



HIRO
Heideler Institut
für Radioonkologie

Nationales Zentrum für
Strahlenforschung in der
Onkologie Heidelberg
getragen von:
Deutsches Krebsforschungszentrum
Universitätsklinikum Heidelberg
Heidelberger Ionenstrahl-Therapiezentrum
Medizinische Fakultät Heidelberg

RadioOnkologie

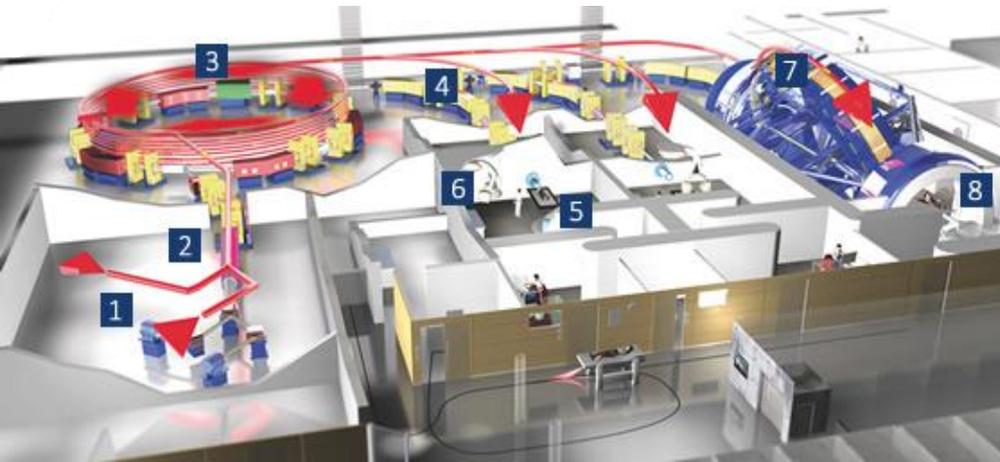


Behandeln
Forschen
Lehren

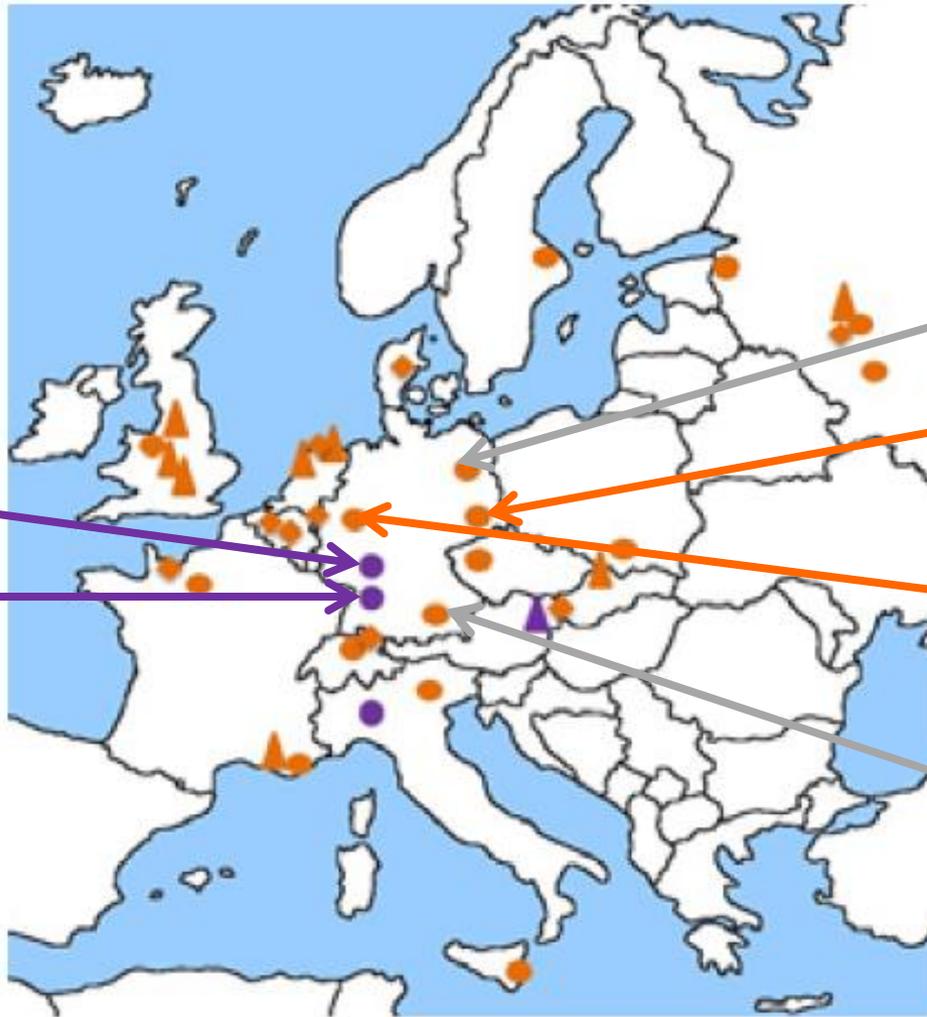


UniversitätsKlinikum Heidelberg
Jürgen Debus

Proton and Ion Therapy: Clinical Trials in Germany



PARTICLE THERAPY CENTRES IN EUROPE - 2015



Protons and carbon ions

- University Hospital Heidelberg
- MIT Marburg
- HIT Heidelberg

Protons

Charité /
Helmholtz-Zentrum
BerlinProtonen

University
Hospital
Dresden

University
Hospital
Essen/ WPE

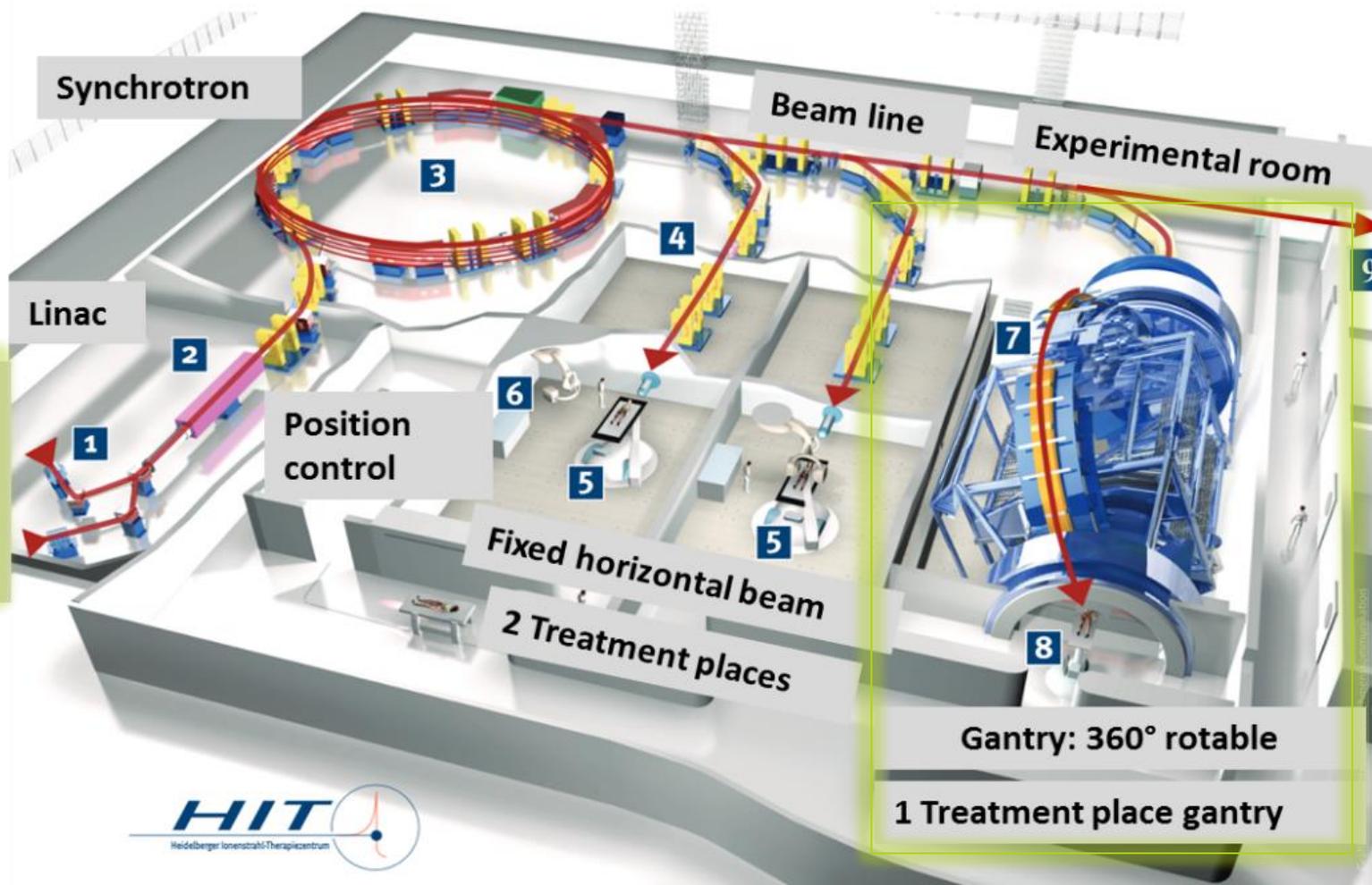
Rinecker Proton
Therapy Center
RPTC

In operation	Under construction	Being planned
● Proton	▲ Proton	◆ Proton
● Dual Ion	▲ Dual Ion	◆ Dual Ion

HIT: Heidelberg Ion Therapy Center

HIT is Europe's first combined treatment facility using **protons and heavy ions** for radiation therapy.

HIT is the world's first heavy ion treatment facility with a **360° rotating beam delivery system (gantry)**.



Ion sources:

- Protons
- Carbon
- Helium
- Oxygen

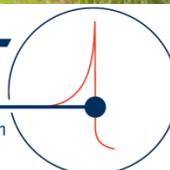


MIT: Marburg Ionbeam Therapy center



MIT

Marburger Ionenstrahl-Therapiezentrum

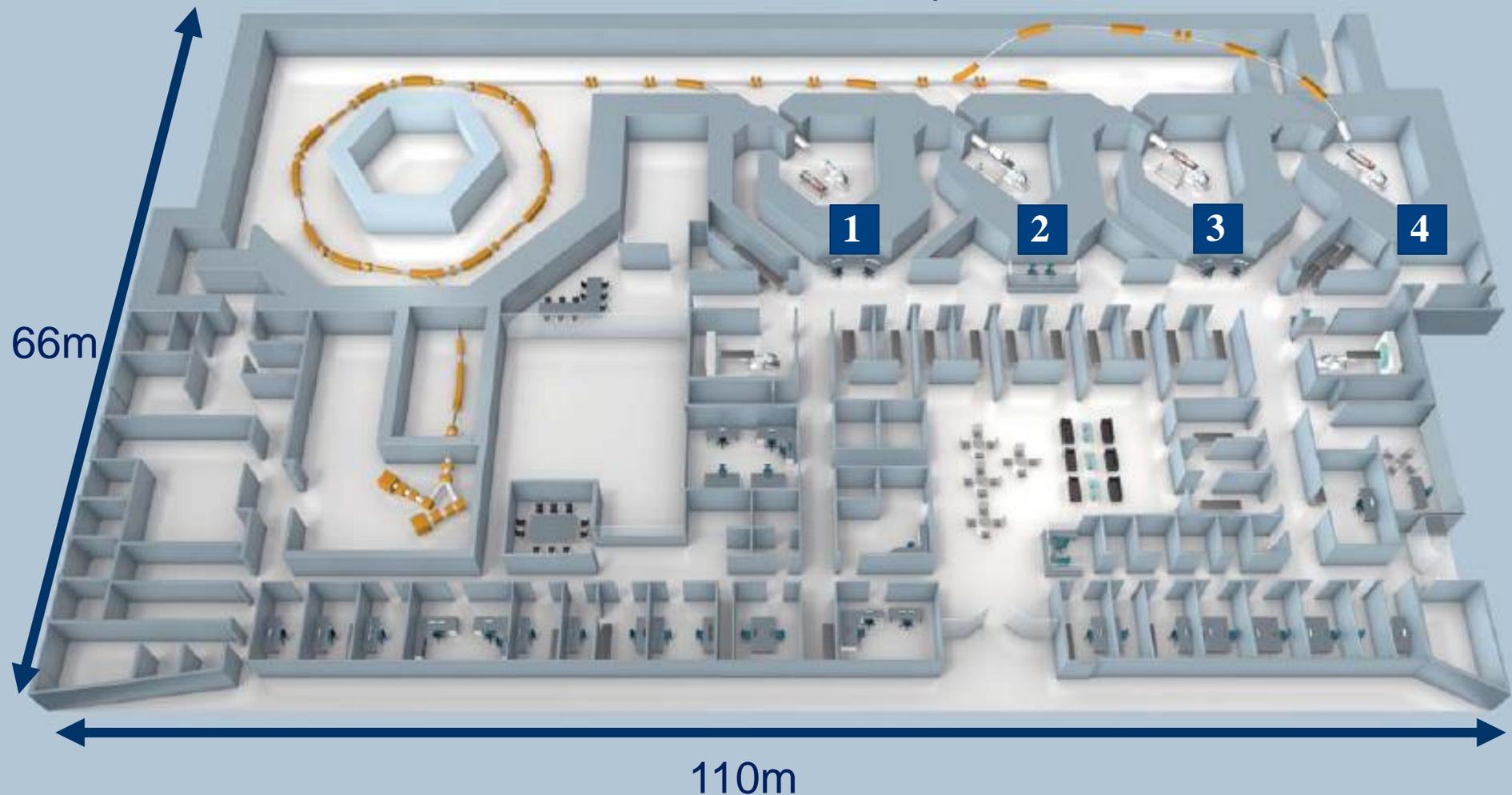


**Operation started in
10/ 2015**



MIT: Marburg Ionbeam Therapy center

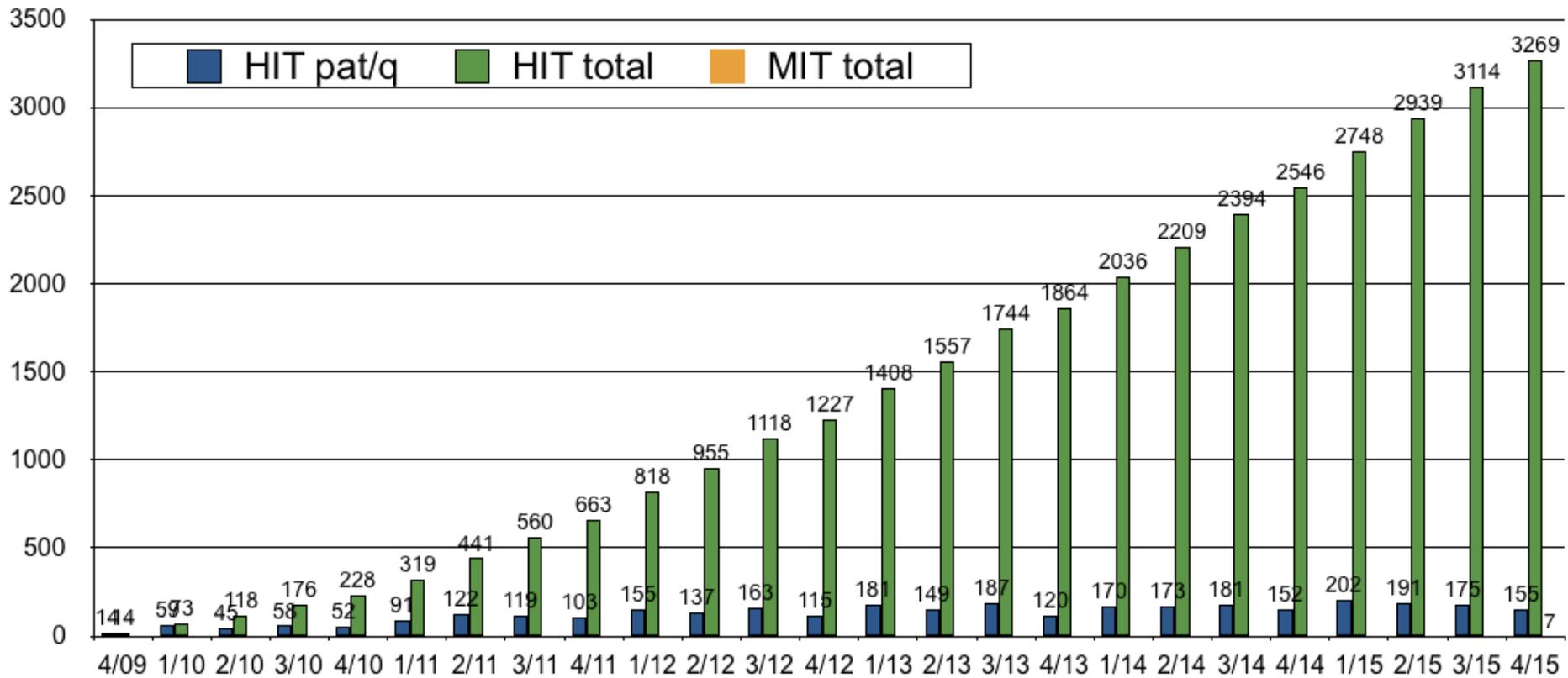
- 3 treatment places at horizontal beam
- 1 treatment places at 45° beam





Patients @ HIT / MIT

Proton therapy since 11/2009, ~3300 patients treated



2009	2010	2011	2012	2013	2014	2015
14	214	435	570	637	676	723 (HIT)



Clinical trials @ HIT

- SB chordomas: H1 vs. C12 **recruiting** (71/319)
- SB chondrosarcomas: H1 vs. C12 **recruiting** (49/154)
- CLEOPATRA (H1 vs. C12 boost RT; prim. glioblastoma) **recruiting** (97/150)
- CINDERELLA (C12 recurrent glioblastoma) **recruiting** (56/56 Phase 1)
- MARCIE (C12 boost RT, meningiomas grade 2) **recruiting** (15/40)
