

# POSTER PRESENTATIONS



## P1 – Perioperative FLOT chemotherapy in real-world setting – single center experience

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**Background:** Gastric cancer remains a global health challenge and represents a significant cause of cancer-related morbidity and mortality worldwide. Perioperative chemotherapy has been widely adopted as the standard of care for locally advanced gastric cancer (LAGC). We have carried retrospective observational study in University Hospital Centre Zagreb to evaluate the efficacy and safety of perioperative chemotherapy with FLOT protocol.

**Methods:** 25 patients who received perioperative FLOT for LAGC between April 2020 and June 2023 were retrospectively identified. Patient characteristics, tumor response rates, DFS, and OS were evaluated. OS was defined as the time from the start of treatment until death or the last follow-up visit, and DFS as the time from the start of treatment until disease progression, relapse, or death, whichever occurred first. Survival (OS and DS) was estimated using the Kaplan–Meier method. Patients were censored with the last follow-up until June 1<sup>st</sup>, 2023.

**Results:** Out of 25 patients, 20 were male (80%). The median age at the start of treatment was 64 years. 17 patients (68%) had gastric cancer, whereas 8 patients (32%) had gastroesophageal junction cancer. 22 patients (88%) received complete 4 preoperative cycles, whereas 3 patients received less than 4 cycles. Dose reduction was necessary in only 3 patients. After preoperative chemotherapy, 24 patients went to surgery while 1 patient had disease progression. Surgery was curative in 20 patients and palliative in 4 patients. 18 patients had their response to neoadjuvant chemotherapy according to the Becker score. In 14 patients score was 3, in 3 patients score was 2, and one patient had a score of 1. No complete responses were found. Only 8 patients (32%) in intent to treat population were able to complete all 4 postoperative FLOT cycles. The estimated DFS was 8.1 months, while OS was not reached.

**Conclusion:** Although our institution's data is not yet mature enough and median follow-up is still short, results in real-world publications appoint to much worse DFS and less tolerability than in the original FLOT-AIO4 study, with low pathological response to perioperative chemotherapy. Further research is warranted to improve survival outcomes in patients with LAGC.

## P2 – Biomarkers of treatment outcome in patients with metastatic melanoma treated with first-line immune checkpoint inhibitors – a single-institution, retrospective analysis

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The use of first-line immune checkpoint inhibitor (ICI) therapy has substantially improved overall survival (OS) in patients with metastatic melanoma. However, a large proportion of patients with metastatic melanoma treated with ICI have or develop resistance to treatment and a reliable biomarker of treatment outcome has not yet been identified. The occurrence of immune-related adverse events (irAE) during ICI therapy is correlated with a positive treatment outcome. On the other hand, increased cancer-associated inflammation that can manifest with systemic inflammatory processes is associated with poorer treatment outcome in various types of cancer. Based on the latter, several blood-based, immune-inflammatory prognostic scores have been developed and previously investigated in cancer patients. Thus, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), systemic immune-inflammation index (SII) and pan-immune-inflammation value (PIV) have all been previously employed to predict treatment outcome in cancer patients. The aim of this study was to evaluate the occurrence of irAE and aforementioned immune-inflammatory prognostic scores as biomarkers of treatment outcome and survival in patients with metastatic melanoma treated with first-line ICI. A single-institution, retrospective analysis was performed. All patients with metastatic melanoma treated with first-line ICI at the Institute of Oncology Ljubljana from January 2018 to December 2020 were included. All prognostic scores were calculated before the start of the 1st (baseline) and 2nd treatment cycle. Their values were labelled as low or high regarding the data obtained from previous studies. Survival rates were obtained using the Kaplan-Meier method; survival between groups was compared using the log-rank test. The significance of irAEs and prognostic scores was analysed using the Cox proportional hazards model with results expressed as hazard ratio (HR) and 95% confidence interval (CI); univariate and multivariate analysis of progression-free survival (PFS) and OS were performed. Of the 129 treated patients, 24 (18.6%) had complete response, 28 (21.7%) had partial response, 26 (20.2%) had stable disease and 51 (39.5%) patients had progressive disease. Patients that developed irAE had a lower risk of disease progression in comparison to patients without irAR (HR 0.41, 95% CI 0.23–0.71,  $p=0.002$ ). Additionally, patients with a high baseline SII had a higher risk of disease progression and death in comparison to patients with a low baseline SII (HR 1.94, 95% CI 1.09–3.45,  $p=0.025$ ; and HR 2.60, 95% CI 0.91–7.50,  $p=0.026$ , respectively). Moreover, patients with a high PLR before the 2nd treatment cycle had a higher risk of disease progression in comparison to patients with a low PLR before the 2nd treatment (HR 1.71, 95% CI 1.03–2.83,  $p=0.038$ ).

In conclusion, the results of this single-institution, retrospective analysis once again confirmed the correlation between the occurrence of irAE and a positive treatment response in patients with metastatic melanoma treated with first-line ICI. They also revealed that high baseline SII and a high PLR before the 2nd treatment cycle are potential early negative predictive biomarkers of response in this setting.

**Keywords:** metastatic melanoma, immune checkpoint inhibitors, biomarkers, immune related adverse events (irAE), immune-inflammatory prognostic parameters

### **P3 – Avelumab as a maintenance therapy in advanced urothelial carcinoma: one-year experience at University Hospital Centre Zagreb**

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Immune-checkpoint inhibitors represent a significant advance in the treatment of metastatic urothelial carcinoma. These drugs are currently used in three clinical scenarios: as first-line treatment in cisplatin-ineligible patients, second-line treatment in case of progression following chemotherapy, and as maintenance therapy in the absence of progression after first-line platinum-containing chemotherapy. Based on the results of the JAVELIN Bladder-100 trial, the anti-PDL-1 antibody avelumab was approved by the FDA in 2020 as maintenance therapy for advanced urothelial carcinoma. Trial update, published earlier this year, indicate a sustained benefit in overall survival and progression-free survival compared to best supportive care. In July 2022, avelumab became available to patients in Croatia as a therapeutic option in the treatment of advanced urothelial carcinoma without progression to first-line chemotherapy. In the one-year period since avelumab has been available for this indication, 13 patients with advanced urothelial carcinoma, without progression to first-line chemotherapy, started treatment with the aforementioned at UHC Zagreb. The youngest patient was 36 years old at the time of diagnosis, while the oldest was 79 years old. 11 patients were treated for localized disease before the diagnosis of distant metastases (e.g. transurethral tumor resection, intravesical chemo- or immunotherapy, radical surgery). The most common metastatic sites have been abdominal or pelvic lymph nodes, followed by bones, lung and liver. Patients received 4-6 cycles of first-line platinum-containing chemotherapy. According to follow-up CT scan, the vast majority of patients (12 of them) had a partial response to chemotherapy, while one had stable disease. The mean time to avelumab initiation was 4 weeks. Despite mandatory use of antihistamine and paracetamol prior to the first 4 infusions of avelumab, three patients had an infusion reaction in the form of chills and rigors, which stopped spontaneously or with additional medication. By July 2023, eight patients, who were progression-free at subsequent follow-up, were still receiving avelumab, while four patients discontinued maintenance therapy due to progression. Immune-related adverse events (irAE) have been observed in 6 patients, including rash and pruritus, asymptomatic elevation of liver enzymes (transaminitis) and hypothyroidism. One patient developed clinical features of psoriasis. Also, renal function worsened in one. Due to adverse events, avelumab was temporarily discontinued in 5 patients. Skin and liver toxicity were successfully managed with topical and systemic steroids, respectively. Hypothyroidism was managed with levothyroxine replacement therapy. Interestingly, all but one patient who developed irAE had a maintained response at subsequent follow-up.

Since the beginning of avelumab administration in this patient population at UHC Zagreb, more than half have a maintained response to first-line treatment. Immune-related adverse events are mostly grade 1-2 and can be successfully managed with steroids and hormone substitution. None of them have so far required permanent discontinuation of avelumab. Constant vigilance is mandatory.

## P4 – Effectiveness of CDK 4/6 inhibitors in the first-line treatment of patients presenting with visceral crisis: real-world data

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**Introduction:** Standard first-line treatment of HR (hormone receptor) positive/ HER2 negative metastatic breast cancer (mBC) without visceral crisis is the combination of CDK 4/6 inhibitors (CDK 4/6i) and endocrine therapy (ET), proven to prolong overall survival (OS). According to the 5th ESO-ESMO international consensus guidelines, visceral crisis is defined as: *severe organ dysfunction, as assessed by signs and symptoms, laboratory studies and rapid progression of disease*. In most breast cancer guidelines, chemotherapy is still the recommended first-line treatment for patients with visceral crisis.

**Methods:** A retrospective study of 369 mBC patients who started CDK 4/6i therapy between January 2018 and December 2022 at University Hospital Centre Zagreb was conducted, with prior Ethics Committee approval. Patients who had visceral crisis at presentation and received a combination of CDK 4/6i and ET as first-line treatment were identified, clinical presentation of disease and therapy information were analyzed. Progression-free survival (PFS) and OS were calculated using the Kaplan-Meier survival analysis with the data cut-off point being July 1st 2023.

**Results:** Of the patients with HR positive / HER2 negative mBC who were treated with first-line therapy CDK 4/6i and ET, 15 out of 221 (6,79%) patients presented with symptomatic disease and visceral crisis: 10 (66,7%) patients had global respiratory insufficiency due to lung metastases and pleural effusion, 3 (20%) had compromised liver function due to extensive liver metastases and 2 (13,3%) had pancytopenia due to bone marrow infiltration. Endocrine resistance was present in 13,33% (2/15) patients and 53,33% (8/15) patients had *de novo* metastatic disease. All three patients with impending liver failure received palbociclib, eleven patients received ribociclib, and one abemaciclib. Most of the patients 86,7% (13/15) were treated with an aromatase inhibitor and only 13,3% (2/15) with fulvestrant. All patients with visceral crisis showed significant clinical improvement during the first 3-4 weeks and significant improvement in laboratory findings and imaging was observed after the first three cycles of treatment with no major adverse effects. Median follow-up was 25 months (6 to 51 months), during which only 3 patients had disease progression. The survival curve for PFS and OS did not drop to 0.5 or below, therefore median time could not be calculated. The 6-month PFS and OS were 100%.

**Conclusion:** Patients with visceral crisis treated by CDK 4/6i had a rapid clinical response without any major adverse effects. According to the results of this case study it can be concluded that patients with HR positive / HER2 negative mBC and visceral crisis could be successfully treated with CDK4/i instead of chemotherapy which was standard for many years, although the value of collected data is limited due to short follow-up and a small number of patients. Future clinical trials should explore the use of CDK4/6i in the setting of visceral crisis.

## P5 – Results of systemic treatment for squamous cell skin cancer at the Institute of Oncology Ljubljana

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**Background:** The management of locally advanced squamous cell carcinoma (laSCC) and metastatic squamous cell carcinoma (mSCC) is possible with radiotherapy, platinum-based chemotherapy, targeted therapy with epidermal growth factor receptor inhibitors or programmed cell death receptor inhibitors. Among these options is cemiplimab, a programmed cell death protein 1 (PD-1) inhibitor, approved for the treatment of locally advanced and metastatic disease where radiotherapy or surgery is not deemed suitable.

**Methods:** The aim of our study is to assess the treatment outcomes with cemiplimab in individuals diagnosed with laSCC and mSCC at the Oncology Institute Ljubljana within the period spanning from May 2020 to February 2023. The study included 28 patients who were administered cemiplimab as their first-line treatment approach. Cemiplimab was administered via a 350 mg dose in 30-minute intravenous infusion every 3 weeks. Participants who did not receive cemiplimab as their first-line treatment regimen were excluded from the study cohort. Patient characteristics, tumor attributes, laboratory metrics, and data concerning immune-related adverse effects were meticulously gathered from medical records and subsequently subjected to analysis.

**Results:** The median progression-free survival (PFS) was 4,4 months (95 % confidence interval 1,5-7,3 months) and the median overall survival (OS) was 7,3 months (95 % confidence interval 4,64-9,89 months). Notably, patients that developed immune-related adverse events (irAE) exhibited a higher response rate; the overall response rate was 43%, and the disease control rate reached 71%. 25 % of patients developed at least one irAE. The most prevalent irAE were skin toxicity (14,29%) and hypothyroidism (3,57%), with a subset of patients (7,14%) manifesting both skin toxicity and hypothyroidism. In our study, we computed several metrics, including the platelet-to-lymphocyte ratio (PLR), pan-immune inflammation value (PIV), systemic immune inflammation value (SII), and neutrophil-to-lymphocyte ratio (NLR). The aforementioned values hold potential as prognostic indicators concerning both irAE development and response to treatment; however, our results are inconclusive.

