ORAL PRESENTATIONS

S1 - THE ROLE OF IMMUNE CHECKPOINT INHIBITORS IN TREATMENT OF TRIPLE NEGATIVE BREAST CANCER

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The triple negative breast cancer (TNBC) had been known for the worst survival rates among all breast cancer subtypes and, from historical point of view, systemic chemotherapy improved median overall survival (OS) for advanced/metastatic TNBC (a/mTNBC) from 5.9 to 12.9 months, making it still the most *uncurable* subtype of breast cancer(1). Considering the early TNBC (eTNBC) the constant challenge are high recurrence rates after primary treatment - surgery and adjuvant/neoadjuvant systemic chemotherapy along with the locoregional radiotherapy(2).

The immune checkpoint inhibitors have been introduced in clinical practise for the treatment of a/mTNBC in 2018 along with the publication of the results of the IMpassion 130 study(3). This study showed significantly longer PFS for the a/mTNBC patients with PD-L1>1%, treated in the first line setting with atezolizumab + nab-paclitaxel compared with nab-paclitaxel alone, PFS 7.5 vs 5.0 months with HR 0.62 (95%CI 0.49-0.8). Moreover, median OS improved from 15.5 to 25.0 months with the addition of atezolizumab with HR 0.62 (95%CI 0.45-0.86) for PD-L1 positive group. In 2020 FDA granted fast approval for another ICI, pembrolizumab, due to primary analysis of KEYNOTE-355 study(4). In this study pembrolizumab was combined with chemotherapy in first line setting for a/mTNBC for the patients with CSP >10, in combination with different chemotherapy back-bone (nab-paclitaxel/paclitaxel/gem-carbo). Patients treated with pembrolizumab + chemotherapy achieved median PFS 9.7 months compared to control treated with chemotherapy alone with PFS 5.6 months HR 0.66 (95% CI, 0.50-0.88). In 2022 final results of the study showed significantly better OS results for pembrolizumab CPS>10 group, 23.0 vs 16.0 months, respectively, with HR 0.73 (95% CI, 0.55-0.95). Today, NCCN guidelines recommend pembrolizumab with chemotherapy as the first line therapy for a/mTNBC while ESMO guidelines recommend both atezolizumab and pembrolizumab in combination with chemotherapy for selected a/mTNBC with positive PD-L1 status(5).

There are numerous ongoing studies exploring further the potential benefit of treatment with ICI in a/mTNBC mostly in combination with antibody drug conjugates (ADC). Particularly noteworthy are the results of the phase 1b/2 BEGONIA study. The study was evaluating combinations of durvalumab (D) with other novel therapies in the first line treatment of a/mTNBC. At the last ESMO meeting the results for Arm 7 were presented where durvalumab was combined with ADC datopotamab-deruxtecan (Dato-DXd). Primary endpoints of the study were safety and tolerability and secondary endpoints were overall response rates (ORR), PFS and duration of response (DoR). At median follow up of 7.2 months ORR was 74%, median PFS was 13.8 months (95% CI, 11.0-NC) and median DoR was 15.5 months (95% CI, 9.92-NC). Although, it was a phase 1b/2 study the results were very promising. In line with the results of BEGONIA Arm 7, TROPION-BREAS-05 study was created, which will compare the standard first line a/mTNBC therapy, pembrolizumab with chemotherapy, versus the combination of Dato-DXd/D. Primary analysis of the study is expected in September 2026.

Quite differently from the mTNBC studies exploring ICI treatment in eTNBC showed positive PD-L1 status in not required nor predictive for ICI treatment response. Many studies with different ICI in different treatment scenarios explored whether addition of ICI to chemotherapy could lead to better event free

survival (EFS) or OS outcomes. In the IMpassion031 study atezolizumab was administered in neoadjuvant setting with nab-pacli/ddAC and then continued after the surgery as adjuvant therapy for one year, versus neoadjuvant chemotherapy(6). The pathologic complete response (pCR) rates for atezolizumab group were 58% vs 44%, 2-EFS years rates for ITT population were 85% vs 80%, numerically improved, but without significant statistical difference. On the other hand, in the NeoTRIPaPDL1 study atezolizumab was given in combination with neoadjuvant chemotherapy (carboplatin + nab-pacli) with control group receiving only neoadjuvant chemotherapy. After the surgery both groups received adjuvant chemotherapy (AC/EC/FEC)(7). The study did not meet endpoints: pCR rates and 5-year EFS rates. Different approach was taken in the GeparNuevo, phase II study, where durvalumab was applied 2 weeks before the start of neoadjuvant chemotherapy and then continued as addition to neoadjuvant chemotherapy (nab-paclitaxel/ddEC), but durvalumab was not given after the surgery in adjuvant setting, the control group was treated with neoadjuvant chemotherapy only(8).The study showed pCR rates of 53% vs 44%, and impressive results of OS; 3-year OS 95% vs 83%, HR 0.24 (95% CI 0.08-0.72). And last but not least, the KEYNOTE-522 study with pembrolizumab along with the neoadjuvant chemotherapy (paclitaxel + carboplatin/AC) and adjuvant pembrolizumab after the surgery for one year, versus control treated with neoadjuvant chemotherapy only(9). The study included T2N0 and T1-T4N+ patients. The pCR rates in this study were 64.8% vs 51.2% and 3-EFS rates were 84% vs 76.8%, respectively, with HR 0.63 $p<0.001$. The result of KEYNOTE-522 made pembrolizumab, in combination with neoadjuvant chemotherapy + adjuvant pembrolizumab, the new standard of care treatment for high risk eTNBC.

There are still many unanswered questions considering eTNBC treatment with ICI. Firstly, taking into account immune related adverse events, which can appear long after the treatment with ICI finished, the question raised how to select patients and which is optimal sequencing, duration and combination to maximise potential benefit from ICI? Ongoing studies are addressing the questions of therapy de-escalation. For example, the Optimice-pCR study is recruiting the patients with pCR after neoadjuvant pembrolizumab + chemotherapy treatment, continuing adjuvant pembrolizumab versus placebo(10). On the other hand, The NeoSTAR, phase 2 study, is questioning de-escalation by omitting anthracyclines from chemotherapy back-bone. The study explores the efficacy of Sacituzumab-govitecan in combination with pembrolizumab in neoadjuvant setting with adjuvant pembrolizumab + chemotherapy that does not contain anthracyclines (paclitaxel/carboplatin)(10). Secondly, what about the patients treated with neoadjuvant pembrolizumab + chemotherapy but without pCR and RCB III? Current studies with adjuvant Sacituzumab-govitecan, datopotamid-deruxtecan or durvalumab will give us valuable information regarding that question(10). Thirdly, we still do not have reliable predictive biomarkers for the treatment of eTNBC with ICI. Hopefully, near future will give us all the answers needed and help us improve furthermore the treatment outcomes for TNBC patients.

Keywords: immune checkpoint inhibitors, triple negative breast cancer

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S2 – NEOADJUVANT AND ADJUVANT TREATMENT OF MUSCLE-INVASIVE BLADDER CANCER

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Urothelial carcinoma of the bladder is one of the most prevalent cancers worldwide, diagnosed as muscle invasive in 25% of cases.

Muscle-invasive bladder cancer (MIBC) is a highly aggressive chemo-sensitive disease with nearly 50% of patients developing metastatic disease, likely owing to the presence of micrometastases at diagnosis and is characterized by an overall poor prognosis with a 5-year overall survival (OS) of ~50%.

