head and neck cancer

**PHASE 2, RANDOMIZED TRIAL (CONCERT-2) OF PANTITUMUMAB (PMAB) PLUS RADIOTHERAPY (PRT) COMPARED WITH CHEMORADIOThERAPY (CRT) IN PATIENTS (PTS) WITH UNRESECTED, LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (LASCCHN)**


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**Background:** We evaluated the safety and efficacy of pmab, a fully human monoclonal antibody against the epidermal growth factor receptor, by comparing PRT with CRT in pts with LASCCHN.

**Methods:** Pts with stage III, IVA, or IVB previously untreated LASCCHN of all sites excluding the nasopharynx were randomized 2:3 to open-label CRT or PRT. CRT included 2 cycles of cisplatin 100 mg/m2 during accelerated fractionation radiotherapy (XRT; 70-72 Gy over 6-6.5 weeks). Pmab included 3 cycles at a dose of 9.0 mg/kg with each cycle administered with XRT. This was an estimation study with no formal hypothesis testing. The primary endpoint was locoregional control (LRC) rate at 2 years; key secondary endpoints were progression free survival (PFS), overall survival (OS), and safety. Preplanned HPV subset analysis (determined by p16 status) was performed on available samples.

**Results:** Of 151 treated pts (90 PRT, 61 CRT), 84% were men; median age was 58 years; EOCG PS 0-4; 64%. Overall, the 2-year LRC rate (95% CI) was 51% (40%–62%) for PRT and 63% (47%–72%) for CRT. For both PFS (hazard ratio [HR] = 1.73 [95% CI: 1.07-2.81]; p = 0.03) and OS (HR = 1.59 [95% CI: 0.91-2.79]; p = 0.10), outcomes favored the CRT arm. Of 99 pts with tumors evaluable for HPV, 24% were HPV+.

**Conclusions:** Trends favored the CRT arm for the primary endpoint (LRC rate at 2 years), as well as other measures of efficacy, in this predominantly HPV- LASCCHN population. Small numbers limit conclusions in the HPV+ group. Both PRT and CRT appeared well tolerated.

**Disclosure:** G. Hatoum: Advisory Board Member for AmgenK. Oliner: Amgen stockA. Vandervelde: Corporate-sponsored research (Amgen), full-time employee of AmgenK.All other authors have declared no conflicts of interest.
Table: 1018O: Tumor HPV status: effects on prognosis and efficacy of CT + cetuximab and CT in R/M SCCHN.

<table>
<thead>
<tr>
<th>Population</th>
<th>Comparison</th>
<th>OS</th>
<th>PFS</th>
<th>ORR</th>
</tr>
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<tbody>
<tr>
<td>CT + cetuximab vs CT</td>
<td>Median (months)/rate (%)</td>
<td>HR/odds ratio 95% CI p</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV- (n = 340)</td>
<td>9.7 (0.647-1.043)</td>
<td>0.822</td>
<td>7.3</td>
<td>5.7</td>
</tr>
<tr>
<td>HPV+ (n = 41)</td>
<td>12.6 (0.295-1.338)</td>
<td>0.628</td>
<td>9.6</td>
<td>5.6</td>
</tr>
<tr>
<td>HPV+ vs HPV-</td>
<td>Median (months)/rate (%)</td>
<td>HR/odds ratio 95% CI p</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT + cetuximab (n = 196)</td>
<td>12.6 (0.319-1.098)</td>
<td>0.592</td>
<td>9.7</td>
<td>5.6</td>
</tr>
<tr>
<td>CT (n = 185)</td>
<td>9.6 (0.504-1.355)</td>
<td>0.827</td>
<td>7.3</td>
<td>3.6</td>
</tr>
</tbody>
</table>

HEALTHCARE ASSOCIATED INFECTIONS IN HEAD AND NECK CARCINOMA PATIENTS TREATED WITH CHEMOTHERAPY AND/OR RADIOTHERAPY

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Background: Healthcare associated infections (HAIs) cause prolonged hospitalization, treatment delay and/or interruption, mortality in cancer patients (pts). Head and neck carcinoma (HNC) pts are predisposed to infections due to risk factors such as malnutrition, comorbidity, immunocompromise, lifestyle, site of tumour and often the presence of CVC, tracheal and gastrostomy. We aimed at HAIs, typing and reporting antibiotics susceptibility.

Materials and methods: We analyzed retrospectively 2288 HNC hospital admissions at our dept between 2005 and 2009. Pts admitted with a suspected infection were studied microbiologically. Contaminants were excluded.

