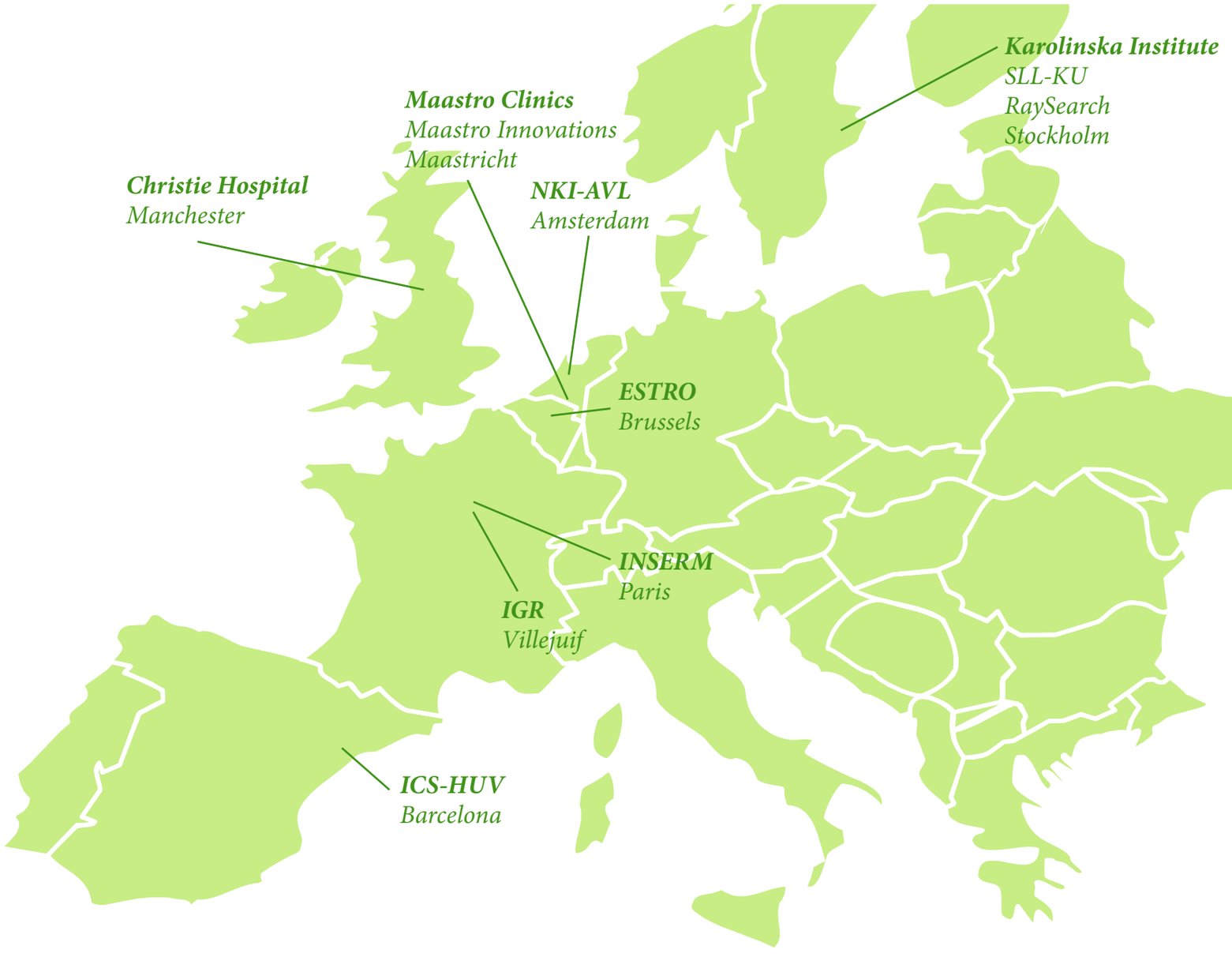
# ADVANCES ON THE ARTFORCE RESEARCH PROJECT

## THE ARTFORCE CONSORTIUM

- 7 European academic hospitals/research institutes
- 2 European SMEs
- ESTRO
- Expertise in basic, translational and clinical research

