# Publikujeme v zahraničí

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## GENITOURINÁRNE MALIGNITY

Timmerman DM, Eleveld TF, Sriram S, Dorssers LCJ, Gillis AJM, **Schmidtova S, Kalavska K**, van de Werken HJG, Oing C, Honecker F, **Mego M**, Looijenga LHJ.

**Chromosome 3p25.3 Gain Is Associated With Cisplatin Resistance and Is an Independent Predictor of Poor Outcome in Male Malignant Germ Cell Tumors**

**J Clin Oncol. 2022 Apr 20:JCO2102809.**

**Purpose:** Cisplatin is the main systemic treatment modality for male type II germ cell tumors (GCTs). Although generally very effective, 5%-10% of patients suffer from cisplatin-resistant disease. Identification of the driving mechanisms of resistance will enable improved risk stratification and development of alternative treatments.

**Methods:** We developed and characterized cisplatin-resistant GCT cell line models and compared their molecular characteristics with patient samples with cisplatin resistance and/or a poor clinical outcome. Subsequently, the association between the overlapping genetic features and clinical data was assessed. Finally, we used Cox regression to determine the prognostic relevance of these features within the currently used risk classification.

**Results:** Gain of chromosome 3p25.3 was detected in all cisplatin-resistant cell lines, and copy number of this region correlated with the level of resistance (R = 0.96, P = 1.5e-04). Gain of this region was detected at low frequencies in primary tumors and at higher frequencies in relapsed and/or cisplatin-resistant tumors. Chromosome 3p25.3 gain was associated with shorter progression-free survival and overall survival, with the strongest association observed in nonseminomas excluding pure teratomas. 3p25.3 gain was more frequently observed in tumors with yolk sac tumor histology and predicted adverse outcome independent of the International Germ Cell Cancer Collaborative Group risk classification and the presence of TP53/MDM2 alterations.

**Conclusion:** On the basis of both in vitro analyses and clinical data, we found 3p25.3 to be strongly associated with cisplatin resistance and poor clinical outcome in male type II GCTs. Using genomic profiling, 3p25.3 status could help to improve risk stratification in male patients with type II GCT. Further characterization of this locus and underlying mechanisms of resistance is warranted to guide development of novel treatment approaches for cisplatin-resistant disease.

**Kalavska K, Sestakova Z, Mlcakova A, Gronesova P, Miskovska V, Rejlekova K, Svetlovska D, Sycova-Mila Z, Obertova J, Palacka P, Mardiak J, Chovanec M, Chovanec M, Mego M.**

**Comprehensive Assessment of Selected Immune Cell Subpopulations Changes in Chemotherapy-Naïve Germ Cell Tumor Patients**

**Front Oncol. 2022 Mar 11;12:858797.**

The pattern of immune cell distribution in testicular germ cell tumors (GCT) significantly differs from the immune environment in normal testicular tissues. The present study aimed to evaluate the role of different leukocyte subpopulation in GCTs. A cohort of 84 chemotherapy-naïve GCT patients was analyzed. Immunophenotyping of peripheral blood leukocyte subpopulations was carried out by flow cytometry. In addition, the data assessing the immunophenotypes and the baseline clinicopathological characteristics of the included subjects were statistically evaluated. Their prognostic value for the assessment of progression-free survival (PFS) and overall survival (OS) was estimated. The percentage of different innate/adaptive immune cell subpopulations was significantly associated with poor risk-related clinical features, including the number of metastatic sites, presence of retroperitoneal, mediastinal, lung, brain and non-pulmonary visceral metastases as well as with the S-stage and International Germ Cell Consensus Classification Group (IGCCCG) risk groups. In univariate analysis, the percentages of neutrophils, eosinophils, dendritic cells type 2, lymphocytes and T cytotoxic cells were significantly associated with PFS, while the neutrophil, non-classical monocyte and lymphocyte percentage were associated with OS. However, all these outcome correlations were not independent of IGCCCG in multivariate analysis. The data indicated a link among different innate/adaptive peripheral immune cell subpopulations in GCT patients. In addition, the association between these subpopulations and tumor characteristics was also investigated. The findings of the present study may contribute to a deeper understanding of the interactions between cancer and innate/adaptive immune response in GCT patients.

