HITRI plus
Heavy Ion Therapy Research Integration

CNAO trials

ESTER ORLANDI

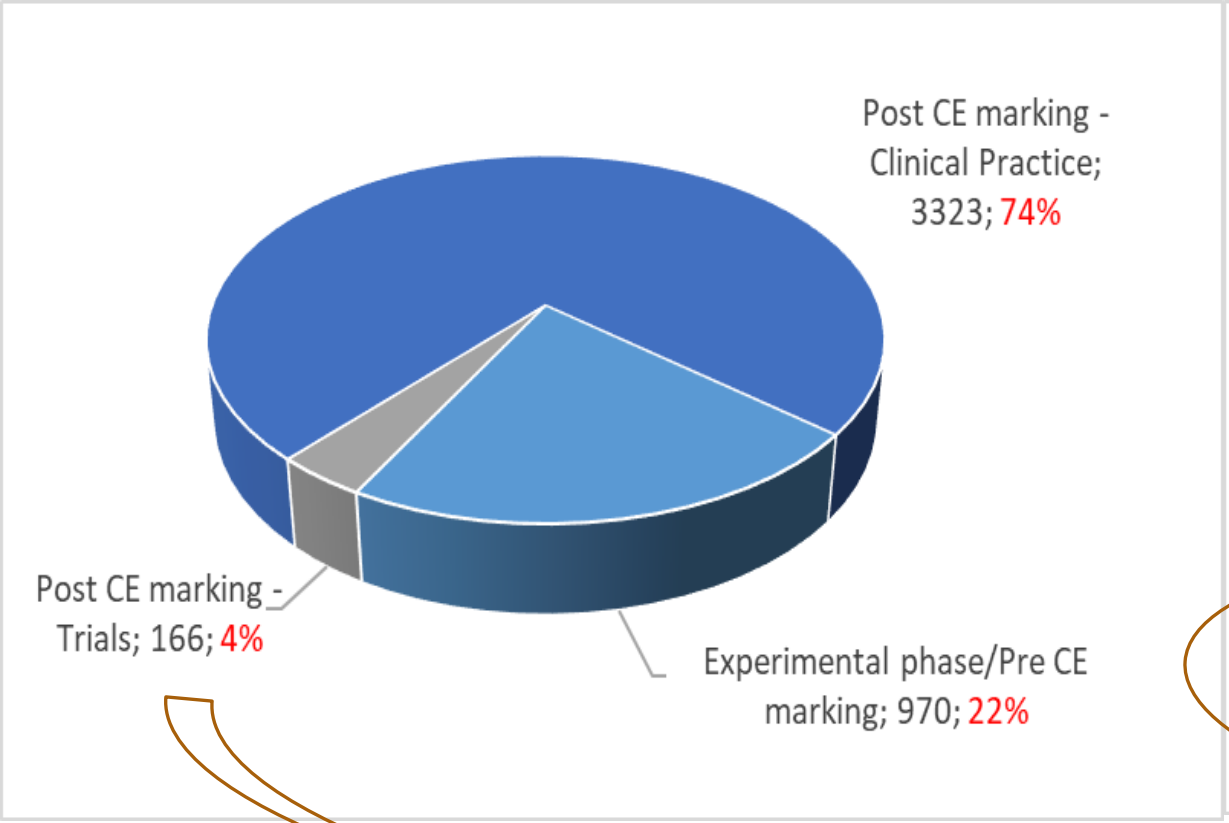
RADIOTHERAPY CLINICAL DEPARTMENT

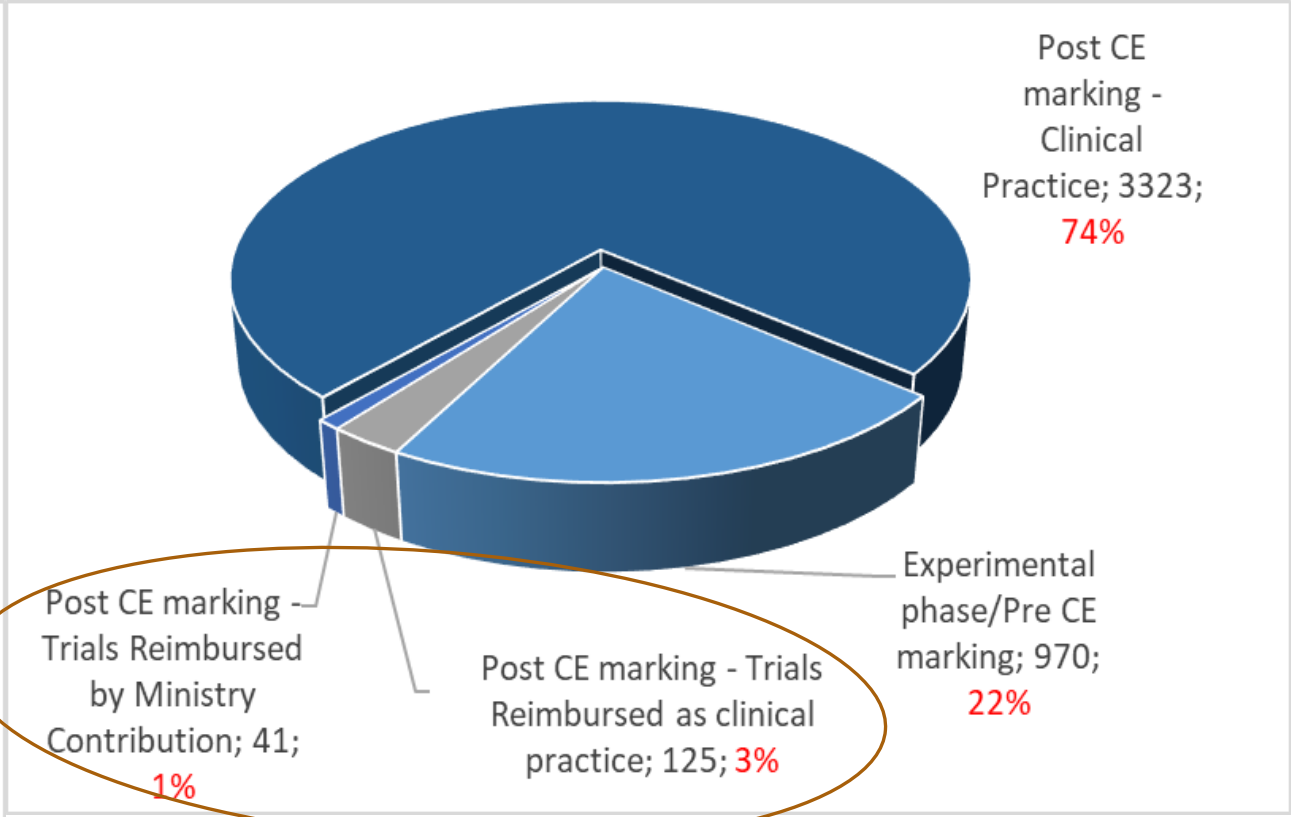
ITALIAN NATIONAL CENTER FOR ONCOLOGICAL HADRONTHERAPY, PAVIA, ITALY

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Phase	Total	Carbon Ion	Proton
Experimental phase/Pre CE marking	970	730	240
Post CE marking - Trials	166	151	15
Post CE marking - Clinical Practice	3323	1417	1906
	4.459	2.298	2.161