**Conclusion:** The obtained data confirms the effectiveness of using cemiplimab as a first-line treatment for mSCC and laSCC, with a satisfactory safety profile. The occurrence of irAE may serve as a positive prognostic factor. Further investigations within larger and more diverse patient groups are imperative to substantiate our findings.

**Keywords:** cutaneous squamous cell carcinoma, cemiplimab, immune-related adverse events (irAE), immune-inflammatory prognostic parameters

## **P6 – Adoption of total neoadjuvant therapy (TNT) for locally advanced rectal cancer: single centre experience from the Institute for Oncology and Radiology of Serbia (IORS)**

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**Background:** Treatment of locally advanced rectal cancer (LARC) involves chemoradiation, surgery and chemotherapy. The concept of total neoadjuvant therapy, in which chemoradiation and chemotherapy are administered prior to surgery, has been developed to optimize delivery of effective systemic therapy upfront, aimed at eradicating micrometastases. This is an observational prospective study in which TNT was established as a new standard of care for LARC at IORS, after a multidisciplinary tumor board decision (MDT).

**Methods:** We defined LARC as adenocarcinoma of the rectum with distal margin of 15 cm or less from the anal verge on endoscopy, staged with magnetic resonance imaging (MRI) as cT3/cT4 N0, or cT (any) cN1/2, according to clinical and histological criteria of the 8th edition of the TNM classification of malignant tumours (TNM8), in line with ESMO, ASCO and NCCN guidelines. Patients were excluded if they had recurrent or metastatic disease, previous surgical treatment for rectal cancer, or concurrent fistulizing inflammatory bowel disease of the rectum. Total neoadjuvant therapy was defined as induction chemotherapy (CHT) in the form of FOLFOX6 or CAPOX protocol, followed by long course radiotherapy (RT) concurrently with infusional 5FU-LV in week 1 and week 5 of RT. We collected demographic data, TNM stage, tumor distance in centimetres from the anal verge, type and duration of induction CHT and adverse events.

**Results:** From May 2022, 30 patients started treatment using this approach. Median age of the patients was 56 (range 34-73), with 20 male (66.6%) and 10 (33.3%) female patients, 17 patients (56%) had cT4 at diagnosis and 13 (44%) had cT3 stage. N2 disease was observed in 25 patients (83%), N1 in 5 patients (17%). 10 patients (33.3%) presented with distal rectal cancer (less than 5 cm from anal verge), 15 (50%) had a tumor between 5 and 10cm above the anal verge, and 5 (16.6%) had a tumor more than 10 cm above the anal verge. Half of the patients (15) were treated with induction FOLFOX chemotherapy, and half (15) with CapOx. At the time of this analysis, 10 patients had completed 4 cycles of CHT and started with chemoradiation. So far, no grade 3 or 4 adverse effects of this treatment were registered. Results regarding efficacy of treatment are still not mature.

**Conclusion:** These are preliminary results of a single institution study which represent a valuable source of real-world data regarding TNT treatment of LARC. So far, the treatment has proven feasible in our setting, and is becoming a new standard of care for selected patients. Measures of treatment efficacy and toxicity are pending, and we hope to present them at a future meeting.



## P7 – Next-generation sequencing (NGS) in routine oncology practice in Croatia

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**Background:** There is no nationally representative data on next-generation sequencing (NGS) tests in routine oncology practice in Croatia. This study aimed to investigate how oncologists in Croatia use NGS tests to evaluate cancer patients and whether NGS results influence treatment decision-making.

**Methods:** In September 2022, research was conducted through an electronic anonymous google form online survey sent to e-mails of oncologists from the database of the Croatian Society for Medical Oncology (N=163, cooperation rate 44%). The goal of the research was to determine how often we use NGS tests in oncology practice in Croatia, in which indications, and for what purpose. We were interested in whether we have problems with the interpretation of NGS results and whether the NGS result affects our decision on patient treatment. We were also interested in possible reasons for not using NGS, general satisfaction with the conditions of molecular testing in Croatia, and the current biggest challenges of molecular testing in Croatia from the perspective of oncologists.

**Results:** Most of the oncologists surveyed reported using NGS tests in their clinical practice (25% often, 60% sometimes, and 15% rarely). Testing is mainly indicated for patients with rare tumors and for patients with advanced refractory disease (57%) as well as for patients with tumors of unknown primary site (50%) to provide patients with insurer-approved targeted therapy (77%), treatment through compassionate or off-label use of the drug (68%) or to determine eligibility for clinical trials (32%). Most respondents have problems with the interpretation of the results of NGS (71% sometimes, 8% often). The results of NGS in the majority of respondents influence the decision on treatment (29% often, 64% sometimes). Oncologists who do not use NGS (N=33) give the following reasons: the impossibility of treatment according to test results (76%), lack of evidence-based guidelines (36%), insufficient information about access to NGS in Croatia (24%), and inability to send material for NGS testing (21%). The majority of respondents are not satisfied with the current conditions of molecular testing in Croatia (60% partially satisfied, 32% dissatisfied). According to the respondents, the biggest challenges of molecular testing in Croatia are the impossibility of treatment according to the test results (81%), the time required to obtain the results (52%), additional financial expenses (38%), and the interpretation of the test results (37%).

**Conclusion:** The majority of oncologists in Croatia use NGS tests in their clinical practice, whereby the results of NGS significantly influence treatment decisions. It is necessary to improve the conditions of molecular testing in Croatia, provide support when interpreting NGS results, and make additional efforts to provide equal access to NGS to all oncology patients who can benefit from new technologies, and then provide therapy according to the test results.

## **P8 – Inflammatory biomarkers as a predictive parameter for the first-line anti-PD1 immunotherapy in metastatic melanoma: Multicentre retrospective study**

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**Background:** Biomarkers derived from complete blood count, considered to be an indirect measure of the immune inflammatory response, have been recognized as the useful prognostic factor in some tumours. We have analysed these biomarkers in patients with metastatic melanoma treated with first-line anti-PD1 immunotherapy.

**Methods:** In this multicentre retrospective study blood samples of 69 melanoma patients (26 females and 43 males) treated with first-line anti-PD1 therapy were collected up to one month before the start of the treatment. The baseline LDH (bLDH) and inflammatory biomarkers [neutrophil to lymphocyte ratio (bNLR), monocyte to lymphocyte ratio (bMLR), lymphocyte to monocyte ratio (bLMR), platelet to lymphocyte ratio (bPLR) and pan-immune inflammation value (bPIV)] were analysed, as well as their correlation with duration of treatment and progression-free survival.

**Results:** Mean value of bNLR, bPLR, bMLR and bPIV in analysed samples were 3.97, 187.39, 0.38 and 571.74, respectively.

Patients with elevated bLDH had significantly higher mean bNLR (4.76 vs 3.45;  $p < 0.05$ ), bPLR (222.75 vs 164.33;  $p < 0.05$ ) and bPIV (906.17 vs 335.17;  $p < 0.05$ ) than patients with normal bLDH. Patients with PFS of more than 12 months had significantly lower mean bNLR (3.85 vs 4.54;  $p < 0.05$ ), bMLR (0.29 vs 0.44;  $p < 0.05$ ) and bPIV (341.72 vs 719.55;  $p < 0.05$ ) when compared to patients with a PFS  $< 12$  months. Also, lower bNLR and bMLR was found in patients with PFS  $> 24$  months ( $p < 0.05$ ). Patients with bNLR and bMLR below cut-off values were associated with duration of therapy  $> 12$  months ( $p < 0.05$ ).

**Conclusions:** This study showed the association between of bNLR, bPLR, bMLR and bPIV values and elevated bLDH, previously recognized as a poor prognostic/predictive marker in patients with metastatic melanoma, as well as correlation of these inflammatory biomarkers and duration of therapy and progression-free survival. Further studies are needed to confirm possible prognostic/predictive value of inflammatory biomarkers.

## **P9 – The prognostic and predictive value of human gastrointestinal microbiome and exosomal mRNA expression of PD-L1 and IFN $\gamma$ for immune checkpoint inhibitors response in metastatic melanoma patients: protocol trial**

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**Background:** Immunotherapy represents the newest and most promising type of treatment for advanced malignant melanoma. However, a large proportion of patients do not respond to the treatment with immune checkpoint inhibitors (ICIs) or they develop serious immune related adverse events (irAE). Preclinical and small cohort studies suggest gastrointestinal microbiome composition, exosomal and tissue mRNA expression of PD-L1 and IFN $\gamma$  from the primary tumor, stool and body fluids as potential biomarkers for response.

**Methods:** In this prospective study we will recruit patients treated with immune checkpoint inhibitors as a first line treatment for metastatic melanoma. Stool samples and peripheral venous blood samples are submitted before the start of treatment, at the 12th (+/-2) week and 28th (+/-2) week. Additionally, the stool and blood samples are taken at the occurrence of event (suspected disease progression/hyperprogression, immune-related adverse event, deterioration). Histological material from the tumor tissue is obtained before the start of immunotherapy treatment. Primary objectives are to determine whether the human gastrointestinal microbiome and the exosomal mRNA expression of PD-L1 and IFN $\gamma$  and its dynamics predicts the response to treatment with PD-1 and CTLA-4 inhibitors and its association with the occurrence of irAE. The response is evaluated radiologically with imaging methods in accordance with the irRECIST criteria.

**Conclusion:** This is the first study to combine and investigate multiple potential predictive and prognostic biomarkers and their dynamics in first line ICI in metastatic melanoma patients.

## P10 – Combined influence of PD-L1 expression and HER2-low status on clinical outcomes of neoadjuvant chemotherapy in early triple negative breast cancer (TNBC)

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**Background:** TNBC is an aggressive breast cancer (BC) subtype, characterized by lack of expression of estrogen, progesterone and HER-2 receptors. Due to its aggressive behavior, high metastatic potential, limited treatment options and frequent treatment resistance, it has worse prognosis than other BC subtypes. TNBC is also characterized by an immunogenic microenvironment with higher rates of tumor-infiltrating lymphocytes and programmed cell death-ligand 1 (PD-L1) expression than other BC subtypes, which led to studies involving immunotherapy in treatment of TNBC. Immune checkpoint inhibitors targeting programmed cell death-1 (PD-1) receptor and PD-L1 have shown promising results in metastatic and early disease setting, in combination with chemotherapy. The aim of this study was to determine whether there is an impact of PD-L1 status on the pathologic complete response (pCR) rate as primary indicator of neoadjuvant chemotherapy (NACT) outcome and its correlation with HER2 low status.

**Methods:** A retrospective study of 82 TNBC cases who received NACT between January 2019 and December 2022 at University Hospital Centre Zagreb, Croatia, was conducted with prior Ethics Committee approval. Histopathological characteristics of tumors available from the hospital information system (BIS), including estrogen and progesterone receptor (ER, PR), HER2 status and proliferation index Ki-67, as well as pCR rates, were analyzed. PD-L1 status at the time of diagnosis was determined by immunohistochemistry using VENTANA PD-L1 (SP142) Assay and results were either positive (>1% PD-L1 stained immune cells) or negative (<1%). NACT consisted of anthracycline and taxane based chemotherapy, without addition of any kind of targeted or immunotherapy. pCR rates were calculated for PD-L1 negative and PD-L1 positive cases. PD-L1 status was correlated with HER2-low status. Chi square test was used to analyze association between pCR rate and PD-L1 status.

**Results:** Among all TNBC patients treated by NACT, altogether 50% (41/82) achieved pCR. After exclusion of cases with missing data, a total of 41 patients were included in the further analysis. Of those, 26 (63.4%) were PD-L1 positive, and 15 (36.6%) were PD-L1 negative. In the PD-L1 positive group, the pCR rate was 53.8%, and in the PD-L1 negative group 26.6% ( $p=0.091193$ ). Similar percentage of HER2-low cases was observed in the PD-L1 positive and PD-L1 negative groups – 12% and 13%, respectively. In the PD-L1 positive group pCR rate for HER2-low cases was 25%, and for HER2 0 cases 54.54%. In the PD-L1 negative group, pCR rate in HER2-low cases was 100%, and in HER2 0 cases 15.4%.

**Conclusion:** Although only a modest number of patients was included in this study and statistical significance was not reached, a trend toward higher pCR rates after neoadjuvant chemotherapy was observed in the PD-L1 positive group. The obtained results are concordant with current literature data suggesting that PD-L1 positive tumors are more likely to achieve pCR. A small number of patients precludes any definitive conclusions regarding correlation of PD-L1 and HER2-low status, although it seems that PD-L1 positive, HER2 0 could be more likely to achieve pCR.