- **COSMIC** (C12 boost RT; salivary glands) **published**
- TPF-C HIT (C12 boost RT; head&neck) **closed**
- IMRT HIT-SNT (C12 boost RT; sinu-nasal cancer) **recruiting** (9/36)
- ACCEPT (C12 boost RT + Erbitux for ACC) **recruiting** (17/49)
- PROMETHEUS (C12 for HCC) **recruiting** (11/36)
- **OSCAR** (H1 + C12 boost; inoperable osteosarkoma) **recruiting** (15/20)
- PANDORA (C12 for recurrent rectal carcinoma) **recruiting** (11/51)
- IPI (C12/H1 for prostate cancer) **f/u phase**
- ISAC (C12/H1 for sacral chordoma) **recruiting** (35/100)
- PROLOG (hypofract. H1 for prostate cancer recurrence) **f/u phase**
- **INKA** (neoadj. C12 for inop. sulcus superior tumors) **recruiting** (5/20)
- KOLOG (hypofract. C12 for Prostate cancer recurrence) **recruiting** (8/40)

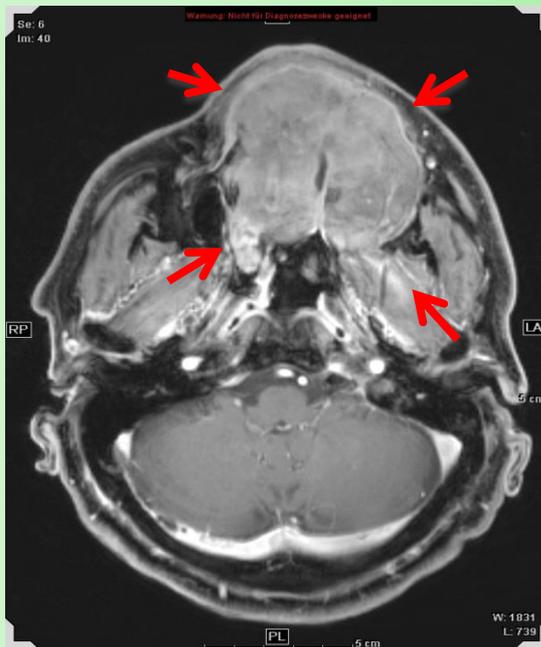
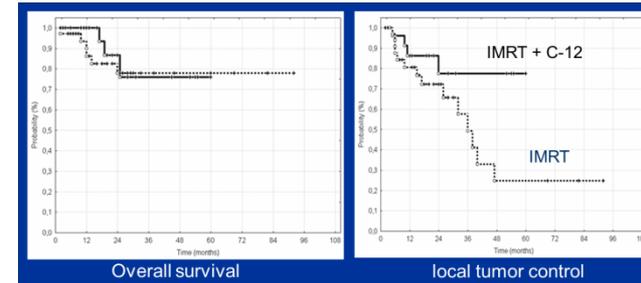
COSMIC- trial