Phase	Total	Carbon Ion	Proton
Experimental phase/Pre CE marking	970	730	240
Post CE marking - Trials Reimbursed as clinical practice	125	110	15
Post CE marking - Trials Reimbursed by Ministry Contribution	41	41	0
Post CE marking - Clinical Practice	3323	1417	1906
	4.459	2.298	2.161





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The clinical research @ CNAO: main topics

- ✓ To collect real world data of patients treated with particles.
- ✓ To assess the effectiveness and safety of CIRT in selected gynecological tumors.
- ✓ To compare surgery and CIRT in selected sarcoma.
- ✓ To clinically test a simoultaneously integrated boost with CIRT in selected HN scenarios.
- ✓ To combine CIRT/PT and immunotherapy.
- ✓ To search predictive biomarkers for outcome and tox following particle therapy.
- ✓ To prospectively longitudinally assess QOL and financial tox in patients managed with particles.
- ✓ to assess the effectiveness and safety of de-escalating elective nodal volume with protons in nasopharyngeal cancer patients.

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CNAO registry – REGAL (NCT05203250)

RECRUITING

Study Design	This is a **longitudinal registry** which will include both retrospective and prospective collection of clinical data derived from diagnostic tests and treatments performed by CNAO for patient management. Only data available from routine clinical practice will be collected. Intervention is not assigned.
Promotor	CNAO
Objectives	**Primary objective:** **To collect real world data of patients** treated with radiotherapy, to support **particle radiotherapy** and to provide evidence of the role of radiation oncology within the multidisciplinary approach. The retrospective enrollment takes into account all patients treated **from 2011 up today. The number of patients enrolled is not limited to a maximum.** **Secondary objectives:** • To analyze the disease course and treatment performed by collecting demographic, disease characteristics and delivered treatment • To collect details about the radiation treatment and radiobiological parameters to develop predictive models (outcome and toxicity) • To collect outcome data (in terms of overall survival, progression free-survival and local control) and to correlate them with the delivered treatment • To define acute, intermediate and late toxicities, according to CTCAE v 5.0 and to correlate it with the delivered treatment • To collect data on standardized QoL questionnaires and PROMS (e,g EORTC C30, EQDL) at 6, 12. 18, 24, 36 months and to correlate them with the delivered treatment • To generate hypotheses for further research

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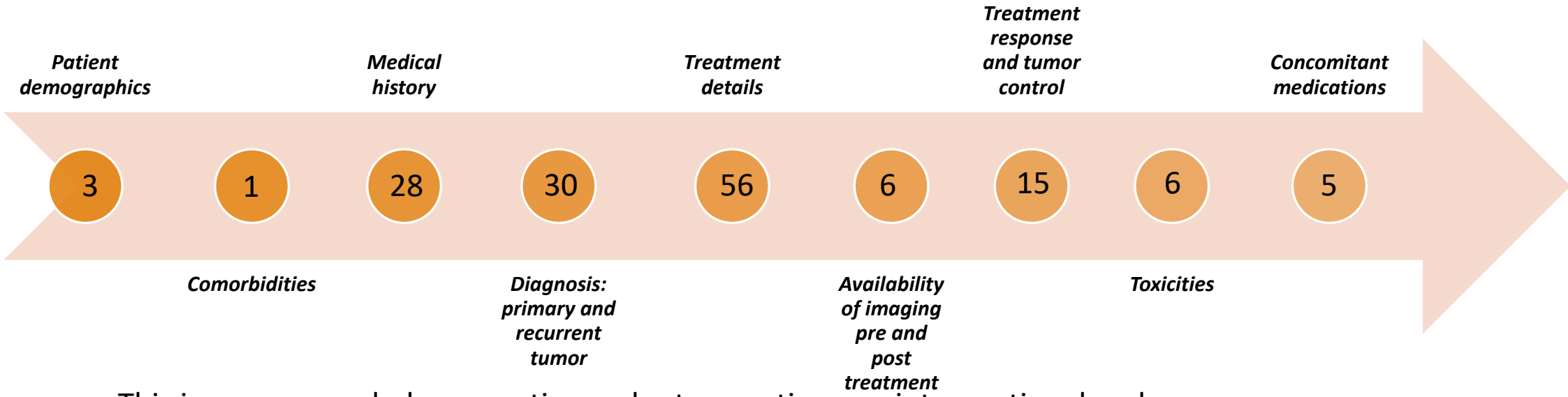
NUMBER OF FIELDS IN REGAL



This is an open ended prospective and retrospective non interventional and non-therapeutic multicohort study. The retrospective enrollment takes into account all patients treated from 2011 up today.
The number of patients enrolled is not limited to a maximum.

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FIELDS IN REGAL

Data Collection Instrument	Baseline	+ Add new Primary Tumor ,	+ Add new Recurrent Tumor ,	+ Add new Follow-up	CTCAE	Concomitant medications
First visit	●					
Comorbidities	○					
Previous cancer	○					
Diagnosis		○	○			
Staging		○	○			
Surgery		○	○			
Systemic treatments		○	○			
Radiotherapy		○	○			
Imaging		○	○			
Follow-up				○		
Patient Status				○		
CTCAE					○	
Concomitant medications						○

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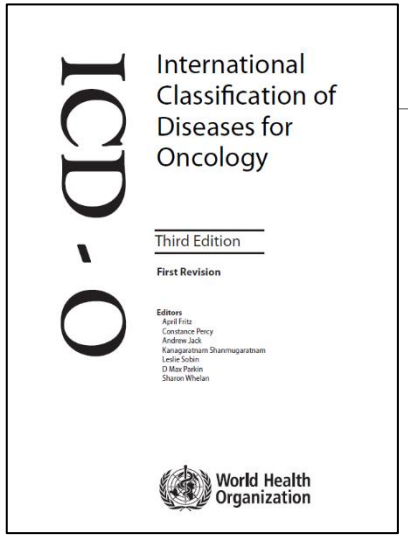
This project has
research and in

