INTEGRATE IIb
Randomized Phase III Controlled Trials of Regorafenib containing regimens versus standard care in Refractory Advanced Gastro-Oesophageal Cancer (AGOC)

AIO-assoziierte-Studie

Studiennummer/-Code:	**AIO-STO-0221/ass - Integrate IIb**
Status:	in Vorbereitung
Rekrutierungszeit:	von: April 2022 bis: ca. Jan 2024
Anzahl Zentren:	geplant: 26 (s.u.) aktuell initiiert: 0 aktiv rekrutierend: 0
Weitere Zentren:	sind erwünscht (Details siehe unten)
Anzahl Patienten:	geplant: 80 (in Europa) aktuell eingeschlossen: 0
Letzte Aktualisierung	28.04.2022

STUDY TYPE	A multicenter, randomized phase III, open label trial with 2:1 (RegoNivo: standard chemotherapy)
PRINCIPAL INVESTIGATOR	Prof. Dr. Markus Möhler Leitung Gastrointestinale-Onkologische Ambulanz, Oberarzt, Johannes Gutenberg-University Mainz, Germany, Universitätsmedizin Mainz, I.Medizinische Klinik und Poliklinik, Langenbeckstraße 1, 55131 Mainz Telefon: +49 (0) 6131-176076, Telefax: +40 (0) 6131-176472 E-Mail: markus.moehler@unimedizin-mainz.de
TRIAL OFFICE	Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main
SPONSOR	Sponsor global: Australasian Gastro-Intestinal Trials Group (AGITG) Level 6, 119-143 Missenden Road Camperdown NSW 2050, Australia Local sponsor, Europe: Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main, Germany
CONDITION	Refractory Advanced Gastro-Oesophageal Cancer
DESIGN	A randomised phase III, open label, trial with 2:1 (RegoNivo:standard chemotherapy) randomisation and stratification by: • Geographic region (Asia vs. Rest of World) • Prior VEGF inhibitors (Y vs N) • Prior immunotherapy (Y vs N)
INDICATION	Refractory Advanced Gastro-Oesophageal Cancer. The study will include patients, who have failed or been intolerant to a minimum of 2 lines of prior anti-cancer therapy for recurrent/metastatic

	disease which must have included at least one platinum agent and one fluoropyrimidine analogue. **Note**: Neoadjuvant or adjuvant chemotherapy or chemoradiotherapy will be considered as first line treatment where people have relapsed or progressed within 6 months of completing treatment; Radiosensitising chemotherapy given solely for this purpose concurrent with palliative radiation will not be considered as a line of treatment. Ramucirumab monotherapy, or immunotherapy with a checkpoint inhibitor, will be considered a line of treatment.
OBJECTIVE(S)	<u>Primary Objective (Endpoint):</u> To determine the effect of RegoNivo on overall survival (OS) (death from any cause) in the overall study population and in the Asian sub-population. <u>Secondary Objectives (Endpoints):</u> To determine the effect of RegoNivo on: • Progression free survival (PFS)(disease progression or death) • Objective tumour response rate (OTRR)((partial or complete response (PR or CR)) according to Response Evaluation Criteria in Solid Tumours (RECIST) version. 1.1, and iRECIST • Quality of life (QoL)(scores from participant-completed questionnaires) • Safety (rates of adverse events) <u>Tertiary/Correlative Objectives:</u> • To identify prognostic and predictive biomarkers (tissue and circulating) for study endpoints (relating to survival, response and safety) • To evaluate regorafenib PK in patient populations from different geographical regions (regorafenib levels).
INTERVENTION(S)	Study Treatments: Participants in the RegoNivo arm will self-administer 90mg (3x30mg) of regorafenib days 1-21 of each 28-day treatment cycle and receive intravenous nivolumab 240 mg day 1 of 14 days until disease progression or prohibitive adverse events as per protocol. After 2 months, patients whose disease is controlled may have nivolumab administered 480 mg every 28 days. Participants in the control arm will receive investigator choice chemotherapy with any of the following agents: taxane, irinotecan or oral trifluridine/tipiracil (TAS102). Both treatment groups will receive Best Supportive Care (BSC).
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	The trial incorporates translational studies (biomarker research) in the trial design. Planned biomarker analyses may include but are not limited to: • Investigation of VEGF-related biomarkers including VEGF, VEGF polymorphisms, circulating VEGF isoforms (VEGF A short isoforms), VEGF family receptors (VEGFR-1, 2, 3) and other proteins downstream of VEGFR, as prognostic and/or predictive markers for those study endpoints relating to survival, response and safety • Other biomarkers relating to angiogenesis and/or tumourigenesis in blood and tumour including FGF pathway, PDGF, vWF, Tie1 and 2. • Evaluation of the prevalence and distribution of the four proposed molecular phenotypes of gastric cancer proposed by the Cancer Genome Atlas Research Network (2014), and their association with angiogenic biomarkers and regorafenib activity. • Regorafenib pharmacokinetics in patients from different geographical regions. • Associations between circulating tumour DNA and clinical outcomes • Associations between autoimmunity and clinical outcomes