Terbuch A, Posch F, Bauernhofer T, Jost PJ, Partl R, Stranzl-Lawatsch H, Baciarello G, Fizazi K, Giannatempo P, Verzoni E, Sweeney C, Ravi P, Tran B, Basso U, White J, Vincenzi B, Oing C, Cutuli HJ, Dieckmann KP, Gamulin M, **Chovanec M**, Fankhauser CD, Heidenreich A, Mohamad O, Thibault C, Fischer S, Gillessen S; International Germ Cell Cancer Collaborative Group.

**Patterns of Disease Progression and Outcome of Patients With Testicular Seminoma Who Relapse After Adjuvant or Curative Radiation Therapy.**

**Int J Radiat Oncol Biol Phys. 2022 Apr 20:S0360-3016(22)00262-0.**

**Purpose:** Radiation therapy is a possible treatment strategy for patients with testicular seminoma after orchiectomy in clinical stage I or II disease. Little is known about the outcome of patients who experience a relapse after radiation therapy.

**Methods and materials:** Data from 61 patients who relapsed after adjuvant or curative radiation therapy from 17 centers in 11 countries were collected and retrospectively analyzed. Primary outcomes were disease-free and overall survival. Secondary outcomes were time

to relapse, stage at relapse, treatment for relapse, and rate of febrile neutropenia during chemotherapy for relapse.

**Results:** With a median follow-up of 9.9 years (95% confidence interval [CI], 7.5-10.9), we found a 5-year disease-free survival of 90% (95% CI, 79-95) and a 5-year overall survival of 98% (95% CI, 89-100). Sixty-six percent of patients had stage III disease at time of relapse and 93% of patients fell into the good prognosis group per the International Germ Cell Cancer Collaborative Group classification. The median time to relapse after radiation therapy was 15.6 months (95% CI, 12-23). Twenty-two (36%) patients relapsed more than 2 years after radiation therapy and 7 (11.5%) patients relapsed more than 5 years after radiation therapy. One-third of relapses was detected owing to patients› symptoms, whereas two-thirds of relapses were detected during routine follow-up. The majority (93%) of cases were treated with cisplatin-based chemotherapy. The rate of febrile neutropenia during chemotherapy was 35%. Five patients experienced a second relapse. At last follow-up, 55 patients (90%) were alive without disease. Only 1 patient died owing to disease progression.

**Conclusions:** Cisplatin-based chemotherapy for patients with seminoma who have relapsed after treatment with radiation therapy alone leads to excellent outcomes. Patients and physicians should be aware of possible late relapses after radiation therapy.

## GASTROINTESTINÁLNE MALIGNITY

Shah MA, Udrea AA, Bondarenko I, Mansoor W, Sánchez RG, Sarosiek T, Bozzarelli S, Schenker M, Gomez-Martin C, Morgan C, Özgüroğlu M, Pikiel J, Kalofonos HP, Wojcik E, Buchler T, Swinson D, Cicin I, Joseph M, Vynnychenko I, Luft AV, Enzinger PC, **Salek T,** Papandreou C, Tournigand C, Maiello E, Wei R, Ferry D, Gao L, Oliveira JM, Ajani JA.

**Evaluating Alternative Ramucirumab Doses as a Single Agent or with Paclitaxel in Second-Line Treatment of Locally Advanced or Metastatic Gastric/Gastroesophageal Junction Adenocarcinoma: Results from Two Randomized, Open-Label, Phase II Studies**