Radical cystectomy (RC) with cisplatin-based neoadjuvant chemotherapy (NAC) has demonstrated improved survival in eligible patients and is the current guideline-recommended treatment. This is based on the randomized Phase III study by Grossman et al, showing a survival advantage for patients treated with neoadjuvant MVAC (methotrexate, vinblastine, adriamycin, cisplatin) followed by RC, compared with RC alone.

Other, more commonly used protocols today are ddMVAC and GC protocol. Dose dense MVAC (ddMVAC), which is similar to MVAC, but administered every 2 weeks with growth factor support, has also been studied in phase II clinical trials in the neoadjuvant setting, and has shown comparable efficacy, shorter duration of administration and better tolerance when indirectly compared with classic MVAC.

Extrapolating from the metastatic setting, another commonly used neoadjuvant regimen is gemcitabine and cisplatin (GC). GC showed similar efficacy but better tolerability compared to classic MVAC. In the neoadjuvant setting, a retrospective multicenter study has shown that neoadjuvant GC and MVAC achieved comparable pCR rates providing further evidence to support its use in this setting.

The first and only prospective randomized Phase 3 study in the perioperative setting to directly compare ddMVAC (6 cycles) and GC (4 cycles) is the GETUG/AFU V05 VESPER study. This study showed a statistically significant overall survival benefit for ddMVAC compared to GC, in the subset of patients treated in the neoadjuvant setting although ddMVAC was associated with a higher toxicity. Recently published results of a randomized trial in almost 500 patients with localized MIBC, ddMVAC improved five-years OS relative to GC (66 versus 57 percent) with a nonsignificant trend toward improvement among those receiving both neoadjuvant and adjuvant treatment (64 versus 56 percent).

Currently all guidelines on the management of MIBC recommend neoadjuvant cisplatin-based combination chemotherapy (ddMVAC or GC) for patients who are eligible for cisplatin, followed by radical cystectomy (RC).

For select patients who are not candidates for radical cystectomy or desire preservation of their native bladder, radiation therapy (RT) plus concurrent chemotherapy known as trimodality therapy (TMT) incorporating maximal TURBT followed by radiation therapy with concurrent radiosensitizing chemotherapy) is indicated rather then chemotherapy or RT as single-modality treatment which is not recommended to be used alone in neoadjuvant setting.

There is an efforts to develop predictive molecular signatures for chemosensitivity in bladder cancer. Studies are investigating gene expression profiling to predict individual responsiveness to neoadjuvant chemotherapy. For example, in a randomized phase II trial (S1314) is evaluated the utility od Co-expression Extrapolation (COXEN) biomarker. In this trial, COXEN score for Gc or ddMVAC were not associated with improved overall survivel within their respective treatment arms. So the role of gene expression profiling in the molecular prognostication of invasive bladder cancer remains experimental.

In recent years, there is interest in investigating the use of checkpoint inhibitor immunotherapy as neoadjuvant treatment, given its efficacy in the treatment of metastatic urothelial cancer. Most studies investigating neoadjuvant immunotherapy in patients who are ineligible for cisplatin-based chemotherapy. Complete pathologic response rates between 30- 40 percent have been reported in early phase studies using neoadjuvant atezolizumab (ABACUS), pembrolizumab (PURE-01) and in the combination of durvalumab and tremelimumab and nivolumab and ipilimumab. Also complete pathologic response rates have been seen in patients receiving immunotherapy in combination with chemotherapy in neoadjuvant setting (pembrolizumab plus GC, nivolumab plus GC and durvalumab plus GC).

For some patients who did not received neoadjuvant therapy, but undergo radical cystectomy, adjuvant treatment is recommended for those with high -risk tumor features as long as no contraindications to cisplatin are present. Although studies suggest that adjuvant chemotherapy is efficacious in such patients, as it may delay recurrences and improve overall survival such data are controversial. The preferred chemotherapy protocol is also cisplatin -based combination therapy (ddMVAC or GC). For patients who did not received neoadjuvant chemotherapy and are ineligible or decline adjuvant cisplatin-based chemotherapy or for those who received neoadjuvant chemotherapy and had persistent muscle invasive or nodal disease FDA approved adjuvant immunotherapy (nivolumab) based on results of randomized study phase III (CheckMate 274) who showed that adjuvant nivolumab improved disease free survival (DFS) over placebo.

This year on ASCO meeting the results of the AMBASSADOR trial was published. AMBASSADOR is phase III randomized adjuvant study of pembrolizumab in muscle-invasive and locally advanced urothelial carcinoma versus observation. The trial showed that adjuvant pembrolizumab demonstrated a statistically significant and clinically meaningful improvement in disease-free survival compared to observation alone in patients with high-risk muscle invasive urothelial carcinoma after radical surgery, regardless of PD-L1 status and these results support adjuvant pembrolizumab as a new therapeutic option for patients with muscle invasive urothelial carcinoma with high risk for recurrence.

There are many drugs such as ADC, alone or in combinations with ICI that are currently being tested in this setting with encouraging results.

The future of patients with muscle-invasive bladder cancer is promising because neoadjuvant therapy in MIBC is rapidly evolving as novel agents previously approved in the metastatic setting are being used and tested in earlier disease states. While cisplatin based neoadjuvant chemotherapy remains an gold standard, either alone or in combination with other agents, ICI and ADCs have shown significant activity in patients who are cisplatin ineligible or intolerant. The use of biomarkers to predict response to cisplatin-based NAC or ICIs is largely investigational, but molecular signatures are showing promise in reshaping selection for treatment and disease monitoring.

Keywords: neoadjuvant therapy, adjuvant therapy, radical cystectomy, immunotherapy, muscle-invasive bladder cancer

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S3 – INTEGRATION OF SBRT AND IMMUNOTHERAPY IN THE TREATMENT OF EARLY STAGE LUNG CANCER

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Approximately 30% of non-small cell lung cancers are diagnosed at an early stage (stage I and II). It is expected that, by implementing the national prevention programme, there will be an increase in a number of patients diagnosed at an early stage of the disease. Surgical resection is „the gold standard" for treatment of early stage non-small cell lung cancers. However, if there are contraindications for surgical resection or considering the patient's preferences, recommended treatment is stereotactic radiation therapy (SBRT) that can provide high rates of local control, preserved quality of life with minimal therapy-specific side effects. Nonetheless, the rates of locoregional and/or distant reccurence are high in these patients. Currently, there are no randomized clinical trials comparing stereotactic radiation therapy and surgical resection in patients with early stage, resectable non-small cell lung cancer. Combination of immunotherapy and stereotactic body radiation therapy is currently being tested in several phase II and III trials in patients with early-stage non-small cell lung cancer. The rationale for this combination is the immunomodulatory effects of radiotherapy and, as we are already familiar with, significantly improved survival in patients with stage III non-small cell lung cancer treated with immunotherapy after concomitant chemoradioterapy. Results from a phase II trial showed a significant improvement in 4-years EFS with I-SBRT compared to SBRT alone in patients with de novo early-stage or lung reccurent, node negative non-small cell lung cancer. Durvalumab after SBRT is currently being tested in a phase 3 trial (PACIFIC 4) versus placebo after SBRT in an early, non-resectable, non-small cell lung cancer. Minimal residual disease is one of the risk factors for recurrence in an early stage non-small cell lung cancer and thus can be used for the selection of patients suitable for new adjuvant strategies. Preliminary clinical results of combination of immunotherapy and SBRT are promising however phase III trial levels of evidence are required to form a definitive conclusion.

