Introduction
To retrospectively assess the feasibility and safety of a sequential proton boost following conventional chemoradiation in high-grade glioma (HGG).

Materials and Methods
Sixty-six consecutive patients with HGG were treated at the Department of Radiation Oncology, University Hospital Heidelberg, Germany with 50.0 Gy photons (range: 50.0–50.4 Gy) in 2.0 Gy (range: 1.8–2.0 Gy) fractions (median PTV volume: 394.6ccm), followed by a proton boost with 10 Gy equivalent (Gy(RBE)) in 2.0 Gy(RBE) fractions (median PTV volume: 134.7ccm). The target volume definition for the proton boost volume was initially defined by the prospective CLEOPATRA protocol (GTV + 5mm) and transferred into clinical routine. Patients were matched one to one with 66 patients with HGG undergoing conventional radiation therapy (RT) with 60.0 Gy photons (range: 59.4–60.0 Gy) in 2.0 Gy fractions (range: 1.8–2.0 Gy)(median PTV volume: 369.4ccm).

Results
Median overall survival was similar in both treatment groups (bimodality RT, 19.1 months [4 to 41 months]; photon-only RT, 20.4 months [3 to 53 months]; p = 0.306). The median PTV volume of the proton boost was significantly smaller compared to the median PTV volume of the photon plans (each p<0.001). Acute toxicity was mild in both treatment groups. Toxicity ≥ grade II was observed in 6 patients (9.1%) receiving bimodality RT and 9 patients (13.6%) receiving photon-only RT. Two types of severe adverse events (CTCAE grade III) occurred solely in the photon-only group: severe increase in intracranial pressure (3 cases; 4.5%); and generalized seizures (2 cases; 3.0%). Median PTV of these patients was 384.4ccm. The intensity of all symptoms decreased after corticosteroid therapy or anticonvulsant therapy.
Pseudoprogression was rare, occurring on average 6 weeks after radiotherapy, and was balanced in both treatment groups (n = 4 each; 7.6%).

Conclusion
Using a sequential proton boost in HGG is safe and feasible. Delivering a proton boost to significantly smaller target volumes when compared to photon-only plans, yielded comparable survival rates at lower CTCAE III toxicity rates. Pseudoprogression occurred rarely and evenly distributed in both treatment groups. Thus, bimodality RT was at least equivalent regarding outcome and potentially superior with respect to toxicity in patients with HGG.