The ARTFORCE (Adaptive and innovative Radiation Treatment FOR improving Cancer patients' treatment outcomE) project. The aim of the project is the improvement of quality and therapeutic ratio in head and neck and lung cancer treatment. To achieve this aim, nine workpackages were designed, including two clinical trials. ▼

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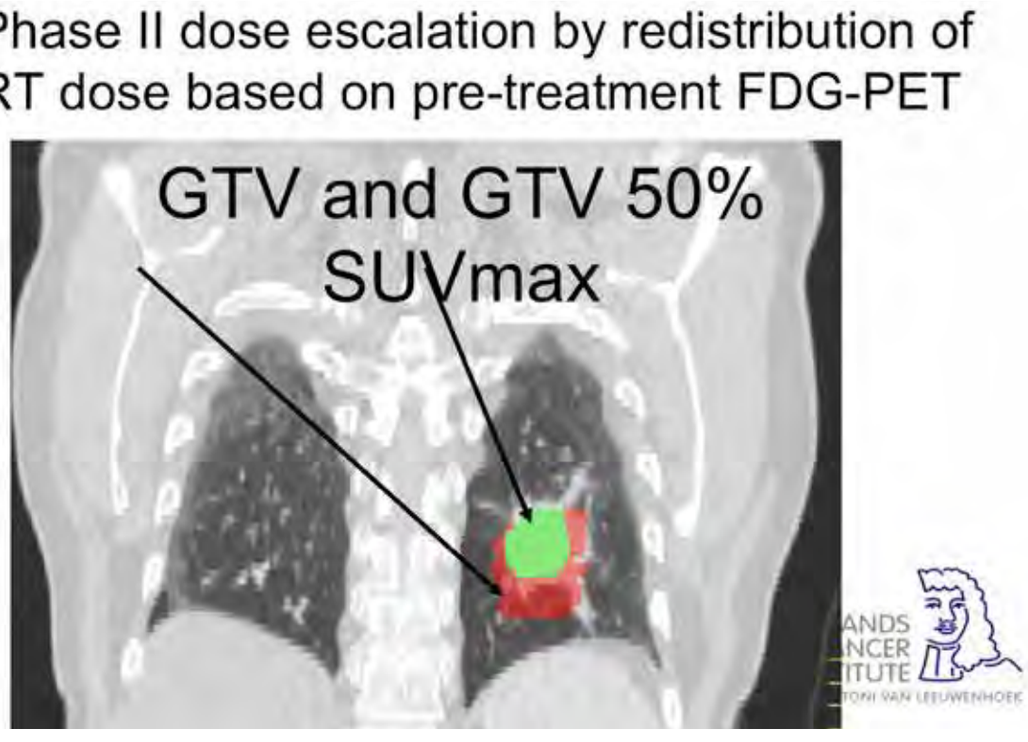
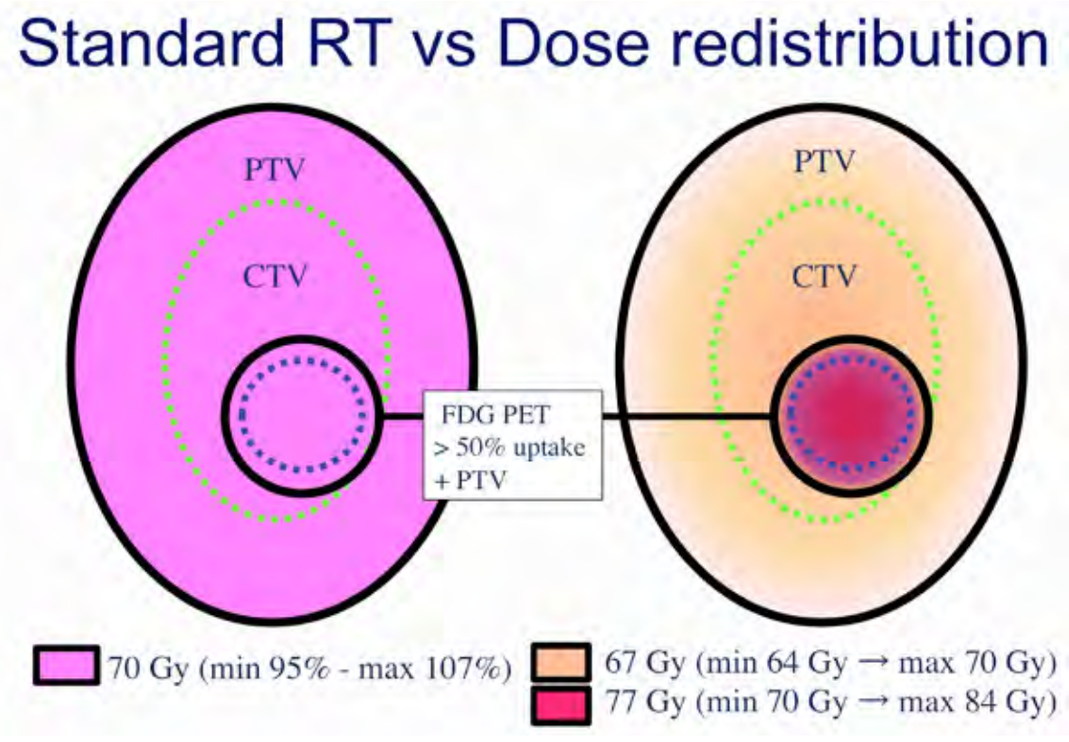
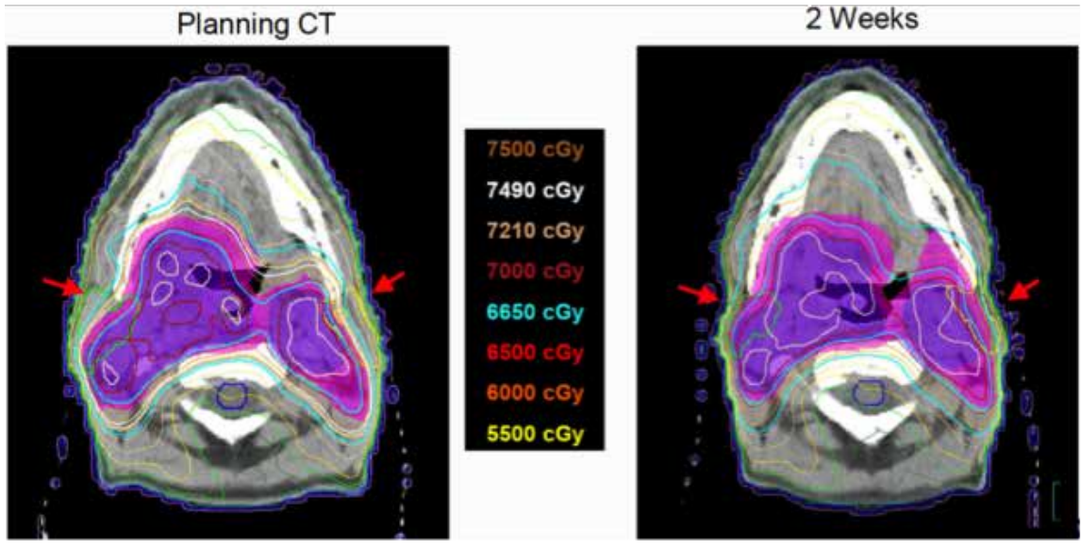