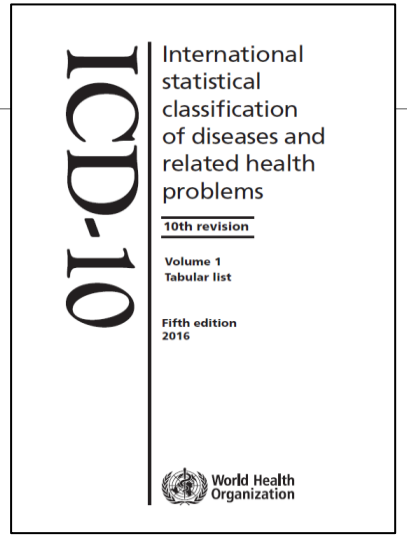
REDCap
Research Electronic Data Capture

n's Horizon 2020
nt No 101008548

SEMANTICS IN REGAL



Histology and Topography



Diagnosis

Toxicities

MedDRA Medical Dictionary for Regulatory Activities

Comorbidities

World Health Organization

Anatomical Therapeutic Chemical (ATC) Classification

Concomitant Medications

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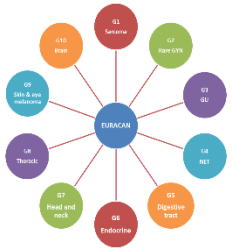
NATIONAL AND INTERNATIONAL REGISTRIES

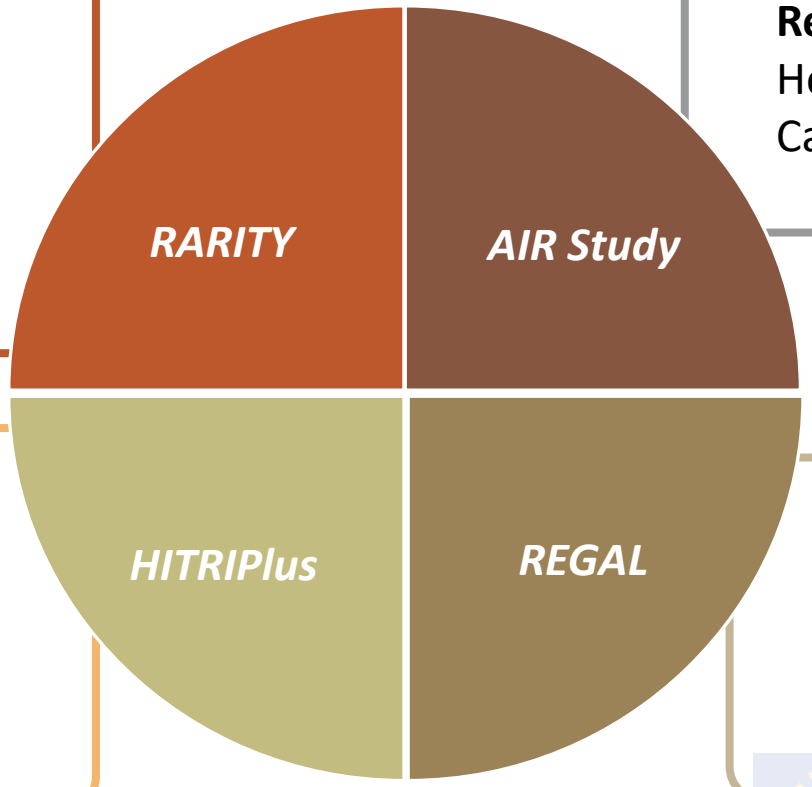
Registry of the European **R**eference **N**etwork on Rare Adult Solid Cancer "EURACAN"

European Reference Network
for rare or low prevalence complex diseases
Network Adult Cancers (ERN EURACAN)



AIOCC **I**talian **Re**gistry on Head and Neck Carcinoma

AIOCC - IHNS
Associazione Italiana Oncologia Cervico Cefalica



Heavy **I**on **T**herapy **R**esearch **I**ntegration plus

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CNAO **REG**istry Tri**AL**

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Carbon ion radiation therapy in the treatment of mucosal melanomas of the female lower genital tract (CYCLE, NCT05478876)

RECRUITING

Study Design	Monocentric, prospective phase II study
Promotor	CNAO
Endpoints	**The primary endpoint** of the study is to estimate **2-year PFS** in patients diagnosed with mucosal melanoma of the lower genital tract, treated with carbon ion radiation therapy. **Secondary endpoints:** •Overall survival (OS) •Toxicity according to Common Terminology Criteria for Adverse Events (CTCAE version 5.0) •Objective response rate (ORR) according to RECIST •Evaluation of the association between the clinical-radiological response at 6 weeks and the late response (> 6 months) •Quality of life.
Treatment	CIRT: The low-dose CTV will receive a total dose of 43 GyRBE in 10 fractions, 4 fractions per week. The high-dose CTV will receive a total dose of 68.8 GyRBE in 16 fractions, 4 fractions/week
Statistical Considerations	Fleming one stage design

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Inclusion Criteria	• **Histological diagnosis** • **N +** (only if confined to the groin and pelvis) • Age > **80 years** • ECOG 0-2 • **No evidence of metastasis** • At least **3 mm away with rectum and bladder wall** • **No previous RT** • Written informed consent • Patient's ability to understand the characteristics and consequences of the clinical trial • **Molecular characterization/ mutational state** • Disease staging (baseline exams)
Exclusion criteria	• Hip prosthesis, or metal prostheses or any other condition that prevents adequate imaging to identify the target volume and calculate the dose in the treatment plan • Psychic or other disorders that may prevent informed consent • Previous invasive tumor unless patient has been disease free for at least 3 years • **Contraindication to MRI** • Pregnancy or breastfeeding in progress

Enrolled patients: 5 (sample size: 9 patients)

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Phase II clinical study on the re-irradiation of lateral pelvic recurrences of gynecological malignancies (CYCLOPS, NCT05457595)

RECRUITING

Study Design	Monocentric, prospective phase II study
Study Population	Patients affected by pelvic recurrence of gynecological neoplasia, already undergone to radiotherapy on pelvis, will be enrolled in the study.
Treatment	PTV will receive a total dose of 48-52.8 GyRBE in 12 fractions, 4 fractions per week. Treatment expected duration is 3 weeks, 4 fractions per week.
Statistical Considerations	Fleming one stage design
Aims	Primary endpoint: 1-year local control (LC) Secondary endpoints: • Overall survival (OS) • Toxicity according to Common Terminology Criteria for Adverse Events (CTCAE version 5.0) • Symptoms control, evaluating pain reduction (screened by NRS scale) and variation in the use of analgesic drugs (decrease or increase) • Subgroup success rate analysis with stratification according to: Histology (adenocarcinoma vs squamo-cellular)

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Inclusion Criteria

- Patients ≥ 18 years of age
- Karnofsky Index ≥ 70
- **Histological or radiological diagnosis** of pelvic recurrence
- **Contraindications for radical surgery**
- No other distant progression or stable disease (SD) of known secondarisms (≥6 months)
- Previous radiation therapy on pelvis
- Distance ≥ 10 mm between tumour and close intestinal tract (small intestine), radiologically evaluated
- **Possibility to perform a surgery to space the intestinal loops, in case of distance < 10mm**
- If needed, **spacer** in biocompatible material (silicon, goretex) or anatomical material (omentum, muscle patch), **non-absorbable.**
- DICOM images of the previous treatment plan availability