Combined therapy of malignant salivary gland tumors with IMRT and carbon ions

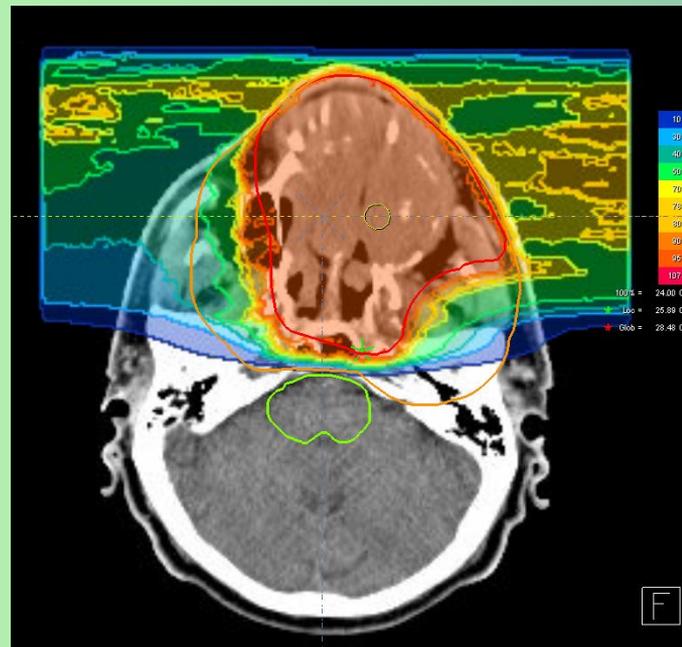
- Phase II feasibility study

- No dose limiting acute toxicity
- Late Toxicität G > CTC grade 2 < 5%

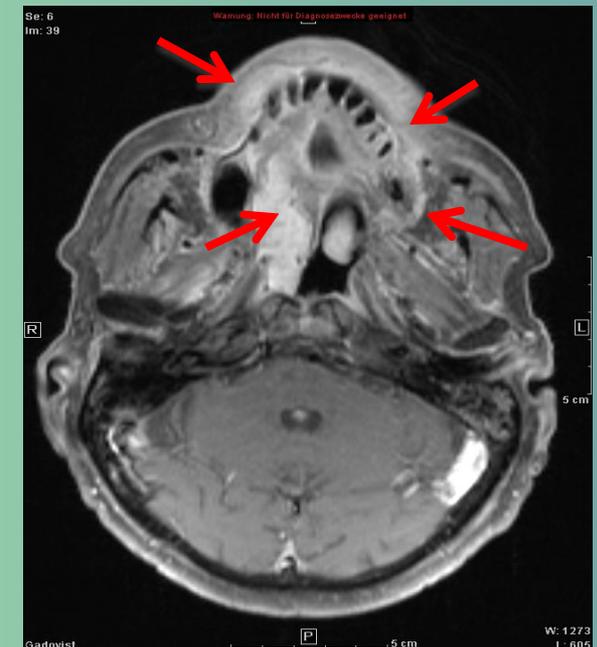
Schulz-Ertner, Cancer. 2005 Jul 15;104(2):338-44



Pre-treatment situation



Treatment planning
C-12 boost

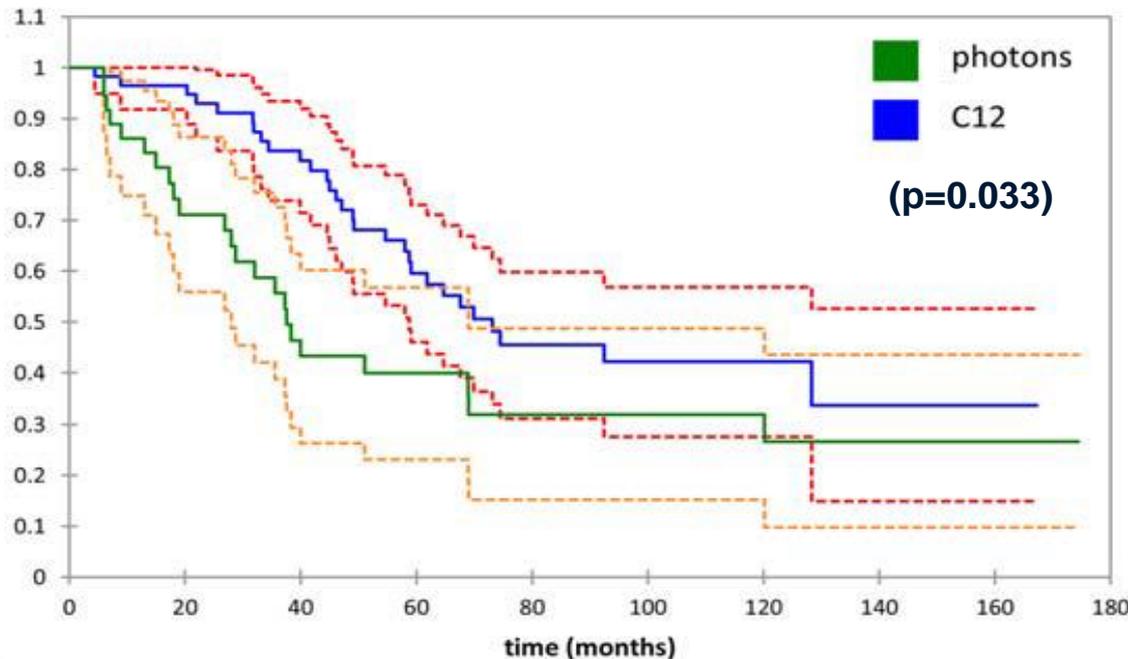


6 weeks post RT

COSMIC- trial

Better local tumor control by C-12 irradiation leads to better long-term survival of locally advanced adenoid cystic carcinoma

Local control



numbers at risk:

C12:	58	55	43	28	17	11	8	5	2
photons:	37	24	15	12	9	7	7	5	2



Original Article

Combined intensity-modulated radiotherapy plus raster-scanned carbon ion boost for advanced adenoid cystic carcinoma of the head and neck results in superior locoregional control and overall survival

Alexandra D. Jensen MD, MSc, Anna V. Nikoghosyan MD, Melanie Poulakis DDS, Angelika Höss MSc, Thomas Haberer PhD, Oliver Jäkel PhD, Marc W Münter MD, Daniela Schulz-Ertner MD, Peter E. Huber MD, PhD, Jürgen Debus MD, PhD

First published: 4 June 2015 [Full publication history](#)

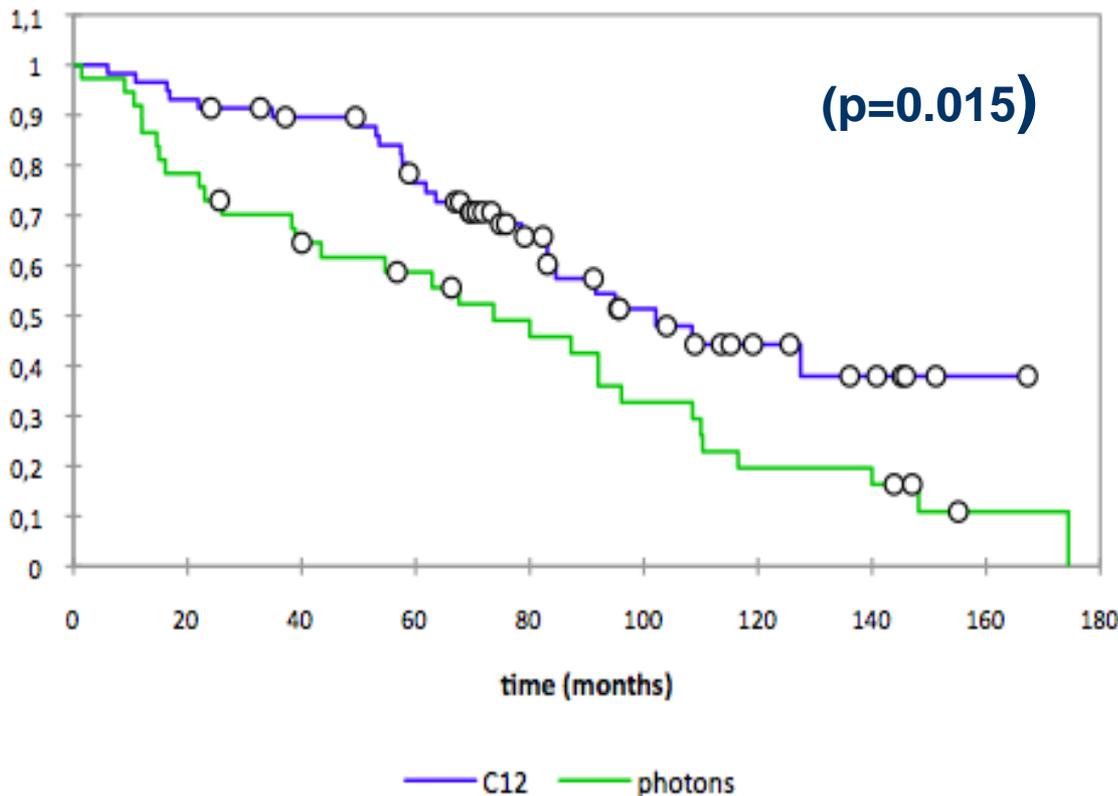
DOI: 10.1002/cncr.29443 [View/save citation](#)

