



COMMENTARY TO HABILITATION THESIS

My habilitation thesis was compiled as an annotated set of publications dedicated to clinical research in the field of gastrointestinal tumours, especially oesophageal and gastric cancer. A key part of my thesis presents the results of my research activities on innovative biomarkers that enable targeted therapy or treatment adaptation. Beyond that, I am outlining the use and implementation of trial results in clinical practice. In the interest of clarity, I have divided the annotated set of 14 publications into chapters that reflect the individual research areas in which I have been active as an investigator. The syllabus of my work summarizes the current knowledge about the epidemiology of gastrointestinal cancer, its molecular background, prognostic and predictive factors for treatment efficacy, and finally, the translation of new knowledge into clinical practice. In the individual sections, I mention specific projects and studies that I conducted or contributed to and whose order is compiled to logically reflect the chronology of cancer study. The introduction includes chapters devoted to the epidemiology of selected gastrointestinal tumours, especially oesophageal and gastric cancer. Over time, these diagnoses have become a major focus of my work, both in research and in the clinical field, and are therefore mentioned in more detail. Understanding cancer's genetic and molecular basis is key to medical advances in cancer research. Thus, the following chapters include our publications devoted to the rare genetic condition Gastric Adenocarcinoma and Proximal Polyposis of the Stomach Syndrome (GAPPS), as well as work on the genomic and molecular characteristics of oesophageal and gastric tumours, the description of which provided hope for a correct understanding and future individualized approach to treatment in 2017.

While in other malignancies such as lung or breast cancer, predictive markers led to profound treatment individualization and improved the course of cancer, in gastrointestinal tumours, which are characterized by high biological heterogeneity, many evaluated molecules failed as predictive markers. During my career as a researcher and co-investigator of sponsored clinical trials, I have gained the opportunity to participate in research and collaborate on studies investigating new molecules and targeted drugs. Contractual clinical studies in which I participated are also mentioned in the text of the habilitation thesis due to the complexity of the entire research issue. However, they are not included in the list of own published works submitted for habilitation.

Selected publications focusing on the study of new targeted drugs for colorectal and gastric cancer are included in the second part of my habilitation thesis.

Novel predictive biomarkers enable the optimization of the treatment approach. An important issue is the innovative use of diagnostic procedures, be it laboratory or imaging methods, to establish possible new biomarkers. Predictive markers and their use to personalize the treatment process are other topics of my habilitation thesis. The use of the biomarkers as indicators of chemotherapy resistance to adapt the treatment algorithm was the source of inspiration for the GastroPET study, which investigates the use of sequential positron emission tomography (PET) imaging and plasma miRNA in locally advanced gastro-oesophageal junction denocarcinoma.

A circulating blood biomarker of prognostic significance in colorectal cancer and also other cancer and chronic diseases is 25-hydroxyvitamin D (25-OHD). Monitoring the level of circulating 25-OHD in the treatment of metastatic colorectal cancer and investigating its significance for treatment outcomes was the subject of my dissertation. I continued this work by analyzing individual patient serum 25-OHD levels from the international multicenter phase III EXPAND study. This study investigated the benefit of the epidermal growth factor receptor (EGFR) antibody cetuximab in combination with standard chemotherapy in the first-line treatment of metastatic gastric cancer. To verify the hypothesis of a potential prognostic and/or predictive role of 25-OHD, we performed an analysis of baseline circulating levels of 25-OHD in patients' serum. Like vitamin D, patients' nutritional status may have predictive or prognostic potential in the treatment of metastatic disease. The clinical condition of patients with metastatic gastric cancer is very often impaired by malnutrition at the time of diagnosis. It can theoretically modify the intensity and thus the success of treatment. Defining the prognostic significance of sarcopenia in patients from the EXPAND trial was the goal of another analysis in which we participated together with the research group of Professor Hacker from Leipzig, Germany. The results were recently published.

Many of our activities were intensely affected by the Covid-19 pandemic, which slowed down or even stopped some research projects and profoundly influenced our professional lives. The pandemic was a particular threat for cancer patients, as they are at high risk for a severe course of infection due to the debilitating nature of cancer and immunosuppressive cancer treatment.