Keywords: early stage of lung cancer, immunotherapy, SBRT

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S4 – IMMUNOTHERAPY IN TREATMENT OF ADVANCED GASTRIC AND EGJ CANCER

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Gastric cancer is the 4th most common cancer and the 4th leading cause of cancer death globally. in the moment of diagnosis it is usually in a advanced stage. the standard of care is the first-line platinum doubled treatment, with trastuzumab in her two positive disease. In the second line but with the cell with or without ramucirumab is usually used for unresectable or metastatic we gastric cancer. however median of survival in this patient is 12 to 15 months so we need a new treatment possibilities. In the last few years immunotherapy become a new standard of treatment in a lot of malignant tumours including advanced ventricular cancer which significant clinical benefit in this population.

Biomarkers for immunotherapy can be categorized into three major groups immunological genetic and virological. The expression of PDL one before treatment can be used as an immunological biomarker that is predictive of of tumor shrinkage. Tumor mutation burden might also be used to predict the benefit of immunotherapy. Ventricular cancer in ancient population has a lower expression of this cell markers and the higher expression of immunosuppressive T cells so we need further investigation to compare benefit and toxicity of immunotherapy in Asian and a non Asian population.

In a phase III ATTRACTION-2 trial nivolumab has shown a better overall survival compared to placebo in patients with advanced ventricular cancer after two and more lines of chemotherapy. These patients had a hazard ratio of 0.67. it also shown a benefit in the overall response rate as in progression free survival.

According to this result nivolumab was approved for a treatment of advanced ventricular cancer in Asian population.

In April 2021 FDA approved nivolumab in combination with fluoropyrimidine and platinum based chemotherapy for the first line of treatment for a patient with metastatic ventricular cancer. as a provent was based on the results of phase III Checkmate-649 trial actions with untreated, her two negative unresectable ventricular cancer, EGJ cancer and eosophageal adenocarcinoma. in this trial patients received chemotherapy with or without nivolumab, end addition of nivolumab resulted in a significant benefit in overall survival and progression free survival. So the combination of nivolumab and chemotherapy become a standard of the first line treatment in a patient with a her two negative advanced ventricular cancer with the CPS score higher or equal 5.

Pembrolizumab is approved in 2017 for patients with unresectable or metastatic solid tumors who had a high microsatellite instability. This approval was based on 5 multicentric global trials with 149 patients who had our overall response rate of 39%.

In June 2020 Pembrolizumab is approved for a treatment of patients with metastatic solid tumors who had a high TMB. Disapproved is based on a retrospective analysis of a 102 patients included in KEYNOTE 358 trial, and they had a response rate of 29% with 4% of complete responses. 50% of patients had duration both response longer then 24 months. According to this pembrolizumab can be used for patients in a second or later lines of therapy who has tumors MSI-H/dMMR, or TMB-H. pembrolizumab also shown or response rate of 11.6% in a third or later lines in a KEYNOTE-059 trial.

In the meantime avelumab didn't show better overall survival compared to chemotherapy in JAVELIN 300 trial.

Dostarlimab-gxly was approved by the FDA in August 2021 for the treatment of patients with dMMR solid tumors who have progressed on or following prior treatments. The majority of patients had endometrial or gastrointestinal cancers overall response rate was 42% with 9% of complete response rate, and the median duration of response was 35 months. Based on this data does sterling mob may be used to treat patients with MSI-H/dMMR tumors.

KEYNOTE-811 trial shown a significant improvement in response rate in combination of pembrolizumab trastuzumab and chemotherapy in patients with healthy positive advanced ventricular cance

In conclusion we can say that addition of immunotherapy in the first line shone a clinical benefit for patients with Her2 negative advanced ventricular cancer. In HER-2 positive disease combination of pembrolizumab trastuzumab and chemotherapy have indicated promising effects. A novel immunotherapy approach using CAR-T cell therapies might be used as a personalized treatment for advanced gastric cancer. Despite these breakthroughs, there is still an urgent need to establish novel biomarkers for immunotherapy and develop new immunotherapies.

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S5 – TARGETED THERAPY IN THE TREATMENT OF GYNECOLOGICAL CANCERS

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During the past decade, considerable progress has been made in the treatment of gynecological cancers.

Endometrial cancer (EC) is the most common gynecological cancer. In recent years, there is a new classification system based on molecular phenotype. The four different molecular subclasses have been identified: POLE- mutant, microsatellite-unstable (MSI), p53 positive (copy-number high) and no specific molecular profile (NSMR or copy-number low). 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 and do not require to receive adjuvant treatment in the early stages of disease regardless of the unfavorable pathohistological characteristics of the tumor. 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.

Currently, the standard chemotherapy regimen for advanced, metastatic or recurrent disease is paclitaxel/carboplatin with or without immunotherapy, 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.

Mismatch repair-deficiency (dMMR), high MSI and high tumor mutation burden (≥ 10 mut/Mb) are effective biomarkers for immunotherapy with checkpoint inhibitors. In patients who are MMR proficient (pMMR) or microsatellite stable (MSS)., the combination of lenvatinib and pembrolizumab is an effective option.

For patient with 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. In those patients with recurrent disease, an excellent results were achieved with trastuzumab deruxtecan.

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.

In patients with T53, 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. Selinexor is an option for the treatment of patients with p53 wild type tumors.

The most commonly used targeted drug for the treatment of cervical cancer is bevacizumab which attaches vascular endothelial growth factor (VEGF). The addition of bevacizumab to chemotherapy in patients with metastatic, persistent or recurrent disease improves tumor response and survival.

Recently, immunotherapy has an increasingly important role in the treatment of metastatic, persistent or recurrent cervical cancer, especially in patients with PD-L1 positive tumors. New trials have also demonstrated the benefit of immunotherapy in locally advanced disease.

The first antibody-drug conjugate targeting tissue factor (TF) is tisotumab vedotin. TF is abnormally expressed in several solid tumors including cervical cancer. The InnovaTV 301 trial demonstrated clini-

cally meaningful and durable antitumor activity with tisotumab vedotin in woman with previously treated recurrent or metastatic cervical cancer. In combination with bevacizumab, carboplatin or pembrolizumab, tisotumab vedotin have also showed encouraging antitumor activity in treatment-naïve and previously treated recurrent and metastatic cervical cancer.

Trastuzumab deruxtecan showed clinical benefit in pretreated patients with HER2-expressing cervical and ovarian tumors.

Ovarian cancer is the leading cause of death from gynecological malignancies. The most important treatment method is still optimal surgery, followed by platinum-based chemotherapy. All patients with advanced disease should receive maintenance therapy. The two most promising targeted agents are anti-angiogenic agents (bevacizumab) and molecular targeting agents (poly-ADP ribose polymerase (PARP) inhibitors. The status of BRCA mutation and homologous recombination deficiency (HRD) must be known before a decision is made. All patients with BRCA mutation or HRD and who have objective response to platinum-based chemotherapy, should receive maintenance therapy with PARP inhibitors or a combination of olaparib and bevacizumab. In HRD-negative tumors, maintenance treatment with bevacizumab or niraparib can be recommended. The choice of treatment should be based on disease and clinical characteristics of the patients.

The treatment of the first recurrence depends on many factors, including duration of initial treatment response, residual toxic effects from previous therapy, performance status, tumor genomics and the preferences of patient herself. Patients, in whom platinum is an option, should be treated with either a platinum-based doublet with bevacizumab or a platinum based doublet followed by maintenance with PARP inhibitors if a response to chemotherapy is achieved and the patient has not been previously exposed to PARP inhibitors. In patients in whom platinum is not an option, single-agent non-platinum chemotherapy is recommended and bevacizumab should be offered if patient has not previously exposed to bevacizumab.

For patients with recurrent low grade serous ovarian cancer, treatment with the MEK inhibitor should be consider.

Keywords: endometrial cancer, ovarian cancer, cervical cancer, targeted therapy

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S6 – LOCALLY ADVANCED PANCREATIC CANCER – MULTIDISCIPLINARITY ON THE TEST

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Pancreatic ductal adenocarcinoma (PC) is the 12th most common malignancy and 7th cause of cancer mortality in the world with the projection to become the 2nd leading cause of cancer deaths in the United States and 3rd in Europe by 2025. Despite significant progress in the understanding of this disease in recent years, the prognosis is still poor with 5-year survival of only 3-11%. Unfortunately, around 50% of patients have metastatic disease already at the time of diagnosis, and potentially curable primary surgical resection is feasible in merely 15-20% of patients. Median overall survival (mOS) of patients treated with upfront surgery followed with 6 months adjuvant chemotherapy is about 34 months or even more but with frequent relapses.

Metastasis-free patients are often divided into 3 groups: resectable, borderline resectable and locally advanced prostate cancer (LAPC). Resectability is defined by several different systems based on the relationship between tumour and blood vessels, among which the National Comprehensive Cancer Network (NCCN) definition is the most commonly used. LAPC is considered tumour encasement greater than 180 degrees of circumference of the superior mesenteric artery (SMA) or celiac artery (CA), an unreconstructable superior mesenteric vein (SMV) or portal vein (PV). However, apart from anatomical criteria resectability, performance status and Ca 19/9 levels are also important. About one third of patients have LAPC. Median survival of treated LAPC patients is 12-25 months. Around 20% of patients with LAPC become eligible for resection after neoadjuvant therapy even in the absence of a clear radiological response. They have similar outcomes to those who were resectable at diagnosis.

Since LAPC patient have subclinical metastases in up to 50% of cases, chemotherapy is the pillar of treatment. mFOLFIRINOX is the preferred regimen for patients with ECOG 0-1 with the pooled mOS in a

meta-analysis 24 months and the resection rate of approximately 30%. In the LAPACT trial (phase II) patients treated with nab-paclitaxel and gemcitabine (NG) had overall response rate (ORR) 33.6%, disease control rate (DCR) 77.6%, mOS 18.8 months and 16% resection rate. NEOLAP trial (phase II) compared 4 cycles of NG with 2 cycles of NG followed by FOLFIRINOX. There was no difference in efficacy and safety. FOLFIRINOX and NG had also comparable efficacy and safety in JCOG1407, while in PRODIGE 29 trial FOLFIRINOX showed significantly prolonged progression-free survival (PFS) (9.7 vs. 7.5 months, $p = 0.03$) in comparison with gemcitabine alone but without difference in mOS (15.6 vs. 15.1 months).

Chemoradiation (CRT) prolonged the OS in clinical trials in comparison to best supportive care. However, the results of randomised trials comparing CRT with chemotherapy are conflicting (FFCD/SFRO 2000-01, ECOG trial). In the LAP-07 trial patients were treated with 4 months of gemcitabine with or without erlotinib and then randomised to continue with 2 more months of gemcitabine or CRT. Although mOS was not improved in the CRT group, CRT was associated with a decreased risk of local progression (32% vs. 46%, $p = 0.03$). The effect of the addition of radiotherapy to neoadjuvant chemotherapy was also investigated in the phase III CONKO-007 trial. Patients were enrolled between 2013 and 2021 to receive 3 months of chemotherapy (85% FOLFIRINOX, 15% gemcitabine) followed by CRT or continuation of chemotherapy in those without progression of the disease. The primary endpoint was changed from OS to R0 resection due to insufficient recruitment. R0 resection rate was significantly higher in CRT group (69% vs. 50%, $p = 0.04$) as well as pathological complete response rate (pCR) (18% vs. 2%, $p = 0.004$). The mOS was significantly improved in resected patients (19 vs. 14 months, $p < 0.001$) but the mOS did not differ between the randomised groups (15 months in both arms).

Therefore, radiotherapy in LAPC is controversial but it is recommended according to the guidelines after up to 6 months of chemotherapy for selected patients without distant metastasis. However, in some randomised trials outdated radiation techniques were performed. In small retrospective cohorts intensity modulated radiotherapy with biologically effective dose more than 70 Gy and high-dose magnetic resonance image-guided radiotherapy improved survival of treated patients.

Numerous randomised trials with stereotactic body radiotherapy (SBRT) are ongoing (MASTERPLAN, SABER, STEREOPAC, LAP-ABLATE, ARCADE) since retrospective data showed previously improved local control along with significantly shorter duration of treatment. Locoregional percutaneous interventional techniques (radiofrequency ablation, microwave ablation, cryoablation, irreversible electroporation, brachytherapy, intra-arterial infusion of chemotherapy, transarterial chemoembolization, intratumoral immunotherapy) are used in specialized centres in the treatment of LAPC. These techniques showed the potential to increase survival as well as the immunomodulatory capacities.

Surgical exploration is the option for patients with a decrease in serum Ca 19/9 level to < 50% of the baseline value and substantial clinical improvement. Imaging can be unreliable in the assessment of resectability due to fibrosis and scar tissue after neoadjuvant therapy. Experienced multidisciplinary tumour board is of paramount importance in the treatment of LAPC.

Finally, PC is genetically and biologically heterogeneous disease. New therapeutic strategies based on the distinct molecular features of the tumour are needed.

Keywords: pancreatic cancer, neoadjuvant, chemotherapy, chemoradiotherapy

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S7 – IMMUNOTHERAPY IN GYNECOLOGICAL CANCERS

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The leading cause of cancer death for women varies significantly depending on geographic location, socioeconomic factors, and access to healthcare. Gynecological cancers significantly contribute to female cancer mortality worldwide. Carcinomas of the uterus, cervix, and ovary in advanced and metastatic stages have poor five-year survival rates, presenting a significant clinical challenge. Immunotherapy using checkpoint inhibitors (ICI) has revolutionized cancer treatment, demonstrating remarkable effectiveness against various tumor types. Immunotherapy shows promising results for treating endometrial and cervical cancers, while research on its efficacy in ovarian cancer is not satisfactory.

The Cancer Genome Atlas (TCGA) identified four molecular subtypes of endometrial cancer. Among these, microsatellite instability (MSI), present in approximately 25-30% of cases, serves as a potential biomarker for immunotherapy response. After progression on platinum-based chemotherapy, two approved treatment options are available for MSI high or mismatch repair-deficient (dMMR) endometrial cancer, pembrolizumab and dostarlimab, both of which are anti-programmed cell death-1 (PD-1) inhibitors. Pembrolizumab received approval based on the phase 2 KEYNOTE 158 study, which demonstrated an objective response rate (ORR) of 48% and not reached duration of response (DOR). Dostarlimab was approved based on the results of the GARNET study with similar ORR and DOR like in KEYNOTE 158 study. Following platinum-based chemotherapy progression, the combination of dostarlimab and lenvatinib (anti VEGF) is currently approved as a second-line treatment for microsatellite stable (MSS) or mismatch repair-proficient (pMMR) endometrial cancer. This approval is based on a phase 3 KEYNOTE 775 study demonstrating its superiority over standard chemotherapy options (doxorubicin or paclitaxel) in ORR, progression-free survival (PFS), and overall survival (OS). Dostarlimab received approval for the first line treatment of advanced or recurrent endometrial cancer with MSI-high/dMMR based on the results of the phase 3 RUBY study. This trial demonstrated the superiority of dostarlimab compared to standard chemotherapy with paclitaxel and carboplatin in terms of ORR, PFS (HR 0.28), and OS (HR 0.30) and change standard of care in first line treatment for MSI-high/dMMR status endometrial cancer.

Pembrolizumab offers a promising option for second-line treatment of advanced cervical cancer. The phase 2 KEYNOTE 158 study demonstrated an ORR of 14.3% in previously treated advanced cervical cancer with PD-L1 positive tumor. The phase 3 EMPOWER study established cemiplimab (anti PD-1) as a second-line treatment option for recurrent or metastatic cervical cancer, demonstrating a survival benefit

over chemotherapy regardless of PD-L1 status. The pivotal phase 3 KEYNOTE 826 study showed that the addition of pembrolizumab to first-line platinum-based chemotherapy, with or without bevacizumab (anti-VEGF), led to a significant improvement in PFS among patients diagnosed with PD-L1 positive persistent, recurrent or metastatic cervical cancer. Consequently, pembrolizumab has approval for this specific indication. The phase 3 KEYNOTE-A18 study investigated pembrolizumab potential in locally advanced cervical cancer. The addition of pembrolizumab to chemoradiotherapy followed by maintenance of pembrolizumab showed promising results in improvement of PFS compared to chemoradiotherapy alone. While pembrolizumab isn't yet approved for this specific use case, and overall survival data is pending, these findings suggest a potential new approach.

Disappointingly, clinical trials published to date haven't demonstrated significant benefit from immunotherapy in advanced ovarian cancer. This includes ICI monotherapy and combinations with chemotherapy, bevacizumab, or PARP inhibitors. Further research is needed for better patient selection, biomarker identification, and novel treatment strategies to improve the efficacy of immunotherapy for ovarian cancer.

Keywords: immunotherapy, gynecologic cancers, endometrial cancer, cervical cancer, ovarian cancer

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S8 - IMPORTANCE OF PROGNOSTIC AND PREDICTIVE TESTS IN ADJUVANT BREAST CANCER THERAPY

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Breast cancer is most frequent cancer in women. Due large number of patients and large heterogeneity of the disease, it's clear that treatment of early breast cancer (BC) has to be more efficacious and less toxic. New technologies identify today a number of biomarkers in BC prognosis and risk prediction. Prognostic factors are used to estimate risk of recurrence and possible benefit of systemic therapy, factors that influence survival and can be changed by therapy. Predictive factors are used to determine optimal therapy for each patient. Prognostic and predictive markers can overlap. These biomarkers enable us to apply optimal treatment for each patient- not to over treat or under treat, improving prognosis and survival of

patients with early BC. Till recently, we used traditional prognostic features (tumour size and grade, lymph node status) and traditional predictive markers: A/ER-the most common predictive marker; B/PR-related to better survival and lower recurrence rates if positive C/ HER2 status, both prognostic and predictive, of which overexpression is connected with aggressive disease and lower survival; D/ Ki67 status that discriminates luminal A and B BCs. Newer markers show potential as markers of survival and risk assessment, as well predisposition to BC. PI3KCA regulates proliferation and protein synthesis and is associated with chemoresistance and reduced survival.TP53 is related to cell cycle, differentiation and apoptosis as well as to predisposition to BC, a feature that shares with BRCA1/2 tumour suppressor genes involved in DNA repair. PTEN, tumour suppressor gene related to cancer cell survival. Its downregulation is associated with worse outcomes, lower sensitivity to CDK4/6 inhibitors and immunotherapy. CHEK2, ATM and PALB genes are involved in cell cycle regulation, DNA repair, apoptosis and increased risk of BC development. CDH1 suppresses spread of tumour cells and is associated with worse prognosis, though its hypermethylation can be reversed. by DNA methylation inhibitors. PD-1/PD-L1 regulate immune response against tumour cells by inhibiting T-cell activation. Antibody mediated PD-L1 degradation enhances effects of radiotherapy and cisplatin. MSI microsatellite instability is associated with malignant tumours development, and is a possible marker for immunotherapy.

Genomic test have changed treatment paradigms with patients with HR+ BC, sparing substantial number of patients of unnecessary chemotherapy and overtreatment. It is emerging strategy of risk prediction and treatment decision based on genomic data. MammaPrint defines 5-10 year recurrence risk and potential benefit from chemotherapy, regardless of ER and HER2 status. Oncotype DX evaluates expression of 21 genes to predict recurrence risk at 10 years. Its use reduced prescription of chemotherapy in low and intermediate risk patients. Prosigna (PAM50) predicts 10-year distant recurrence survival assuming five years of ET. Endopredict assay determines 10-year risk of distant recurrence and to determine benefit of chemotherapy. Breast Cancer Index (BCI) assesses early and late distant recurrence risk and predicts which patients could benefit from extended ET. Single-cell-based genomic technologies and in situ spatial methods provide more personalized therapy approach- a serial monitoring of cell heterogeneity, spatial and temporal cell mapping, epigenetic mechanisms of resistance..., identifying potential treatment targets for new drugs

Keywords: breast cancer biomarkers, personalized therapy, genetics of breast cancer

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S9 – ANTIBODY-DRUG CONJUGATES IN THE TREATMENT OF BLADDER CANCER

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Despite introduction of immune checkpoint inhibitors in the treatment armamentarium for advanced urothelial cancer (aUC), only a minority of patients respond to this therapy. Even in the era of immune checkpoint inhibitors, aUC is still characterized by rapid disease progression and poor survival. Antibody drug-conjugates (ADC) represent the novel concept of targeted therapy for urothelial carcinoma that can overcome resistance mechanisms associated with immunotherapy failure. ADC therapy can be considered as a breakthrough as it allows the combination of a target-specific monoclonal antibody covalently conjugated via a linker to a cytotoxic agent (payload) to be directed against tumor cells. aUC is a perfect candidate for this therapeutic approach since it is particularly enriched in antigen expression on its surface and each specific antigen can represent a potential therapeutic target. ADCs can deliver chemotherapy drugs to a specific target with greater therapeutic efficacy and less toxicity.

Enfortumab Vedotin (EV) is an ADC developed to target nectin-4. The open-label, single-arm phase II trial (EV-201) evaluated the efficacy of EV in patients pretreated with immunotherapy enrolled in two cohorts: cohort 1 enrolled patients previously treated with platinum-containing therapy; and cohort 2 platinum-ineligible patients. The ORR in cohort 1 (125 patients) was 44% and the median duration of response (mDOR) was 7.6 months. The estimated median PFS was 5.8 months and the median OS was 11.7. Responses were observed in all subgroups, including patients unresponsive to ICI. Adverse events (AEs) seen in more than 20% of patients included fatigue (50%), alopecia (49%), rash (48%), loss of appetite (44%), peripheral sensory neuropathy (40%), and dysgeusia (40%). The EV-301 study, a randomized, open-arm phase III trial of EV versus investigator-choice chemotherapy (docetaxel, paclitaxel, and vinflunine) enrolled 608 patients progressing after platinum-containing chemotherapy and ICI. The study reached its primary endpoint, obtaining a median OS of 12.9 and 9.0 months respectively for EV and chemotherapy (hazard ratio (HR): 0.70; 95% confidence interval (CI) 0.56 to 0.89; p = 0.001). Based on these data, EV received FDA and EMA approval for the treatment of patients previously treated with platinum-containing chemotherapy and ICI. In first-line setting, EV has also been shown to have a synergistic effect when combined with ICI in the cohort A of the ongoing phase Ib/2 EV-103 trial, showing an ORR of 73%, with 15.6% of CR and median PFS of 12.3 months, in cisplatin-unfit patients.

Sacituzumab Govitecan Sacituzumab Govitecan (SG) is an ADC conceived to specifically target human trophoblastic cell surface antigen 2 (Trop-2). SG consists of a monoclonal antibody against Trop-2 conjugated to SN-38, an active metabolite of irinotecan, through a hydrolysable linker.

In a phase I/II study 45 patients with metastatic urothelial carcinoma who progressed after ≥1 prior systemic therapy were treated with SG at 10 mg per kg on days 1 and 8 of 21-day cycles, until progression or unacceptable toxicity. The ORR was 31% with a clinical benefit rate of 47%. The median DOR was 12.6 months. The mPFS and mOS were 7.3 and 18.9 months, respectively. The most common grade 3 or higher reported side effects were neutropenia (38%), anemia (11%), hypophosphatemia (11%), diarrhea (9%) fatigue (9%), and febrile neutropenia (7%). The TROPHY-U-01 study is an open-label, single-arm phase II

study evaluating the efficacy of SG in patients progressing after platinum-containing chemotherapy and a checkpoint inhibitor. Preliminary data from cohort 1, including 113 patients with locally advanced or unresectable or metastatic UC who had progressed after prior platinum therapy and ICI, showed an ORR of 27% with a mPFS and mOS of 5.4 months and 10.9 months, respectively.

Disitamab Vedotin is a novel ADC consisting of a humanized monoclonal antibody directed against HER-2 conjugated to MMAE through a cleavable linker with a DAR of 4. A recent phase II study reported encouraging results in 43 patients with HER-2+ metastatic urothelial cancer previously treated with at least one line of systemic treatment platinum-based chemotherapy. The ORR was 51%, mPFS and mOS were 6.9 and 13.9 months, respectively. Another phase II trial enrolling a larger population is starting to test the efficacy of this agent in HER-2+ UC metastatic patients.

Trastuzumab Deruxtecan (DS-8201a) is an ADC consisting of a monoclonal antibody targeting HER-2 conjugated to a topoisomerase I inhibitor (DXd) at a DAR of 7–8. This ADC has shown significant activity even in tumor cells expressing low levels of HER-2. In early trials conducted in heavily pretreated metastatic breast cancer patients DS-8201 showed a high response rate. A phase II trial evaluating the efficacy of DS-8201 in several tumors including metastatic UC is currently ongoing (NCT04482309). Some preclinical data have also shown the role of DS-8201 in the immunogenic modulation of the tumor microenvironment. Trials testing the association of DS-8201 and ICIs such as Nivolumab are ongoing to evaluate the safety and efficacy of combinations.

Keywords: urothelial carcinoma, antibody-drug conjugates, ADC, Enfortumab vedotin, ADC resistance mechanism

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S10 – TREATMENT OF UNRESECTABLE STAGE III NON-SMALL CELL LUNG CANCER IN CROATIA

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Stage III non-small cell lung cancer (NSCLC) comprises a highly heterogenous group of patients regarding patient fitness and tumour size and distribution, resulting in a wide range of treatment goals and therapy options. Curative-intent treatment for stage III NSCLC is multimodal, consisting of a combination of chemotherapy, radiotherapy (RT), and/or surgical resection, although the optimal sequence and modality is debated and highly case-specific. The extensive staging work-up required to assess the feasibility for curative-intent treatment, and the need for consultation with a multidisciplinary team further complicates the optimal, individualized management of stage III patients. In patients with unresectable disease who are fit (ECOG 0–1), have adequate lung function, and have a disease that can be encompassed within a radical radiation volume, chemoradiotherapy (CRT) using platinum-based chemotherapy is the standard of care. Concurrent CRT (cCRT) is typically favoured for these patients, owing to its superiority to sequential CRT. As cCRT can be curative in 20–30% of patients with stage III NSCLC, it is critical that newly diagnosed patients be assessed for cCRT treatment eligibility. Within the last few years, immunotherapy has been introduced into stage III treatment regimens as a consolidation therapy following cCRT and substantially improved survival outcomes. In the 5-year update of the phase III PACIFIC trial, durvalumab following cCRT led to a significant improvement in overall survival and progression- free survival versus placebo in patients with stage III NSCLC with only a 4% increase in grade 3/4 adverse events from the addition of durvalumab. Consolidation durvalumab is nowadays a standard of care for patients with stage III unresectable NSCLC whose disease has not progressed following platinum-based cCRT. Despite the practice-changing results of the PACIFIC trial and availability of durvalumab, real- world data show that the percentage of patients receiving optimal treatment is low, with many country- related factors contributing to the underusage of cCRT in clinical practice.

In Croatia there are approximately 3200 newly diagnosed patients with lung cancer each year. Population registries do not show accurate distribution by stage and histology, but according to the world lung cancer statistics, 20-25% of patients have stage III, of which up to 80% are unresectable. Thus, we can

assume that unresectable stage III NSCLC is diagnosed in at least 400 patients. For the purpose of this work, data about management of patients with stage III NSCLC in year 2023 have been collected from five academic centers in Croatia.

Clinicians in Croatia are facing many challenges regarding timely and accurate diagnostics for stage III NSCLC. Comprehensive diagnostic procedures including endoscopies, invasive mediastinal staging, imaging (including PET/CT and brain MRI), pathological and molecular diagnostics, as well as the multidisciplinary evaluation are mainly performed in five university hospital centers, but there is no established oncological network which could enable fast patient flow from general hospitals to academic centers. Other factors contributing to delay in diagnosis at some institutions include insufficient number of endoscopy facilities, as well as the availability of specialists, such as radiologists, pathologists, pulmonologists performing endoscopic procedures (EBUS, rEBUS, EUS, etc). Some lung cancer guidelines suggest diagnostic work-up should be completed within 26–30 days of referral, with an additional 7–15 days before treatment initiation. In Croatia, average time to establish diagnosis is often longer than recommended due to above mentioned reasons. Multidisciplinary teams are functional in all academic centers, but there are differences in the extent of suggested staging procedures (especially invasive mediastinal staging and PET/CT).

Regarding treatment, there are different approaches among institutions, but ≥ 50% of patients undergo cCRT (others, mostly fragile or patients with comorbidities are treated with sequential chemotherapy followed by hypofractionated RT or RT alone). In patients undergoing cCRT, some centers begin treatment with two induction cycles of chemotherapy (with other two given concurrently with RT); this is the case in institutions with longer waiting- time for initiation of RT.

The main challenge in timely delivery of cCRT in Croatia is related to insufficient number of linear accelerators; there are only ten LINACs in five university hospitals and most of these machines are older than 10 years, so treatment disruptions or delays are very common. Accordingly, modern treatment planning (4D CT, respiratory gating) and radiotherapy delivery (IMRT/VMAT) techniques which reduce severe cCRT toxicities, have not been implemented as a standard of care; in most institutions 3D- conformal RT is still dominant RT technique. Concurrent chemoradiotherapy poses many other challenges; approximately 15% of patients do not complete the treatment for reasons like distance from treatment centres, lack of logistical support, management of adverse events during treatment, poor coordination between institutions delivering chemo- and RT, etc.