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COSMIC- trial

Better local tumor control by C-12 irradiation leads to better long-term survival of locally advanced adenoid cystic carcinoma

Overall Survival



Original Article

Combined intensity-modulated radiotherapy plus raster-scanned carbon ion boost for advanced adenoid cystic carcinoma of the head and neck results in superior locoregional control and overall survival

Alexandra D. Jensen MD, MSc [✉](#), Anna V. Nikoghosyan MD, Melanie Poulakis DDS, Angelika Höss MSc, Thomas Haberer PhD, Oliver Jäkel PhD, Marc W. Mürter MD, Daniela Schulz-Ertner MD, Peter E. Huber MD, PhD, Jürgen Debus MD, PhD

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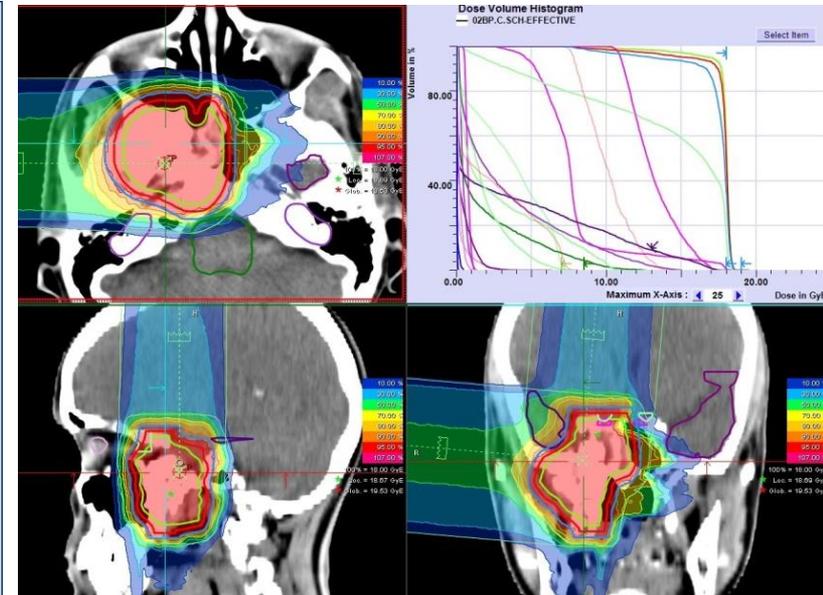
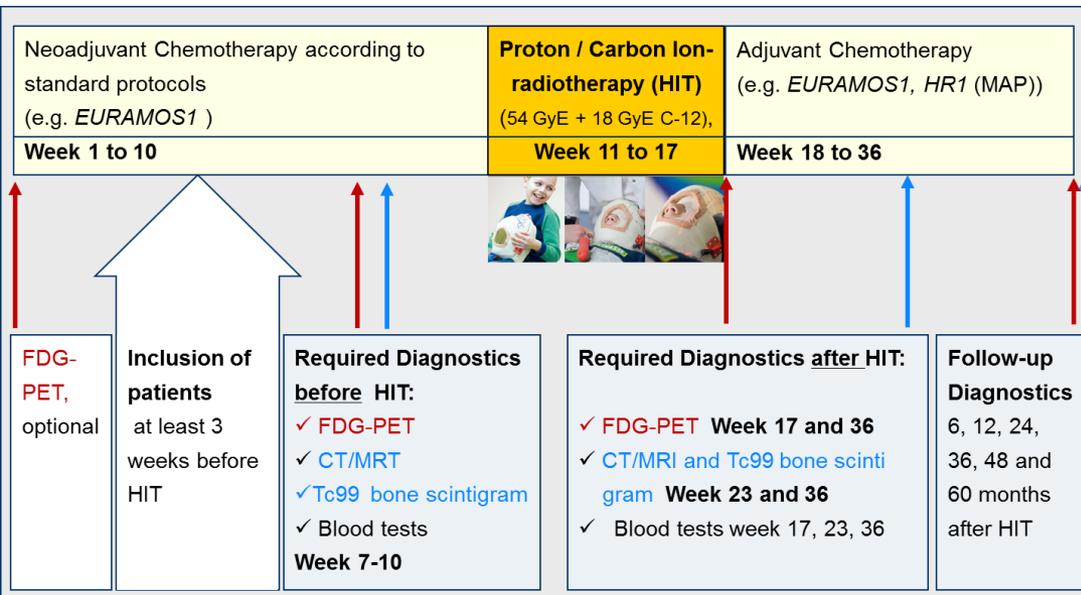
DOI: 10.1002/cncr.29443 [View/save citation](#)

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OSCAR- trial

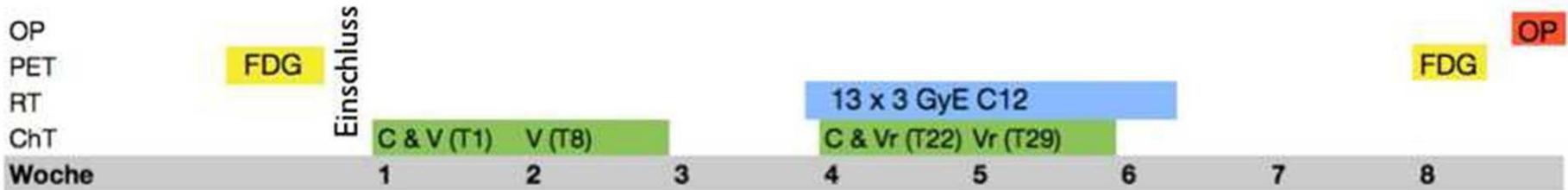
OSteosarcoma – CArbon Ion Radiotherapy: Phase I/II therapy trial to determine the safety and efficacy of heavy ion radiotherapy in patients with inoperable osteosarcoma

Secondary endpoints: local control disease-free and progression-free survival, Overall survival, role of **FDG-PET** in response monitoring

