Based on this result, we decided to account for the differences in T stage, overall treatment time and concomitant treatment for the statistical analysis of outcome and toxicity. Mean follow up was 5.68 years in the group without ND and 5.83 years in the group with upfront ND. Local, regional and distant control after 2 years were 91.07% and 85.96% (\( p = 0.09 \)), 89.22% and 83.27% (\( p = 0.12 \)) and 76.74% and 75.13% (\( p = 0.92 \)) in the group with and without upfront ND, respectively. We observed worse OS after 2 years in the subgroup with upfront ND (48.01% vs. 70.79%, \( p = 0.01 \)). The difference in OS can be explained by more secondary primaries in this subgroup with upfront ND and more non-disease related deaths. We did not find a significant difference between both groups regarding edema and atrophy at 6, 12, 18 and 24 months (Figure 1). Regarding fibrosis, we found an overall trend towards worse outcome in the ND group at all time-points (\( p = 0.06 \)). A significantly higher proportion of severe fibrosis (grade ≥2) was present in the ND group (\( p = 0.01 \)) at all time points (Figure 1).

Conclusion: Both treatment regimens have a comparable local, regional and distant control. However, fibrosis and more specifically fibrosis grade ≥2 is more prominent following upfront ND and CRT when compared to CRT alone.

PV-0518
Phase 1 study of Debio 1143 in combination with Concurrent Chemoradiotherapy in LA-SCCHN

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Purpose or Objective: Chemo-radiotherapy (CRT) plays a major role in the management of patients with locally advanced squamous cell carcinoma of head and neck (LA-SCCHN). However, loco-regional (LR) failure remains a significant problem due to the resistance to radiotherapy and chemotherapy. Inhibitors of Apoptosis Proteins (IAPs) are expressed in various cancers and are able to block caspase activation and modulate NF-kB signalling pathways. As such, they represent attractive targets to overcome resistance to both chemo- and radio-therapy. Debio 1143 is a potent orally-available IAP antagonist currently in clinical development able to radiosensitize and ameliorate the effects of platinum derivatives in multiple SCCHN models both in vitro and in vivo. A previous phase I study showed Debio 1143 as a single agent was well tolerated up to 400 mg/day q14d21. This Phase I study defined the dose limiting toxicities (DLTs), maximum tolerated dose (MTD), safety, pharmacokinetic (PK) and pharmacodynamic (PD) of Debio 1143 in combination with CRT.

Material and Methods: Treatment-naïve LA-SCCHN (stage III/IV), negative HPV status for oropharynx, were treated with CRT (70 Gy in 7 weeks + cisplatin 100 mg/m2 every 3 weeks) and escalating doses of Debio 1143, administered orally once daily on days 1-14 every 3 weeks for a maximum of 3 cycles. The starting dose of Debio 1143 was 100 mg/day. Doses were escalated using a Bayesian Continuous Reassessment Method (CRM) until MTD, based on dose limiting toxicities (DLTs) observed within the first 9 weeks
from start of study drug administration. Dose escalation decision and recommended dose (RD) were made by an independent safety committee. Blood PK and PD samples were serially drawn along the 3 cycles.

Results: Fourteen patients were included in the study. DLTs per dose level (DL) are shown in the table with 3 patients experiencing more than one DLT. The RD of Debio 1143 to be combined with CRT was 200 mg/day (=MTD). Debio 1143 exposure increased proportionally with dose and did not accumulate over time. Amylase/lipase and ALT/AST increase as the percentage of the initially prescribed dose; and drug - regimen (6 fractions/week). The compliance was estimated\n
Conclusion: Combination of Debio 1143 with CRT was tolerated, exhibited favourable PK in combination with CRT with significant PD activity. The MTD was found to be 200 mg/day and is now being used in a randomized phase 2 study initiated by GORTEC to evaluate the anti-tumor activity of this combination in LA-SCCHN.