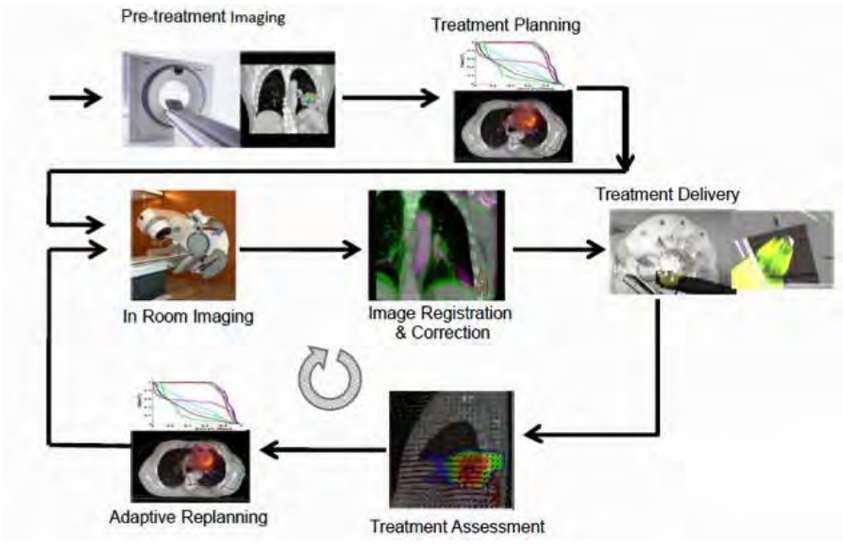




Within the lung cancer study, the concept of FDG PET-based dose redistribution is evaluated in a randomised phase II trial. Patients are randomised to either a maximum dose escalation to the primary tumour, while respecting organ-at-risk tolerance limits, or redistribution of the escalated dose based on dose painting by segments by prescribing at least a standard dose (66 Gy in 24 fractions) to the whole primary tumour and maximally escalating the dose to the sub-volume defined by the 50% of the $SUV_{max}$ (Maximum Standardised Uptake Value). Both arms are normalised to the mean lung dose. The maximum dose is 98.4 Gy in the redistribution arm while in the conventional radiotherapy arm, 80 Gy is given to the primary tumour. Additional studies include Hx4 PET imaging and dynamic contrast enhanced CT scans to investigate additional imaging biomarkers.

Currently, 71 patients have been registered of whom 45 have been randomised to receive this technically feasible treatment. Up to now, the toxicity is in agreement with the known toxicity after radical radiotherapy for lung tumours. The Head and Neck cancer trial uses a factorial design for a randomised phase II study, comparing weekly cisplatin (40 mg/m2) with weekly cetuximab (250 mg/m2) and conventional RT (70 Gy x 35 fx) versus dose redistribution with adaptive radiotherapy (highest dose of 84 Gy in the primary tumour and adaptive replanning after 2 weeks).

At the beginning of this year, the first patients were entered and it appears that in spite of the complex techniques, the treatment is feasible. The toxicity was in agreement with the expected toxicity seen in the treatment of advanced head ▼




and neck tumours with combined modality treatment. In the cetuximab arms, in a few patients the typical cetixumab skin side effects were observed.

This head and neck trial is accompanied by fundamental molecular research aiming first of all at prediction of the cisplatin response. Therefore, in vitro research is being performed using genome-wide siRNA screens investigating cisplatin response modifiers. This research has resulted in the identification of 32 genes which, if "switched off", sensitise the tumour to cisplatin. Thirty-five genes are cytoprotectors, their depletion augments the cisplatin-induced cell death. This has been confirmed in four head and neck cell lines. Already, one of these genes can be used for immunohistochemical detection of susceptibility in biopsies of head and neck cancer patients. Frozen tumour biopsies will be taken from all patients and full blood samples collected to investigate and validate the predictive value of these genes and other gene profiles.

The uptake of cetuximab in the primary tumour, as a predictor of sensitivity to cetuximab, is estimated with 89Zirconium-labelled cetuximab in patients using CT-PET scans. The influence of the presence of HPV on treatment outcome will be evaluated using a Multiplex assay, where 27 different HPV types (including 15 high risk types) are simultaneously assayed by broad spectrum PCR followed by bead base analysis in a Magpix instrument from Luminex. In addition, the biological activity of HPV will be tested and the presence of E5/E6/E7 mRNA will be investigated, in parallel with testing p16 expression (by immunohistochemistry).

## DOSIMETRIC IMPACT OF PAROTID SHRINKAGE

A separate workpackage on adaptive radiotherapy aims to develop and validate software which takes into account the changes in morphology of patients undergoing radiotherapy, for example shrinkage of parotid glands after two weeks of radiotherapy.

Additionally, the daily images acquired for image guidance will be used to estimate the delivered dose that will subsequently be correlated to treatment outcome. ▼

A special work package develops and implements *in vivo* dosimetry by electronic portal imaging devices (EPID) to provide patient-specific QA in both trials for every fraction.

Conclusions: The first periodic report presented to the EU was well received and continued funding has been secured. This will allow the cooperating centres to complete their joint activities divided over the nine workpackages. It is anticipated that the final outcome will lead to considerable progress in the treatment of both head and neck and lung cancer. An update of the progress of the project will be presented at ESTRO 33 in Vienna (April 5, 2014, 14.30 hrs). *(ARTFORCE is an EU project/grant agreement nr. 257144)*

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