Exclusion criteria

- prosthesis, metal prostheses or any other condition that prevents adequate imaging to identify the target volume and calculate the dose in the treatment plan
- **Intestinal infiltration**
- **Bladder infiltration**
- **Vessel infiltration**
- Previous therapy with **anti-angiogenesis drugs**
- Psychic or other disorders that may prevent informed consent
- Previous invasive tumor, with the exception of skin cancer (excluding melanoma) unless disease-free for at least 3 years
- **Spacer in absorbable material (i.e. vycril)**
- Distance < 10 mm between tumour and close intestinal tract (small intestine), radiologically evaluated
- Impossibility to assess MRI

Enrolled patients: 5 (sample size: 55 patients); Ongoing emendament with inclusion criteria changes (oligoprogrssive disease not only in the plevis or in re-irratition setting) in order to improve the accrual)

A technical framework for combining multi-parametric imaging with advanced modelling in personalized radiotherapy (AIRC IG 2020 – n. 24946)

RECRUITING

Study Design	The study design consists of the retrospective collection of routinely-acquired data (CT, MRI and dose maps, along with relevant clinical information) and the prospective acquisition of optimized non-invasive MR imaging data, of **skull-based chordoma** patients treated with particle therapy (PT) at the National Center for Oncological Hadrontherapy (CNAO, Pavia, Italy).
Promotor	CNAO and Politecnico di Milano
Objectives	**Primary objective:** A1. Derive imaging biomarkers for treatment outcome prediction, by discriminating between respondent vs. non-respondent patients undergoing PT. This will allow supporting clinical decision, along with the personalization and optimization of PT, tumour characterization and patients' stratification **Secondary objectives:** B1. Derive personalized TCP and NTCP models relying on imaging biomarkers from A1, coupled with dosimetric parameters and clinical information. B2. Derive microstructural biomarkers able to describe tumour microstructure in patients' undergoing PT, thus allowing a better understanding of radiation-tissue interaction.

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Inclusion Criteria	• Patients with histologically confirmed diagnosis of chordoma of the skull base • Particle therapy with curative intent • Karnofsky Performance status greater than or equal to 60 • Patients with macroscopic disease detectable at pre-radiotherapy imaging • Patients undergoing PT with standardized treatment procedures • Patients who have signed the written informed consent for research • Patients ≥ 18 years old
Exclusion criteria	• Metastatic disease • Palliative treatment • Other malignancies with disease-free interval < 5 years (excepting pre- cancerous lesions) • Pregnancy • Simultaneous CHT or Immunotherapy • Extensive metal instrumentation/implants • Patients with autoimmune diseases (ADs) -including collagen-vascular (CVD) and inflammatory bowel (IBD).

Enrolled patients: 8 (simple size for the prospective study: 35 patients; for retrospective cohorts 150 patients

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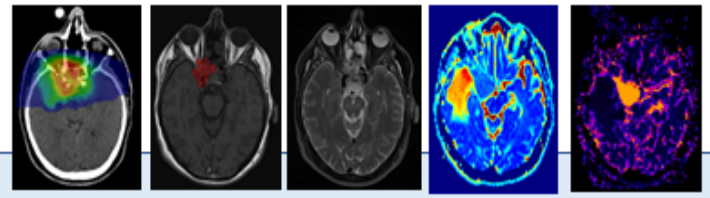
Radiomics, Dosiomic …

strategies for individual treatment optimization and outcome prediction (Collaboraboration with PoliMi)

AIRC IG-2020 n. 24946
PI: Prof. Baroni G.



CT + dose maps
Anatomical MRI (T1-w, T2-w)
Quantitative MRI (DWI, PWI,…)

Technical framework

MULTI-PARAMETRIC IMAGING

PRE-PROCESSING
image segmentation, intensity normalization, …

FEATURE EXTRACTION
Radiomics, Dosiomics, candidate features, biomarkers, …

MACRO
modelling of properties at the MACRO level (e.g. DWI, PWI,…)

MICRO
modelling of properties at the MICRO level (e.g. cellularity)

MACHINE LEARNING-BASED MODELS

KNOWLEDGE-BASED RADIOBIOLOGICAL / STRUCTURAL MODELS
Tumour control probability (TCP), NTCP, microstructural model, …

VALIDATION

TECHNICAL

BIOLOGICAL – CLINICAL

Immune checkpoint inhibitors and Carbon iON radiotherapy In solid Cancers with stable disease (ICONIC, NCT05229614)

RECRUITING

Study Design	Non-randomized, open label, single arm, phase II clinical trial
Promotor	CNAO
Objectives	**Primary objective:** to estimate the effect, in terms of clinical response, of immunotherapy associating carbon ion treatment in the palliative setting across different malignancies, for which immunotherapy is currently the standard of care. **Secondary objectives:** 1. to describe the safety profile of the association of carbon ion radiation therapy and systemic immunotherapy in the palliative setting across different malignancies, for which immunotherapy is currently the standard of care; 2. to estimate the effect, in terms of survival, of immunotherapy with the association of carbon ion radiation treatment in the palliative setting across different

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Enrolled patients: 2/27

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Inclusion Criteria	• Histologically-proven primary head and neck ACC; • unresectable stage or residual macroscopic disease after surgery or multiple microscopic margins after surgery; • patient with resectable tumor but refusing surgery • cN0/pN0 – cN1/pN1 patients (only ipsilateral neck levels I and II) • Absence of distant metastases or oligometastatic status (patients with ≤ 3 metastatic lung or bone lesions, excluding other sites; • No previous radiotherapy in head and neck region; • Karnofsky Performance Status ≥ 70; • Age ≥ 18 years; • Written informed consent • Patients' ability to understand the characteristics and consequences of the clinical trial.
Exclusion criteria	• local conditions contraindicating CIRT (e.g., active infection or previous history of recurrent infections in or close to the tumour site; intratumoral necrosis in strict proximity of vessels; pre-existing skin, bone or soft tissue fistula; extended mucosal involvement by the tumor; previous surgery with flap reconstruction); • tumor site in nasopharynx, pharynx and tongue base (where an exclusive CIRT treatment could be at high risk of toxicity); • tumor disease involving ≥ 50% of the palate with consequent high risks of serious anatomical damage in case of significant and rapid disease response to CIRT • nodal involvement > cN1/pN1 or cN1/pN1 outside ipsilateral levels I and II • tumor surrounding carotid artery > 180° or infiltrating the vessels • Titanium surgical implants or metal prostheses or any other condition that prevents adequate imaging to identify the target volume and may determine uncertainties in CIRT dose distribution during treatment planning • Presence of any comorbidity deemed to impact on treatment toxicity; • Psychic or other disorders that may prevent informed consent • active autoimmune disease (e.g. systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis) • Contraindication to MRI • Pregnancy or breastfeeding in progress

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Inclusion Criteria	• Signed written informed consent • Histologic confirmation of malignancies under treatment with single agent anti-PD1/PDL1 immunotherapy per clinical practice (see cohort specific inclusion criteria) with immune checkpoint inhibitors approved by Italian national drug regulatory agencies (Agenzia Italiana del Farmaco, AIFA) • Having a disease stability as assessed by AIFA monitoring sheet • Presence of at least 2 measurable target lesions, of which at least one to be followed up as per RECIST and one suitable for CIRT • Willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study • Females and males, 18 years of age or older (no upper limit for age) • Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 • Subjects must have measurable disease by CT or MRI per RECIST 1.1
Cohort-specific inclusion criteria	*Melanoma* □ Drug: pembrolizumab (Keytruda) monotherapy □ Unresectable or metastatic melanoma □ Disease assessment = SD after 12 weeks from treatment start or later *NSCLC* □ Drug: pembrolizumab (Keytruda) monotherapy □ Locally advanced or metastatic NSCLC with TPS ≥ 1 % already treated with chemotherapy □ Untreated metastatic NSCLC with TPS ≥ 50 % □ Disease assessment = SD after 9 weeks from treatment start or later *HNSCC* □ Drug: pembrolizumab (Keytruda) monotherapy □ Untreated recurrent/metastatic HNSCC with CPS ≥ 1 □ Disease assessment = SD after 9 weeks from treatment start or later *Urothelial carcinoma* □ Drug: pembrolizumab (Keytruda) □ Locally advanced or metastatic urothelial carcinoma pre-treated with platinum-based chemotherapy □ Disease assessment = SD after 9 weeks from treatment start or later

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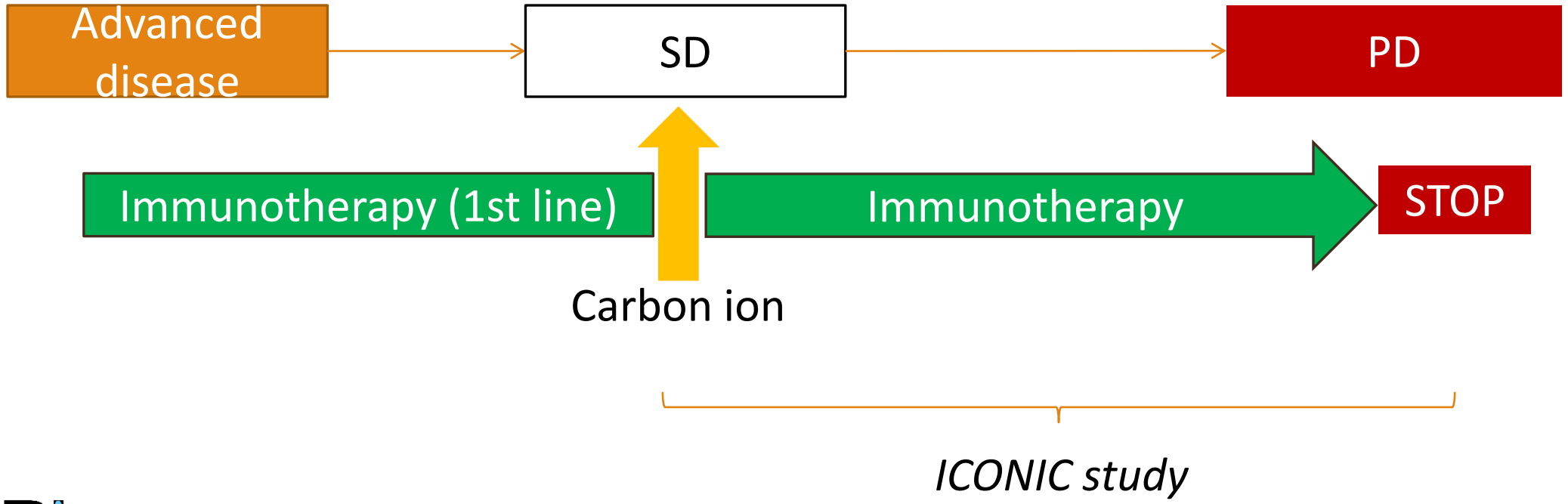
ICONIC: Study intervention



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Study intervention - CIRT

Hypofractionated carbon ion boost to one site of disease

Radiation to a single lesion:

- total dose of 24 Gy[RBE]
- 8 Gy[RBE]/fraction
- one fraction/day, for 3 days

According to radiobiological equivalence, based on the linear quadratic model, the proposed fraction size with CIRT is equivalent to 12 Gy/fraction, total prescription dose of 36 Gy with photon SBRT

The biological efficacy and safety of the proposed regimen is, in principle, comparable to a conservative fractionations, widely used in SBRT, for oligometastatic disease

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Study intervention - Immunotherapy

Inclusion of cancer pts:

Under treatment with pembrolizumab per clinical practice (AIFA)

If best response = SD after at least 9-12 weeks from pembro start

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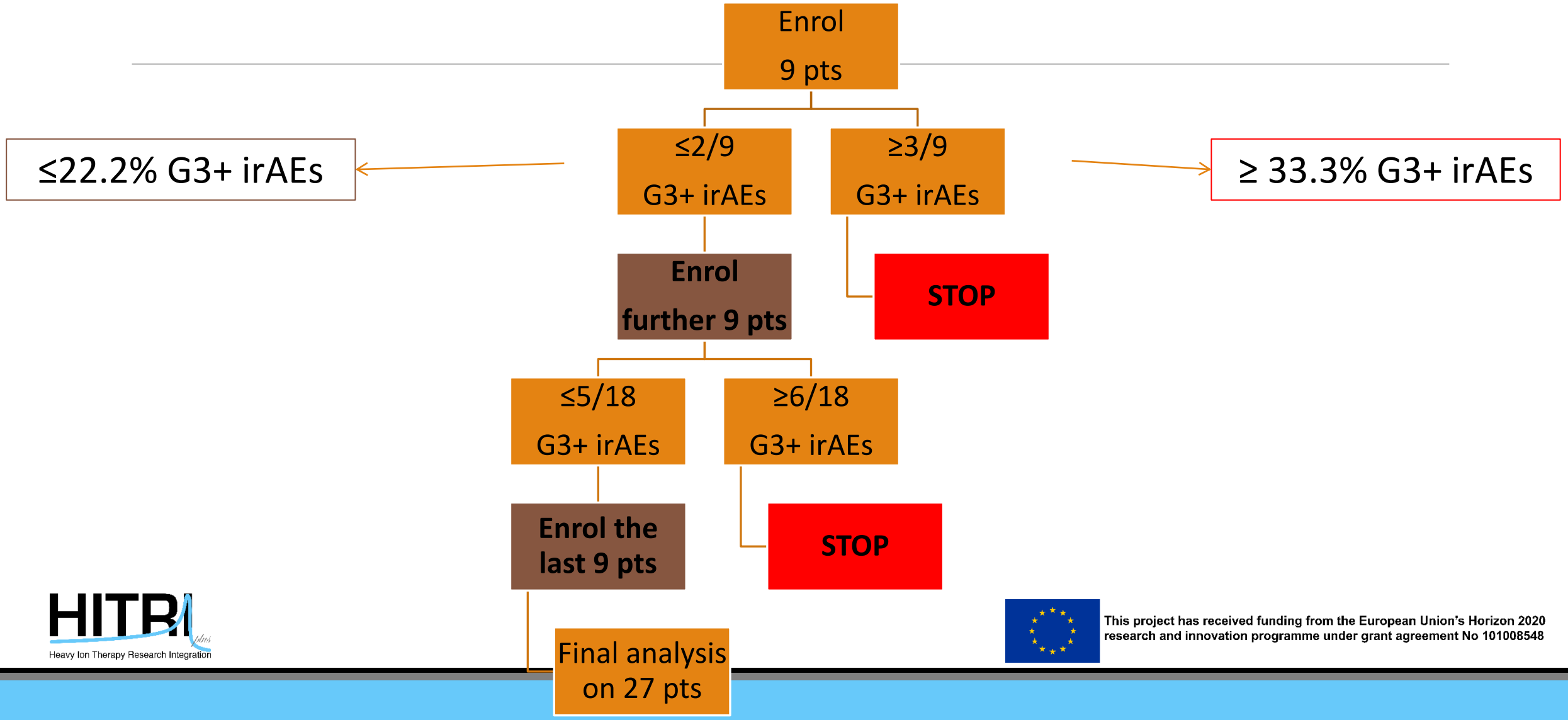
ICONIC - Safety run-in



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Health related quality of life (HRQoL) in patients with solid tumors treated with hadrontherapy (HadroQoL).

RECRUITING

Study Design	This is a mono-institutional, longitudinal prospective trial.
Promotor	CNAO
Endpoint	**Primary objective:** To assess QoL in subjects treated with curative hadrontherapy at different timepoints investigated by global score according to SF-12 and to compare it with SF-12 results in healthy population (cohort A and B) **Secondary objectives:** • to assess QoL in subjects treated with curative hadrontherapy at different timepoints investigated by global score according to EORTC QLQ-C30 and to compare it with EORTC QLQ-C30 results obtained from relevant literature in similar study population if available (cohort A and B). • to investigate QoL determinants in relation to clinical patients characteristics (age, gender, site of primary tumor), type of received radiation, prevalence of late toxicity recorded according to CTCAE scale v 5.0; (cohort A and B). • to investigate QoL determinants in relation to: 1. psychological variables (anxiety and depression according to HADS questionnaire, optimism, self-esteem, life satisfaction and coping according to BRIEF-cope questionnaire) (cohort A). 2. socio-cognitive factors (presence of caregiver and social support) (cohort A and B). 3. resilience according to Brief Resilient Copy Scale (BRCS) (cohort A and small sample of Cohort B). • to investigate feasibility and acceptability of pts study engagement by means of teleconsultation and ad hoc designed surveys (cohort A). • to explore financial toxicity through administration of PROFFIT questionnaire (cohort B). • to compare the QoL pre-treatment and 1 year after therapy in a patients' cohort (cohort B).

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Inclusion Criteria	Cohort A (“survivors”): • Patients with at least a follow up of 5 years with head and neck, skull base and brain tumors and no evidence of progressive disease. • Patients ≥ 18 years of age • The patient is able to give consent Cohort B: • Histological and/or radiological diagnosis of head and neck tumors • Patients candidate for curative intent hadrontherapy • Patients ≥ 18 years of age • The patient is able to give consent
Exclusion criteria	Cohort A (“survivors”): • Re-irradiation. • Second tumor. • Known cases of any psychiatric and neurological diseases leading to disability (eg, manic disorder, schizophrenia etc..), which could impair compilation of questionnaires or affect quality of life. Cohort B: • Re-irradiation. • Second tumor • Known cases of any psychiatric and neurological diseases leading to disability (eg, manic disorder, schizophrenia etc..), which could impair compilation of questionnaires or affect quality of life • Presence of diffuse metastasis

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Enrolled patients
- Cohort A: 12
- Cohort B: 7

For cohort A: about 80 patients with at least a 5 year follow up will be enrolled in two years from January 2023 to December 2025.
For cohort B: 100 patients will be enrolled from February 2023 to September 2024

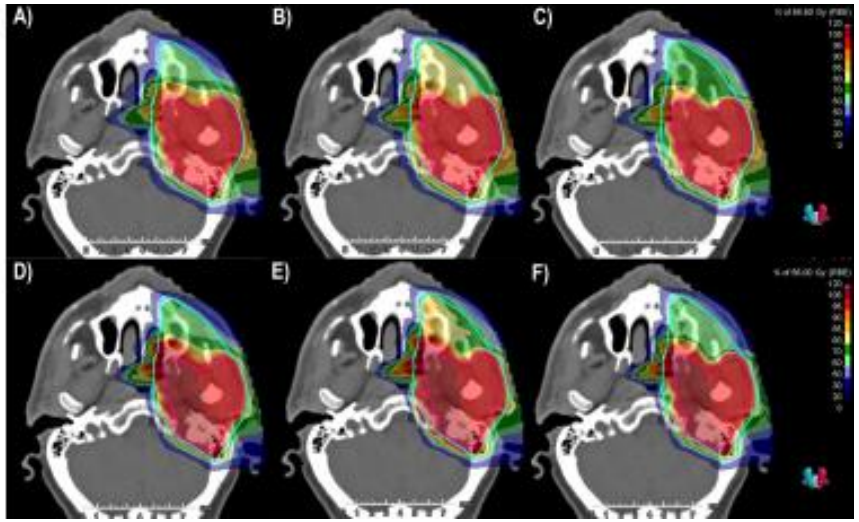
Carbon ion radiation therapy (CIRT), with a superior dose distribution and high relative biological effectiveness (RBE) compared to photons, showed in previous studies good efficacy and toxicity profile for Head and neck adenoid cystic carcinoma .

The CIRT standard planning approach is a sequential (SEQ) strategy:

first 9-10 fractions delivered to the low-risk clinical target volume (LR-CTV) followed by a boost of 6–7 fractions to the high risk CTV (HR-CTV) (unique nominal dose per fraction).

At CNAO (National Center for Oncological Hadrontherapy), we observed in silico that a CIRT Simultaneous integrated boost (SIB) strategy has superior conformality and homogeneity indexes compared to SEQ, reducing the unintended dose to the LR-CTV.

SEQ SIB 54.4 SIB 48



frontiers in Oncology

ORIGINAL RESEARCH
published: 13 December 2021
doi: 10.3389/fonc.2021.772580

In Silico Feasibility Study of Carbon Ion Radiotherapy With Simultaneous Integrated Boost for Head and Neck Adenoid Cystic Carcinoma

Edoardo Mastella[1], Silvia Molinelli[1], Giuseppe Magro[1], Stefania Russo[1], Maria Bonora[1], Sara Ronchi[1], Rossana Ingargiola[1], Alexandra D. Jensen[2,3], Mario Ciocca[1], Barbara Vischioni[1†] and Ester Orlandi[1†]*

Basing on these preliminary results, we built up a prospective clinical trial to investigate whether SIB in CIRT can significantly reduce toxicity without affecting Local Control (LC).

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Open to accrual

SIBACIRT: Simultaneous Integrated Boost (SIB) planning Approach in Carbon ion RadioTherapy for head and neck adenoid cystic carcinoma (NCT05733910)

INDAGA
project ID 3438215
funded by Fondazione Regionale per la Ricerca Biomedica, Regione Lombardia, call Unmet Medical Needs

Monocentric, single arm prospective phase II clinical trial

Study duration: 36 months

42 head and neck ACC patients (unresectable or after surgery)

CIRT with SIB approach
total dose to HR-CTV of 65.6 GyRBE in 16 fractions (4.1 GyRBE/fraction)
LR-CTV simultaneously receiving a total dose of 54.4 GyRBE (3.4 GyRBE/fraction) or 48 GyRBE (3 GyRBE/fraction) depending on different prognostic factors

Primary endpoint:
acute and subacute toxicity (within 180 days after the end of treatment) (CTCAE v5.0.)

Secondary endpoints:
1) Local Control (at least 12 months after starting of treatment)
2) development of multivariate predictive models, including clinical and dosimetric parameters, for different toxicity endpoints;
3) Quality of Life (EORTC QLQ C30 and QLQ 43 questionnaires assessed at baseline, at the end of treatment and every 6 months after the end of treatment)

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CNAO
Centro Nazionale di Adroterapia Oncologica

Fondazione Regionale per la Ricerca Biomedica

Regione Lombardia

ved funding from the European Union's Horizon 2020 on programme under grant agreement No 101008548

Inclusion criteria:

- Histologically-proven primary head and neck ACC;
- Unresectable stage/residual macroscopic disease after surgery/multiple microscopic margins after surgery
- Patient with resectable tumor but refusing surgery
- cN0/pN0 – cN1/pN1 (only ipsilateral neck levels I and II)
- cM0 or oligometastatic status (≤ 3 metastatic lung or bone lesions, excluding other sites)
- No previous RT in head and neck region;
- KPS ≥ 70;
- Age ≥ 18 years;
- Written informed consent
- Patients' ability to understand the characteristics and consequences of the clinical trial.

Exclusion criteria:

- Local conditions contraindicating CIRT (e.g., active infection/previous history of recurrent infections in/close to the tumor site/intratumoral necrosis in strict proximity of vessels; pre-existing skin, bone or soft tissue fistula; extended mucosal involvement by the tumor; previous surgery with flap reconstruction);
- Tumour site in nasopharynx, pharynx and tongue base (where an exclusive CIRT treatment could be at high risk of toxicity);
- Tumor disease involving ≥ 50% of the palate (high risks of serious anatomical damage in case of significant and rapid disease response)
- Nodal involvement > cN1/pN1 or cN1/pN1 outside ipsilateral levels I and II
- Tumor surrounding carotid artery > 180° or infiltrating the vessels
- Titanium surgical implants or metal prostheses (may determine uncertainties in CIRT dose distribution during treatment planning)
- Presence of any comorbidity deemed to impact on treatment toxicity;
- Psychic or other disorders that may prevent informed consent
- Active autoimmune disease
- Contraindication to MRI
- Pregnancy or breastfeeding in progress

SIBACIRT
INDAGA project ID 3438215
funded by Fondazione Regionale per la Ricerca Biomedica, Regione Lombardia,
call Unmet Medical Needs

A pilot study of Lower-Neck **S**paring **P**rot**O**n Therapy in **NA**sopharyngeal Carcinoma **P**atients with **U**ninvolved **N**ec**K** (SPONAPUNK):

To be submitted to EC

- **Promotore: CNAO ,Pilot multicenter AIRO study**

- To estimate the 2 year-regional free survival (RFS) with **IMPT de-escalated nodal volumes strategy** (upper neck irradiation, UNI of the uninvolved neck, omitting bilateral level IV and Vb) in a cohort of patients with NPC **staged as T1N0, T2N0 and T3 N0 (T1-3N0)** treated at CNAO.

- Benefit/risk ratio :
  - **reduction in toxicity**, without jeopardizing regional control. This benefit depends on the potentiality of protons to better spare normal tissues.
  - to provide **information about the safety and efficacy** of this experimental strategy.
  - If a patient experiences a **nodal failure during follow-up**, he will be effectively managed with neck dissection with low morbidity rate.

HITRI
Heavy Ion Therapy Research Integration

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Primary Endpoint

- To estimate the **2-year RFS rate** with IMPT de-escalated volumes strategy (UNI) in a cohort of patients with T1-T3 N0 NPC treated at CNAO compared to historical data from non-endemic area.

Secondary Endpoints

- **2y-local control** (LC) rate and **2y-distant failure free survival** (DFFS) and **2y-progression free survival** (PFS)
- **Pattern of nodal recurrence** in terms of nodal levels involved according to international guidelines (Biau J Radiotherapy Oncology, 2019)
- Longitudinally analyse changes **in safety and benefit on acute/late toxicity profile** (CTCAE version 5.0)
- **Quality of life** (EORTC QLQ- C30 and EORTC QLQ-H&N43 questionnaires from the beginning of therapy until 60 months after therapy completion)
- Longitudinally explore **significance of peripheral blood absolute counts**, including **lymphocyte count** from the beginning of therapy to the first follow-up, after completing RT, and its impact on the outcome.
- To investigate **imaging biomarkers** for primary **tumour microstructure characterization on MRI imges** and treatment outcome prediction in the proposed treatment framework
- To longitudinally analyse **patients' financial toxicity (FT)** following cancer diagnosis and treatment evaluated according to **Patient Reported Outcome for Fighting Financial Toxicity (PROFFIT**) questionnaire from the beginning of therapy until 60 months after therapy completion

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Simple size and Study Treatment Procedures

- 30 patients
- IMPT as a **curative setting** (**with or without** concomitant standard **chemotherapy**)

- IMPT will be planned according to **SIB strategy in 33 fractions** as follows:
  ***HR-CTV**: 70 GyE /2.12 GyE per fraction*
  ***LR-CTV**: 56.1 GyE/1.7 GyE per fraction*
  ***IR-CTV** (optional): 59.4 GyE/ 1.8 GyE per fraction*

- **Robust plan optimization** will be pursued. Treatment plans will be **re-calculated and re-optimized** with **variable RBE models** following an investigational in- silico approach.
- **Parameters describing target coverage, OAR dose and LET distributions** will be collected and correlated to treatment outcomes to evaluate the potential impact of RBE modelling on tumour control and tissue complication probabilities.