**Cancers (Basel). 2022 Feb 24;14(5):1168.**

Studies JVDB and JVCZ examined alternative ramucirumab dosing regimens as monotherapy or combined with paclitaxel, respectively, in patients with advanced/metastatic gastric/gastroesophageal junction (GEJ) adenocarcinoma. For JVDB, randomized patients (N = 164) received ramucirumab monotherapy at four doses: 8 mg/kg every 2 weeks (Q2W) (registered dose), 12 mg/kg Q2W, 6 mg/kg weekly (QW), or 8 mg/kg on days 1 and 8 (D1D8) every 3 weeks (Q3W). The primary objectives were the safety and pharmacokinetics of ramucirumab monotherapy. For JVCZ, randomized patients (N = 245) received paclitaxel (80 mg/m2-D1D8D15) plus ramucirumab (8 mg/kg- or 12 mg/kg-Q2W). The primary objective was progression-free survival (PFS) of 12 mg/kg-Q2W arm versus placebo from RAINBOW using meta-analysis. Relative to the registered dose, exploratory dosing regimens (EDRs) led to higher ramucirumab serum concentrations in both studies. EDR safety profiles were consistent with previous studies. In JVDB, serious adverse events occurred more frequently in the 8 mg/kg-D1D8-Q3W arm versus the registered dose; 6 mg/kg-QW EDR had a higher incidence of bleeding/hemorrhage. In JVCZ, PFS was improved with the 12 mg/kg plus paclitaxel combination versus placebo in RAINBOW; however, no significant PFS improvement was observed between the 12 mg/kg and 8 mg/kg arms. The lack of a dose/exposure-response relationship in these studies supports the standard dose of ramucirumab 8 mg/kg-Q2W as monotherapy or in combination with paclitaxel as second-line treatment for advanced/metastatic gastric/GEJ adenocarcinoma.

## INFEKCIE V ONKOLÓGII

**Palacka P, Polanova M, Svobodova A,** Zigmond J**, Zanchetta K, Gombarova V, Vulganova M, Slopovsky J, Obertova J, Drgona L, Mego M, Pechan J.**

**Effectiveness, Adverse Events, and Immune Response Following Double Vaccination with BNT162b2 in Staff at the National Comprehensive Cancer Center (NCCC)**

**Vaccines (Basel). 2022 Apr 4;10(4):558.**

Vaccination remains the leading strategy against COVID-19 worldwide. BNT162b2 is among the first licensed vaccines with high effectiveness. However, the role of antibody and cell immunity response monitoring after vaccination remains unclear. We conducted a 6-month prospective study involving the employees of NCCC in Slovakia, who were tested for IgG antibody and cell immune responses after double vaccination with BNT162b2. IgG antibodies were detected at 3, 7, and 26 weeks, respectively. At 6 months, blood samples were tested by two different interferon-γ release assays to determine responses to spike protein antigen and nucleocapsid protein antigen of the novel coronavirus. Results were stratified by gender and body mass index (BMI). Statistical significance was set at $p = 0.05$. The medical records of 94 respondents (71 females) were analyzed. The mean age was 40.2 years and the mean BMI was 26.4 kg/m2. At 6 months after double vaccination, effectiveness was 97.9%. The side effects of the BNT162b2 vaccine were similar after both doses, with no serious adverse events or new safety signals recorded. The IgG index declined rapidly ($p < 0.0001$), and 42.6% of subjects had positive and 57.4% borderline or negative immune cell response at 6 months ($p < 0.0001$). Both T cell activation and IgG counts were lower in morbidly obese patients when compared to some other BMI categories. This study confirmed an acceptable toxicity profile and the high efficacy of BNT162b2 despite a rapid decline of IgG level and negative cell-mediated immunity response in most subjects. An individualized approach to vaccination could be considered in morbidly obese individuals.

Albasanz-Puig A, Durà-Miralles X, Laporte-Amargós J, Mussetti A, Ruiz-Camps I, Puerta-Alcalde P, Abdala E, Oltolini C, Akova M, Montejo JM, Mikulska M, Martín-Dávila P, Herrera F, Gasch O, **Drgona L,** Morales HMP, Brunel AS, García E, Isler B, Kern WV, Retamar-Gentil P, Aguado JM, Montero M, Kanj SS, Sipahi OR, Calik S, Márquez-Gómez I, Marin JI, Gomes MZR,

Hemmati P, Araos R, Peghin M, Del Pozo JL, Yáñez L, Tilley R, Manzur A, Novo A, Pallarès N, Bergas A, Carratalà J, Gudiol C, On Behalf Of The Ironic Study Group.

