PROTOCOL SYNOPSIS

EU CT Number	2025-523055-55-00
Full Title	A phase II, open-label, randomized, multi-center study comparing the efficacy and safety of Sacituzumab govitecan (SG) versus investigators choice in patients with cancer of unknown primary (CUP) who are relapsed after or refractory to platinum-based chemotherapy
Clinical Trial Code	SACICUP
Background and hypothesis	The outcome of 2nd or further line chemotherapy in unfavorable CUP is poor. The study tests the hypothesis that SG improves outcome as compared to standard chemotherapy in this group.
Primary Objective and Endpoint	Progression-free survival (PFS) of SG versus chemotherapy arm
Main Secondary Objectives and Endpoints	• Overall survival (OS), Overall response rate (ORR), Duration of clinical benefit (DCB) • Patient reported outcomes (Quality of life, Pat. reported AEs) • Safety
Trial Design	Controlled, open; randomized, cross over, multi-center; national trial with a post-treatment observation period duration of trial per participant: depending on time of inclusion 24 to 48 months
Sample Size	To be screened: 150 To be enrolled: 100 To be analyzed: 100
Clinical Trial Population	Key Inclusion Criteria: • Age ≥ 18 years • ECOG performance status of 0-2 • unfavorable CUP diagnosed according the 2023 ESMO Clinical Practice Guidelines for CUP, adeno-, squamous cell and undifferentiated histology allowed • at least one measurable lesion according to RECIST • disease relapse or progression after at least three cycles of a platinum-based standard chemotherapy • recovery from active infections and prior relevant toxicities • adequate hematologic, hepatic and renal function Key Exclusion Criteria • favorable CUP subsets according to ESMO guidelines • prior therapy with topoisomerase inhibitors (e.g. irinotecan) • active brain metastsases or leptomeningeal disease • significant cardiovascular disease • active hepatits or HIV infection • pregnancy or breastfeeding
Interventions and Treatments	Participants will be randomized in a 1:1 ratio between the experimental arm (SG) and the arm with chemotherapy according to investigator´s choice. The regimen for SG is 10mg/kg body weight on day 1,8 of a three-weekly cycle.

	The following chemotherapy compounds are standard of care and therefore classified as AxMPs and used for investigator´s choice: carboplatin / paclitaxel, carboplatin / docetaxel, cisplatin / gemcitabine, carboplatin / gemcitabine, gemcitabine as well as oxaliplatin / 5-FU. Restaging with CT or MRI is performed at 3-monthintervals during routine check-ups. At progression, participants randomized to the investigator´s choice chemotherapy arm may cross-over to the SG arm, if they are still eligible. Administration of SG or chemotherapy according to investigator's choice is possible for until twelve months after the randomization of the last participant. The last SG cross-over participant can be treated additionally for a maximum of twelve months.
Ethical Considerations	Patients with relapsed / refractory unfavorable CUP have poor outcomes on currently available treatments and, hence, have a high unmet medical need for new therapeutic approaches. SG is an antibody-drug conjugate composed of a humanized anti-Trop-2 IgG antibody conjugated to SN-38, the topoisomerase I-inhibitory active component of irinotecan. SG displays therapeutic benefit across a broad spectrum of carcinoma entities; this pan-carcinoma efficacy makes SG a promising compound for the treatment of CUP. In view of the rationale for using Sacituzumab govitecan in participants with CUP a favorable benefit/risk proposition exists to support the conduct of this study. The safety profile for SG is well established from other cancer entities.
Number of Sites	11