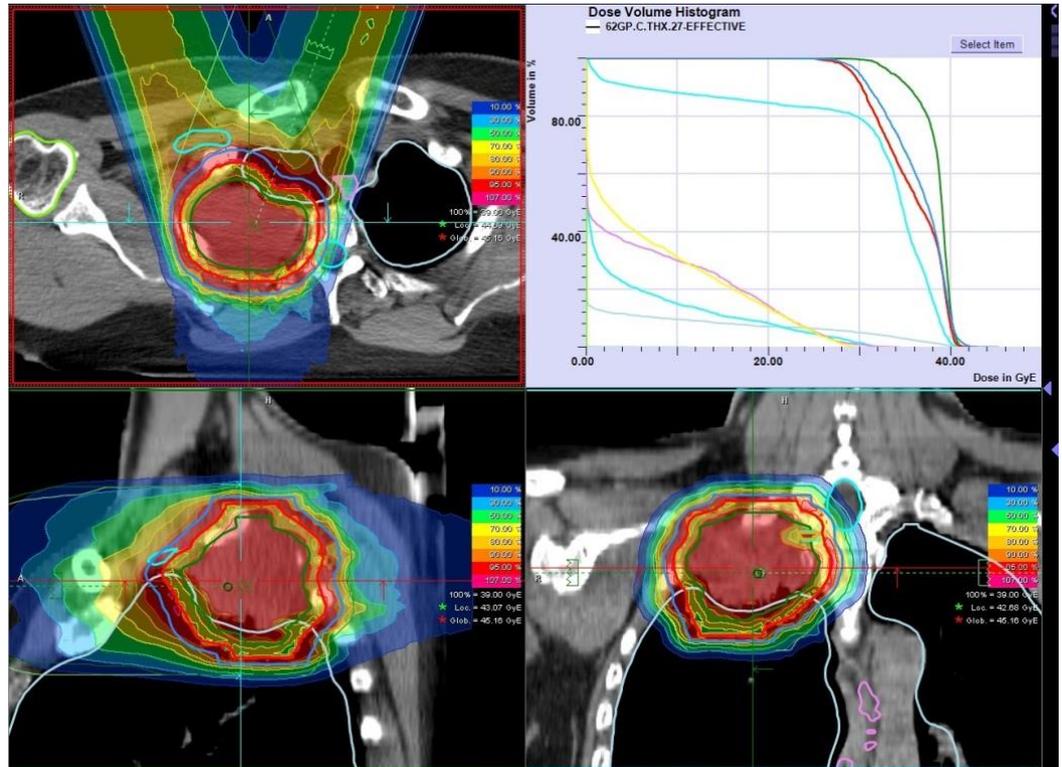


INKA-trial

Prospective pilot-study to determine the safety and feasibility of primary ion radiotherapy in patients with pancoast-tumors within a trimodal treatment concept.



C = Cisplatin 80 mg/m² KOF
 V = Vinorelbin 25 mg/m² KOF
 Vr = Vinorelbin (reduziert) 15 mg/m² KOF





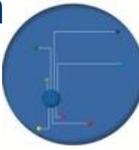
Future Clinical trials @ HIT

- Pancreatic Carcinoma (C12 only)
- PROCEED (Esophagus Carcinoma (C12 Boost))
- Anal Carcinoma (C12 Boost)

Current clinical studies at Westdeutsches Protonentherapiezentrum Essen (WPE)

Proton therapy since 12/2014, 120 patients treated

- ❖ **Registry study for adult patients** as a basis for future therapy studies
- ❖ **Registry study for pediatric patients** as a basis for future therapy studies
- ❖ **Prospective quality-of-life study** on children with tumors of brain and skull base before and after proton therapy including toxicity and specific side effects; in co-operation with University Hospital Münster
- ❖ **Prospective study on endocrine effects** after cranial irradiation with protons in children



Joint activities: A multicentre explorative study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG)

Radiobiological profiling for biologically stratified radio-chemo-therapy of HNSCC

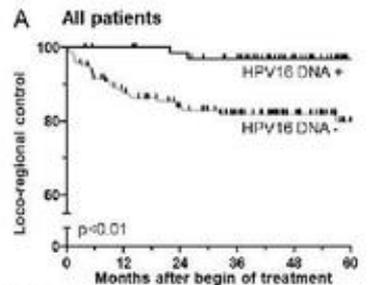
Retrospective
exploratory cohort
(2012 - 15)

Prospective validation
cohort
(2014 - 17)

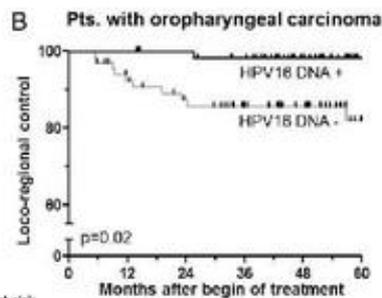
Interventional study
(2016 - ...)

HPV16 DNA status is a strong prognosticator of loco-regional control after postoperative radiochemotherapy of locally advanced oropharyngeal carcinoma.

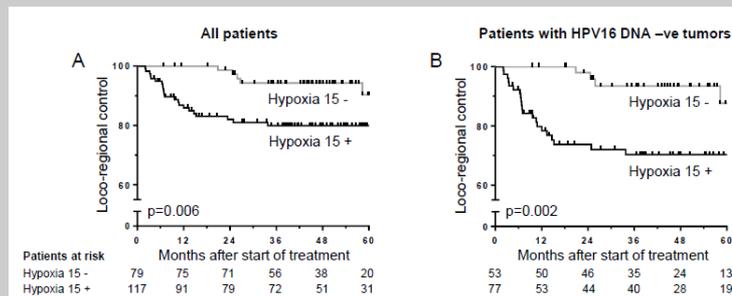
Low CSC marker expression and low hypoxia identify good prognosis **subgroups in HPV(-) HNSCC**



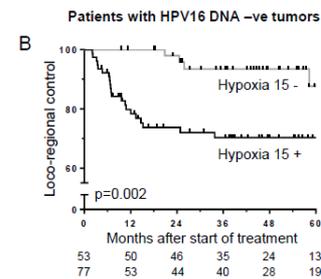
Patients at risk	0	12	24	36	48	60
HPV16 DNA +	72	69	65	58	43	24
HPV16 DNA -	143	115	102	86	60	36



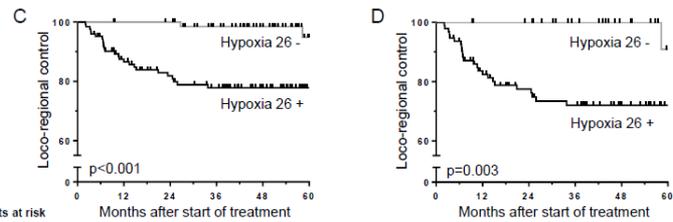
Lohaus et al. Radiother Oncol, 2014



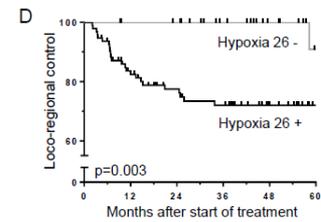
Patients at risk	0	12	24	36	48	60
Hypoxia 15 -	79	75	71	56	38	20
Hypoxia 15 +	117	91	79	72	51	31