## P11 – Breakdown of biological subtypes in breast cancer patients with germline *BRCA 1/2* and beyond-*BRCA* mutations treated with neoadjuvant chemotherapy

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**Background:** Neoadjuvant chemotherapy (NACT) found its role in breast cancer treatment as an effective tool for downstaging, allowing for less radical surgery and less postoperative complications, while also evaluating the effectiveness of systemic therapy. Studies show that different biological subtypes exhibit different responses to chemotherapy. In recent years more and more breast cancer patients in the Department of Oncology in University Hospital Centre Zagreb are subjected to genetic testing. We aimed to examine the distribution of biological subtypes among the germline *BRCA 1/2* and beyond-*BRCA* mutated patients who received chemotherapy in a neoadjuvant setting.

**Methods:** 778 patients were subjected to genetic testing and medical records of 110 breast cancer patients harboring germline pathogenic or likely pathogenic variants of *BRCA1/2* genes and beyond-*BRCA* genes (*ATM*, *PALB2*, *TP53*, *CHEK2*, *NBN*, *MUTYH*, *BLM*, *NTHL1*, *RAD50*) were reviewed selecting the ones treated with NACT. The clinicopathological variables which included age at the time of diagnosis, biological tumor subtype (luminal A like, luminal B like, HER2+, triple negative breast cancer like), chemotherapy regimen and type of surgery (breast-conserving vs. mastectomy) were collected. The data was analyzed using binary logistic regression.

**Results:** In total 47 patients were included, the *BRCA* subgroup was comprised of 28 patients of which 19 (67.9%) were triple negative (TNBC), 7 (25%) luminal B like and 2 (7.1%) HER2+. The beyond-*BRCA* subgroup included 19 patients of which 15 (78.9%) were luminal B like, 2 (10.5%) HER2+ and 1 (5.3%) luminal A like. One patient with a mutated *CHEK2* gene had bilateral disease (HER2+ and HER2-). The median ages of the subgroups were 38 (TNBC), 42 (luminal A like), 42 (luminal B like) and 43 (HER2+). Furthermore, hormone receptor status was found more likely to be positive among the beyond-*BRCA* subgroup (p-value 0.001302, OR 75.11, 95% CI [5.399, 1044]). No statistically significant difference in age at diagnosis, HER2 status, chemotherapy regimen and type of surgery was identified.

**Conclusion:** The most represented subtype among the *BRCA* subgroup was TNBC which is in accordance with studies reporting association between *BRCA* status and TNBC. Among the beyond-*BRCA* subgroup the exceedingly dominant subtype was luminal B like. Additionally, our sample demonstrated a statistically significant association between hormone receptor positivity and beyond-*BRCA* mutations. In summary, knowing the representation of different breast cancer subtypes within a group allows for personalized treatment decisions, assessment of prognosis and risk, identification of genetic associations, and advancements in research and clinical practice.

## P12 – Anticoagulant therapy in patients with malignancies/risk assessment during chemo-radiotherapy treatment

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**Introduction:** Patients with previously diagnosed malignancies are 4-7 times more likely to develop venous thromboembolism (VTE), which represents second most common and potentially preventable cause of death. Therefore, severe bleeding in patients on chronic anticoagulant therapy is twice as often as in the control group. There are numerous additional risk factors, such as large tumour masses, malignant neoplasms of gastrointestinal tract, otorhinolaryngological region, gynaecological tumours, as well as personal characteristics of a patient, comorbidities and therapeutic approach. Furthermore, older people are more prone to hypercoagulable conditions and usually dependent on anticoagulant therapy. When applied, chemoradiotherapy (CRT) interacts with anticoagulants leading to increased risk of severe bleeding, especially in elderly. Aforementioned interaction could cause hemostasis disorders, azotemia, hematological toxicity, electrolyte imbalance etc. and consequently bleeding.

**Case report:** 63-years-old patient, a long-time smoker, retiree. Anamnestic data reveals paroxysmal valvular atrial fibrillation (AF), dilated veins in lower extremities and previous surgical treatment of the abdominal aortic aneurysm. Chronic therapy included amiodarone 200mg 1x1, doses of acenocoumarol appropriately adjusted in accordance with INR and amlodipine. In February 2023, he was diagnosed with locally advanced laryngeal squamous cell carcinoma. The treatment started with total laryngectomy, radical tongue resection and bilateral neck dissection, and afterward followed by CRT. During the CRT, he reported a presence of multiple hematomas: the biggest, about 7cm in diameter, was found on his right shoulder area, whereas multiple smaller were present on the back. Hemostasis parameters were following: INR 8.66; PTV 116.8 and aPTT 58.2. There were no signs of hematologic toxicity or additional bleeding on visible mucous membranes. First step was discontinuation of acenocoumarol, and potential application of freshly frozen plasma (FFP) in case of an additional bleeding. After two days, hemostasis test was repeated and control INR was below 1.5. In consultation with the hematologists, further administration of oral anticoagulant therapy (OAC) was replaced with low-molecular-weight-heparin (LMWH), dalteparin-sodium, starting with a dose of 5000 IU twice a day with corresponding anti-Xa control test.

**Conclusion:** In older patients suffering from malignancies with multiple comorbidities including valvular and non-valvular AF, stroke or coronary disease, risk burden in anticoagulant therapy should be well assessed, based on CHA2DS2-VASC risk factors, Khorana Score, Wells Score. Evaluation of the risk factors represents a crucial precondition for an accurate assessment of an anticoagulant therapy's benefit/risk ratio in vulnerable patients. *OAC-Warfarin:* anticoagulant effect occurs a few days after the first administration. Usually, initial dose of warfarin is 5-10mg on the first day, switching to a corresponding maintenance dose (3-9mg) adjusted in accordance with INR value. Introduction of OAC require frequent laboratory control of INR in order to achieve the optimal dosage. The main side effect is bleeding. In case of severe bleeding, it is necessary to discontinue warfarin and apply 5-10mg of phytomenadione (vitamin K) along with FFP and prothrombin complex concentrate. Furthermore, due to high affinity for plasma proteins, CYP450 dependent metabolism and a small therapeutic range, warfarin and other coumarin-based anticoagulant drugs enter clinically significant interactions with numerous other medications. New anticoagulant drugs (NOAC), such as direct thrombin inhibitors (dabigatran) and anti-Xa factors (rivaroxa-

ban, apixaban and edoxaban) can often replace standard anticoagulants. Clinical studies have shown supremacy in efficacy and safety profile of NOACs compared to warfarin. On the other hand, the main problems of NOACs are lack of laboratory tests for anticoagulant effect monitoring and deficiency of an antidote. Therefore, the application of LMWH for the treatment of VTE in cancer patients remains a standard in clinical practice for a long-term treatments. However, LMWH is underused, primarily due to problems with application, costs and patient preferences.

### **P13 – Impact of HER2-low status on effectiveness of first line treatment with CDK4/6 inhibitors in patients with HR-positive, HER2-negative metastatic breast cancer (mBC): single institution experience**

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**Background:** Standard of care in the first line treatment of hormone receptor (HR) positive, HER2-negative mBC is combination of CDK4/6 inhibitors and endocrine therapy (ET). More recently, new entity called HER2-low BC emerged within HER2-negative BC, characterized with specific clinical features and defined by immunohistochemical (IHC) score of 1+, or 2+ without amplification of *HER2* gene determined on in situ hybridization (ISH). Currently, there are a lot of research undertaken to define influence of HER2-low status on course of mBC. This aim of this study was to determine the prognostic significance of HER2-low status in HR-positive, HER2-negative mBC treated with first-line combination therapy – ET plus CDK4/6 inhibitors.

**Methods:** This retrospective study was investigating patients with HR-positive, HER2-negative mBC who started first line treatment with ET and CDK4/6 inhibitors from January 2018 through December 2022 at University Hospital Centre Zagreb, with prior Ethics Committee approval. The inclusion criterion was assessment of HER2 status by IHC with or without ISH. Patient demographics and clinical presentation, tumor characteristics and treatment information were collected. Progression-free survival (PFS) and overall survival (OS) analysis was done with the final data cut-off date being June 1st, 2023. Type 1 right censoring was performed. The data was analyzed using the Kaplan-Meier method and Cox proportional-hazards regression for clinically relevant covariates (*de novo* metastatic disease, ET resistance, liver metastases, and bone marrow infiltration).

**Results:** The overall number of 221 patients treated in the first line setting with combination of ET and CDK4/6 inhibitors were included in this study. Of those, 43.4% (96/221) were determined to have HER2-low and 40.3% (89/221) to have HER2-0 disease, while for 16.3% (36/221) HER2 status was defined as HER2 positive or negative without determined IHC score. After median follow-up of 23 months, median PFS in HER2-low subgroup was 23 months (95% confidence interval (CI):18-29) versus 24 months (95% CI:22-47) in the HER2-0 subgroup. Further on, median OS in HER2-low subgroup was 47 months (95% confidence interval (CI): 34-51) in comparison to 41 months (95% CI: 32-42) in the HER2-0 subgroup. Using multivariable analysis, an adjusted hazard ratio of 1.30 (95% CI:0.84-2.01; p-value 0.236) was calculated. Covariates

associated with a statistically significant increased risk of disease progression were the presence of ET resistance (HR 2.86, 95% CI 1.48-5.51, p-value 0.0017) and liver metastases (HR 1.70, 95% CI 1.09-2.66, p-value 0.0192).

Interestingly, 20.8% (20/96) of patients with HER2-low tumors had liver metastases in comparison to 60.7% (54/80) of patients with HER2-0 tumors, where as 11.5% (11/96) of HER2-low and 65.2% (58/80) HER-0 tumors were ET resistant.

**Conclusion:** HR-positive, HER2-low mBC had numerically almost identical PFS but longer OS in comparison to HER2-0 mBC, without reaching statistical significance. Patients who had liver metastases and ET resistant tumors were more likely to experience disease progression, but patients with HER2-low tumors less often presented with liver metastases and were less often ET resistant therefore they probably had numerically longer OS. Larger cohort and longer follow-up are required to make final conclusions.

## **P14 – Diffuse large B-cell lymphoma: 5 years single institution experience (Institute for Oncology and Radiology of Serbia)**

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**Background:** Diffuse large B-cell lymphoma (DLBCL), the most common type of Non-Hodgkin lymphoma (NHL), is a heterogeneous group of diseases in terms of morphology, genetics, biological and clinical behavior, as well as response to treatment.

**Methods:** This is a retrospective database analysis which includes 125 patients (pts) with DLBCL treated at Institute for oncology and radiology of Serbia between 2017 and 2021. The aim is to overview demographic data, disease characteristics, treatment modalities and response in patients with DLBCL treated and followed over a 5 year period. The source of data was the patient's records. Progression free survival (PFS) was defined as the time from the beginning of treatment to disease progression for patients who achieved complete or partial remission and was calculated using Kaplan-Meier curve.

**Results:** Out of 125 pts, 73 were females (58,4%) and 52 were males (41,6%). The average age at initial diagnosis was 60 (range 23-85). Bulky disease was observed in 35% pts, and 54% of pts presented with B major symptoms. By cell of origin (COO), 28% was germinal center B-cell (GCB) DLBCL, 30% activated B-cell (ABC) DLBCL, and the rest of DLBCL was unclassified. Patients were categorized as IPI 'low' (n=41; 32,8%), 'low-intermediate' (n=39; 31,2%), 'high-intermediate' (n=26; 20,8%) and 'high' (n=19; 15,2%) risk.

All of the pts received first line treatment; most of them (75; 60%) received combination of chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisolone – CHOP) and monoclonal anti-CD20 antibody rituximab (R-CHOP) and 50 pts (40%) received R-CHOP-like regimens. Complete (CR) and partial response (PR) was achieved in 101 pts (80,8%). In the IPI 'low-risk' group, 34 pts (83%) had a CR/PR, while in 'low-intermediate', 'high-intermediate' and 'high' risk groups CR/PR were achieved in 84,6%, 80% and 74% of pts. Median PFS was 15 months (range 7-60 months). After two year follow-up, 64,6% pts were still in remission (treated from 2017 to 2019), six pts (9,2%) were lost to follow-up, while after five years remission was maintained in 62,5% pts (treated in 2017).



**Conclusion:** DLBCL, despite variable biological and clinical behavior, remains highly curable disease treated with combination of anthracycline-based chemotherapy and monoclonal anti-CD20 antibody, which presents standard of care for the first line treatment. These results represent a valuable source and mostly correspond with real world data. The follow-up is still ongoing.

## **P15 – Outcomes of ramucirumab combined with paclitaxel among Slovenian patients with metastatic gastric/gastroesophageal junction adenocarcinoma: a retrospective study**

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**Background:** Systemic treatment with ramucirumab in combination with paclitaxel is standard of care second-line treatment of metastatic gastric/gastroesophageal adenocarcinoma. This retrospective analysis aimed to evaluate outcomes of ramucirumab plus paclitaxel in real world setting.

