they also responded to the combination of everolimus and letrozole.

Mismatch repair-deficiency (dMMR), high MSI and high tumor mutation burden (≥ 10 mut/Mb) are effective biomarkers for immunotherapy with checkpoint inhibitors. Pembrolizumab and dostarlimab are PD-1 inhibitors which have been approved for patients with dMMR/MSI-H recurrent EC. Single agent immunotherapy is less effective in tumors that are MMR proficient (pMMR) or microsatellite stable (MSS). In these patients, the combination of lenvatinib and pembrolizumab is an effective option.

Patients with TP53 mutated tumor have the poorest outcomes. In this group, therapy with PARP inhibitors has been investigating.

In patients with recurrent uterine serous cancer, an oral Wee1 inhibitor (adavosertib) has shown clinical activity and demonstrated reduction in disease progression.

With increasing knowledge of the molecular alterations of EC, their prognostic and predictive value, it is expected that treatment decisions will be based on tumor molecular characteristics.

Keywords: endometrial cancer, molecular subtype, targeted therapy

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S22 – VULVAR CANCER-CASE REPORT

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Background: Vulvar cancer is a rare gynecological malignancy and accounts for about 5% of all gynecologic neoplasms. The population incidence rate of vulvar cancer is approximately 2.6 per 100,000 in the United States and the incidence has been gradually increasing during the past few years. According to the Croatian National Cancer Registry the incidence rate of vulvar cancer in 2020 per 100 000 women was 4.8. Squamous cell carcinoma is the most common histologic type of vulvar cancer, comprising over 90 percent of cases. Other histologies include melanoma, basal cell carcinoma, Bartholin gland adenocarcinoma, sarcoma and Paget disease. Risk factors include HPV infection, vulvar or cervical intraepithelial neoplasia, a prior history of cervical cancer, cigarette smoking, vulvar skin conditions (lichen sclerosus) and immunosuppression. The average age at the time of diagnosis is about 70 years. The most common presenting symptom is a persistent lump or sore on the vulva. Diagnosis is confirmed by biopsy of the affected area. Staging is based on the size and extent of the tumor, involvement of lymph nodes and distant organs. Treatment options depend on the stage and location of the tumor. Surgery is the mainstay of treatment with options including radical local excision, radical vulvectomy and lymph node dissection. For patients with unresectable, locally advanced disease chemoradiation is preferred. For patients who initially present with stage IVB chemotherapy with the combination of carboplatin and paclitaxel is a preferred treatment option. Patients with FIGO stage I or II have a 5-year disease-free survival (DFS) rates of 86% and 60 %. Patients with stages III and IV tend to recur and metastasize very often and have 5-year DFS of 49% and 22%. Overall, early detection and prompt treatment are essential for improving the prognosis of vulvar cancer. Regular gynecologic exams and HPV vaccination can help prevent the development of this disease.

Case: In January 2022, a 70 year old female presented with a large, exophytic necrotic vulvar mass which destroyed the entire external genitalia. Urethra was infiltrated and the patient was unable to urinate so suprapubical cystostomy was performed. She was also unable to sit down because of the pain due to the large tumor mass. ECOG PS was 1-2. In medical history: Arterial hypertension; Mild mitral valve insufficiency; Tobacco use for more than 50 years. Biopsy confirmed a well differentiated HPV related invasive

squamous cell carcinoma. CT revealed inhomogeneously imbibed vulvar mass 147x55 mm with infiltration of the urethra. Retroperitoneal, bilateral inguinal and parailiac lymph nodes were enlarged. These findings confirmed the diagnosis of FIGO IVB stage and neoadjuvant chemotherapy was initiated with paclitaxel and carboplatin. After 2nd cycle she already had a marked local response and was able to sit down without pain. After 4nd cycle genitourinary exam revealed significant reduction of tumor mass by more than half. At the completion of 6th cycle CT showed normalization of the prior enlarged retroperitoneal and bilateral parailiac lymph nodes from 12 to 6 mm and reduction of inguinal lymph nodes from 16 to 10 mm. Three weeks after completion of neoadjuvant chemotherapy she started chemoradiation. Radiotherapy was performed by VMAT technique. She received radiation to the distal paraaortic region, pelvis, vagina and vulva in a dose of 45 Gy in 25 fractions with a weekly application of Cisplatin a total of 5 times. Simultaneously she received boost integrated radiation on enlarged inguinal lymph nodes to a total dose of 60 Gy in 25 fractions. After 25 fractions sequential boost radiation (20Gy/10x) on the vulva and vagina to a total dose of 65 Gy was performed. During radiotherapy there was one break of 2 weeks due to the development of radiation dermatitis. She finished her therapy in November 2022. One week ago she came to the first control exam after therapy. Subjectively she is in a good general condition, ECOG PS 0-1, denies any major pain. On control CT there is no visible mesenteric end retroperitoneal lymphadenopathy, and in the inguinal area several nodes from 6-10 mm. Genitourinary exam revealed large ulceration affecting the labia majora and minora on the left with a deep necrotic bottom. Citology was performed-findings: Atypical squamous cells (ASC). Then a biopsy was made-findings: Inflammatory and necrotic detritus. She was referred for a PET/CT scan for insight into the metabolic activity of primary disease and decision on further procedure. The documentation and the tissue sample from the initial biopsy are submitted for Foundation Medicine testing.

Keywords: vulvar cancer; chemotherapy; VMAT

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S23 – CHALLENGES IN TREATMENT OF HER2 POSITIVE AND HER2 LOW BREAST CANCER

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In breast cancer, HER2 overexpression is seen in about 20% of cases and it is known for its aggressive nature and behavior. In recent years knowledge of HER2 status and its importance is rapidly changing and now the milieu od HER2 nature is more complex, especially since we have therapies with efficacy in HER2 low breast cancer. Targeted therapies substantially improve prognosis, decrease risk of recurrence and improve survival both in early and advanced breast cancer. In early breast cancer, all HER2 positive tumors bigger than two centimeters in diameter and/or N+, should receive neoadjuvant chemotherapy with with pertuzumab and trastuzumab. In this setting approach without antracyclins is possible, as was shown in TRAIN-2 clinical study which included carboplatin with same rates of pCR. After neoadjuvant therapy and surgery, adjuvant approach depends on response of the disease. If pCR is achieved with initally N+ disease, dual therapy with pertuzumab and trastuzumab continues, according to results of APHINITY trail. After 8.4 years mFU s benefit of dual blockade was seen with improved IDFS by 23% in N+ patients. In N0 patients and achieved pCR, adjuvant trastuzumab is recomended. In absence of pCR, HER2 therapy should be changed to trastuzumab-emtanzine (T-DM1), as seen in KATHERINE trial (51% risk reduction of disease relapse). Recently published data on adjuvant neratinib (EXTENET trial), showed in early breast cancer significantly improved iDFS in patients with HR+/HER2+ breast cancer. No improved OS was found, although there was a trend favoring neratinib (HR of 0.79).

In advanced disease, preferred first line of therapy includes pertuzumab and trastuzumab, initially with chemotherapy, and in prolonged treatment with dual HER2 blocade +/- endocrine therapy. Final analysis of CLEOPATRA trial, after 8 years of FU showed improved mOS - one and a half years longer. After progression, new second line treatment is established. According to DESTINY Breast03 trial, trastuzumab-deruxtecan (T-dxD) showed significantly better PFS and OS when compared to T-DM1. At 12 months PFS was 75.8% vs 34.1% and OS 94.1% vs 85.9%. Destiny breast 04 was clinical trial with T-dxD, which showed unprecedented efficacy in HER2 low metastatic breast cancer, in previously treated patients. In HR+ cohort (88.7% pts) mPFS was 10.1 vs 5.4 months, and mOS 23.9 vs 17.5 months. Among all patients, the mPFS was 9.9 vs 5.1 months and mOS 23.4 vs 16.8 months. The results of this trial opened a whole new chapter in treating breast cancer. There are new ADCs targeting other members of HER family, inluding patritumab-deruxtecan which is anti-HER3 inhibitor. In phase1/2 trial median treatment duration was 5.9 months and efficacy was shown in HR+, TNBC and HER2+ MBC. In patients with active untreated brain metastases, as in ITT population, substantial impact showed tucatinib (in combination with trastuzumab and capecitabine). HER2CLIMB clinical trial and included patients that previously progressed on trastuzumab, pertuzumab and TDM-1. Other TKIs that showed efficacy include lapatinib (now in later lines), and neratinib in combination with capecitabin when compared to lapatinib/capecitabin (NALA trial). Another ADC, trastuzumab duocarmycin (SYD985), in the phase III TULIP study was associated with significant improvement in PFS in patients with HER2+ MBC with mPFS od 7.0 vs 4.9 moths. In PHOEBE trial patients that previously received trastuzumab and chemotherapy, were included to recieve pyrotinib (pan-HER inhibitor) or lapatinib with capecitabin. Combination with pyrotinib improved mPFS: 12.5 vs 6.8 months and ORR 67.2% vs 51.5%. In PANACEA trial with pembrolizumab and trastuzumab, 15%

response was seen in PDL1+ patients. KATE2 trial that combined atezolizumab and TDM1 showed numeric trend to better PFS and OS in PD-L1+ patients. Moreover, CDK4/6 and HER2 signaling association has been proved. In MonarcHER trial, patients received trastuzumab and fulvestrant with abemaciklib, abemaciclib or chemotherapy with a trastuzumab. Improved PFS was observed in triplet combination (8.3 vs 5 months), and ORR (33% vs 14%).New HER2 targeting therapies include bispecific antibodies , directed at two distinct domains of HER2 receptor, or at HER2 and immune cells. Zanitamab (ZW25) is bispecific antibody with activity in pretreated patients, it is under investigtion in luminal HER2 positive BC with fulvestrant and palbociklib or with CD47 blocker in HER2 low BC. New antibody showing promising results is KNO26 in heavily pretreated patients with ORR of 28% and mPFS od 6.8 months. Zenocutuzumab is bispecific antibody inhiting HER2–HER3 signalling. In triplet with trastuzumab and vinorelbine demonstrated a CBR of 35% at 6 months in patients which progressed on prior anti-HER2 therapies.

Although major aprovements are seen, many questions and challenges still lie in front of clinicians.

Keywords: breast cancer; HER2 positive; HER2 low

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S24 – NEOADJUVANT AND ADJUVANT TREATMENT OF TRIPLE NEGATIVE BREAST CANCER

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Triple-negative breast cancer (TNBC) is a term historically applied to cancers lacking expression of hormonal receptors and HER2 protein which behave more aggressively than other breast cancer (BC) subtypes.

Early TNBC can be treated with neoadjuvant systemic therapy (NAT) applied before or, nowadays less often, with adjuvant therapy (AT) applied after the surgery.

Generally, NAT is preferable approach in patients with locally advanced BC or in those who cannot obtain adequate cosmetic outcome with breast conservation techniques as well as in those with aggressive subtypes like TNBC or HER2 positive BC. Achievement of pathological complete response after NAT is associated with improvement in disease-free survival (DFS). Patients with smaller TNBCs (under 2 cm) can also be offered NAT as they might be candidates for additional treatment in the adjuvant setting in the case of residual disease.

Standard NAT for TNBC is still chemotherapy based on anthracyclines and taxanes. Some recent trials confirmed benefits of platinum addition to the NAT in the context of improved pCR rate, followed by improvement of event-free survival (EFS) and DFS, particularly in young patients and irrespective of eventual addition of immunotherapy with checkpoint inhibitor.

Nowadays, standard NAT for TNBC should also incorporate immunotherapy pembrolizumab in patients who do not have contraindication. Pembrolizumab continuation is also recommended after surgery irrespectively of response to NAT, although benefit of checkpoint inhibition in the adjuvant setting is still matter of investigation. At this point of time, it is unknown who could benefit most from addition of pembrolizumab as PD-L1 expression was not confirmed to be useful.

In patients with residual disease, AT with capecitabine as well as with PARP inhibitor olaparib in patients with germline BRCA mutation, can be used. Some smaller studies suggest that combinations of those drugs – capecitabin and olaparib with checkpoint inhibitor pembrolizumab have acceptable safety profiles and can be considered in certain circumstances.

Patients diagnosed with TNBC who initially underwent surgery are in the majority of cases candidates for AT most often chemotherapy based on anthracyclines and taxanes. Chemotherapy can only be omitted in very small tumors, smaller than 5 mm and node negative. Although, in some patients with tumors close to 5 mm, it is reasonable to proceed with chemotherapy. In high-risk patients with germline

BRCA mutation, who initially underwent surgery and are node positive or have tumor ≥ 2 cm, following adjuvant chemotherapy, it is reasonable to proceed with adjuvant treatment with PARP inhibitor olaparib.

Patients with TNBC who did not respond well to the NAT represent significant unmet need subgroup. Therefore, there are many ongoing trials investigating possible candidate drugs like antibody-drug conjugates such as sacituzumab govitecan and datopotamab deruxtecan, which have shown to be active in chemo-refractory tumors in the advanced setting and are now under investigation in post-neoadjuvant setting.

Keywords: triple negative breast cancer, neoadjuvant treatment, adjuvant treatment

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S25 – CHECKPOINT INHIBITOR THERAPY FOR METASTATIC TRIPLE-NEGATIVE BREAST CANCER

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Immunotherapy has changed the paradigm of cancer treatment and become a standard of cancer treatment in many malignancies, though its application in breast cancer remains limited. Of the breast cancer subtypes, triple-negative breast cancer (TNBC) is characterized by immune activation and infiltration and more commonly express biomarkers associated with response to immunotherapy. Immunotherapy can provide a durable response in tumors characterized by tumor cell or infiltrating immune cell PD-L1 (programmed death-ligand 1) positivity, a ligand which typically binds to PD-1 on T lymphocytes to inhibit immune clearance of tumor cells. By blocking this interaction with PD-1/PD-L1 inhibitors, the immune system becomes able to recognize and eliminate tumor cells.

Immune checkpoint inhibitors showed modest response rates as monotherapy only in a select group of patients. Further efforts have been made through the evaluating these agents in combination with chemotherapy, hypothesized that additional agent may help create an inflamed tumor microenvironment that stimulates responses to immunotherapy, knowing that chemotherapy administration may lead to releasing of high level of antigens from tumor cells, suppressive immune cells depletion and PD-L1 upregulation.

Till now, atezolizumab (PD-L1 inhibitor) and pembrolizumab (PD-1 inhibitor) have approval for metastatic PD-L1 positive TNBC cancer, both in combination with chemotherapy.

Atezolizumab and nab-paclitaxel as the first line treatment for mTNBC with PD-L1 expression was analyzed in Impassion130 phase III trial. Patients were randomized 1:1 to receive atezolizumab plus nab-paclitaxel compared with placebo plus nab-paclitaxel. The chemotherapy agent nab-paclitaxel was chosen to mitigate the need for pre-treatment steroids which can cause immunosuppression. PD-L1 expression was defined as >1% staining positive on tumor-infiltrating immune cells. In both treatment arms, 41% of patients had PD-L1-positive tumors. The primary endpoint was progression free survival (PFS). Median PFS was 7.2 months with atezolizumab and nab-paclitaxel, as compared with 5.5 months with placebo plus nab-paclitaxel, (HR:0.80, p=0.0025). Among patients with PD-L1-positive tumors, median PFS was 7.5 months and 5 months, respectively, which was statistically significant ($p \leq 0.001$). The trial met its PFS endpoint in the intent-to-treat (ITT) and PD-L1-positive group. The median OS in the ITT was not significantly different between the study arm (21.3 vs 17.6 months, p=0.08). In the PD-L1-positive subgroup, final

OS analysis showed improvement of 7.5 months (24.5 vs 17.9 months). But, formal statistical testing could not be conducted due to the pre-specified hierarchical statistical analysis plan requiring a statistically significant median OS in the ITT population.

Phase III IMpassion131 trial tried to answer the question whether paclitaxel could replace nab-paclitaxel in combination with atezolizumab in the first line setting. There were not improvements either in PFS or OS. Reasons are not clear.

Pembrolizumab has been evaluated in KEYNOTE-355, phase III study in patients with metastatic TNBC, which randomized eligible patients 2:1 to receive chemotherapy with or without pembrolizumab. This study evaluated the efficacy of combination chemotherapy-immunotherapy with taxane and non-taxane based regimen. Eligible patients were treatment naïve in the advanced setting and had a disease-free interval (DFI) of ≥ 6 months from completion of adjuvant chemotherapy. The PFS benefit was reported with the addition of pembrolizumab to chemotherapy in patients who had a CPS ≥10 (9.7 vs 5.6 months, HR 0.65, p=0.0012). The PFS benefit was larger in a taxane regimen (HR 0.51, 95%CI 0.33–0.78). Benefit from the addition of pembrolizumab was greater for patients with CPS ≥10 than CPS ≥1.This trial supports the use of a non-taxane regimen combined with a checkpoint inhibitor that can be used in the first-line setting for metastatic TNBC and can be considered to treat patients with a DFI as short as 6 months. Od note, in those trials, study population is slightly different, also PD-L1 positivity was defined by two different tests.

A variety of targeted agents have also been evaluated in combination with immunotherapy in the treatment of metastatic TNBC such as PARP, CDK4/6, AKT and MEK inhibitors and vaccines (1). Antibody-drug conjugates (ADCs) in the treatment of mTNBC is also an area of intense interest as well as dual CTLA4 and PD-L1 blockade.

In conclusion, according to currently available data, checkpoint inhibitor therapy should be offered to metastatic TNBC patients with an identified biomarker predictive of response (i.e., PD-L1 overexpression or an elevated CPS). Patients should be evaluated for biomarkers of response at time of initial diagnosis, with immunotherapy utilized in the first-line setting when possible. It is not clear if one checkpoint inhibitor is better than another, nor which biomarker assay most reliably predicts for response.

Keywords: triple-negative breast cancer, metastatic, immunotherapy, checkpoint inhibitor

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