olaparib as radiosensitizer to efficacy of olaparib as single agent in cell systems with different genetic backgrounds.

**Materials and Methods:** Mouse mammary tumor cell line with BRCA2 deficiency, its isogenic control cell line with restored BRCA2 function and a panel of human head and neck squamous cell carcinoma (HNSSC) cell lines were treated with different doses of olaparib and radiation. Survival was quantified using proliferation and clonogenic assays. To assess the effect of olaparib and radiation on PARP activity, we measured PAR levels using an ELISA-based immunoassay.

**Results:** As reported previously, olaparib alone has efficacy at significantly lower concentrations in BRCA2-proficient cells than in BRCA2-deficient cells. Efficiency of olaparib alone differed among the human HNSSC cells. Olaparib radiosensitized all tested cell lines, however, to a different extent and at different dose ranges. Importantly, in all but one HNSSC cell line that is hypersensitive to olaparib alone, effective radiosensitization always established at ten-fold lower concentrations than single agent activity. Radiation increased PAR levels in both BRCA2-deficient and BRCA2-proficient cells. Olaparib reduced PAR levels in a dose-dependent fashion and to a similar extent in BRCA2-deficient and BRCA2-proficient cells. Low doses of olaparib that result in effective radiosensitization without concomitant single agent activity fully abolished PAR induction by radiation, without fully abolishing baseline PAR levels.

**Conclusions:** Our results show that olaparib acts as an effective radiosensitizer at significantly lower doses than those required for single agent activity. We conclude that olaparib-induced radiosensitization occurs by the prevention of PAR induction upon radiation, rather than by full PARP inhibition as proposed to be required for single agent activity. From these data we would predict that radiosensitization may be present at low olaparib dose levels in the clinic. This study emphasizes the importance to evaluate the concept of biological optimal dosing in novel radiation-targeted agent combinations.

**OC-0618**

**Evaluation of the therapeutic optimality in radiotherapy for breast cancer with targeted gold nano-particles**

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**Purpose/Objective:** In recent years there has been considerable interest on the use of gold nanoparticles (GNPs) combined with radiotherapy to improve tumor control. Radiosensitization in cancerous cells in presence of GNP has been demonstrated both in vitro and in vivo at kilo- and mega-voltage energies [1,2,3,4]. GNPs exhibit unique physical and chemical properties, and can be designed to interact with various biomolecules, resulting in improved diagnosis and treatments efficacy when bound to molecules that target specific cell receptors. A quantification of the expected clinical improvements is however still lacking. In this work a new approach for estimating the improved nanoparticle-driven radiosensitivity is presented and a quantification of the treatment optimality as a function of GNP uptake is performed.

**Materials and Methods:** In order to assess the biological effects, a stochastic radiobiological model derived from the Local Effect Model (LEM) [5,6] approach was coupled with Monte Carlo simulations performed using Geant4 toolkit, so as to estimate the local dose deposited from secondary electrons at the nanometric level. A closed analytical formulation of the model was also derived for MV irradiation. The model was benchmarked for MDA-MB-231 breast cancer cells with varying gold concentration and then used to investigate breast cancer cases for planned treatments with both 6 MV and 15 MV photons. Treatment simulations of 6 patients were performed for each energy, in which a parametrization of the GNPs uptake with varying tumor selectivity was introduced. The expected treatment optimality as a function of the spatially varying gold uptake was quantified in terms of Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP).

**Results:** Results show good agreement between simulations and experimental clonogenic survival assays for both 6 MV and 15 MV, suggesting that the models could be used to estimate the experimental outcomes in a clinical setup. The breast cancer treatment simulations show improved tumor control when GNPs bound to targeting agents are present. For both treatments with 3 Gy per fraction and 13 fractions (START A) and 2.67 Gy with 15 fractions (START B) [8], a maximum TCP increase of 20% was observed in the 6 MV case, assuming a maximum concentration of 12 μG NGP in the tumoral region.

**Conclusions:** A model to account GNP uptake and tissue radiosensitization was implemented and included in the simulation of breast cancer treatments. In addition to the improved treatment efficacy, the possibility of a short course of fractionation in combination with GNP was also quantified.

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**OC-0619**

**Targeting HSP90 with the small-molecule inhibitor NW457 sensitizes human glioblastoma cells to ionizing radiation**

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**Purpose/Objective:** A common characteristic of glioblastoma multiforme is radioresistance. Hence, novel treatment concepts involve the application of molecularly targeted agents that interfere with pathways mediating glioma cell radiosensitivity and invasiveness. One molecule contributing to glioblastoma cell growth and survival is the heat shock protein 90 (HSP90), a chaperone that regulates the proper folding and stability of numerous client proteins which are involved in promoting tumorigenesis, proliferation, invasion, and survival.

The novel pochoxime-based HSP90 inhibitor NW457 binds to the N-terminal ATP binding site of HSP90, thus leading to the destabilization and proteasomal degradation of crucial client proteins. Here, we report on the mechanisms involved in NW457-mediated radiosensitization of human glioblastoma cell lines as well as on the impact of NW457 on the migratory phenotype.