	• Immunoprofiling including: immune cell infiltration, expression of immune checkpoint molecules including PD-1 and PD-L1 • Tumour mutational burden (TMB) • Cellular and molecular signatures associated with immune-related adverse events. Since the identification of new biomarkers correlating with disease activity and the efficacy or safety of treatment are rapidly evolving, the definitive list of biomarkers remains to be determined.
BACKROUND/RATIONALE	Advanced Gastro-oesophageal Carcinoma (AGOC) has a poor prognosis, and there is no established standard treatment following failure of first- and second-line chemotherapy. Regorafenib (BAY 73-4506) is an investigational oral multi-targeted tyrosine kinase inhibitor (TKI) which targets angiogenic (VEGF, TIE-2), stromal (PDGF-β), and oncogenic (RAF, RET and KIT) receptor tyrosine kinases, and has shown activity in other solid tumours. Regorafenib was shown to prolong PFS across all regions/subgroups in INTEGRATE The INTEGRATE II trial is currently a randomised phase III, controlled trial aiming to determine if regorafenib improves overall survival in refractory AGOC. Immune checkpoint inhibitors enhance anti-tumour T-cell activity through the inhibition of immune checkpoints such as the programmed death-1 (PD-1) receptor. Nivolumab is a fully human IgG4 monoclonal antibody inhibitor of PD-1, shown to be effective in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens in the ATTRACTION-2 study. Biologic rationale exists for synergy between anti-angiogenic therapy (anti-VEGF and others) and anti-PD-1/PD-L1 therapy through changes in the tumour microenvironment. The regorafenib and nivolumab combination (RegoNivo) showed manageable toxicity and encouraging activity in patients with refractory advanced gastric cancer in a Phase Ib trial, including in patients having received prior nivolumab. Current practice in countries participating in INTEGRATE IIb has evolved to use chemotherapy in 3rd and subsequent lines of therapy in fit patients. Agents with demonstrated activity in the 2nd line setting (vs Best supportive Care alone) are utilised, including taxanes (paclitaxel and docetaxel), irinotecan, and oral trifluridine/tipiracil (TAS 102). With the shift in practice in AGOC resulting in use of multiple lines of therapy, the use of new immunotherapy agents, and the promising activity of RegoNivo, this amended trial is proposed to compare the effectiveness of RegoNivo in pre-treated patients with AGOC to the current standard therapy (i.e.: chemotherapy).
KEY EXCLUSION CRITERIA	○ Prior anti-VEGF targeted therapy using small molecule VEGF TKIs. Prior anti- VEGF targeted monoclonal antibody therapies (e.g. bevacizumab and ramucirumab) are permitted. ○ Any prior use of more than one immune checkpoint inhibitor ○ Treatment with any previous drug therapy within 2 weeks prior to first dose of study treatment ○ Uncontrolled metastatic disease to the central nervous system ○ History of another malignancy within 2 years prior to randomization ○ Patients who require high dose systemic corticosteroids < 14 days prior to randomization ○ Pregnancy, lactation, or inadequate contraception.
KEY INCLUSION CRITERIA	○ Adult patients with metastatic or locally recurrent gastro-oesophageal cancer that **a.** has arisen in any primary gastro-oesophageal site; and

	b. is of adenocarcinoma or undifferentiated carcinoma histology; and **c.** is evaluable according to Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1); and **d.** has failed or been intolerant to a minimum of 2 lines of prior anti-cancer therapy (at least one platinum agent and one fluoropyrimidine analogue) o ECOG Performance Status of 0 or 1 o Adequate bone marrow, renal and liver function
OUTCOME(S)	o Overall Survival (OS) *(Death from any cause)* o Progression Free Survival (PFS) *(Disease progression or death)* o Objective Tumour Response Rate (OTRR) o Quality of Life (QoL) o Safety o Tertiary/Correlative
STATISTICAL ANALYSIS	A statistical analysis plan for INTEGRATE IIb will be prepared and finalised prior to database release for analysis. The primary analysis of efficacy endpoints will be performed on the analysis set comprising all randomised patients in accordance with the intention-to-treat analysis principle. The safety population will comprise all randomised participants who received at least one administration of study medication. Participants will be analysed according to the regimen they actually received for the purposes of the safety analysis.
SAMPLE SIZE	A sample of 450 participants (globally; 80 patients in Europe) randomised in a 2:1 ratio (RegoNivo: chemotherapy) and followed until 380 deaths occur (e.g. over a 24 month recruitment period plus an additional follow-up period of at least 12 months) provides 90% power to detect a hazard ratio (HR) for OS of 0.70 with a 2-sided α of 0.05.
TRIAL DURATION	Globally: a 24-month recruitment period plus an additional follow-up period of at least 12 months.
PARTICIPATING CENTERS	Up to 26 sites in Germany and in other European countries.
FURTHER CENTERS DESIRED?	Yes
NUMBER of PATIENTS	450 randomized patients globally; 80 in the European countries.
CURRENT NUMBER of PATIENTS	Recruitment in the European countries has not started yet.