**Methods:** We conducted a retrospective study of patients with metastatic gastric/gastroesophageal adenocarcinoma who were treated with ramucirumab plus paclitaxel between January 2016 and July 2023 at the Institute of Oncology Ljubljana. Objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS) were assessed. Tumor response was evaluated with RECIST version 1.1., PFS and OS were evaluated with Kaplan-Meier method.

**Results:** A total of 146 patients were included. Median age was 62,9 years. Median duration of response was 4 months. The ORR was 16% and DCR 32%. The difference in ORR among the lines of treatment was not statistically significant. Median PFS and OS were 3.3 (95% IC 2.84-3.79) and 6.5 months (95% IC 5.29-7.70), respectively. Median PFS and OS for second-line were 3.3 (95% IC 2.72-3.97) and 6.6 months (95% IC 5.35-7.77), respectively. There was no statistically significant difference in PFS or OS among second- and third-line of treatment.

**Conclusion:** In our cohort, the overall response rate, disease control rate, progression free survival and overall survival were lower than in the RAINBOW trial.

**Keywords:** ramucirumab, paclitaxel, gastric adenocarcinoma, outcome.

## **P16 – Is there a difference in the mechanisms of development of skin toxicity between EGFR TKIs: A case presentation of severe skin adverse event during treatment with afatinib**

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**Background:** Afatinib is a small molecule EGFR tyrosine kinase inhibitor (TKI) widely used for treatment of patients with non-small cell lung cancer (NSCLC) whose tumours harbour EGFR activating mutations such as exon 19 deletion. The primary dermatologic adverse event associated with all EGFR TKIs is acneiform rash, whose incidence varies from 30 to even 80% of patients, with grade 3 and 4 rash occurring in about 15% of patients. It is a class toxicity of all EGFR inhibitors, but some differences between drugs have been described. We present a case of severe skin adverse reaction in a patient treated with afatinib, which did not re-occur during further treatment with erlotinib.

**Case presentation:** A 78 year old patient presented with long-lasting, non-productive cough and difficulty breathing in July of 2022. He is a smoker, 35 pack/years, with history of hypertension, atrial fibrillation and COPD, ECOG PS 1. A CT scan of thorax and abdomen showed tumour masses in both lungs, with the biggest mass located in the upper right lobe, up to 7cm in diameter, and mediastinal lymphadenopathy, staged as T3N2M1a. Bronchoscopy and biopsy of the tumour confirmed adenocarcinoma with exon 19 deletion in the *EGFR* gene, ALK negative, PD-L1 TPS 20%. Primary treatment was started with TKI afatinib 40mg daily in November of 2022. After one month of therapy, in December 2022 the patient presented with erythematous annular plaques and papules with adherent crusts on extremities, face and lower abdomen, covering over 50% of skin surface, along with pruritus. This skin toxicity was graded as grade 4 and the treatment with afatinib was stopped. The patient was hospitalized in the Clinic for dermatology for further evaluation and treatment. Biopsy of the skin changes showed interface dermatitis with scarce eosinophils which is consistent with cutaneous drug reaction, DIF test was negative, additional immunological analyses including C3, C4, RF, SSA/SSB, ANA, ANA Hep2, ENA screen and anti-dsDNA antibodies were within normal range. The patient was treated with systemic antibiotics (intravenous clindamycin 600mg q8h for one week; followed by doxycycline caps a 100 mg twice daily, with dose de-escalation to 100mg daily after 2 weeks), antihistamines (cetirizin 5 mg, twice daily) and corticosteroid, antimicrobial and emolient creams (hydrocortison ung., metronidazole gel and clindamicin sol.) locally. The total duration of the treatment was 4 weeks, after which the skin toxicity downsized to grade 1 with acneiform rash remaining on the lower parts of abdomen. Considering the registered skin toxicity grade 4, afatinib had to be permanently discontinued. The MTB at our institution decided to introduce a reversible TKI erlotinib (150mg) in February of 2023. The patient is still taking erlotinib, his ECOG PS is 1, and no adverse events have been recorded to this day. The best response during the treatment is partial regression PR (RECIST 1.1). His last visit was in July 2023.

**Conclusion:** The severe skin adverse event that occurred in our patient was connected only to exposure to afatinib, but not erlotinib, so we wonder if it could be an adverse reaction to the drug itself rather than a representation of the known class toxicity of EGFR TKIs, even though all the tests performed did not point to a likely mechanism of development of the reaction.

## P17 – Clinical outcomes of neoadjuvant treatment in locally advanced rectal cancer: multi-institutional experience

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**Background:** Rectal cancer makes 30-60% of all colorectal cancer deaths. Treatment outcome was improved by the introduction of total mesorectal excision and neoadjuvant therapy (NAT) as standard of care for locally advanced rectal cancer (LARC). NAT implies short-course radiotherapy (S-CRT) or long-course chemoradiotherapy (LC-CRT). More recently, improvement of prognosis was obtained by implementation of total neoadjuvant therapy (TNT) – addition of oxaliplatin based chemotherapy to S-CRT or LC-CRT delivered prior to surgery. Treatment response to NAT is defined as tumor regression grade (TRG) according to modified Ryan classification as TRG 0 (complete), 1 (near complete), 2 (partial) or 3 (poor or no response). Half of rectal cancers are down staged and downsized during NAT, but only about 10-30% will achieve TRG 0 which is associated to favorable long-term outcome – low recurrence rates and excellent overall survival. The aim of the conducted study was to determine correlation of disease stage at diagnosis, modality of NAT and treatment response defined according to modified Ryan classification.

**Methods:** Multi-institutional retrospective study investigating outcome of LARC treated with NAT was conducted in Clinical Hospital for Tumors, University Hospital Center (UHC) Sisters of Mercy, and UHC Zagreb with prior Ethics Committee approval. Data for 163 patients treated between 2017 and 2022 were obtained from the hospital information system. Baseline characteristics – clinical and radiological stage, treatment modality, and final pathological stage defined at surgery, were analyzed. Patients with unknown disease stage, treatment modality or pathological outcome at surgery were excluded.

**Results:** Of all included patients, 19.6% (32/163) were treated with S-CRT, 63.8% (104/163) with LC-CRT and 16.5% (27/163) with TNT. Most of the patients had stage III (86.5%, 141/163) and only 13.5% (22/163) stage II disease. TRG 0 was obtained in 12.3% (20/163) of all patients who underwent NAT. None of the patients treated with S-CRT achieved TRG 0, whereas TRG 0 was achieved in 13.5% (14/104) of patients treated with LC-CRT and 22.2% (6/27) treated with TNT. Most of the patients, 90% (18/20), achieving TRG 0 had stage III and only 10% (2/20) had stage II rectal cancer. All patients treated with TNT had stage III disease.

**Conclusion:** Results of the conducted study showed trend toward higher TRG 0 rates after NAT with TNT, especially in patients with stage III LARC. In concordance with the obtained results and available literature findings, this subgroup of patients should be considered for TNT, an increasingly used approach in everyday practice. Further studies are needed to better define factors predictive of complete response in the NAT of rectal cancer.

## P18 – Effect of body mass index (BMI) on pathological response after neoadjuvant therapy in locally advanced rectal cancer

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**Background:** Rectal cancer accounts for approximately one third of all colorectal cancer and has been shown to have worse prognosis. The standard of care in locally advanced rectal cancer (LARC) is neoadjuvant treatment (NAT) followed by surgery. Worse clinical outcome is attributed to its anatomical features, extraperitoneal position and lack of serosa, facilitating tumor growth in the perirectal space and making surgical resection more difficult. High BMI, abdominal obesity and diabetes type II are known risk factors of poor clinical outcome of rectal cancer. Multiple studies have shown that both, extremely low as well as extremely high BMI, can lead to worse survival when compared to normal BMI.

The aim of the conducted study was to analyze the effect of BMI on pathohistological response to NAT of LARC, obtained at surgery.

**Methods:** Multi-institutional retrospective study, including 123 patients with LARC, who received NAT followed by surgery at Clinic for Tumors, University Hospital Centre (UHC) Sisters of Mercy and UHC Zagreb, was conducted with prior Ethics Committee approval. Patients' data: BMI, type of NAT and definitive pathohistological findings at surgery were obtained from the hospital information system (BIS). The applied NAT was short course radiotherapy (SCRT), long course chemoradiotherapy (LCCRT) or total neoadjuvant therapy (TNT). Pathohistological results were defined according to modified Ryan scale as tumor regression grade (TRG) 0 – complete, 1 – near complete, 2 – partial, 3 – poor or no response. Pearson correlation test was used to analyze correlation between BMI and definitive pathohistological findings at surgery.

**Results:** After exclusion of patients with missing data, a total of 123 patients were analyzed. Of those, 37.4% (46/123) patients had normal BMI, 43.9% (54/123) were overweight and 18.7% were obese. None of the patients was underweight. Obese patients were more often men than women 73.9% (17/23) vs 26.1% (6/23) respectively.

Complete response was achieved in 15.5% (19/123) of all analyzed patients. TRG 0 was achieved in 19.6% (9/46) of patients with normal BMI and in 13% of overweight (7/54) and 13% of obese (3/23) patients. Poor or no response to NAT was observed in 23.6% (29/123) of all included patients. Among patients with normal BMI, poor or no response was observed in 19.6% (9/46), whereas poor or no response was observed in 27.8% (15/54) of overweight and 21.7% (5/23) of obese patients. Pearson correlation test was used to analyze correlation between BMI and TRG at surgery following NAT. A weak positive correlation between high BMI and worse pathohistological response ( $p=0.5138$ ), approaching statistical significance, was observed.

**Conclusion:** Although there was no statistically significant correlation between high BMI and poor response to NAT of LARC, a tendency towards poorer therapeutic response was observed in patients with higher BMI. Interestingly, male patients with higher BMI were more likely to have worse treatment response. Further studies are needed to define correlation between response to NAT, gender, or BMI.

## P19 – The frequency of HER2-low breast cancer among patients diagnosed at the Institute of Oncology Ljubljana from 2011 to 2021

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**Introduction:** Human epidermal growth factor receptor 2 (HER2) is a transmembrane glycoprotein with tyrosine kinase activity that belongs to the epidermal growth factor receptor family (EGFR/ErbB). The development of anti-HER2 drugs has significantly improved the prognosis of patients (pts) with HER2-positive breast cancer (BC). This subtype of BC is defined according to the 2018 American Society of Clinical Oncology and College of American Pathology HER2 testing guidelines by HER2 overexpression on an immunohistochemical (IHC) assay (score 3+) and/or gene amplification on an *in situ* hybridization (ISH) assay. The remaining majority of BCs (80-85%) that do not overexpress HER2 are currently defined as HER2-negative, as traditional HER2-targeted therapies are not effective in these cases. So-called HER2-low tumors are defined as IHC expression of HER2 1+ or 2+ without amplification on the ISH assay.

Until recently, HER2-low expression has never influenced clinical practice, as these tumors were considered ineligible for anti-HER2 therapies. The development of new anti-HER2 drugs such as trastuzumab deruxtecan (T-DXd), which has also been shown to be effective in BC with lower HER2 expression, has changed the binary classification of HER2 status by introducing a new entity, HER2-low. The recent randomized phase 3 trial DESTINY-Breast04, in which pts with HER2-low metastatic BC who had 1-2 prior lines of chemotherapy for metastatic disease were treated with T-DXd, demonstrated that treatment with T-DXd successfully prolongs progression-free survival (PFS) and overall survival (OS) among pts categorized as having unresectable and/or metastatic HER2-low BC compared with physician's choice of standard single-agent chemotherapy, confirming that targeting HER2 provides a clinically relevant benefit for pts with HER2-low metastatic BC. There are currently ongoing studies that are examining the effectiveness of anti-HER2 drugs also in early HER2-low BC. Data from the literature on the proportion of HER2-low BCs are inconsistent. They are estimated to represent 45-55% of BCs. The aim of our study was to determine the proportion of HER2-low BC in the population of pts treated at the Institute of Oncology Ljubljana (IOL).

**Methods:** We identified pts from an institutional database and included all pts with invasive BC treated at IOL between 2011 and 2021. HER2 protein was determined immunohistochemically. Until 2012, Hercep test from DAKO was used, and from 2012, Ventana Roche. IHC results were evaluated according to ASCO guidelines. The HER2 gene was also determined in all invasive BCs by ISH with STK "HER-2 PathVysion" manufactured by Abbott Vysis.

We analyzed the average and annual values of proportion of pts with:

IHK scores 3+,

IHC scores 2+, with HER2 gene amplification,

IHC scores 2+, without HER2 gene amplification,

IHC scores 1+,

IHC score 0.

HER2-low was defined as HER2 IHC 1+, or 2+ with non-amplified FISH.