PV-0519
The hypoxic radiosensitizer, nimorazole, in RT of HNSCC: pharmacokinetics, toxicity and compliance M.A.H. Metwally1, J. Overgaard1
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Purpose or Objective: Study of pharmacokinetics (PK), toxicity, and compliance with nimorazole (NIM) which is currently investigated for its efficacy in three large randomized clinical trials (NIMRAD, EORTC 1219/DAHANCA 29, and DAHANCA 30)

Material and Methods: The PK of NIM was studied in 63 patients with HNSCC treated in the DAHANCA-5 trial. While the toxicity and compliance were studied in HNSCC patients treated with NIM, in combination with radiotherapy (RT) or chemo-radiotherapy (CRT), in Denmark between 1990 and 2013. Plasma concentration measurements were done using high pressure liquid chromatography following the first day dose; and plasma concentration profiles were subjected to non-compartmental PK analysis using validated PC-based software. The different PK parameters were calculated and correlated with the different patient- and treatment-related variables. Nimorazole was administered as oral tablets in doses of approximately 1.2 g/m² BSA before the first daily radiation treatment. A second dose of 1 g was given before the second RT fraction in the accelerated fractionation regimen (6 fractions/week). The compliance was estimated as the percentage of the initially prescribed dose; and drug-related side effects were reported from the DAHANCA database.

Results: A linear relationship between peak plasma concentration and administered dose was detected. The mean peak concentration was 36.8 ± 1.3 µg/ml, and the time of peak concentration ranged between 30 and 180 min (median 60 min). Plasma elimination occurred with a mean half-life of 3.35 ± 0.09 h. There was a statistically significant correlation between area under the concentration-time curve (mean 191 ± 6 µg·h/ml) and administered dose, especially when expressed as g/m². A statistically significant longer elimination half-life in men relative to women (mean difference 0.40 h; 95% confidence interval 0.77-0.03; P 0.03) was detected. A total of 1649 patients were investigated for toxicity and compliance with NIM. The compliance was fair, with both conventional and accelerated RT as well as CRT schedules, with 58% of patients received the full prescribed total dose. Nausea and vomiting were the major complaints representing 87% of the known side effects that caused dose reduction. All side effects ceased when treatment was interrupted, and neither severe nor long lasting side effects were observed. Female patients, and patients received accelerated CRT were significantly less compliant with NIM, and more likely to have nausea and vomiting; while patients who received less than 1100 mg/m² per day were significantly more compliant, and less likely to have nausea and vomiting.

Conclusion: The current nimorazole administration practice in clinical trials is acceptable, and the compliance to the drug is fair, either with the conventional or accelerated RT as well as CRT, with tolerable acute, but neither persistent nor late, toxicity.

Symposium: Dose painting: those pending issues

SP-0520
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Purpose To demonstrate that dose painting (DP) is a promising tool to decrease overall treatment time (OTT), to reduce toxicity, to improve palliation or enhance tumor control. The present state of DP will be illustrated through 2 types of applications. We will also speculate about the potential of DP to integrate with novel systemic treatment approaches.

Materials and methods
A. Topographical DP (TDP) in breast irradiation. TDP distributes dose as function of the spatial distribution of subclinical cancer deposits nearby the primary tumor in breast cancer. Patients (n=170) were randomized between prone whole breast irradiation (WBI) followed by a boost (WBI-SeqB; OTT=4 weeks) and WBI with simultaneous integrated boost (SIB) using TDP (WBI-TDP-SIB; OTT=3 weeks). Acute moist desquamation rate was the primary endpoint.

B. DP against bone metastasis pain. There is no dose-response relationship above 8 Gy single dose for the control of pain by uncomplicated bone metastases. This observation triggered the hypothesis that cytokine cascades counteracting palliation are activated by radiation and that their activity is function of the irradiated volume. DP was employed to drastically reduce the irradiated volume. Patients (n=45) were randomly assigned (1:1:1) to receive a single fraction of either 8 Gy with conventional radiotherapy (Conv-8Gy) or 8 Gy with DP (dose range 6-10 Gy) (DP-8Gy) or 16 Gy with DP (dose range 14-18 Gy) (DP-16Gy). The trial was designed for selection of the experimental arm worthwhile of continuing in phase III.

C. DP in loco-regionally advanced head/neck cancer. 18F-FDG-PET-guided DP-treated patients enrolled in 3 dose-escalation studies (n = 72) were matched with standard IMRT-treated patients (n=72) irradiated during the same time period. Median dose in the DP-group was 70.2-85.9 Gy/30-32