Patients at risk	0	12	24	36	48	60
Hypoxia 15 -	53	50	46	35	24	13
Hypoxia 15 +	77	53	44	40	28	19



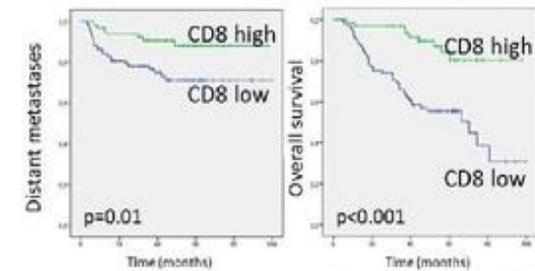
Patients at risk	0	12	24	36	48	60
Hypoxia 26 -	72	69	68	56	40	23
Hypoxia 26 +	124	97	82	72	49	28



Patients at risk	0	12	24	36	48	60
Hypoxia 26 -	36	33	32	23	16	9
Hypoxia 26 +	94	70	58	52	36	23

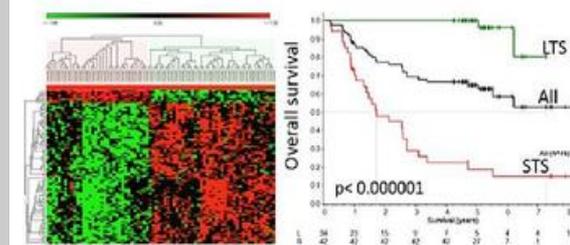
Linge et al. Clin Cancer Res. 2016 Jan 11

Tumour infiltrating lymphocytes (TILs)



Balermipas et al. Int J Cancer. 2016 Jan 1

Methylation patterns in HPV -ve tumours

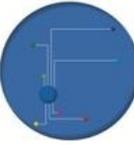


STS: short-term survival; LTS: long-term survival

Green: hypomethylated

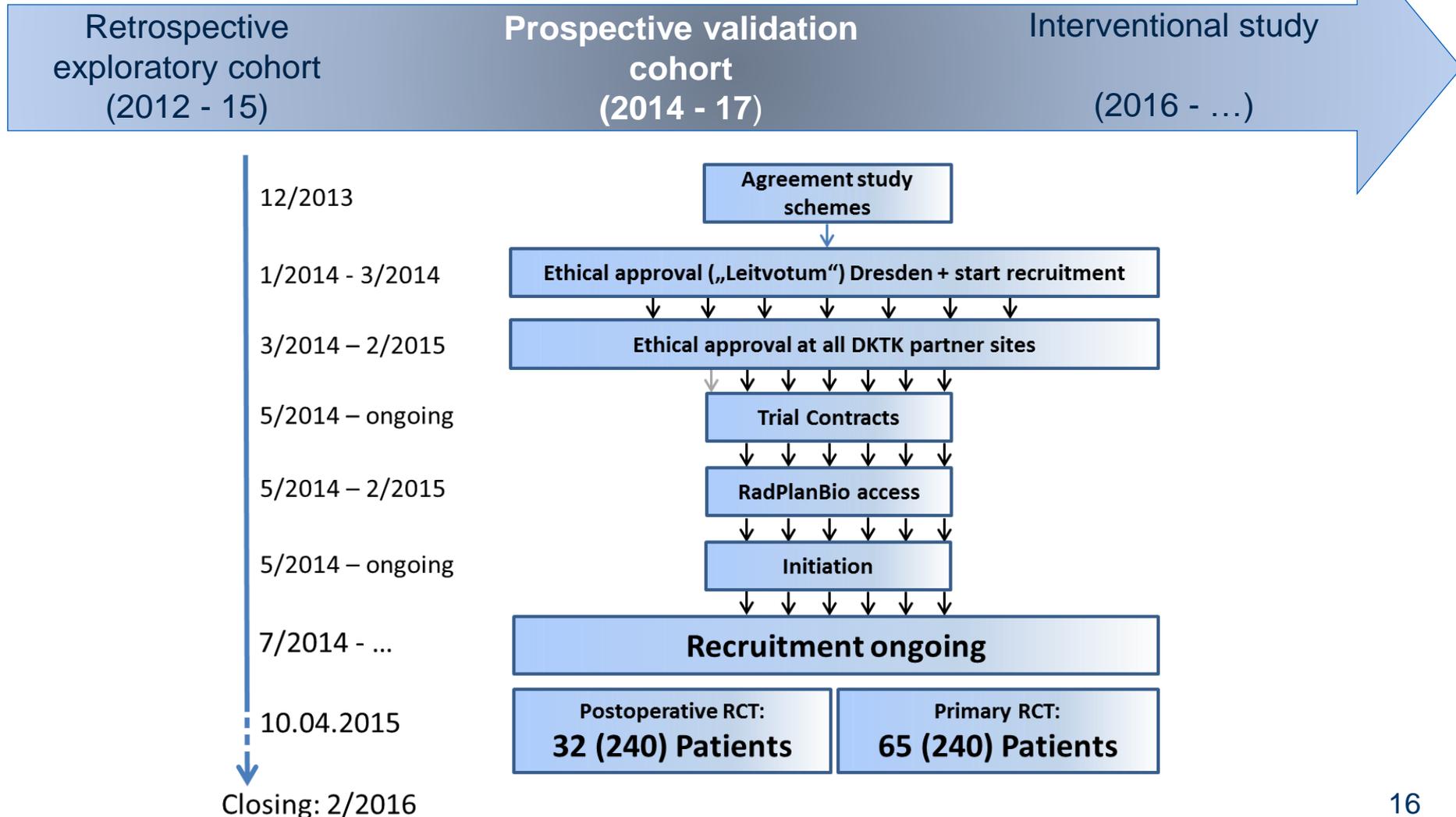
Red: hypermethylated

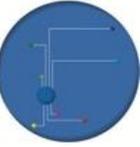
Abdollahi, Debus et al. in preparation



Joint activities: A multicentre explorative study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG)

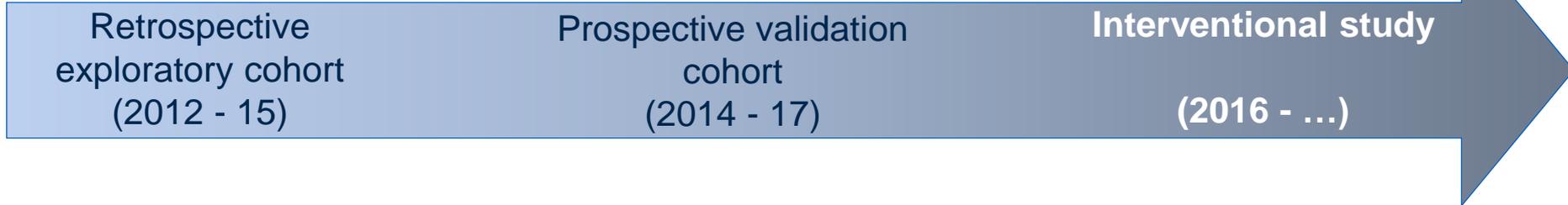
Ongoing and future research: Radiobiological profiling for Biologically stratified radio-chemo-therapy of HNSCC





Joint activities: A multicentre explorative study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG)

***Ongoing and future research:* Radiobiological profiling for Biologically stratified radio-chemo-therapy of HNSCC**



In preparation:

- **Interventional de-escalation study**
(patients with HPV-positive OPSCC)