**Results:** 11.234 consecutive pts with invasive BC were included. The distribution of HER2 status is shown in Table 1. The proportion of HER2-low invasive BCs was 52.9% in all pts and varied slightly over

the years, ranging from 45.7% to 59.4%, being higher in the last few years. HR-positive/HER2-low pts and HR-negative/HER2-low pts comprised 56.1% and 29.2%, respectively, of the total number of pts studied.

Table 1.

*Distribution of HER2 status in all pts and in pts with positive and negative hormonal receptor status*

	All (N)	IHC 0 N (%)	IHC 1 N (%)	IHC 2 FISH- N (%)	IHC 2 FISH + N (%)	IHC 3 N (%)
HR+	9736	3325 (34.2)	3391 (34.8)	2074 (21.3)	218 (2.2)	728 (7.5)
HR-	1337	580 (43.4)	263 (19.7)	127 (9.5)	20 (1.5)	347 (26.0)
All	11073	3905 (35.3)	3654 (33.0)	2201 (19.9)	238 (2.1)	1075 (9.7)

**Conclusions:** The average proportion of HER2-low BC in our population is 52.9%. The proportion of HER2-low status is higher in pts with positive HR status (56.1%) and lower in pts with negative HR status (29.2%). The proportion of pts with HER2-positive status was stable during the observed period, however, the proportion of HER2-low tumors slightly increased in the last few years, probably due to the pathologist's awareness of the importance of the HER2-low entity.

## P20 – Biomarker guided first-line treatment of metastatic triple negative breast cancer

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**Introduction:** Immunological factors are known to play an important role in breast cancer and have recently become a major target in the treatment of triple negative breast cancer (TNBC) with research focusing mainly on programmed death ligand 1 (PD-L1). PD-L1 is a transmembrane protein that is predominantly expressed on tumour-infiltrating immune cells rather than tumour cells and plays an important role in suppressing the adaptive immune system by inhibiting the function of activated T cells, identifying the PD-1/PD-L1 pathway as a key immune response checkpoint and therefore a useful treatment target. The phase III IMpassion130 study has demonstrated that the addition of atezolizumab to nab-paclitaxel for the treatment of PD-L1-positive metastatic TNBC (mTNBC) resulted in an increase in progression-free survival (PFS). Similar results were seen in KEYNOTE-355, which showed that the addition of pembrolizumab to chemotherapy resulted in significantly longer PFS as well as overall survival (OS) compared to chemotherapy alone. Subsequently, two PD-L1 assays were developed to determine patients (pts) eligibility for the use of specific checkpoint inhibitors (CPIs) in TNBC pts, including the 22C3 assay for pembrolizumab based on the results of the KEYNOTE-355 clinical trial and the SP142 assay based on the results of the IMpassion130 clinical trial. These testing methods have become standard practice with CPIs being the standard first-line treatment for PD-L1-positive mTNBCs. Cancer cells with deleterious mutations in breast cancer susceptibility genes 1 or 2 (BRCA1/2) lack the mechanism to repair DNA dou-

ble-strand breaks. As a result, these tumours rely heavily on the single-strand break repair pathway. In BRCA1/2 mutant cells, inhibiting poly (ADP-ribose) polymerase (PARP) causes cell death through the build-up of irreparable DNA damage. The EMBRACA and OlympiAD studies have shown that the use of the PARP inhibitors olaparib and talazoparib in pts with advanced breast cancer (BC) and a germline BRCA1/2 mutation (gBRCAm) significantly prolongs PFS compared with standard chemotherapy. The aim of our study was to determine PD-L1 and BRCA status as well as first-line treatment for the first manifestation of metastatic disease.

**Methods:** PD-L1 expression status was determined by immunohistochemical (IHC) method at the Department of Pathology. For SP142 IHC, we used the VENTANA PD-L1 assay, which shows PD-L1 protein in tumor cells and tumor-infiltrating immune cells. SP142 expression in immune cells was estimated as the fraction of the tumor surface occupied by PD-L1 positive immune cells of any intensity. A result of IC < 1 was scored as negative, and a result of IC 1 as positive. 22C3 IHC was performed with the Dako PD-L1 IHC 22C3 pharmDx, which was evaluated using the combined positive score (CPS), i.e. the number of cells stained with 22C3 (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. BRCA mutation status was determined with the Next-Generation Sequencing method at the Department of Molecular Diagnostics. Data was obtained from electronic medical records. Descriptive statistical methods were used for analysis.

**Results:** We evaluated 110 pts with mTNBC and known PD-L1 status treated at the Institute of Oncology Ljubljana from April 2019 until July 2023. The PD-L1 status was positive in 74/110 pts (67.3%) and negative in 36/110 pts (32.8%). BRCA 1 status was positive in 16 pts (14.5%), BRCA2 in 2 pts (1.8%), negative in 72 pts (65.5%) and not determined in 20 pts (18.2%). Among PD-L1 positive pts, 15/74 (20.3%) had positive gBRCA1/2m status and 3/36 (8.3%) among pts with negative PDL1 status. Difference was not statistical significant (Chi-Square test,  $p=0.22$ ). Among pts with PD-L1 positive status, the most common first line therapy was atezolizumab in combination with *nab*-paclitaxel ( $n=38$ , 51.4%) and among pts with PD-L1 negative status either a combination of gemcitabine and cisplatin ( $n=7$ , 19.4%), taxanes ( $n=7$ , 19.4%) or capecitabine ( $n=7$ , 19.4%). The therapy used is presented in Table 1.

Table 1.

First line treatment of mTNBC based on the PD-L1 status

	PDL1+		PDL1-	
	Number	%	Number	%
Atezolizumab + <i>nab</i> -paclitaxel	38	51.4	0	0
Pembrolizumab + gemcitabin + cisplatin	4	5.4	0	0
Pembrolizumab + other	0	0	1	2.8
Gemcitabin + cisplatin	7	9.5	7	19.4
Taxanes	5	6.8	7	19.4
Capecitabine	8	10.8	7	19.4
PARPi	3	4.1	2	5.6
None	5	6.8	4	11.1
Other	0	0	7	19.4
Unknown	1	1.4	1	2.8

**Conclusion:** In our population of pts with mTNBC, 67% of pts had PDL-1 positive tumours and 16.6% of pts were carriers of gBRCAm. Majority of pts with PDL-1 positive tumours received CPI in first line treatment of metastatic disease.

## P21 – Pembrolizumab in neoadjuvant setting for early TNBC – real world data

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**Introduction:** Triple-negative breast cancer (TNBC) is an aggressive subtype characterised by the absence of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) expression. Despite advances in cancer therapy, TNBC remains challenging to treat due to its intrinsic molecular heterogeneity and limited therapeutic options. In recent years, immunotherapy has emerged as a promising approach to cancer treatment, with pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, showing significant potential in several malignancies. The Keynote 522 study, a landmark clinical trial, has played a pivotal role in evaluating the efficacy of neoadjuvant pembrolizumab in TNBC. This randomised phase III trial evaluated the combination of pembrolizumab with chemotherapy as neoadjuvant treatment in patients (pts) with early-stage TNBC. The results showed a significant improvement in pathological complete response (pCR) rates compared to chemotherapy alone, highlighting the potential of pembrolizumab to improve outcomes. This real-world data analysis aimed to review the current evidence and clinical outcomes of neoadjuvant pembrolizumab treatment in pts with TNBC, focusing on its efficacy, safety and impact on pCR rates.

**Methods:** This retrospective analysis included 29 consecutively treated pts with early TNBC who received pembrolizumab in the neoadjuvant setting at the Institute of Oncology, Ljubljana, between 4 January 2022 and 17 July 2023. According to the Keynote 522 protocol, pembrolizumab was administered in cycles 1-4 in combination with carboplatin and paclitaxel, and in cycles 5-8 in combination with anthracyclines and cyclophosphamide. In some cases, pembrolizumab was added to the standard chemotherapy regimen at a later point in time, outside of the protocol. Data were obtained from electronic medical records and included tumor size, nodal status, UICC stage, BRCA status, residual cancer burden (RCB), as well as the frequency and type of adverse events (AE) (according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5). Descriptive statistical methods were used for analysis.

**Results:** The median age at diagnosis was 48 years (range 24-72). Median follow-up was 4.6 months. At diagnosis, the majority of pts had stage 2A disease (n=14, 48.3%), followed by stage 2B (n=9, 31%), 3B (n=4, 13.4%) and 3A (n=2, 6.9%). Node-positive disease was found in 16 pts (55.2%). The most common

Table 1.

Adverse events, AEs

Side effect	Grade 1 (number of pts)	Grade 2 (number of pts)	Grade 3 (number of pts)	Grade 4 (number of pts)
Autoimmune endocrinopathies				
Adrenal insufficiency				2
Hyperthyroidism		1		
Hypothyroidism		1		
Insulin-deficient diabetes mellitus			1	
Hypophysis			1	
Hepatopathy		1	1	
Encephalitis				1
Colitis			1	
Skin toxicity	2			



tumour size and extent was T2 (n=17, 58.6%). Of the 25 pts who were tested for a BRCA mutation, 5 (20%) were positive for BRCA1 and 2 (8%) were positive for BRCA2. Most pts (n=25, 86.2%) were treated according to the Keynote-522 protocol and only 4 pts (13.8%) were not, as pembrolizumab was added later in the course of neoadjuvant treatment. AEs were observed in 11 pts (37.9%), with grade III and IV AEs being the most common (n=7, 29.2%). The most common AEs were autoimmune endocrinopathies, with adrenal insufficiency as the leading subtype (n=2, 6.9%). Hepatopathy was the most frequently observed non-endocrine AE (n=2, 6.9%). The full list of AEs is shown in Table 1. Of the 29 pts, 15 had already undergone surgery. According to the final pathological reports, only 4 pts had a pCR (26.7%) and 11 pts (73.3%) did not. Of the 11 pts without pCR, 5 pts had RCB score 2 (45.5%) and 6 pts had score 3 (54.5%).

**Conclusion:** Evidence from real-world clinical practice complements and extends the findings from clinical trials and underscores the relevance of pembrolizumab as a valuable neoadjuvant therapeutic option. In our analysis, we have seen promising results with pembrolizumab in combination with chemotherapy, however, compared to the Keynote 522 trial, we have seen a lower percentage of pCRs and a higher percentage of AEs. The difference from the pivotal trial may be due to a small sample size and we will continue to collect data. Ongoing collaboration between oncologists, researchers and policymakers is needed to address challenges such as cost, long-term safety and optimal treatment duration. By addressing these critical areas, we can better define the role of pembrolizumab in the neoadjuvant setting.

## P22 – Real-world outcomes with sacituzumab govitecan in a single-centre study

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**Introduction:** Triple-negative breast cancer (TNBC) is an aggressive subtype defined by the absence of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) expression. It is associated with a high risk of recurrence and generally poor prognosis. Chemotherapy, although associated with low response rates and short progression-free survival, has long been the main treatment for metastatic TNBC. Recently, new treatment options have emerged with promising results. In addition to polyadenosine diphosphate-ribose polymerase inhibitors (PARPi) for patients (pts) with BRCA mutations and check point inhibitors for pts with PD-L1-positive tumours, another new drug has recently been introduced for the treatment of metastatic TNBC – sacituzumab govitecan (SG). SG is an antibody-drug conjugate consisting of an anti-trophoblast cell surface antigen 2 (Trop-2) IgG1 kappa antibody coupled through a proprietary hydrolyzable linker to SN-38, the active metabolite of irinotecan, which acts as a topoisomerase I inhibitor. Trop-2 is a transmembrane calcium signalling transducer that is highly expressed in several tumour types, including breast cancer (>90%). The ASCENT study was a landmark clinical trial that played the most important role in evaluating SG efficacy in metastatic TNBC. This randomised phase III trial compared SG with single-agent chemotherapy of the physician's choice (eribulin, vinorelbine, capecitabine or gemcitabine) in pts with relapsed or refractory metastatic TNBC. The results showed that SG significantly increased median progression-free survival from 1.7 to 5.6 months and median overall survival from 6.7 to 12.1 months compared to single-agent chemotherapy in metastatic TNBC. The aim of this real-world analysis was to evaluate clinical outcomes and safety of SG in our pts with metastatic TNBC.

**Methods:** This retrospective analysis included 15 consecutively treated pts with metastatic TNBC who received SG at the Institute of Oncology, Ljubljana from December 14, 2022, to June 28, 2023. Clinical and pathological variables including demographics, site of metastases, prior lines of therapy, adverse events (AEs, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5) and clinical outcomes were collected. Descriptive statistical methods and Kaplan-Meier plots were used for analysis.

**Results:** The median age at diagnosis was 50 years (range 38-74). Median follow-up time was 4.7 months (2.6-6.7 months). The median number of prior treatment lines in the metastatic setting was 3 (range 1-7) and 60% of pts (9/15) received  $\geq 3$  prior treatment lines. 80.8% (12/15) had  $\geq 3$  metastatic sites. The common sites of metastases included bones (66.7%), soft tissues (60%), lung (53.3%), liver (26.6%) and CNS (33.3%). None of the pts had BRCA mutation, therefore none of the pts were treated with PARPi. Prior to SG, checkpoint inhibitors (CPIs) were received by 6 pts (40%). All pts received primary or secondary prophylaxis with granulocyte colony stimulating factor. At the time of analysis, stable disease was reported among 26.7%, 26.7% of pts had disease progression, none of the pts had complete response and one (6.7%) pts had partial response. In 40% of pts response could not be evaluated yet. 3 pts died. The median progression-free survival was 5.5 months and median overall survival was not yet reached due to the relatively short median follow-up. AEs were observed in 13 pts (86.7%), with all of AEs being  $\leq$  Grade 3. The most common AEs were neutropenia (n=11, 84.6%). Diarrhea was the most common non-hematological AE observed (n=4, 30.8%). The full list of AEs is shown in Table 1. Due to the AEs, the delay of the treatment was needed in 11 pts (73.3%) and dose reduction in 2 pts (13.3%).

Table 1.

*Adverse events, AEs*

Side effect	Any Grade number of pts (%)	Grade 3 number of pts (%)
Any AEs	13 (86.7)	9 (60)
Hematological AEs		
Neutropenia	11 (73.7)	7 (46.7)
Anemia	2 (13.3)	0
Stomatitis	1 (6.7)	1(6.7)
Hepatopathy	1 (6.7)	1(6.7)
Diarrhea	4 (26.7)	0
Fatigue	6 (40)	0

**Conclusion:** In our analysis, we have seen encouraging results with the use of SG in metastatic TNBC. Compared to ASCENT trial, the progression-free survival was almost identical, as were the AEs, with neutropenia and diarrhea being the most clinically relevant. We will continue to collect data to complement future findings.

## P23 – Metaplastic breast cancer: a single center retrospective study

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**Introduction:** Metaplastic breast cancer (MBC) is a rare and aggressive subtype of breast cancer (BC) that accounts for up to 1% of all primary invasive BC. It is histologically heterogeneous and defined by presence of both epithelial and mesenchymal components. It usually presents as triple negative phenotype. Positive estrogen receptor status has no prognostic significance and, like HER2 status, does not affect breast cancer-specific survival. Most patients (pts) present with stage II or more advanced disease, mostly due to the size of the primary tumour. MBC is more likely to present with metastatic disease and distant metastases may have a sarcoma-like distribution with a known predilection for the lungs and pleura. MBC comprises low- and high-grade (HG) variants. HG variants are more aggressive and have a higher risk of recurrence and a shorter disease-free and overall survival. The aim of our study was to estimate the prevalence of HG-MBC among the Slovenian population and determine the characteristics of pts and tumours and the disease outcome.

**Patients and methods:** Our retrospective study included pts diagnosed with HG-MBC at the Institute of Oncology Ljubljana from January 1983 until January 2021. Clinicopathologic characteristics of the tumor as well as presence of germline BRCA mutation status were determined. The survival analyses were performed using the Kaplan-Meier method. The Cox proportional hazard model examined the association between risk factors and survival outcomes.

**Results:** We evaluated 113 HG-MBC pts among a total of 27700 pts diagnosed with BC over 38 years (0.41%). The median age was 61.6 years (range 29.7 -93.9), majority of pts were postmenopausal (78.69%). The median follow-up was 15.5 years. The most common tumour subtype in our cohort was mixed MBC (53 cases, 46.9%), followed by MBC with mesenchymal differentiation (24 cases, 21.2%), squamous cell carcinoma (20 cases, 17.7%) and spindle cell carcinoma (16 cases, 14.2%). From the 113 evaluated pts, we obtained data about the stage in 105 pts, pathological tumour size in 100 pts, number of positive lymph nodes in 99 pts, HR status in 95 pts, HER2 status in 76 pts, grade in 97 pts, LVI in 85 pts, MIB-1 in 41 pts and TIL in 77 pts. At diagnosis, 17/105 pts (16.2%) had stage I disease, 59/105 pts (56.2%) stage II, 25/105 pts (23.8%) stage III and 4/105 pts (3.8%) stage IV. Most tumours were poorly differentiated (90/97, 92.2%) without LVI (60/85, 70.6%). Only 6/95 (6.3%) pts had positive HR, 7/76 (9.2%) pts had positive HER-2 status and 8/77(10.4%) pts intensive TIL. Overall, 13 pts were tested for BRCA germline mutation, among which only 1 (7.7%) had BRCA1 mutation. Modified radical mastectomy was the most frequent type of surgery (63.5%); 49.5% of the pts received radiotherapy. In total, 66/113 pts received CT: from 1983 to 2000, 16/36 (44.4%), and after 2000 50/77 (74.9%). In the first period, most pts received CMF (14/16; 87.5%) and anthracyclines and taxanes (27/50; 54%) in the second period. The disease progressed at 37 pts. At 19 pts, new malignancies were found. 55 pts died, 37 of them because of BC. Five- and 10-year disease-free survival (DFS) was 61.7% and 54.1%, while 5-and 10-year overall survival (OS) was 67.1 % and 56.7%, respectively. However, DFS and OS did not differ between the pre-2000 and post-2000 periods. The best outcome was found in pts with squamous cell carcinoma (5- and 10-year DFS 83.5% and 77.0% and 5-and 10- year OS 89.4 % and 83.0%). A subtype of MBC (squamous cell vs other) was the only predictive factor in multivariate analysis for both DFS (HR 0.21; 95% CI 0.05-0.92; p = 0.038 and OS (HR 0.27; 95%CI 0.09-0.78; p = 0.016), no association was seen between survival and tumour size, nodal status, stage, HR and HER2 status, grade, LVI and TILs.

Median OS after the first progression was only 0.9 years. Visceral organs were the most common localization of distant metastases (21/37, 56.8%). Metastases in CNS occurred in 9/37(24.3%) pts.

**Conclusions:** the proportion of HG-MBC in our cohort of pts is 0.41%. Disease outcomes are poor; the 10-year OS of pts with early HG-MBC is only 56.6% and has not improved during the last decades. Squamous cell differentiation predicts a better outcome and is the only independent predictive factor of DFS and OS among HG-MBC pts.

## P24 – Efficacy and safety of abemaciclib in the treatment of HR+ HER2- advanced breast cancer: real world data

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**Introduction:** Abemaciclib is a CDK4/6 inhibitor approved for the treatment of HR+ HER2- advanced breast cancer (ABC) in combination with endocrine therapy (ET). In randomised clinical trials, the combination with an aromatase inhibitor (AI) or fulvestrant in the first- or second-line setting has shown a clear benefit in terms of prolonging progression-free survival (PFS). This combination is associated with additional toxicity and cost, as many patients can achieve durable disease remission with ET alone. The objective of the study was to evaluate the clinical experience with the drug in terms of both efficacy and safety.

**Methods:** An institutional retrospective analysis of patients treated with abemaciclib between November 2019 and February 2022 for HR+ HER2- ABC was performed. Data on the number of patients treated with abemaciclib were retrieved from the Slovenian National Institute of Public Health and the Slovenian Cancer Registry. Patient data and treatment characteristics were collected from electronic health records. Univariate and multivariate analyses were performed using the Cox regression model. The following variables were included in the univariate analysis: liver metastases, line of treatment, age>75 years, tumour grade, PR>10%, bone disease only. In the multivariate model, only variables found to be significant in the univariate analyses were included ( $p \leq 0.05$ ). Prognostic significance was expressed as hazard ratio (HR) and 95% confidence intervals (95% CI). All statistical analyses were performed with SPSS v.24 (IBM Corp.). The primary outcome was real-world PFS (rwPFS), and secondary outcomes were overall survival (OS) and safety.

**Results:** Between November 2019 and February 2022, a total of 168 patients were treated with abemaciclib in Slovenia, 134 (79.8%) at the Institute of Oncology Ljubljana, 133 were women and only one man. The median age at treatment initiation was 62 years (range 30-85 years). 51.1% (n=69) of patients received abemaciclib in combination with ET as first-line treatment for ABC. Partner ET was an AI in 68.1% (n=47) of patients and 31.9% (n=22) of patients received abemaciclib in combination with fulvestrant. 23.9% (n=2) of patients were treated with abemaciclib in the second-line setting and 24.6% (n=33) in the third-line setting or later. The median follow-up time was 24 months. Median rwPFS in first line of treatment was 23.0 months (95% CI; 13.3-32.7), in second line 20.0 months (95% CI; 6.4-33.6) and 7.0 months (95% CI; 4.2-9.8) if patients were treated with abemaciclib plus ET as third or late line. Median OS for first and second line was not reached, and was 26.0 months for third or later line. Adverse prognostic factors were analysed

in univariate analyses. Only liver metastases and treatment line were found to be significant for rwPFS and OS. They were included in the multivariate model. Only liver metastases were identified as an independent adverse prognostic factor for PFS and OS, with a median rwPSF of 9 months for patients with liver metastases and 28 months for patients without liver metastases (HR 2.43, 95%CI 1.5-3.8,  $p<0.001$ ), median OS was 20 months for patients with liver metastases. Median OS was not reached for patients without liver metastases (HR 3.31, 95%CI 2.67-6.47,  $p<0.001$ ).

Median OS from the diagnosis of metastatic disease for the whole group of patients was 83 months. The most common adverse events were diarrhoea (67.1%,  $n=90$ ), anaemia (64.2,  $n=86\%$ ), increased serum creatinine (57.5%,  $n=77$ ), neutropenia (45.5%,  $n=61$ ) and fatigue (37.3%,  $n=50$ ). Other commonly reported adverse events were macrocytosis (34.3%,  $n=46$ ), thrombocytopenia (18.7%,  $n=25$ ), nausea (21.6%,  $n=39$ ), abdominal pain (20.9%,  $n=28$ ) and hepatotoxicity (16.4%,  $n=22$ ). Grade 3 or 4 adverse events were reported in 21.6% ( $n=29$ ) of patients. Abemaciclib dose reductions occurred in 44.0% ( $n=59$ ) of patients. The most common adverse event leading to dose reduction was diarrhoea (32.2%,  $n=19$ ). 70.9% ( $n=95$ ) of patients discontinued abemaciclib; the most common reasons for discontinuation were disease progression (66.3%,  $n=63$ ) and adverse events (24.2%,  $n=23$ ).

**Conclusion:** Abemaciclib is a relatively new agent for the treatment of HR+ HER2- ABC. Although it is not possible to make a direct comparison with the results of the registration trials, the results of the present analysis confirm its efficacy in terms of OS and PFS in routine clinical practice, irrespective of the treatment line. Although the present cohort represents a selected patient population, the median OS from diagnosis of metastatic disease of more than 5 years indicates a significant benefit from the addition of CDK4/6 inhibitors in the treatment of HR+ HER2- ABC. The only independent adverse prognostic factor identified was the presence of liver metastases. Safety data were consistent with the known safety profile of abemaciclib and no new adverse events were identified. Experience on how best to manage adverse events and maintain patient compliance is crucial as the drug is approved for use in the adjuvant setting.

## P25 – Thrombotic complications associated with DA-EPOCH-R therapy for non-Hodgkin’s lymphoma

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**Introduction:** DA-EPOCH-R is a combined immunotherapeutic and chemotherapeutic protocol used in the treatment of several types of aggressive non-Hodgkin’s lymphomas, in particular Diffuse large B-cell lymphoma (DLBCL). The constituent drugs used in the protocol are Etoposide (E), Prednisone (P), Vincristine (O), Cyclophosphamide (C), Doxorubicin (D), Rituximab (R). In our practice we’ve noticed a trend of clinically significant thromboembolic events in patients after receiving therapy. In this case report we will describe two patients in whom a venous thromboembolism (VTE) occurred concomitant with drug administration via Port-a-Cath.

**Patients:** Retrospectively we’ve analyzed the occurrence of VTE in two patients during administration of DA-EPOCH-R chemotherapy. Both patients were Caucasian males and both were receiving treat-

ment for advanced stage DLBCL. The first patient had DLBCL non-GCB centroblastic type BCL2 and BCL6 positive confirmed by fluorescent in situ hybridization (FISH). The second also had DLBCL GCB with an extra-nodal localization, while FISH analysis didn't show BCL2 or BCL6 positivity. Both had high CD20 positivity so for the first line therapy DA-EPOCH-R was chosen. The Thrombosis lymphoma predictive score (ThroLy) was calculated for both patients, the patients had scores of 0 and 1 respectively. Because of the low probability of thromboembolic events no prophylaxis was initiated. The first patient, after receiving the third cycle of therapy, developed cephalgia and syncope. A MSCT head scan was performed and an ischemic stroke was confirmed. After completion of the therapeutic cycle the second patient developed isolated unilateral arm oedema. A color doppler scan showed a VTE in multiple localizations. The subclavian, axillary and cephalic veins were involved. In both cases anticoagulant therapy was initiated and continued until full recanalization of blood vessels was confirmed.