**Materials and Methods:** DNA damage response regulators were analyzed by qPCR. Treatment response of LN229 and T98G to ionizing radiation in the presence or absence of...
NW457 was assessed by Western blot, flow cytometry, caspase activity, colony formation, wound healing, viability, and transmigration assays. Results: The novel small-molecule HSP90 inhibitor NW457 interferes with the radiodisruptive phenotype of human glioblastoma cells as it sensitized LN229 and T98G cells towards irradiation-induced clonogenic cell death and potently induced apoptosis. NW457 provoked destabilization of critical regulators of the DNA damage response (ATM, ATR, CHK1 and CHK2) and induced activation of caspase-3 with subsequent PARP cleavage. Additionally, NW457 demonstrated potent anti-invasive activities by decreasing the inherent migration of LN229 cells as well as inhibiting irradiation-induced hypermigration. Conclusions: Taken together, our data on HSP90 inhibition as a clinically relevant, novel glioblastoma treatment concept suggests that the novel small-molecule inhibitor NW457 might improve the efficacy of radiotherapy via a dual mechanism involving (i) attenuation of radioresistance through induction of apoptosis and impairment of the DNA damage response and (ii) inhibition of both inherent and radiation-induced migration.

Proffered Papers: Physics 11: Quantifications of imaging for response prediction

OC-0620 Experimental validation of FMISO simulations on tumor xenografts: a question of O2 consumption? L.J. Wack1, D. Mönnich1, A. Yaromina1, D. Zips1, M. Baumann1, D. Thorwarth1
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Purpose/Objective: Tumor hypoxia is prognostic for poor outcome after radiotherapy (RT). A method for non-invasive assessment of hypoxia is positron emission tomography (PET) using radiotracers that accumulate in hypoxic tissue volumes. However, many factors that impact tracer accumulation are not yet fully understood. Here, mathematical simulations may help to further investigate hypoxia PET image formation. The purpose of this study is to validate a dedicated simulation model against experimental data. The model can readily be adapted to a variety of conditions, such as different human head and neck cancer (HNC) cell lines (CLs).

Materials and Methods: Immunohistochemically stained sections of tumor xenografts were available for nine HNC cell lines, providing information on hypoxia (pimonidazole), perfusion (Hoechst 33342), and vessel distribution (CD31). They were used to generate 2D maps of perfused blood vessels, based on which tissue oxygenation and the distribution-retention dynamics for the hypoxia PET tracer FMISO were mathematically simulated in order to generate FMISO distribution patterns four hours post injection. The model includes a Michaelis-Menten relation to describe the oxygen consumption inside the tissue. M0, representing the maximum oxygen consumption, was chosen as parameter for CL-specific optimization as this parameter strongly influences tracer distribution. Simulations were optimized for M0 on each tumor slice to reach optimum correlations between FMISO concentration and pimonidazole staining intensity.

Results: After optimization, very high point-to-point correlations up to R² = 0.85 were found for individual tissue sections. Experimental pimonidazole staining and simulations showed good visual agreement, confirming the validity of the approach. Mean correlations per CL varied significantly (p² ranging from 0.24 to 0.53). The derived maximum oxygen consumption rate M0 differed significantly (p0) was found to correlate significantly with the previously published BrdU labeling index for these CL (p < 0.05). No correlation was found with TCD50.

Conclusions: It is technically feasible to simulate FMISO distributions that match the pimonidazole retention patterns observed in vivo. Good agreement can be obtained for multiple CLs by optimizing the individual oxygen consumption rate, M0, whose optimum value differed significantly between CLs. Optimized M0 correlated with the proliferation marker BrdU, but not with TCD50.

OC-0621 Comparison of perfusion CT parameters and [18F]-FDG uptake in head and neck cancer patients. M. Nesteruk1, S. Lang1, S. Stieb1, H. Hemmatazad1, S. Glatz2, P. Veit-Halbach1, M. Guckenberger1, S. Klöck1, O. Risterer1
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Purpose/Objective: Tumor physiology predicts response to radiotherapy. The aim of this study was to examine and correlate tumor vascularity and glucose metabolism based on [18F]-FDG uptake and perfusion maps.

Materials and Methods: 42 patients with head and neck cancer (15 patients T1/T2 and 27 T3/T4), who underwent [18F]-FDG PET/CT (270 - 410 MBq FDG) examination together with simultaneous perfusion CT (CTP) (40 mL of contrast, 1 s rotations time with 1 image/s, cine duration 50 s, 80 mA, 100 kV), were included in the study. A radiation oncologist contoured primary tumor (GTVPT) and lymph node metastases (GTVLN) in CTP. Using the gradient-based method GTV_H was auto-segmented. Perfusion maps were calculated using singular value decomposition method with in-house developed software. Blood volume (BV), blood flow (BF),