In planning phase:

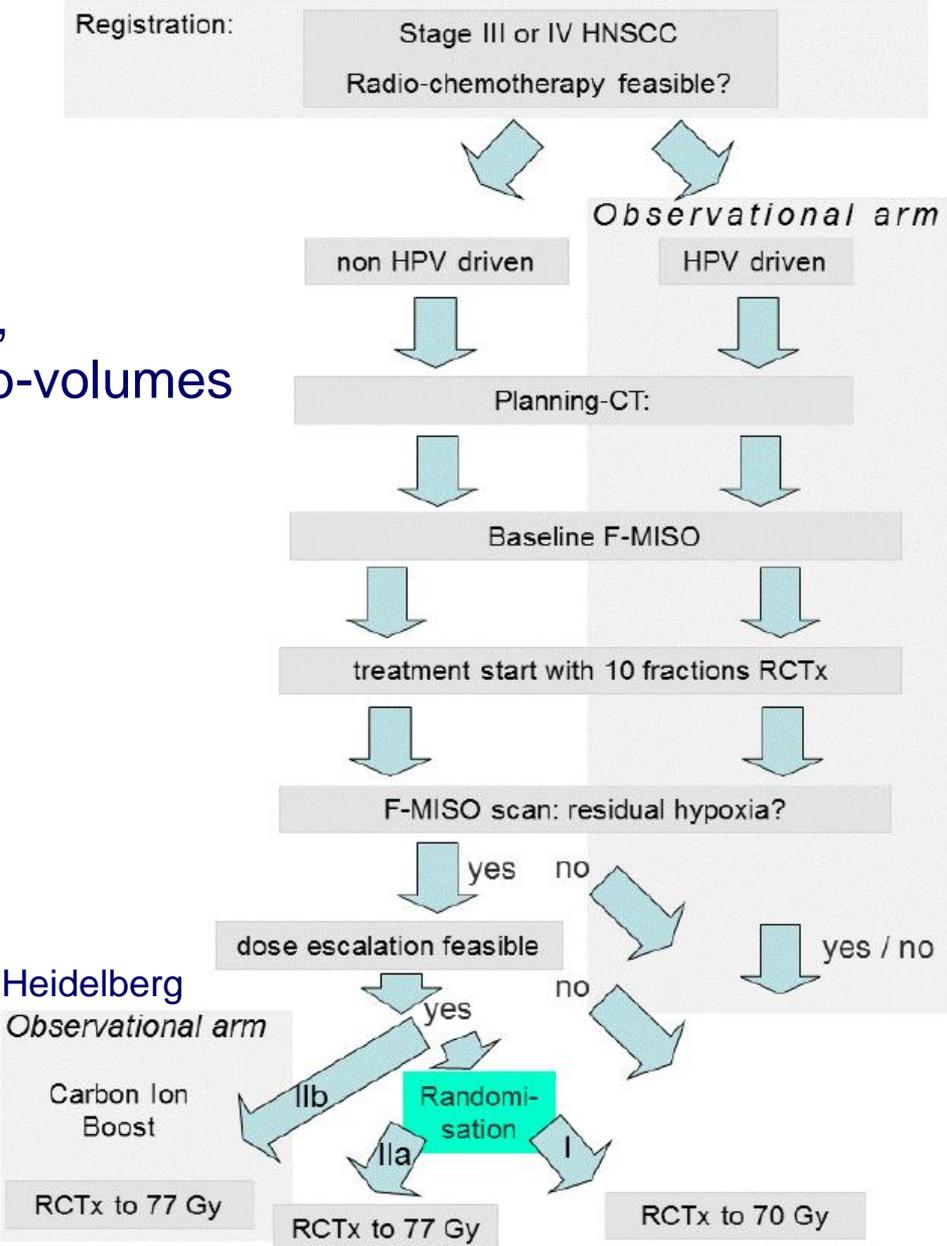
- **Interventional escalation study**
(patients with HPV-negative HNSCC +
additional biomarkers, t.b.d.)

Joint activities: A multicentre explorative study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG) + Rome + Poznan + Vienna

Intervention study:

(waiting for BfS approval)

- in high risk patients
- dose escalation on total GTV,
- non- selective on hypoxic sub-volumes



Proton therapy since 12/2014, ~120 patients treated

- First studies in 2015 with non-randomised standard dosing and standard fractionation
- Primary endpoint: chronic toxicity
- Secondary endpoints: Acute toxicities, Quality of life, survival
- ❖ Own study protocol Proto-R-Brain
- ❖ Own study protocol PETra
- ❖ Own study protocol Proto-R-Scull base
- ❖ Proto-Choice Prostate (74-78 Gy RBE) prospective matched pair protons vs. photons
- ❖ ReKo Study (HNSCC, re-RT 60-66 Gy, in high dose pre-irradiated area)
- ❖ Primary Radiochemotherapy of NSCLC: randomised proton vs. photon RT

Future Studies in Dresden

- ❖ PANAMA: Dose escalation in atypical anaplastic meningeoma, multicentric

- ❖ Dresden is involved in national studies (GPOH) and national registries (RISK)
- ❖ **Data base** (under construction): data from pediatric patients who received RT with photons **as a reference collective** for comparison with patients irradiated with protons
- ❖ Cooperation with Essen and Heidelberg for follow-up-analysis and quality of life in children (start 2015/16)



Registry for Clinical Trials in Proton and Iontherapy in Germany

www.studien-protonen-ionen.de
 email: contact@studien-protonen-ionen.de

Under construction

Study ID	Study Name	Phase	Start Date	End Date	Center	Country	Status	Patients
TRITON	Prostate	III	01.07.2008	01.12.2011	31	Germany	Completed	1
TRITON	Head and Neck Cancer	III	01.07.2010	30.06.2012	54	Germany	Completed	2
TRITON	Prostate	III	01.10.2010	01.10.2012	48	Germany	Completed	3
TRITON	Cervix/Neck/Brain	III	01.08.2010	31.08.2014	180	Germany	Completed	4
TRITON	Prostate (non Prostate)	III	01.08.2012	01.08.2018	92	Germany	Completed	5
TRITON	Prostate	III	26.11.2011	28.08.2018	200	Germany	Completed	6
TRITON	Cervix/Neck/Brain	III	01.09.2010	01.09.2018	435	Germany	Completed	7
TRITON	Prostate	III	22.02.2010	31.12.2018	20	Germany	Completed	8
TRITON	Other	III	01.02.2010	01.02.2018	40	Germany	Completed	9
TRITON	Prostate	III	01.08.2010	31.08.2012	184	Germany	Completed	10
TRITON	Head and Neck Cancer	III	30.10.2010	ongoing	40	Germany	Completed	11
TRITON	Prostate	III	01.08.2013	01.08.2014	40	Germany	Completed	12
TRITON	Chondroma	III	01.07.2010	revised	310	Germany	Completed	13
TRITON	Prostate	III	01.10.2015	revised	20	Germany	Completed	14
TRITON	Chondroma	III	01.10.2012	revised	100	Germany	Completed	15
TRITON	Liver	I	01.10.2010	revised	33	Germany	Completed	16

- List of all currently recruiting clinical studies with proton or ion therapy
- Contact information for patients and researchers
- Background information for patients
- In german and english



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NCRO

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Heidberger Institut für Radioonkologie

Partners:

