Protocol summary

Title of the Study	Stereotactic body radiotherapy in addition to standard of care treatment in patients with rare oligometastatic cancers (OligoRARE): a randomized, phase 3, open-label trial

Objective(s)	The primary objective of this trial is to assess if the addition of stereotactic body radiotherapy (SBRT) to standard of care treatment improves overall survival (OS) as compared to standard of care treatment alone in patients with rare oligometastatic cancers.
	
	Secondary objectives:
	• To assess the toxicity profile of radiation treatment (SBRT and/or palliative radiotherapy (RT) in patients with rare oligometastatic cancers
	• To determine if the addition of SBRT improves
	  • progression-free survival
	  • disease-specific survival
	  • time to disease progression
	  • time to development of new metastatic lesions
	  • time to development of polymetastatic disease of these patients
	  • time to progression in oligometastatic lesions initially present at randomization
	• To assess the impact of the addition of SBRT on the health related quality of life of the patients measured by the EORTC-QLQ-C30 and EQ-5D-5L questionnaires

Methodology	This is a randomized open-label multicentre Phase III superiority study of the effect of adding SBRT to the standard of care treatment on overall survival in patients with rare oligometastatic cancers. Patients will be randomized in a 1:1 ratio between current standard of care treatment vs. standard of care treatment + SBRT to all sites of known metastatic disease. Randomization is conducted using a dynamic allocation approach with stratification factors: country, number of oligometastases (1-3 versus 4-5), disease-free interval (≤ 2 years versus > 2 years) and type of pre-specified systemic therapy (immunotherapy/targeted therapy/hormone therapy versus cytotoxic therapy versus observation) Three safety reviews (after 25%, 50% and 75% of accrual) by the independent data monitoring committee (IDMC) are planned in this study. At the third safety review, an optional futility interim look of the primary endpoint will be implemented. This interim look will only be triggered if at the time of the third safety review the predicted study duration based on the actual accrual, drop-out and overall death rates

	observed so far results in a markedly increased study duration as compared to the originally planned study duration of 7.8 years
Number of patients Number planned (Statistical design)	200 patients in total The study is sized to detect a hazard ratio (HR) of 0.65 with a 1-sided significance level of 0.05 and 80% power. Assuming a 5-year OS rate of 20% in the standard arm, this corresponds to an increase of 15% in the 5-year OS rate in the experimental arm. A total of 134 deaths (OS events) are needed to be observed for the statistical test to meet the above requirements. Anticipating that a total of 200 patients will enter the study in 5.5 years, 134 deaths are expected to have occurred 7.8 years after first patient in (total study duration) if the target treatment effect is true or earlier if the null hypothesis is true.
Number analysed	200 in total (intention-to-treat population)

Diagnosis and main criteria for inclusion	**Inclusion criteria**
	• Histologically confirmed malignancy with metastatic disease detected on imaging. Biopsy of metastasis is preferred, but not required
	• Controlled primary tumour, defined as:
	  • at least 3 months since original tumour treated definitively, with no progression at primary site
	• Total number of oligometastases of 1-5 including:
	  • Brain metastases amenable to radiosurgery or fractionated stereotactic radiotherapy (patient who had neurosurgical resection before trial inclusion are allowed and resected brain metastases count to the total number of oligometastases)
	• All sites of disease can be safely treated based on the judgement of an experienced radiation oncologist
	• ECOG score 0-2
	• Life expectancy > 6 months
	
	Exclusion criteria
	• Primary cancer of prostate, breast, lung or colorectal
	• Serious medical comorbidities precluding radiotherapy
	• Substantial overlap with a previously treated radiation volume
	• Brain metastases only, without extra-cerebral metastases
	• Malignant pleural effusion, malignant ascites, meningeal carcinomatosis and peritoneal carcinomatosis
	• Maximum size of 6 cm for lesions outside the brain, except:
	  • Bone metastases over 5 cm may be included, if in the opinion of the local radiation oncologist it can be treated safely (e.g. rib, scapula, pelvis)

Treatment Test product, dose and mode of administration Duration of treatment	The experimental arm consists of SBRT (and standard of care systemic therapy). Each lesion may be treated with 1, 3, or 5 SBRT fractions of 16-24 Gy, 24-33 Gy or 25-40 Gy, respectively, depending on the local practice and size & location of oligometastases. Three-fraction regimens will deliver a fraction every second day, and five-fraction regimens are delivered daily. All treatments must be completed within 2 weeks (10 working days) in order to avoid delays in starting systemic therapy. Patients treated with prior or concomitant systemic therapy are eligible for this study. Use of chemotherapy regimens, targeted therapy or immunotherapy containing potent enhancers of radiation damage (e.g. gemcitabine, doxorubicin) can be postponed or interrupted for a duration of one month after radiation.
Reference therapy, dose and mode of administration	Radiotherapy for patients in the standard arm should follow the principles of palliative radiotherapy. Recommended dose fractionations in this arm will include 8 Gy in 1 fractions, 20 Gy in 5 fractions, and 30 Gy in 10 fractions. Systemic therapy will be pre-specified based on the standard of care approach for that patient, and it may include cytotoxic, targeted, hormonal, immunotherapy or observation.
Criteria for evaluation Efficacy	 The primary efficacy endpoint is overall survival. Overall survival is defined as the time interval from the date of randomization to the date of death whatever the cause of death. Patients who are alive are censored at the last date known to be alive. Secondary efficacy endpoints: • Progression-free survival • Disease-specific survival • Time to disease progression • Time to development of polymetastatic disease • Time to development of new metastatic lesions • Time to progression in oligometastatic lesions initially present at randomization
Safety	Adverse events graded according to the National Cancer Institute Common Terminology Criteria for adverse events (NCI-CTCAE) version 5.0
Patient reported outcome	Health-related quality of life evaluated using self-administered EORTC QLQ-C30 and EQ-5D-5L questionnaires

Statistical methods	The analysis of all efficacy endpoints will be performed in the intention-to-treat population. All analyses are performed at the 1-sided 5% significance level and confidence intervals (CI) are 2-sided at the 90% confidence level. Overall survival and progression-free survival will be described using Kaplan-Meier curves in the two treatment arms. The median survival time and its associated nonparametric confidence interval will be calculated. The treatment effect hazard ratio (HR) with its CI is estimated using an adjusted Cox regression model, adjusted by the stratification factors used at randomization: number of oligometastases, disease-free interval, and systemic therapy (except country). The Wald test from the Cox model will be used to assess the statistical significance of the treatment effect. The proportionality of the hazards between the two treatment arms will be assessed using the graphical and numerical methods proposed by Lin, Wei and Ying. Disease-specific survival, time to disease progression, time to development of new metastatic lesions, time to development of polymetastatic disease and time to progression in oligometastatic lesions initially present at randomization that are subject to competing risks are analysed by means of a Fine-and-Gray model adjusted for the stratification factors used at randomization (except country). The hazard ratios with their CI will be estimated. The cumulative incidence function will be estimated by the Aalen-Johansen estimator. The analysis of the toxicity related to RT will be performed in the safety population.
Quality of Life	Health related quality of life is an important secondary endpoint. The main objective is to describe the impact of the addition of SBRT on the health related quality of life of patients. Two validated questionnaires will be used in this trial: the EORTC QLQ-C30 and the EQ-5D-5L. Together, these two questionnaires present 36 questions to the patients.