

European Association of NeuroOncology Magazine

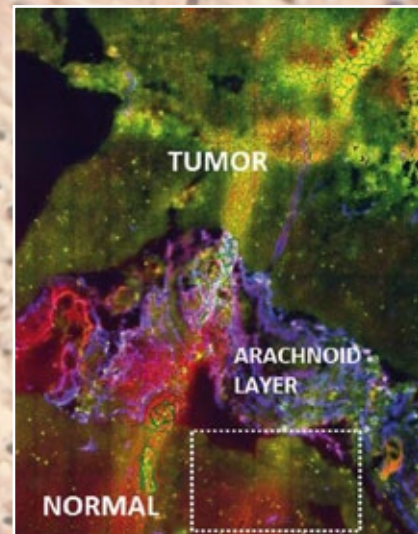
Neurology · Neurosurgery · Medical Oncology · Radiotherapy · Paediatric Neuro-
oncology · Neuropathology · Neuroradiology · Neuroimaging · Nursing · Patient Issues

**Interview with Dr Stephanie E
Combs, Heidelberg University
Hospital, about the Phase-II Trial
Evaluating Carbon Ion Radiotherapy
for the Treatment of Primary
Glioblastoma (CLEOPATRA)**

Abacioglu U

*European Association of
NeuroOncology Magazine 2014; 4 (1)*

47-48



Homepage

**[www.kup.at/
journals/eano/index.html](http://www.kup.at/journals/eano/index.html)**

**Online Database Featuring
Author, Key Word and
Full-Text Search**



THE EUROPEAN ASSOCIATION OF
NEUROONCOLOGY

Member of the



Indexed in EMBASE

Interview with Dr Stephanie E Combs, Heidelberg University Hospital, about the Phase-II Trial Evaluating Carbon Ion Radiotherapy for the Treatment of Primary Glioblastoma (CLEOPATRA)

Ufuk Abacioglu

From the Department of Radiation Oncology, Neolife Medical Center, Istanbul, Turkey

Q: Dr Combs, what can you tell us about the ongoing phase-II trial on carbon ion radiotherapy in newly diagnosed glioblastoma? What are its background and objective?

A: Glioblastomas are highly treatment-resistant tumours, and an improvement of the therapeutic window is being intensively sought for in several disciplines and aspects. As far as radiation is concerned, they are known as radio-resistant lesions, therefore, methods of dose escalation have been studied with more or less success. Particle therapy is characterised by a distinct physical profile, with a sharp dose deposition within the Bragg peak and a steep dose fall-off thereafter. Thus, normal tissue can be spared effectively. Carbon ions are also associated with a higher relative biological effectiveness (RBE). In my group, we could show that this RBE lies between 3 and 5, depending on the cell line and endpoint, and several analyses have shown additive effects together with chemotherapeutic agents. Thus, the CLEOPATRA trial evaluates a carbon ion boost to the macroscopic tumour with the aim of exploiting the biological benefit of carbon ions.

Q: How is the trial designed? Which patients are eligible?

A: The trial is designed as a randomised phase-II trial, the primary endpoint is overall survival at 12 months. Main inclusion criteria include histologically confirmed primary glioblastoma after biopsy or partial resection and indication for combined chemoradiation with temozolomide.

Q: Previous dose escalation studies have been disappointing with regard to improving outcome and showed increased toxicity. What is the rationale behind this trial to change the dismal prognosis?

A: The aim is not only to exploit dose escalation but also the biological properties of the carbon ion beam. Several preclinical studies have shown a higher RBE and the physical properties of particle beams allow dose deposition precisely to the defined tumour while sparing surrounding tissue. Also, in contrast to older dose escalation trials, improved imaging for target volume delineation including modern MR sequences as well as PET imaging has been implemented. This is also likely to improve the therapeutic window.

Q: What are the dose and fractionation schedules in both arms?

A: In both arms, patients are treated with 50 Gy photon radiotherapy as chemoradiation with temozolomide to the T2-

hyperintense region including the necessary safety margin. Thereafter, randomisation is performed, in both arms particle therapy is applied. The standard arm includes 10 Gy E, 5 fractions of 2 Gy E up to a total dose of 60 Gy with protons, in the experimental arm 18 Gy E of carbon ions in 6 fractions are applied.

Q: What are the target volume definitions in the trial?

A: Gross Tumour Volume (GTV) is defined as the contrast-enhancing lesion on MRI as well as PET-positive regions. For the base plan, the clinical target volume (CTV) includes the GTV, the T2-hyperintense regions including a safety margin of 2–3 cm. The boost is defined with a boost CTV including the GTV plus a 5-mm safety margin. The PTV is added according to institutional guidelines, as the 50-Gy base plan can also be applied in external institutions and patients come to Heidelberg for boost treatment only.

Q: Are you planning to conduct any translational studies?

A: At our department, blood samples are being collected from all patients within a clinical protocol for subsequent translational projects. Moreover, molecular markers for glioblastoma will be correlated with outcome to identify potential subgroups of patients showing distinct responses and outcomes. However, these measures are not part of the inclusion criteria and immediate study protocol.

Q: How is response assessed in this trial? Do you use specific imaging modalities for response assessment and follow-up?

A: Of course, response criteria include, as outlined in the most recent RANO guidelines, clinical as well as imaging parameters. MRI is used as a regular follow-up and amino-acid-PET is scheduled for specific questions, ie, to differentiate pseudoprogression, radiation reaction, and tumour progression.

Q: How is accrual progressing and when can we expect final data?

A: We are currently still recruiting patients, aiming at a projected number of 150 patients. So, we hope to be able to report some data from the interim analysis when the patient and event numbers defined have been reached.

Q: Finally, can you comment on the very unique names chosen for your trials?

A: I myself always find it difficult to remember trials whose identification only consists of numbers, such as EORTC or RTOG trials. Therefore, I find it helpful to give each trial a special name. It makes it easy for our treating physicians, physicists, and study nurses to keep track on the trial and the patients in them. Also, I found it very positive when patients can remember the name of “their trial” and identify themselves as being members of that trial. Currently, CLEOPATRA has also some Disney sisters, CINDERELLA for recurrent gliomas and MARCIE for atypical meningiomas, but we are also recruiting into some trials with names based on Greek-mythology characters, such as PROMETHEUS, PANDORA, and PHOENIX.

Thank you!

Dr Stephanie Combs is currently vice chairman of the Department of Radiation Oncology in Heidelberg, Germany, and the study coordinator of the CLEOPATRA trial.

Contact Details:

*Stephanie E Combs, MD
Department of Radiation Oncology
University Hospital of Heidelberg
Im Neuenheimer Feld 400
69120 Heidelberg
Germany
e-mail: Stephanie.Combs@med.uni-heidelberg.de*

Correspondence to:

*Ufuk Abacioglu, MD
Department of Radiation Oncology
Neolife Medical Center
Yucel Sok # 6
I. Levent, Besiktas
34340 Istanbul
Turkey
e-mail: ufuk.abacioglu@neolife.com.tr*