**Conclusion:** According to available data there is a trend of increased thrombotic events in patients receiving DA-EPOCH-R when compared to other treatment options. Further evaluation of thrombotic risk scores and prophylactic strategies is needed.

## P26 – Neoadjuvant treatment outcomes in patients with germline *BRCA 1/2* and beyond-*BRCA* mutations: examining pathological complete response rates

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**Introduction:** Over the years germline mutated *BRCA 1/2* status has been associated with higher pathological complete response (pCR) rates among breast cancer patients treated with neoadjuvant chemotherapy (NACT) but few studies have explored the predictive value of beyond-*BRCA* breast cancer susceptibility genes in the NACT setting. Our aim was to compare the NACT outcomes in *BRCA* and beyond-*BRCA* mutated breast cancer patients in the Department of Oncology in University Hospital Centre Zagreb from February 2019 to February 2023.

**Methods:** From 778 patients tested, 110 were detected to carry pathogenic or likely pathogenic variants of germline *BRCA 1/2* (72) and beyond-*BRCA* (38) mutations. Among that group 47 (42.7%) patients were treated with NACT, 28 *BRCA 1/2* and 19 beyond-*BRCA*. The beyond-*BRCA* gene mutations in our study were *ATM* (6), *PALB2* (2), *TP53* (1), *CHEK2* (7), *NBN* (2) and *MUTYH* (1). The medical records were reviewed and data on age at diagnosis, biological tumor subtype, chemotherapy regimen, type of surgery (mastectomy vs. breast-conserving) and pathological complete response (pCR) were collected. The *BRCA 1/2* and beyond-*BRCA* subgroups were compared based on whether or not they achieved pCR and the data was analyzed using the  $\chi^2$  test.

**Results:** In total 19 patients (40.4 %) achieved pCR, 14(50%) in the *BRCA 1/2* mutated subgroup and 5(26.3 %) among the beyond-*BRCA* mutated subgroup, the obtained p-value was 0.1044 (significance

$p < 0.05$ ). The median age at the time of diagnosis of the *BRCA 1/2* subgroup was 39, compared to the beyond-*BRCA* subgroup which was 41. Age at diagnosis, chemotherapy regimen and type of surgery had no statistically significant effect on the odds of achieving pCR in our sample.

**Conclusion:** The *BRCA 1/2* subgroup was more likely to achieve pCR than the beyond-*BRCA* subgroup even though our sample did not yield a statistically significant difference which could be attributed to its size. Given that specific immunohistochemical characteristics that identify surrogate breast cancer subtypes exhibit different NACT susceptibility, we can assume that the varying distribution of said subtypes among the *BRCA* and beyond-*BRCA* subgroups results in different pCR rates. The role of neoadjuvant chemotherapy in beyond-*BRCA* mutated patients remains unclear, but as we gain more and more insight it is fair to suggest the need to continue to gather data of NACT treated breast cancer patients and search for independent significant predictors for pCR.

## P27 – Treatment of pancreatic ductal adenocarcinoma with liposomal irinotecan with 5-fluorouracil and leucovorin in Institute of Oncology Ljubljana

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**Introduction:** Ductal adenocarcinoma is the most frequent malignant tumor of the pancreas. In Slovenia it is among the cancers with the worst prognosis. At the time of diagnosis only 15-20% are operable. For all the others the only option is palliative systemic treatment. One of the regimens is liposomal irinotecan in combination with 5-fluorouracil and leucovorin (nal-IRI + 5-FU/LV). This treatment is registered for patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy.

**Patients and methods:** In retrospective observational study data was gathered on patients treated for pancreatic ductal adenocarcinoma with nal-IRI + 5-FU/LV in any line of treatment in Institute of Oncology Ljubljana from September 2019 till July 2023.

**Results:** There were 47 patients (pts), most of which received nal-IRI + 5-FU/LV in second or third line (41 pts), only few in fourth or subsequent lines of treatment (5 pts) and one in first line. Median time of receiving the treatment was 3,5 months (8 patients were excluded from this calculation, because they are still on this line of treatment). The median progression free survival was 3,8 months. The most common best response to treatment with nal-IRI + 5-FU/LV was disease progression, while disease control rate was 40 %. Some patients were excluded from the last calculation due to adverse effects that led to discontinuation of the treatment (3 pts), some due to the fact, that they began the treatment lately and have not yet had evaluating imaging (8 pts) and one patient was excluded because of death due to other causes (acute ischemic stroke).

**Conclusions:** Patients with metastatic pancreatic ductal adenocarcinoma can be treated with liposomal irinotecan in combination with 5-fluorouracil and leucovorin after being previously treated with gemcitabine-based therapy. This regimen improves overall survival, progression-free survival, disease control rate and has an acceptable safety profile with manageable adverse effects. Patients, treated with this treatment in Institute of Oncology, have comparable results with the patients in NAPOLI-1 study.

## **P28 – Comparison between estimated T/N stage by MRI and pathological findings in patients with locally advanced rectal cancer after neoadjuvant therapy: multi-institutional experience**

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**Introduction:** Rectal magnetic resonance imaging (MRI) plays a key role in the pre- and posttreatment evaluation of rectal cancer. The tumor/node/metastasis (TNM) system is used to describe the extent of cancer. The initial local staging is performed to diagnose locally advanced rectal cancers (LARC), for which neoadjuvant chemoradiotherapy (CRT) is indicated, or to plan surgery in those not requiring CRT. After treatment with neoadjuvant CRT, restaging is performed and rectal MRI can help evaluate clinical response and tumor regression before surgery. The aim of the study was to evaluate the concordance between T and N stage measured on magnetic resonance imaging and pathological findings in patients who underwent neoadjuvant chemoradiotherapy (CRT) and operative procedure.

**Material and methods:** Multi – institutional retrospective study investigating concordance of estimated T/N stage by MRI and pathologic findings in patients with LARC after neoadjuvant CRT was conducted in University hospital Center (UHC) Zagreb and Clinical Hospital for Tumors, UHC Sisters of Mercy, with prior Ethics Committee approval. Data for 88 patients treated between 2017 and 2022 were obtained from the hospital information system. Radiological stage according to MRI, and final pathological stage defined after surgery were analysed. Patients who have not received neoadjuvant CRT, and those without preoperative MRI staging after neoadjuvant treatment were excluded.

**Results:** In 28,41% (25/88) of patients, pathological T/N stage after surgery was equal to stage estimated by MRI. The radiological stage was overestimated in 50% (44/88) and underestimated in 21,59% (19/88) of patients.

Independently, pathological T stage was equal to radiological in 45,45% (40/88) of patients. Radiological stage was overestimated in 42,05% (37/88) and underestimated in 12,50% (11/88) of patients. N stage was equal in 65,91% (58/88) of patients. Radiological stage was overestimated in 19,32% (17/88) and underestimated in 14,77% (13/88) of patients.

**Conclusion:** Our results show that, on average, MRI staging tends to overestimate the actual pathological stage of rectal cancer in patients with LARC after neoadjuvant CRT.

Radiological and pathological stages are more consistent when T and N are compared independently.

**Keywords:** chemoradiotherapy, rectal cancer, MRI staging



## P29 – Synovial sarcoma – where are we?

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**Introduction:** Synovial sarcoma is a rare soft-tissue malignancy, mainly initiated by reciprocal t(X; 18) translocation. The SS18-SSX fusion protein behaves as an aberrant transcriptional dysregulator of the corresponding oncogenic signalling pathways resulting in sarcoma genesis. Even though it is considered to be more chemosensitive in comparison with other soft tissue sarcomas, the prognosis in the metastatic disease remains poor with overall survival no longer than 22 months. Wide surgical resection in combination with chemoradiotherapy represents a main therapeutic option. Given that molecular targeted therapeutic approaches are presently unavailable, numerous researchers have been investigating the relevance of possibly fundamental molecules, including the transcription factor CREB and its' downstream targets (especially Bcl-2).

**Aim:** The aim of our study was to evaluate the epidemiological parameters of patients diagnosed with synovial sarcoma, treated at the Institute of Oncology and Radiology of Serbia, analyse an immunohistochemical profile and aggressiveness, as well as to estimate the overall 2-year survival (OS) and progression free survival (PFS) after doxorubicin and ifosfamide based therapy.

**Materials and methods:** We conducted a retrospective national center observational study on patients treated at the Institute for Oncology and Radiology of Serbia between June 2018 and June 2023. A total of 52 patients were included in the research. The diagnosis of synovial sarcoma was obtained according to formalin-fixed paraffin-embedded histological specimens evaluated at the Institute of Pathology, Faculty of Medicine, University of Belgrade. Analysis of the corresponding medical data was performed, and clinical data, including age, gender, histology, immunohistochemistry, resection line infiltration, oligo-metastatic and metastatic disease appearance, treatment modality and follow up time was collected. Descriptive statistics was applied in order to evaluate epidemiological data. OS was defined as the time passed from the first line therapy to death of an individual, whereas PFS was defined as the time between treatments aimed at shrinking or controlling the cancer and signs that it has started to grow again. Survival analysis was performed using Kaplan-Meier method.

**Results:** We have examined a total of 52 patients (20 male and 32 female). Mean age was 46.62 years (range 18-78 years). They were diagnosed with high-grade (n=48; 92.3%) or low-grade (n=4; 7.7%) synovial sarcoma. SS18-SSX rearrangement was tested in 65.4% (n=34) patients, and proven in 82.35% of tested samples. 73% of specimens were tested for bcl-2 positivity, and 36 out of 38 were found to be positive (94.7%). Ki-67 positivity varied from 5 up to 80% and was not significantly correlated with OS. All the patients included in our study were treated with neoadjuvant or adjuvant doxorubicin and ifosfamide based therapy (n = 52), followed by high-dose ifosfamide chemotherapy in 26.9% patients (n=14). Microscopic resection line infiltration after surgical treatment was positive in 57.7% of cases, whereas in 19.2% we had a lack of data. Local recurrence was discovered in 23%, whereas 57.69% developed lung metastases, 19.2% skeletal metastases and 3.85% brain metastases. PFS ranged from 3 months to 5 years, and the median PFS was 13 months. During this period, no progression was detected in 26.9% of patients (n=14), and 7.69% were lost in follow up. Overall survival was 50% and the 2-year survival was 75%.

**Conclusion:** Even though wide surgical treatment in combination with neoadjuvant or adjuvant doxorubicin and ifosfamide based therapy remains the leading treatment option, to the best of our knowledge, this modality does not appear to provide protection from metastatic disease.

### **P30 – Body mass index (BMI) and adult comorbidity evaluation 27 (ACE-27) as a prognostic factor of overall survival (OS) in locally advanced head and neck (H/N) cancer patients**

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**Introduction:** Locally advanced H/N cancer patients represent heterogeneous group of patients with prognostic factors that are not clearly defined. Malnutrition is recognized as a factor of worse outcome in these patients.

**Patients and methods:** One hundred patients with locally advanced squamous H/N cancer, treated at the Institute for Oncology and Radiology of Serbia from July 2002 until January 2007 were included in this prospective study. Patients were categorized in 4 groups according to BMI: underweight (BMI<18,5); healthy weight (BMI 18,5-24,9); overweight (BMI 25-29,9); obese (BMI≥30). All patients were treated with chemotherapy and then underwent through follow-up period. Primary endpoint of this study was OS. ACE-27 was categorized in 4 groups: none, mild, moderate or severe. Kaplan-Meier survival analysis was conducted to compare the BMI and ACE-27 groups with a log rank test to determine if there were differences in the survival.

**Results:** Among patients, 23 were underweight, 53 patients were with healthy weight, 18 were overweight and 6 were obese. There was not a statistically significant difference in Objective Overall Response (ORR) and Tumor Treatment Response (TTR) between BMI and ACE-27 groups. For all patients median OS was 11.50 months (95%CI, 9.92-13.08). Among BMI groups, median OS (months) was: 9.59 (CI 95% 4.81-14.38) for BMI<18.5; 12.02 (CI 95% 9.58-14.47) in BMI 18.5-25 group; 13.11 (CI 95% 12.02-14.20) in BMI 25-30group; and 13.04 (CI 95% 0.00-27.55) in >30 BMI. There was a statistically significant difference in median OS among groups (Log rank, p 0,038) with most prominent difference among underweight and patients with healthy weight (0.005). There was a statistically significant difference in median OS among ACE-27 groups (Log rank, p 0.031), most prominent in comparison between the group with none (median OS 15.67 (CI 95% 12.41-18.93)) and with comorbidities (median OS 10.81 (CI 95% 9.74-11.88)), p 0.009.