Durvalumab is reimbursed in Croatia since September 2020 for all patients with stage III NSCLC (PD-L1 positive) with non- progressive disease after cCRT. Penetrance of consolidation treatment with durvalumab is lower than expected due to reasons such as non- completion of cCRT, adverse events, disease progression or death. The main reasons for interruption of maintenance immunotherapy are adverse events (mainly pneumonitis) and disease progression.

In conclusion, there is a need for regional- and institutional-level evaluation of care pathways in Croatia. Better organized referral system, access to timely assessments, increased capacities of daily hospitals and radiotherapy facilities for delivery of modern, high quality radiotherapy are key to ensure more eligible patients with stage III NSCLC can receive curative treatment options. In context of upcoming adoption of new TNM classification and perioperative chemoimmunotherapy, multidisciplinary team collaboration will be crucial in optimizing outcomes for these patients.

Keywords: stage III non- small cell lung cancer, unresectable, treatment, Croatian practice

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S11 – OPEN QUESTIONS IN TARGETED THERAPY OF NON-SMALL CELL LUNG CANCER

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Targeted therapies have greatly improved the survival in non-small cell lung cancer (NSCLC) patients with actionable mutations. Despite that, there are still many unresolved questions and a lot of possibilities for further progress.

The main obstacles for a more comprehensive and even more efficient application of targeted therapy are drug resistance, toxicity and high costs of the therapy itself that limit the access for the NSCLC patients. Essential for improving treatment results is better understanding of resistance mechanisms and developing combination therapies.

The efficacy of combination therapy has been shown in the first-line treatment of patients with advanced EGFR mutation positive NSCLC in two phase III studies.

In FLAURA study, combination of osimertinib and chemotherapy resulted in a significantly better progression-free survival (PFS) in comparison with osimertinib monotherapy (median PFS 25,5 vs 16,7 mo; HR 0.62; P<0.001).

Combination of amivantanab and lazertinib also resulted in a significantly better efficiency than osimertinib in MARIPOSA study (median PFS 23,7 vs 16,6 mo; HR 0.70; P<0.00).

However, considering higher toxicity of combined treatment in comparison to osimertinib monotherapy and immature survival data, it is still unclear what the optimal first-line treatment is for the majority of these patients.

Another challenge which, without doubt, requires better solutions is the further treatment of patients who progressed on all available (EGFR) tyrosine kinase inhibitors (TKIs). Subsequent treatment depends on patient and disease characteristics, genomic findings and the patient's possibilities to access the treatment. Therefore, a precondition for improvement in treatment efficacy is to provide an environment in which retesting (tissue or liquid biopsy) can easily be carried out for all patients who progressed on TKIs.

Unfortunately, at least for now, the majority of these patients continues to be treated only with chemotherapy.

Recently published phase III study MARIPOSA 2 provides new treatment options for these patients: combination of amivantanab and chemotherapy, with or without lazertinib, in patients who progressed on EGFR TKIs including osimertinib, significantly improved PFS in comparison with chemotherapy treatment.

It is very important to define whether the application of checkpoint inhibitor immunotherapy is reasonable in patients with targetable mutations.

In CheckMate 722 and KEYNOTE-789 phase III studies, which compared the efficacy of adding nivolumab or pembrolizumab to chemotherapy in patients with advanced EGFR mutation positive NSCLC who progressed on TKIs, immunotherapy did not result in significant improvement of neither PFS nor overall survival (OS). One of the possible explanations for negative results of these studies is an immunosuppressive tumor microenvironment associated with EGFR mutation positive NSCLC. Therefore, it is reasonable to investigate whether combining chemoimmunotherapy with immunomodulatory drugs, like those targeting vascular endothelial growth factors (VEGFs), can improve efficacy.

Exploratory analysis of patient subpopulation with EGFR mutation positive NSCLC in IMpower150 study showed that combination of atezolizumab, bevacizumab and chemotherapy provides OS and PFS benefit in comparison with combination of bevacizumab and chemotherapy.

The phase III IMpower151 study compared two almost the same drug regimens in a similar patient population with EGFR mutation. Unfortunately, the trial did not meet its primary endpoint – significant improvement of PFS.

On the other hand, in ORIENT 31 study with a similar patient population, adding immunotherapy or immunotherapy with anti-VEGF to chemotherapy significantly improved PFS but, for now, without improvement in OS.

Based on the data in the resectable and metastatic setting, there is a rationale to believe that EGFR TKIs may improve outcomes in patients with unresectable EGFR mutation positive stage III NSCLC. Unfortunately, for now there are no approved targeted treatments for these patients due to lack of robust evidence from the existing clinical trials. Meta-analysis showed that combination of radiotherapy (RT) and TKIs and combination of chemo-radiotherapy (CRT) and TKIs have significantly longer PFS than CRT ± immunotherapy, with uncertainty regarding the tolerability.

Keywords: non-small cell lung cancer, targeted therapy, treatment strategy, treatment outcomes

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S12 – NEOADJUVANT MELANOMA TREATMENT – THE IMMINENT FUTURE

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Clinical stage III melanoma encompasses approximately 15% of new melanoma cases, with additional patients presenting with recurrent nodal disease. The current standard of care for these resectable clinical stage III melanoma patients is surgical resection, consisting of therapeutic lymph node dissection (and/or resection of in-transit metastases) and subsequent adjuvant systemic therapy, either targeted or immunotherapy, and occasionally adjuvant radiotherapy.

However, even with adjuvant systemic therapies applied, these patients have suboptimal long-term outcomes and are at high risk of regional recurrence and/or progression to metastatic disease, highlighting the need for better treatment options.

With the success of targeted therapy and immunotherapy in the adjuvant and metastatic settings, the use of these agents in the neoadjuvant setting has been an emerging area of research interest.

Neoadjuvant therapy involves administering systemic treatment before the primary treatment, in the case of melanoma, before surgical intervention.

The neoadjuvant approach has multiple potential advantages. Early systemic intervention can reduce the tumor size and potentially downstage it, thus facilitating subsequent less invasive surgical resection and reducing perioperative morbidity. By shrinking the tumor before surgery, neoadjuvant therapy may increase the likelihood of achieving clear surgical margins, which is crucial for minimizing the risk of recurrence.

Moreover, by treating the systemic disease upfront, neoadjuvant therapy addresses potential micrometastases, thereby reducing the risk of distant metastasis and improving long-term outcomes.

Initiating treatment before surgery provides an opportunity to assess treatment response at an early stage, enabling clinicians to tailor adjuvant therapy accordingly (or omit it altogether), thus maximizing therapeutic efficacy and minimizing toxicity.

The ability to early evaluate response or resistance to treatment in the neoadjuvant setting is an ideal platform for quick evaluation and development of new treatment approaches.

Neoadjuvant immunotherapy provides an opportunity to better understand the tumor microenvironment while the patient is on active treatment; it also allows for gathering and exploring biomarkers predictive of therapy response/resistance, which is still a great unmet need in melanoma treatment.

The rationale for neoadjuvant immunotherapy arises from the concept that the administration of immune checkpoint inhibitors (ICIs), while the primary tumor is still present, will lead to a more robust systemic antitumor immune response compared to the one in the adjuvant setting due to more numerous and more various tumor antigens presented to the immune system. This theoretic concept was proven preclinically as well as in several clinical trials, demonstrating the increased ability to generate tumor-specific CD8 T-cells, greater expansion of the existing clones of tumor-specific T-cells, and detection of the higher number of new clones of T-cells in comparison to adjuvant therapy.

With neoadjuvant therapy, the assessment of response to treatment is feasible after surgical resection, which provides valuable prognostic data from tissue pathology, including intratumoral T-cell expansion, presence of tertiary lymphoid structures, and percentage of viable tumor cells.

