**Annex. CIRT administration details**

**Simulation CT**

Before the Radiation treatment the patient will receive a CT simulation aimed to obtain images of the target lesion to be irradiated. Each patient will be immobilized by a thermoplastic mask in treatment position on a flat table. CT will be carried out in the same conditions of position and immobilization of the patient of each session of treatment.

A volumetric treatment planning CT study will be required to define gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV).

Contiguous CT slices, having 3 mm thickness are required through the region harboring the region of interest (gross tumor and adjacent slices that are within the path of non-coplanar beams or containing critical structures).

The GTV, CTV, PTV and normal organs will be outlined on all appropriate CT cross-sectional slices. Based on the location of the target lesionthe need of Intravenous (IV) contrast during the planning CT will be evaluated case by case. If contrast is used, the contrast scan must be registered to a non-contrast scan for planning purposes.

In case of patients with thoraco-abdominal tumour(s) moving targets (i.e. hepatic or lung lesions), simulation 4DCT data will be acquired specifically. 4DCT will be acquired without contrast agent to provide necessary data for treatment planning and when needed with contrast agent, in order to better delineate the tumor. The patient will be positioned on the CT couch: a custom rigid cushion (CIVCO AccuForm, USA) is molded below the patient and a semi-rigid mask of thermoplastic material is tightly shaped on the body surface. This guarantees patient immobilization and thoraco-abdominal compression during imaging and irradiation, while allowing a limited displacement for volume variations caused by breathing. The 4DCT will be acquired by means of a Siemens SOMATOM Sensation Open CT scanner and retrospectively sorted using a pressure sensor (ANZAI AZ-733V), which is placed between the patient’s skin and the mask. After image acquisition, the 4D reconstruction is performed by the medical physicist through the scanner software. The following volumes are usually reconstructed: the end-exhale respiratory phase (0 ex), used for treatment plan optimization; two phases representing adjacent and symmetrical respiratory phases with respect to end-exhale during breath out and breath in, ideally in correspondence of gating window start and end end-inhale phase, needed for the assessment of the total range of motion.

**Target Volumes /OAR/ Treatment Planning/Treatment Delivery**

**Target Volumes**: The definition of volumes will be in accordance with the ICRU 62 report.

(ICRU Report 62. Prescribing, Recording, and Reporting Photon Beam Therapy (Supplement to ICRU Report 50). International Commission on Radiation Units and Measurements. 1999).

**GTV:** The Gross Tumor Volume consists of the selected metastatic lesion suitable for the intent of the study (see inclusion criteria).

**CTV:**Clinical Target Volume is defined as the GTV plus a 0.3-0.5 cm margins to account for microscopic tumor extension.

**ITV**:Internal Target Volume is defined (in case of moving target) as the union of the CTV volumes contoured on each 4D CT data set and includes the envelope that encompasses the tumor motion for a complete respiratory cycle.

**PTV:**PTV consists of CTV + Setup margin + Tumor motion margins (in case of moving target)

*4D CT Approach (Required Tumor Volumes: GTV, ITV, PTV)*

*Normal Anatomy (i.e. organs at risk) has to be defined on Treatment-Planning CT Images.*

**Prescription dose, Fractionation and dose constraints**

Doses of carbon ion are expressed in photon equivalent doses, defined as the physical doses multiplied by the relative biologic effectiveness of the carbon ions. Patients will receive CIRT at the 24 Gy [RBE], 8 Gy RBE/fraction, prescribed to the PTV. Treatment will be carried out in 3 consecutive fractions. The dose limits for critical organs are derived from the clinical experience of NIRS. As a precaution, these limits are not converted from the Japanese model to the LEM model. This leads to a greater saving of about 10% of the dose, these more restrictive limits are theoretically possible thanks to the greater spatial precision in depositing the dose of the active scan system.

The dose constraints for OAR used are listed :

* Spinal cord: Dmax 30 Gy [RBE]
* Stomach and small bowel: Dmax 38 Gy [RBE], D5cc < 36 Gy [RBE] 310
* Liver: V18Gy < 700 cc
* Kidney: Dmean < 15 Gy [RBE]
* Lung: V20 Gy RBE <30%

**Total duration of treatment**

The expected duration of treatment is 3 consecutive days. Treatments longer than 5 total days will not be considered suitable for the final analysis of data.

**Treatment Planning**

CIRT treatment plans will be optimized with the Raystation Treatment Planning (Raysearch Medical Systems) on the simulation CT scan.

In case of moving target treatment plan will be optimized on the 4D CT acquisition corresponding to the maximum expiration phase (0 ex) and it will be delivered using respiratory gating and rescanning methodology to further minimize uncertainties due to movement.

**Technical Factors**

Beam Energy ranging between 115-400 MeV/u will be used.

Beam Shaping: spot scanning technique.