**Effect of Combination Antibiotic Empirical Therapy on Mortality in Neutropenic Cancer Patients with Pseudomonas aeruginosa Pneumonia**

**Microorganisms. 2022 Mar 29;10(4):733.**

To assess the effect of combination antibiotic empirical therapy on 30-day case-fatality rate in neutropenic cancer patients with Pseudomonas aeruginosa (PA) bacteremic pneumonia. This was a multinational, retrospective cohort study of neutropenic onco-hematological patients with PA bloodstream infection (BSI) (2006-2018). The effect of appropriate empirical combination therapy, appropriate monotherapy and inappropriate empirical antibiotic therapy [IEAT] on 30-day case-fatality was assessed only in patients with PA bacteremic pneumonia. Among 1017 PA BSI episodes, pneumonia was the source of BSI in 294 (28.9%). Among those, 52 (17.7%) were caused by a multidrug-resistant (MDR) strain and 68 (23.1%) received IEAT, mainly when the infection was caused by an MDR strain [38/52 (73.1%) vs. 30/242 (12.4%); p < 0.001]. The 30-day case-fatality rate was higher in patients with PA bacteremic pneumonia than in those with PA BSI from other sources (55.1% vs. 31.4%; p < 0.001). IEAT was associated with increased 30-day case-fatality (aHR 1.44 [95%CI 1.01-2.03]; p = 0.042), whereas the use of appropriate combination empirical treatment was independently associated with improved survival (aHR 0.46 [95%CI 0.27-0.78]; p = 0.004). Appropriate empirical monotherapy was not associated with improved overall survival (aHR 1.25 [95%CI 0.76-2.05]; p = 0.39). Combination antibiotic empirical therapy should be administered promptly in febrile neutropenic patients with suspected pneumonia as the source of infection.

Nemethova V, Mazancova P, Selc M, Jakic K, Uhelska L, Nemethova B, Poturnayova A, **Drgona L**, Babelova A, Razga F.

**Effective Reduction of SARS-CoV-2 RNA Levels Using a Tailor-Made Oligonucleotide-Based RNA Inhibitor**

**Viruses. 2022 Mar 25;14(4):685.**

In only two years, the coronavirus disease 2019 (COVID-19) pandemic has had a devastating effect on public health all over the world and caused irreparable economic damage across all countries. Due to the limited therapeutic management of COVID-19 and the lack of tailor-made antiviral agents, finding new methods to combat this viral illness is now a priority. Herein, we report on a specific oligonucleotide-based RNA inhibitor targeting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It displayed remarkable spontaneous cellular uptake, >94% efficiency in reducing RNA-dependent RNA polymerase (RdRp) RNA levels in transfected lung cell lines, and >98% efficiency in reducing SARS-CoV-2 RNA levels in samples from patients hospitalized with COVID-19 following a single application.

Bergas A, Albasanz-Puig A, Fernández-Cruz A, Machado M, Novo A, van Duin D, Garcia-Vidal C, Hakki M, Ruiz-Camps I, Del Pozo JL, Oltolini C, DeVoe C, **Drgona L**, Gasch O, Mikulska M, Martín-Dávila P, Peghin M, Vázquez L, Laporte-Amargós J, Durà-Miralles X, Pallarès N, González-Barca E, Álvarez-Uría A, Puerta-Alcalde P, Aguilar-Company J, Carmona-Torre F, Clerici TD, Doernberg SB, **Petrikova L**, Capilla S, Magnasco L, Fortún J, Castaldo N, Carratalà J, Gudiol C.