In a pooled analysis, Menzies et al. showed that pathologic complete response (pCR) correlated with improved recurrence-free survival (RFS) and disease-free survival (DFS) and suggested that pCR should be an early surrogate primary endpoint for clinical trials. Moreover, detecting poor response enables altering the planned adjuvant therapeutic regimen, and obtaining pCR can potentially de-escalate further treatment.

However, there are still potential pitfalls and challenges in the neoadjuvant setting. One significant concern is the potential for disease progression during the neoadjuvant period, leading to delayed surgery or compromised resectability. Furthermore, adverse effects of neoadjuvant immunotherapy can also postpone surgery. Neoadjuvant therapy is more demanding logistically, requiring precise coordination of systemic therapy, diagnostic procedures, and surgery. Pseudoprogression due to neoadjuvant therapy can be misinterpreted as a progressive disease and remains difficult to evaluate.

Additionally, not all patients respond favorably to neoadjuvant treatment, highlighting the need for predictive biomarkers to identify responders and non-responders accurately.

The optimal duration and sequencing of neoadjuvant therapy remain areas of ongoing research, requiring prospective studies to elucidate.

Neoadjuvant targeted therapy with dabrafenib and trametinib in BRAF-V600-positive stage III. melanoma patients, although having high overall response rates (ORR) and a high percentage of pathologic complete response (pCR) of almost 50%, has proven to be of short duration, with high percentages of patients recurring shortly after the neoadjuvant treatment and subsequent surgery.

In contrast, immunotherapy, either dual/combined anti-PD-1 antibody and anti-CTLA-4 antibody (primarily nivolumab and ipilimumab) or monoimmunotherapy with anti-PD-1 antibody pembrolizumab, has emerged as a cornerstone in melanoma treatment.

The efficacy of neoadjuvant therapy in melanoma has been supported by a growing body of clinical evidence, including prospective trials, retrospective studies, and meta-analyses.

Several landmark trials have demonstrated impressive response rates and favorable outcomes with neoadjuvant targeted therapy and immunotherapy.

OpACIN clinical trial was the first to show significant benefit and improved patients' outcomes by applying neoadjuvant immunotherapy with two standard doses for melanoma (ipilimumab 1 mg/kg + nivolumab 3 mg/kg) versus adjuvant nivolumab monoimmunotherapy.

The opACIN-neo clinical trial was designed to explore different schedules of dual neoadjuvant immunotherapy with ipilimumab and nivolumab, aiming to identify the schedule with the best efficacy-to-toxicity ratio. Modified dosing (ipilimumab 1 mg/kg + nivolumab 3 mg/kg) was identified as the best, with maintained efficacy (pathologic response rate of 77%), but twice lower the incidence of grade 3 or 4 adverse effects (20%) in comparison to standard dosing (40%).

PRADO clinical trial further explored the personalization of neoadjuvant therapy by excising and analyzing the so-called "index lymph node" (the largest regional metastatic lymph node) as the representative for the whole regional lymph node basin after the application of neoadjuvant dual immunotherapy. Based on the achieved pathologic response to treatment in the index lymph node, further activities were stratified as – observation only (if pCR or near-pCR was achieved); total lymph node dissection (TLND) followed by observation if pathologic partial response (pPR) was achieved; or TLND and subsequent adjuvant therapy if pathologic no response (pNR) occurred. Patients in the PRADO – trial had 71% of pRR, with an impressive 61% of pCR or near-pCR.

SWOG1801 trial in 2022, surprisingly, showed PFS benefit by moving three cycles of monoimmunotherapy with pembrolizumab from the adjuvant to the neoadjuvant setting (while the remaining 15 cycles were applied adjuvantly) in comparison to 18 cycles of adjuvant pembrolizumab (HR=0.58; p=0.004).

Eagerly awaited are the results of the ongoing stage III neoadjuvant NADINA trial, which is comparing response-driven neo-adjuvant combination of ipilimumab + nivolumab versus adjuvant nivolumab.

The ongoing clinical trials further explore new therapeutic combinations in the neoadjuvant setting, such as the combination of nivolumab and relatlimab.

Based on these results, neoadjuvant immunotherapy has already been included in clinical practice guidelines for melanoma treatment, although it is still not formally registered for this indication.

In conclusion, neoadjuvant melanoma treatment represents a paradigm shift in the management of melanoma, offering the potential to improve outcomes through early intervention, tumor downstaging, and systemic disease control.

It is most likely the imminent future in the management of patients with clinical stage III melanoma.

Keywords: neoadjuvant treatment, melanoma, immunotherapy, anti-PD-1 therapy

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S13 – BREAST CANCER AND PREGNANCY

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Breast cancer is the most commonly diagnosed cancer during pregnancy. An estimated incidence is of 1 case every 1000 pregnancies(1). The incidence is likely to rise due to later maternal age at first pregnancy.

Breast cancer during pregnancy is associated with a lower prevalence of hormone receptor expression, thus with a predominance of more aggressive subtypes that are peculiar for younger ages, such as triple-negative or HER2-positive(2,3). The diagnosis occurs more frequently at more advanced stages in comparison with non-pregnant patients, potentially due to the teratogenicity of most radiological imaging procedures, and suboptimal staging and management.

Breast cancer during pregnancy is a challenging and delicate situation requiring a multidisciplinary team work to establish the best strategy for assuring safe care for both the mother and the child(4).

To date, data regarding breast cancer care occurring during pregnancy are mostly derived from retrospective reports, thus the inclusion of patients in dedicated registries is advisable.

The different treatment strategies can be combined according to the gestational age.

Breast surgery is feasible throughout the pregnancy while radiotherapy should be postponed after delivery.

Patients diagnosed with breast cancer during pregnancy can be safely treated with chemotherapy starting from the second trimester while it is contraindicated in the first trimester due to the high risk of fetal malformations(4,5). The choice of the regimen should follow the guidelines for non-pregnant patients, anthracyclines and taxanes being the standard of care after the first trimester(5).

Endocrine therapy and targeted therapies are not indicated in pregnant patients and should be postponed after delivery(5).

Targeted therapies for the treatment of breast cancer have been increasingly used in the last few years. Current guidelines contraindicate the use of trastuzumab during pregnancy, mainly due to the increased risk of developing oligo- and/or anhydramnios. Up to now, no data available for administration of newer

anti HER therapy, pertuzumab, trastuzumab-emtansine (T-DM1) and neratinib, in early breast cancer during pregnancy, thus they are contraindicated.

To date, no data on the safety of CDK4/6i during pregnancy are available, so currently their use is contraindicated during pregnancy(5).

Patients with breast cancer during pregnancy should undergo a close fetal monitoring, and a full-term delivery should be reached to reduce the risk of long-term complications(4).

Immunotherapy with antibodies directed against programmed cell death protein 1 (PD-1) or its ligand (PD-L1) is becoming a relevant option for triple-negative subtype. During pregnancy, the mother develops an immune tolerance towards the fetus, involving the PD-1/PD-L1 pathway; therefore, its inhibition could potentially result in an immune response against the fetus(6,7,8).

The treatment landscape of breast cancer is rapidly evolving, but very few data have been reported about the safety of new compounds during pregnancy. The collection of prospective data regarding patients with breast cancer during pregnancy into dedicated registries is highly recommended, in order to enrich current knowledge on this topic and to improve the counseling of patients and their caregivers.

Considering the young age of patients with breast cancer during pregnancy, proper genetic counselling should be offered.

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