An effort to further specify the immune response to vaccination in actively treated cancer patients led us to initiate the academic clinical study of COVIGI. We examined the side effects of vaccination in cancer patients but mainly focused on changes in humoral and cellular immunity of actively treated patients with a specific view on individual treatment modalities such as chemotherapy, radiotherapy, immunotherapy, and targeted treatment. Collaborating on contractual clinical trials and answering frequently asked research questions in clinical practice has led me to academic clinical research to implement my academic projects and studies at the national level. Similarly, as a member of the European Organisation for Research and Treatment on Cancer (EORTC) Gastrointestinal Tract Cancer Study Group, I have had the opportunity to collaborate on the design of academic clinical trials since 2013 and being appointed co-chair of the Individualised Cancer Therapy Task Force since 2018. Within this task force, we designed an international clinical trial on advanced biliary tract cancer (Pamiparib in Patients with Platinum Sensitive Biliary TraCt Carcinoma [PAMICC] study). This activity is also mentioned in my habilitation thesis.

As an essential part of clinical research, clinical trials are the first step leading to the entry of a new drug or therapeutic procedure into clinical practice. Evidence-based medicine is also inextricably linked to correctly interpreting data from clinical trials, which is a fundamental step toward successfully treating a cancer patient. The last part of my habilitation thesis describes my participation in National treatment recommendations for oesophageal and gastric cancer and the European guidelines for the treatment of oesophageal cancer.

As part of my habilitation thesis, I selected the 14 most important articles. My contribution to these articles is summarized in the following tables, with special emphasis on experimental work, student supervision, manuscript preparation, and research direction.

[1] FORETOVA, L., M. NAVRATILOVA, M. SVOBODA, P. GRELL, L. NEMEC, L. SIROTEK, **R. OBERMANNOVA**, I. NOVOTNY, M. SACHLOVA, P. FABIAN, R. KROUPA, P. VASICKOVA, J. HAZOVA, E. STAHLLOVA HRABINCOVA a E. MACHACKOVA. GAPPS – gastric adenocarcinoma and proximal polyposis of the stomach syndrome in 8 families tested at Masaryk memorial cancer institute – prevention and prophylactic gastrectomies. *Klinická onkologie*. 2019, 32, 2S109-2S117.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
-	20	40	40

[2] **OBERMANNOVA, R.** a F. LORDICK. Insights into next developments in advanced gastric cancer. *Current Opinion in Oncology*. 2016, 28(4), 367–375. ISSN 1040-8746.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	20	60	-

[3] MOEHLER M. M., A. HÖGNER, A. D. WAGNER, **R. OBERMANNOVA**, M. ALSINA, P. THUSS-PATIENCE, H. VAN LAARHOVEN, E. SMYTH. Recent progress and current challenges of immunotherapy in advanced/metastatic esophagogastric adenocarcinoma. *European Journal of Cancer*. 2022, 176, 13–29. ISSN 0959-8049.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
-	-	40	20

[4] **OBERMANNOVA, R.**, E. VAN CUTSEM, T. YOSHINO, G. BODOKY, J. PRAUSOVA, R. GARCIA-CARBONERO, T. CIULEANU, P. GARCIA ALFONSO, D. PORTNOY, A. COHN, K. YAMAZAKI, P. CLINGAN, S. LONARDI, T. W. KIM, L. YANG, F. NASROULAH a J. TABERNERO. Subgroup analysis in RAISE: a randomized, double-blind phase III study of irinotecan, folinic acid, and 5-fluorouracil (FOLFIRI) plus ramucirumab or placebo in patients with metastatic colorectal carcinoma progression (euro). *Annals of Oncology*. 2016, 27(11), 2082–2089. ISSN 0923-7534. Dostupné z: doi: 10.1093/annonc/mdw402.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	50	60	30

[5] BENCSIKOVA, B., E. BUDINSKA, I. SELINGEROVA, K. PILATOVA, L. FEDOROVA, K. GREPLOVA, R. NENUTIL, D. VALIK, **R. OBERMANNOVA**, M. A. SHEARD a L. ZDRAZILOVA-DUBSKA. Circulating T cell subsets are associated with clinical outcome of anti-VEGF-based 1st-line treatment of metastatic colorectal cancer patients: a prospective study with a focus on primary tumour-sidedness. *Bmc Cancer* [online]. 2019, 19, 687. ISSN 1471-2407.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	20	30	30

[6] **OBERMANNNOVA, R.**, D. VALIK, D. HASENCLEVER, L. ZDRAZILOVA-DUBSKA, U. HACKER, R. DEMLOVA, I. SELINGEROVA a F. LORDICK. High prevalence of severe hypovitaminosis D in patients with advanced gastric cancer treated with first-line chemotherapy with or without anti-EGFR-directed monoclonal antibody (EXPAND trial) showing no prognostic impact. *European Journal of Cancer*. 2019, 116, 107–113. ISSN 0959-8049.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
70	90	70	70

[7] HACKER U.T., D. HASENCLEVER, R. BABER, N. LINDER, H. BUSSE, **R. OBERMANNNOVA**, L. ZDRAZILOVA-DUBSKA, D. VALIK a F. LORDICK. Modified Glasgow prognostic score (mGPS) is correlated with sarcopenia and dominates the prognostic role of baseline body composition parameters in advanced gastric and esophagogastric junction cancer patients undergoing first-line treatment from the phase III EXPAND trial. *Annals Oncology* 2022, 33(7), 685-692. doi: 10.1016/j.annonc.2022.03.274.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	-	20	20

[8] **OBERMANNNOVA, R.**, I. SELINGEROVA, Z. REHAK, V. JEDLICKA, M. SLAVIK, P. FABIAN, I. NOVOTNY, M. ZEMANOVA, H. STUDENTOVA, P. GRELL, L. ZDRAZILOVA DUBSKA, R. DEMLOVA, T. HARUSTIAK, R. HEJNOVA, I. KISS a R. VYZULA. PET/CT-tailored treatment of locally advanced oesophago-gastric junction adenocarcinoma: a report on the feasibility of the multicenter GastroPET study. *Therapeutic Advances in Medical Oncology*. 2021, 13, 17588359211065152.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
80	90	80	80

[9] SLAVIK, M., P. BURKON, I. SELINGEROVA, P. KRUPA, T. KAZDA, J. STANKOVA, T. NIKL, R. HEJNOVA, Z. REHAK, P. OSMERA, T. PROCHAZKA, E. DVORAKOVA, P. POSPISIL, P. GRELL, P. SLAMPA a **R. OBERMANNNOVA**. Preoperative Chemoradiotherapy for Gastroesophageal Junction Adenocarcinoma Modified by PET/CT: Results of Virtual Planning Study. *Medicina-Lithuania* [online]. 2021, 57(12), 1334. ISSN 1010-660X.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	50	40	30

[10] **OBERMANNNOVA, R.**, M. REDOVA-LOJOVA, P. VYCHYTILOVA-FALTEJSKOVA, P. GRELL, W. C. CHO, M. SACHLOVA, M. SVOBODA, R. VYZULA a Ondrej SLABY. Tumour Expression of miR-10b, miR-21, miR-143 and miR-145 Is Related to Clinicopathological Features of Gastric Cancer in a Central European Population. *Anticancer Research* [online]. 2018

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	80	50	160

[11] LORDICK, F., C. MARIETTE, K. HAUSTERMANS, **R. OBERMANNNOVA** a D. ARNOLD. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* [online]. 2016, 27, v50–v57. ISSN 0923-7534.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
-	-	30	-

[12] **OBERMANNNOVÁ, R.**, M. ALSINA, A. CERVANTES, T. LEONG, F. LORDICK, M. NILSSON, N.C.T. VAN GRIEKEN, A. VOGEL, E.C. SMYTH. ESMO Guidelines Committee. Oesophageal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology*. 2022, 33(10), 992–1004. ISSN 0923-7534.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
-	70	50	20

[13] KROESE, T.E., R. VAN HILLEGERSBERG, S. SCHOPPMANN, P.R.A.J. DESEYNE, P. NAFTEUX, **R. OBERMANNNOVA**, M. NORDSMARK, P. PFEIFFER, M.A. HAWKINGS, E. SMYTH, S. MARKAR, G.B. HANNA, E. CHEONG, A. CHAUDRY, A. ELME, A. ADENIS, G. PIESSEN, C. GANI, C.J. BRUNS, M. MOEHLER, T. LIAKAKOS, J. REYNOLDS, A. MORGANTI, R. ROSATI, C. CASTORO, D. D'UGO, F. ROVIELLO, M. BENCIVENGA, G. DE MANZONI, P. JEENE, J.W. VAN SANDICK, C. MUIJS, M. SLINGERLAND, G. NIEUWENHUIJZEN, B. WIJNHOFEN, L.V. BEEREPOOT, P. KOŁODZIEJCZYK, W.P. POLKOWSKI, M. ALSINA, M. PERA, T.F. KANONNIKOFF, M. NILSSON, M. GUCKENBERGER, S. MONIG, D. WAGNER, L. WYRWICZ, M. BERBEE, I. GOCKEL, F. LORDICK, E.A. GRIFFITHS, M. VERHEIJ, P.S.N. VAN ROSSUM, H.W.M. VAN LAARHOVEN, C. ROSMAN, H. RÜTTEN, E.C. GOOTJES, F.E.M. VONKEN, J.M. VAN DIEREN, M.A. VOLLEBERGH, M. VAN DER SANGEN, G.-J. CREEMERS, T. ZANDER, H. SCHLÖSSER, S. CASCINU, E. MAZZA, R. NICOLETTI, A. DAMASCELLI, N. SLIM, P. PASSONI, A. COSSU, F. PUCCHETTI, L. BARBIERI, L. FANTI, F. AZZOLINI, F. VENTORUZZO, A. SZCZEPANIK, L. VISA, A. REIG, T. ROQUES, M. HARRISON, B. CIŚEŁ,

A. PIKUŁA, M. SKÓRZEWSKA, H. VANOMMESLAEGHE, E. VAN DAELE, P. PATTYN, K. GEBOES, E. CALLEBOUT, S. RIBEIRO, P. VAN DUIJVENDIJK, C. TROMP, M. SOSEF, F. WARMERDAM, J. HEISTERKAMP, A. VERA, E. JORDÁ, F. LÓPEZ-MOZOS, M.C. FERNANDEZ-MORENO, M. BARRIOS-CARVAJAL, M. HUERTA, W. DE STEUR, I. LIPS, M. DIEZ, S. CASTRO, R. O'NEILL, D. HOLYOAKE, U. HACKER, T. DENECKE, T. KUHN, A. HOFFMEISTER, R. KLUGE, T. BOSTEL, P. GRIMMINGER, V. JEDLIČKA, J. KŘÍSTEK, P. POSPÍŠIL, A. MOURREGOT, C. MAURIN, N. STARLING a I. CHONG. Definitions and treatment of oligometastatic oesophagogastric cancer according to multidisciplinary tumour boards in Europe. *European Journal of Cancer*. 2022, 164, 18–29.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	20	20	20

[14] LUTZ, M. P., J. R. ZALCBERG, M. DUCREUX, A. ADENIS, W. ALLUM, D. AUST, F. CARNEIRO, H. GRABSCH, P. LAURENT-PUIG, F. LORDICK, M. MOEHLER, S. MONIG, R. OBERMANNOVA, G. PIESSEN, A. RIDDELL, C. ROECKEN, F. ROVIELLO, P. M. SCHNEIDER, S. SEEWALD, E. SMYTH, E. VAN CUTSEM, M. VERHEIJ, A. D. WAGNER a Florian OTTO. The 4th St. Gallen EORTC Gastrointestinal Cancer Conference: Controversial issues in the multimodal primary treatment of gastric, junctional and oesophageal adenocarcinoma. *European Journal of Cancer*. 2019, 112, 1–8. ISSN 0959-8049.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	20	20	20