**Real-Life Use of Ceftolozane/Tazobactam for the Treatment of Bloodstream Infection Due to Pseudomonas aeruginosa in Neutropenic Hematologic Patients: a Matched Control Study (ZENITH Study)**

**Microbiol Spectr. 2022 Apr 27:e0229221.**

We sought to assess the characteristics and outcomes of neutropenic hematologic patients with Pseudomonas aeruginosa (PA) bloodstream infection (BSI) treated with ceftolozane-tazobactam (C/T). We conducted a multicenter, international, matched-cohort study of PA BSI episodes in neutropenic hematologic patients who received C/T. Controls were patients with PA BSI treated with other antibiotics. Risk factors for overall 7-day and 30-day case fatality rates were analyzed. We compared 44 cases with 88 controls. Overall, 91% of episodes were caused by multidrug-resistant (MDR) strains. An endogenous source was the most frequent BSI origin (35.6%), followed by pneumonia (25.8%). There were no significant differences in patient characteristics between groups. C/T was given empirically in 11 patients and as definitive therapy in 41 patients. Treatment with C/T was associated with less need for mechanical ventilation (13.6% versus 33.3%; P = 0.021) and reduced 7-day (6.8% versus 34.1%; P = 0.001) and 30-day (22.7% versus 48.9%; P = 0.005) mortality. In the multivariate analysis, pneumonia, profound neutropenia, and persistent BSI were independent risk factors for 30-day mortality, whereas lower mortality was found among patients treated with C/T (adjusted OR [aOR] of 0.19; confidence interval [CI] 95% of 0.07 to 0.55; P = 0.002). Therapy with C/T was associated with less need for mechanical ventilation and reduced 7-day and 30-day case fatality rates compared to alternative agents in neutropenic hematologic patients with PA BSI. IMPORTANCE Ceftolozane-tazobactam (C/T) has been shown to be a safe and effective alternative for the treatment of difficult to treat infections due to Pseudomonas aeruginosa (PA) in the general nonimmunocompromised population. However, the experience of this agent in immunosuppressed neutropenic patients is very limited. Our study is unique because it is focused on extremely immunosuppressed hematological patients with neutropenia and bloodstream infection (BSI) due to PA (mainly multidrug resistant [MDR]), a scenario which is often associated with very high mortality rates. In our study, we found that the use of C/T for the treatment of MDR PA BSI in hematological neutropenic patients was significantly associated with improved outcomes, and, in addition, it was found to be an independent risk factor associated with increased survival. To date, this is the largest series involving neutropenic hematologic patients with PA BSI treated with C/T.

## INÉ

Thallinger C, **Berzinec P**, Bicakcic E, Dan A, Fabian G, Gales LN, Kuhar CG, Janzic U, Kahan Z, Mencinger M, Penthedourakis G, Sgouros J, Simetic L, Sirbu D, Vosmik M, Wrona A, Zielinski C.

**Establishment of a virtual transborder tumor board for cancer patients in Central and Southeastern Europe : An initiative of the Central European Cooperative Oncology Group (CECOG)**

**Wien Klin Wochenschr. 2022 Mar 21:1–8.**

**Purpose:** To establish a transborder virtual tumor board (VTB) fostering state-of-the-art management of cancer patients by exchanging knowledge and expertise among oncologists in Central and Southeastern Europe (CEE).

**Methods:** We established and implemented a VTB based on the WebEx platform. This allowed for password-protected and secure upload of patient cases to be presented and discussed among colleagues from various oncology centers scattered throughout CEE in order to arrive at a recommendation for further diagnoses and/or treatment.

**Results:** A total of 73 cases from 16 oncology centers located in 11 CEE countries were uploaded by 22 physicians; 71 were discussed over the course of 17 virtual meetings between June 2018 and May 2019 and 12 different kinds of malignant diseases were discussed with lung cancer (46.6%), melanoma (19.2%) and bladder cancer (13.6%) being the most commonly presented tumor entities. Of the discussed patients, 93.3% had stage IV disease at the time of presentation, 62.6% received chemotherapy or targeted treatment and 67.1% were treated with immune checkpoint inhibitors (ICPIs). The most common causes for presentation and discussion of patient cases were related to the use of ICPIs (80%).

**Conclusion:** When the need for expertise exceeds locally available resources, web-based VTBs provide a feasible way to discuss patient cases and arrive at conclusions regarding diagnoses and/or treatment across large geographic distances. Moreover, VTBs provide an innovative way for proper, state-of-the-art management of patients with malignant diseases in times of social distancing and the resulting need for restricted interaction during the current SARS-CoV-2 (severe acute respiratory syndrome coronavirus type 2) pandemic.