Phase II Trial to assess the Efficacy of Low Radiation Dose of 20 Gy for the Treatment of Marginal Zone Lymphoma or Follicular Lymphoma Stage I-II localized in the Stomach or the Duodenum

ISRT 20 Gy in Localized Indolent **G**astric or **D**uodenal **L**ymphoma
(GDL-ISRT 20 Gy)

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1.1 Synopsis

Title:	Phase II Trial to assess the Efficacy of Low Radiation Dose of 20 Gy for the Treatment of Marginal Zone Lymphoma or Follicular Lymphoma Stage I-II localized in the Stomach or the Duodenum
Short Title:	ISRT 20 Gy in Localized Indolent **G**astric or **D**uodenal **L**ymphoma
Acronym	GDL-ISRT 20 Gy
Protocol version identifier:	01, 12.05.2020
Register-No.	NCT04097067 (ClinicalTrials.gov)
Lead Investigators:	Prof. Dr. med. H.Th. Eich/ Dr. med. G. Reinartz
Indication/ Medical condition:	Primary indolent (marginal zone or follicular) gastric or duodenal lymphoma
Study Design:	Prospective single-arm multicenter study
Active substance/ Medicinal product	None
Intervention(s):	Involved Site RadioTherapy (ISRT) with 20 Gy

Treatment plan	-Study enrollment, **blood draw** for **biomarker-analysis** (at baseline visit/ after 4 Gy/ after 10 Gy / after 20 Gy RT/ at 3 and 6 months after RT) -CT-based planning of RT -**ISRT** with **IMRT** (oder 3D-CRT)**/ IGRT, daily 2 Gy ad 20 Gy**
Objectives:	-Prove the effectiveness of 20 Gy and non-inferiority to 30 Gy with respect to response rate. -Recording of survival rates, quality of life (QoL), radiogenic toxicities and inflammation relevant molecules. *-Primary Objective*: Response rate 6 months after end of treatment, 4 categories according to GELA-criteria: CR (complete remission) = CR or pMRD (probable minimal residual disease), PR (partial remission) = rRD (responding residual disease), NC (no change), PD (progressive disease) *-Secondary Objectives:* QoL according to EORTC (QLQ C30 and STO22). EFS=Event-free survival (time to any failure or death from any cause, all patients), PFS=Progression-free survival (time to progression of lymphoma or death from any cause, patients in PR or SD), RFS=Recurrence-free survival (time to recurrence of lymphoma or death from any cause, patients in CR), LSS=Lymphoma-specific survival (time to death related to lymphoma or associated with the treatment, all patients), OS=Overall survival (time to death from any cause, all patients). Level of cytokines IL-1β, IL-4, IL-8, TNFalpha and other inflammation relevant molecules Syndecan1, MMP-2 and S100 proteins. Acute toxicities during treatment according to NCI-CTC, chronic toxicities according to NCI-CTC/ LENT-SOMA. Monitoring of Adverse Events (AEs) and Serious Adverse Events (SAEs) -Assessment of safety: Monitoring of Adverse Events (AEs) and Serious Adverse Events (SAEs)
Inclusion Criteria:	-primary indolent gastric or duodenal lymphoma -pathology: marginal zone lymphoma (MZL) or follicular lymphoma (FL) -stage: clinical stage I or II (Ann Arbor classification) -H. pylori negative or antibiotic resistant lymphoma -any FLIPI score low – high (0-4) -any size of tumor or affected lymph nodes -male or female with age ≥ 18 years -performance status ECOG 0 – 3 -written informed consent by the patient
Exclusion Criteria:	-prior radiation treatment of the gastrointestinal lymphoma -stage: clinical stage III or IV (Ann Arbor classification)-unability to understand the informed consent or unwillingness to participate in the study -severe comorbidity or organ dysfunction contraindicating the use of RT (liver cirrhosis Child-Pugh C, chronic obstructive pulmonary disease GOLD 4, heart insufficiency NYHA IV, dialysis dependent renal insufficiency, uncontrolled epilepsy) -known seropositivity for HIV -acute hepatitis B or C infection -chronic inflammatory bowel disease

	-prior malignant disease (exclusion: basalioma, non-metastasized solid tumor in constant remission diagnosed >3 years ago) -pregnancy or breastfeeding -active substance abuse or severely compromised compliance
Statistical Methods:	Primary endpoint analysis: The primary endpoint is the overall response rate (ORR) 6 months after end of treatment. It will be analysed by a one-sample non-inferiority binomial test. The one-sided significance level is 2.5%, the power is 80%. It will be tested whether ORR will be non-inferior to 0.95, with non-inferiority margin (difference) 0.1, i.e. it will be tested whether the lower limit of the one-sided 97.5% confidence interval by Clopper-Pearson will be greater than 0.85. Secondary endpoint analysis: The pre-specified secondary endpoints will be analysed with appropriate statistical methods depending on the type of variable, e.g. rates are analysed by binomial test and exact 95%-confidence interval, time-to-event endpoints by one-sample log-rank test.
Number of Patients/ Sample size:	**To be assessed for eligibility:** n = 88 **To be assigned to the trial:** n = 83 **To be analyzed:** n = 79
Participating Centers:	University Hospitals of: Beijing, Essen, Heidelberg, Kiel, Gießen-Marburg, Muenchen LMU, Muenchen TU, Muenster, New York MSKCC, Rochester, Singapore, Tokyo, Torino, Tuebingen, Boston, San Francisco, Toronto. Other expert hospitals: Bielefeld Franziskus Hospital, Mönchengladbach Kliniken Maria Hilf. Participating (Inter-) national centers after approval of their Ethics Committee/ Institutional Review Board.
Trial duration /Schedule:	Planned recruitment duration: 1.5 years Duration of single patient participation: RT intervention of two weeks plus 6 months after end of treatment Planned overall duration of the study: 2 years Planned start of recruiting/data collection: September 01, 2019 Planned end of data collection: August 31, 2021 Planned final report of study results: August 31 2022
Visits:	Visits summary: Baseline visit, first day of RT treatment, second day (after 4 Gy), 5th day of RT (after 10 Gy), last day of RT (after 20 Gy), 6 weeks after end of RT±5 d, 3 and 6 and 9 months after end of RT±3 weeks, 1 year after end of RT±3 weeks, 2 years after end of RT±3 weeks.
Financial Support:	An application for funding was submitted to the IZKF Muenster and to the DLH-foundation.