**Conclusion:** Our study has shown that malnutrition and high ACE-27 score is a negative prognostic factor of OS in locally advanced H/N cancer patients treated with chemotherapy.

### **P31 – Olaparib as a first-line maintenance treatment for BRCA-positive ovarian cancer patients: single-institution experience**

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**Introduction:** We all acknowledge that olaparib is most effective when used as maintenance therapy following a positive response to platinum-based regimens in patients with newly diagnosed advanced high-grade serous ovarian cancer (HGSOC).

**Purpose:** The aim of this paper is to present our firsthand experiences with utilizing olaparib as a first-line treatment.

**Methods:** At the Institute of Oncology and Radiology of Serbia, we treated a total of 14 patients, with 7 patients testing positive for *BRCA2* and another 7 patients testing positive for *BRCA1* mutations. *BRCA* positivity was confirmed in all patients through the analysis of somatic mutations, and in one patient a germline *BRCA* mutation was additionally confirmed by a blood analysis. Out of the total patients, nine were diagnosed with FIGO stage IIIa, while five patients were diagnosed with stage IVa, based on positive cytology of pleural effusion.

**Results:** The majority of our patients underwent surgery with a significant residual tumor burden. Out of 9 patients who underwent surgery, 3 patients achieved no evidence of disease (NED), while 5 patients were initially treated with neoadjuvant systemic therapy for inoperable disease due to large tumor burden. After a follow-up period of max22-month, the progression-free survival (PFS) was observed to be 12 months. The most frequently achieved response was partial remission in 8 patients, with 3 patients maintaining NED stadium. One patient had rapid progression of the disease, while 2 patients achieved complete remission. Two patients experienced a severe level of grade 3 anemia, and one patient had grade 3 thrombocytopenia. These listed toxicities necessitated a temporary interruption of therapy and a subsequent dose reduction after correcting the hematological toxicity. Two patients exhibited grade 2 renal impairment, which was effectively managed through appropriate hydration measures.

**Conclusions:** The limitations of our analysis lie in the small sample size and the relatively short duration of patient follow-up. Furthermore, compared to the existing literature data and the SOLO1 study, the patients included in our analysis exhibited a notably higher tumor burden and disease extent, and consequently, they bear greater resemblance to the patients enrolled in the PAOLA1 study. Despite these limitations, our analysis clearly demonstrates significant effectiveness and excellent outcomes with adequate safety profiles in ovarian cancer patients with *BRCA* mutations who received olaparib maintenance therapy following favorable responses to platinum-based therapy.

**Keywords:** *BRCA*- mutated HGSOc, olaparib, maintenance therapy

### **P32 – New therapeutical approach in treatment of nasopharyngeal cancer: sequential chemotherapy Epirubicin-Cisplatin combined with radiotherapy, a eighteen years of follow up**

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**Background:** Nasopharyngeal cancer (NPC) is rarer type of head and neck cancer than squamocellular carcinoma with different geographical distribution, biology and treatment. The cornerstone of treatment are chemotherapy and radioterapy. We herein report the results of our single institutional expirience.

**Material and Methods:** From 2005 to 2012 we have treated patients with advanced nasopharyngeal cancer (NPC). There were 73 patients with previously untreated stage III (41,1%), IVa (19,3%) and IVb

(38,6%). This is significant number of patients for this part of the world. The median age was 52 years. Two cycles of neoadjuvant chemotherapy consisting of Epirubicin and Cisplatin, 90mg/m<sup>2</sup> of each, were administered followed by CHRT with two same cycles but at the dose of 60mg/m<sup>2</sup> of each drug and once-daily RT 2Gy/day (median RT dose was 70Gy). Finally, patients received adjuvant chemotherapy at the same dose as neoadjuvant approach.

**Results:** Response to neoadjuvant therapy was 72,6%: complete response (CR) 1,4% and partial response (PR) 71,2%. After that 15,5% of patient had neck dissection. 69 patients completed CHRT. Response to CHRT was 92%: CR 37,7% and PR 53,6% 57 of patients received adjuvant treatment. There were 98,2% response, CR 84,2% and PR 14%. The progression free survival (PFS) at 3 and 5 years was 56% and 48% respectively. Overall survival (OS) at 3 and 5 years was 57% and 49%. Kaplan-Meier curves were done to determine PFS and OS. Median PFS for our group of patients was 141,60 months. 95% CI was non confirmed because 48% were still alive. Median OS was 155,27 months.

**Conclusions:** Treatment of NPC with neoadjuvant, concomitant CHRT and adjuvant CHT resulted in very good RR. A phase III study to definitely test this treatment strategy is warranted.

### P33 – Neurological immune related adverse events associated with immune checkpoint inhibitors – real world data from single cancer center

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**Background:** Immune checkpoint inhibitors (ICIs) can induce a wide spectrum of neurological immune-related adverse events (NirAEs) with estimated incidence of 1-5% and time to onset from 6 to 13 weeks. They are often severe with high morbidity and fatality rate of around 10%.

**Methods:** We did a retrospective study of 11 cancer patients (pts) that were treated with ICIs and developed NirAE between July 2020 and July 2023. All pts were treated at the Institute of Oncology Ljubljana. Grade of a NirAE was defined by the Common Terminology Criteria for Adverse Events v5.0. Median follow-up time was 17.7 months (range 8.9-33.7 months).

**Results:** We identified 11 pts with NirAE. Median age was 69 (range 49-87) years, 6 (55%) were males, none had history of autoimmune disease, all had metastatic disease, 2 with central nervous system (CNS) metastases. ICI treatments were nivolumab-ipilimumab (n=4) pembrolizumab (n=4), nivolumab (n=2) and cemiplimab (n=1). Underlying malignancies were non small cell lung cancer (n=4), kidney cancer (n=4), urothelial carcinoma (n=1), melanoma (n=1) and cutaneous squamous cell carcinoma (n=1). We identified 6 peripheral nervous system (PNS) and 5 central nervous system (CNS) NirAEs. PNS NirAEs were myasthenic syndrome with overlapping myopathy (n=2), myopathy (n=1), acute polyradiculoneuritis (n=1), acute motor axonal neuropathy (n=1) and sensorimotor polyneuropathy (n=1). CNS NirAEs were encephalitis (n=2), rhombencephalitis (n=1), meningoencephalitis (n=1) and optic neuritis (n=1). Time to onset was shorter for PNS (median 4 weeks, range 0-6 weeks) than CNS NirAEs (median 18 weeks, range 10-36 weeks). Out of all NirAEs 9 were grade 3, 2 were grade 2, none were grade 1 or 4 and no pt died due to NirAE. Both pts with overlapping myasthenic syndrome and myopathy had anti titin antibodies, thymic

malignancy was excluded. No antibodies were identified in other pts. 2 pts with encephalitis had concurrent hypophysitis. ICIs were permanently discontinued in all pts, 10 were treated with corticosteroids, 2 with addition of pyridostigmine and 1 with only pyridostigmine. 10 pts achieved complete or major improvement, 6 were able to stop corticosteroids. Objective response to ICIs was achieved in 9 pts (82%).

**Conclusions:** We collected data of pts with various NirAEs associated with different ICIs. Peripheral NirAEs developed earlier, the occurrence was similar to central NirAEs. Majority of events were serious, corticosteroids led to partial or complete recovery in most patients, no patient died due to NirAE. 82% of pts with NirAE achieved objective response to ICI treatment. Better outcomes with lower fatality rate compared to other reported cases were probably due to prompt recognition of symptoms and centralised treatment in a specialised cancer center with early involvement of neurologist.

### **P34 – FOLFIRINOX in initially metastatic pancreatic cancer: a single-center retrospective study**

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**Introduction:** Pancreatic cancer is the 7th leading cause of cancer-related death worldwide and the 3rd most frequent gastrointestinal cancer. The five-year survival rate for unresectable pancreatic cancer is less than 5%. Recent evidence anticipates a rising incidence of pancreatic cancer.

**Methodology:** We conducted a retrospective study on patients presented at the Clinic of Oncology, Clinical Center University of Sarajevo, with initially metastatic pancreatic cancer between January 2021 and January 2023. Patients unfit for FOLFIRINOX as a first-line treatment were excluded from the analysis. Baseline characteristics of the population were collected retrospectively from patients' medical documentation. Tumor markers (CEA, CA 19-9, CA 125), neutrophil-to-lymphocyte ratio (NLR), neutrophil-to-platelet ratio (NPR), and initial metastatic site were evaluated as potential predictive and prognostic factors using Cox regression statistical analysis.

**Results:** We retrospectively analyzed 33 patients with initially metastatic pancreatic cancer who were treated with FOLFIRINOX as a first-line treatment. The median age of patients (range) was 64 (38-76) years old, including 18 males and 15 females. The median overall survival (OS) (95% CI) was 21.7 (10.5-32.9) months, while the median progression-free survival (PFS) (95% CI) of first-line FOLFIRINOX treatment was 10.0 (8.2-11.8) months. We identified a statistically significant negative correlation between the neutrophil-to-lymphocyte ratio (NLR) and overall survival of patients ( $r=-0.464$ ,  $p=0.045$ ). Patients with initial liver metastasis had numerically worse median overall survival (95% CI) of 16.3 (5.1-27.5) months compared to patients with non-liver locations of metastasis (median overall survival was not reached) (log-rank  $p$ -value=0.058). Three patients (9%) had initially multiple metastatic sites. Tumor markers, NLR, NPR, and initial metastatic site were not identified as independent predictive and prognostic markers of PFS and OS.

**Conclusion:** Patients with initially metastatic pancreatic cancer treated with FOLFIRINOX at our site exhibited better PFS and OS results compared to clinical studies that established this regimen. A larger analysis should be conducted to identify new predictive and prognostic markers in this group of cancer patients.

**Keywords:** pancreatic cancer, metastatic disease, FOLFIRINOX, neutrophil-to-lymphocyte ratio (NLR)

### **P35 – Slovenian experiences of vandetanib efficacy and toxicity in advanced/metastatic medullary thyroid cancer**

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Medullary thyroid cancer (MTC) is a rare endocrine malignancy, which accounts for around 5% of all thyroid cancers. Two multikinase inhibitors, vandetanib and cabozantinib are approved for the treatment of advanced/metastatic MTC. Since 2023, vandetanib usage is restricted to rearranged during transformation (RET) mutation positive MTC. We aimed to present the efficacy and toxicity of vandetanib in the treatment of advanced/metastatic MTC patient in Slovenian population. Since reimbursement in 2020 to analysis in 2023, 10 patients (7 males, 3 females) were treated with vandetanib (8 patients in first-line and 2 patients in second-line). Median age was 55 years (min 41, max 81). Six patients had RET mutation (4 germline, 2 somatic), in 3 patients RET status was unknown, in 1 it was negative. Median progression-free survival was 30.3 vs 2.3 months ( $p=0.001$ ) in RET-mutant vs RET-unknown/negative. 2/6 and 4/6 RET-mutant had partial remission and stable disease, resp., however, 4/4 patients with RETunknown/negative tumors progressed. After median follow-up of 27 months, 6/6 patients with RET-mutant tumors were alive, 2/4 patients with RET-unknown/negative tumors died ( $p=0.016$ ). Mean overall survival of all patients was 33 months (95% CI 23–43). Vandetanib treatment was accompanied with plenty of adverse effects. 9/10 pts had fatigue (8 grade (G) 1, 1 G2), 8/10 pts had diarrhoea (5 G1, 2 G2, 1 G3), 7/10 pts had skin rash G1, 5/10 had arterial hypertension G2, 4/10 had QTc interval prolongation (G1), 4/8 had dispnea G1 and anxiety G1, 3/10 had hand-foot syndrome, 2/8 pts had hair problems G1 and 1/10 eye discomfort, weight loss or deep vein thrombosis (all G1) and 1/10 pts had an immune-related thrombocytopenia G4. Dose reduction of vandetanib was needed in 5/10 pts (in 3 pts to 200 mg/d and in 2 pts to 100 mg/d), 1/10 pts discontinued treatment due to immune-related thrombocytopenia of G4.

Our results support the fact of the efficacy of vandetanib in RET-mutant MTC only, as presented by updated analysis of registrational trial ZETA. For RET-negative MTC cabozantinib is the treatment option. During vandetanib treatment a careful monitoring of QTc and blood pressure is warranted, as well as appropriate supportive treatment of diarrhoea and a hand-foot-skin toxicity.