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Inclusion Criteria

- **Histologically confirmed** EBV unrelated or related NPC

- AJCC 8 th edition: Stage **T1-T3N0M0**
- Age **≥18 years old**
- Karnofsky Performance Status **≥ 70**
- **Suitable for radical treatment** (definitive IMPT with or without concomitant platinum -based CT)
- Available **blood chemistry** (including at least lymphocytes absolute counts and hemoglobin) before PT, at the end of PT, and at the first follow-up
- **Adequate cognitive ability** to complete QoL questionnaires
- **Willingness to comply with the protocol**, including travel to the proton centre for PBT treatment and undergoing required imaging procedures at CNAO
- Written **informed consent**

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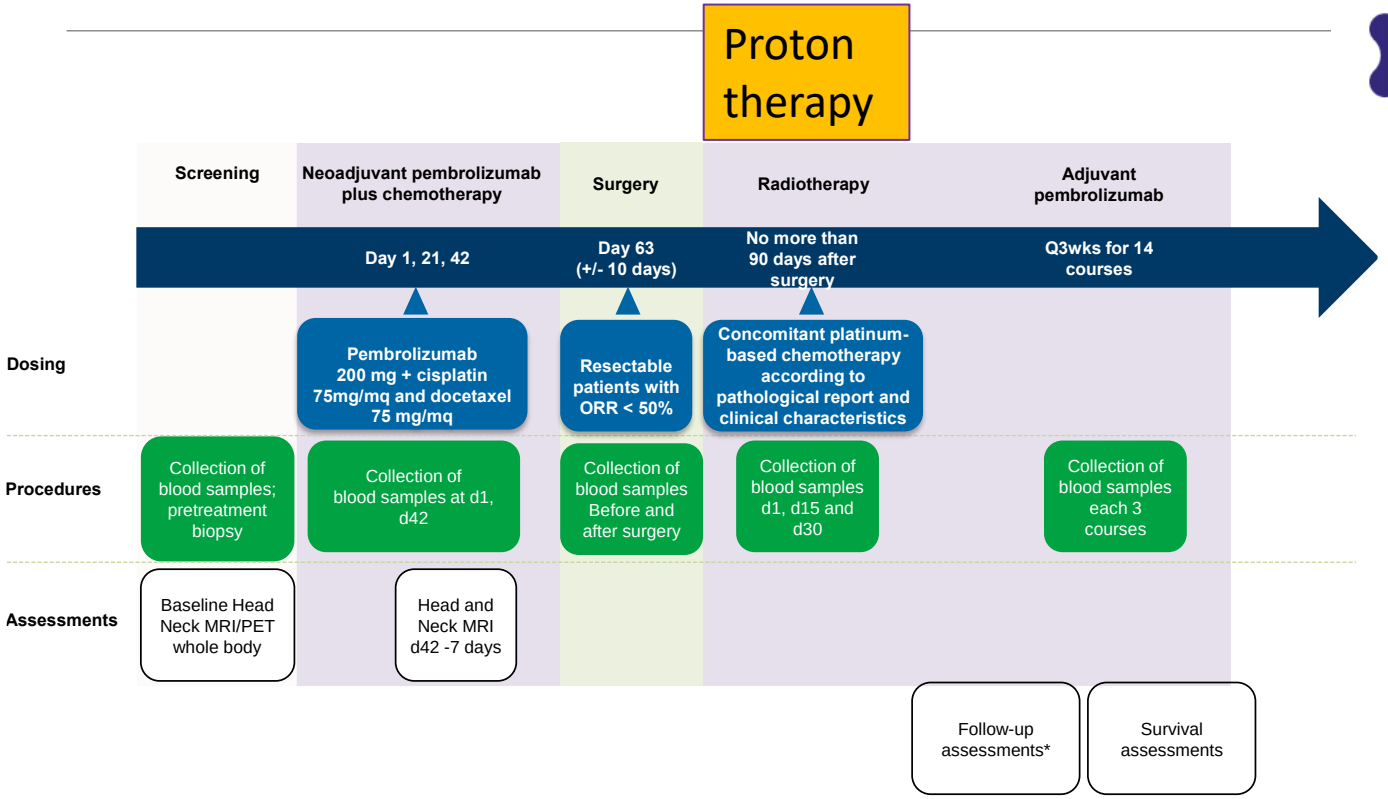
Neoadjuvant pembrolizumab plus chemotherapy in local advanced Undifferentiated sinonasal carcinoma (USNC):phase II trial

To be submitted to EC



- University of Pavia
- CNAO
- National Canner Institute of Milan
- Spedali Civili of Brescia

30 pts to be enrolled
For each pt included in the clinical trial, we will collect baseline tumor biopsy, surgical specimen (when applicable), blood (plasma) samples at different time points

- Single cell analysis
- Spatial trascriptomics
- Liquid biopsies
- Bulk RNAseq/DNAseq

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Objectives	
	Primary Clinical Objectives: Safety and activity of pembrolizumab plus chemotherapy as neoadjuvant treatment in locally advanced SNUC. **Primary Clinical Hypotheses:** Activity of neoadjuvant chemotherapy in locally advanced SNUC has been already demonstrated; we hypothesize that the addition of pembrolizumab as neoadjuvant and adjuvant agent might confirm the results, obtained with a combined treatment strategy including chemotherapy, decreasing the burden of treatment-related side effects **Primary Translational Objectives:** - To investigate the behavior of exhausted CD8+ T in response to pembrolizumab in SNUC and the relationships between T cell clusters. To this aim, single-cell RNA sequencing, 2D space diffusion maps, and spatial transcriptomics will be done in tumor and at peripheral level before and after pembrolizumab. - To assess the persistence of tumor-specific T-cell clones after the treatment of primary cancer, potentially contributing to a durable immune response. Single cell/spatial-transcriptomics sequencing will be applied to the blood samples collected after surgery (in case of response less than 50%) and during follow up. **Exploratory Objectives**

Endpoints	
	Primary clinical Endpoint: Neoadjuvant therapy objective response rate (ORR, defined as the sum of complete remission (CRs) and partial responses (PRs) by RECIST v. 1.1 criteria will serve as the primary efficacy endpoint. **Secondary clinical Endpoint:** - Duration of response (DoR) - Progression free survival (PFS) - Overall free survival (OS) - Safety profile (eg. safety of multimodality approach including immunotherapy; perioperative complications rate; rate of treatment-related adverse events > G3) - Organ sparing rate and avoid surgical procedure rate (for those patients with response > 50%). The impact of pembrolizumab on surgery (rate of complete resections; number of pCR; rate of surgery delay; rate of complications, etc) will be recorded. - Amount of chemotherapy spared with the proposal approach compared to the benchmark used in the SINTART1 (NCT02099175) and 2 (NCT02099188) trials.

We would even investigate the biological mechanisms of pembrolizumab resistance in non-responding patients. We hypothesized that genomic aberrations associated with pembrolizumab resistance are pre-existing in the tumor mass due to the intratumor heterogeneity and adaptively selected in response to treatment. The acquiring of resistance is largely due to drug-refractory subclones within heterogeneous tumors (single-cell NGS).

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THANK YOU!

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