Results: One hundred forty HAIs were confirmed in 84 admissions out of 71 pts. Thirty-three pts had more than 1 HAI (range 2-7) and 25 pts had concomitant HAIs (range 2-4). HAIs occurred in pts with advanced disease (56% stage III/IV) or recurrence (33%), during chemoradiotherapy (60%) or CT alone (28%). Moreover 74% of pts had CVC, 47% gastrostomy and 16% tracheostomy. We isolated 140 colonizers pathogens: 49% Gram +, 35% Gram + and 16% fungi. Table1 reports the frequency and site of infection by microorganisms. Eighty-eight percent of P. aeruginosa and 100% of Enterobacteriaceae were sensible to meropenem and piperacillin/tazobactam. Methicillin-resistant S. aurei (MRSA) were 42%, all responsive to daptomycin, linezolid, rifampicin, tetracycline, teicoplanin, vancomycin.

Conclusions: We observed more Gram-related HAIs especially into the respiratory tract. The high frequency of MRSA may require to tailor antibiotics first approach of HNC pts treated with CT and/or RT.

Disclosure: All authors have declared no conflicts of interest.

Table: 1019O

| Infectious Site | Gram + N 49 (35%) | Gram - N 69 (49%) | Fungi N 22 (16%) | | |
|----------------|------------------|------------------|------------------| | |
| Respiratory tract | S. aureus 9 (15%) | P. aeruginosa 18 (30%) | Aspergillus species 2 (3%) | | |
| | Corinbacterium species 3 (5%) | Enterobacteriaceae 16 (27%) | Total 140 (100%) | | |
| | S. pneumoniae 3 (5%) | H. influenzae 6 (10%) | | | |
| Surgical | S. aureus 5 (13%) | P. aeruginosa 6 (15%) | | | |
| | Others 6 (15%) | Enterobacteriaceae 5 (12%) | C. albicans 9 (22%) | | |
| | C. species 5 (13%) | C. glabrata 4 (10%) | 40 (29%) | | |
| Blood | S. epidermidis 9 (26%) | | | | |
| | S. aureus 4 (12%) | | |
| Other | S. aureus 8 (80%) | | | | |

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same CT/RT; Arm B2: 3 cycles of induction TPF followed by CET/RT. A total of 204 deaths (420 pts including the 101 randomized in the II part of the study comparing CT/RT with or w/o induction TPF) were required to detect a HR of death of 0.675 (A1 + A2 vs. B1 + B2: 2-sided a = 0.05, b = 0.20) and a 10% difference in G3-4 in-field mucosal toxicity (A1 + B1 vs. A2 + B2). Results: Accrual was completed (421 pts) in April 2012. By May 2012, 348 patients were evaluable for toxicity during the planned concomitant treatments. 82% of pts were male; median age was 60y; PS of 0 (77.8%) or IV (69%). Sites of disease were: oral cavity: 21.7%, oropharynx: 54.8%, hypopharynx: 23.5%. Data on G3-4 in-field toxicity (primary endpoint) and compliance to CT/RT vs CET/RT are shown in table 1.

<table>
<thead>
<tr>
<th>CT/RT N</th>
<th>CET/RT N</th>
<th>p</th>
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<tbody>
<tr>
<td>215</td>
<td>133</td>
<td></td>
</tr>
<tr>
<td>In-field mucositis Grade 3 Grade 4</td>
<td>37% 4%</td>
<td>35% 2%</td>
</tr>
<tr>
<td>In-field skin reaction Grade 3 Grade 4</td>
<td>13% 1%</td>
<td>20% 1%</td>
</tr>
<tr>
<td>RT median dose, Gy (range)</td>
<td>70 (8-70)</td>
<td>70 (14-70)</td>
</tr>
<tr>
<td>RT median duration, weeks (range)</td>
<td>7 (1-11)</td>
<td>8 (1-14)</td>
</tr>
<tr>
<td>Pts with RT interruption &gt;3days</td>
<td>32%</td>
<td>38%</td>
</tr>
<tr>
<td>RT modification due to acute toxicity</td>
<td>37%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Conclusions: No advantage for CET/RT over CT/RT were observed regarding G3-4 in-field toxicities and feasibility. Pts were therefore followed-up to assess OS. Table 1: Disclosure: All authors have declared no conflicts of interest.

1023PD MODULATION OF THE PERITUMORAL MICROENVIRONMENT BY CETUXIMAB: A WINDOW PRE-OPERATIVE STUDY IN PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (SCCHN)

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Background: Only a subset of SCCHN pts benefits from anti-EGFR mAbs. Trials with pre- and post-therapy tumor biopsies (windows studies) in treatment-naïve patients are crucial to better characterize the molecular pathways involved in treatment response or resistance.

Methods: Cetuximab (C) 400mg/m2 first wk followed by 250mg/m2/wk was given pre-operatively during 2 wks (day 15 until day 1-3) infusions before surgery (day 0) to 20 treatment-naïve SCCHN pts selected for primary curative surgery. As controls, 5 additional pts were included without C treatment but with the same CT/RT; Arm A1: 3 cycles of induction TPF followed by CT/RT; Arm B1: 3 cycles of induction TPF followed by CET/RT. A total of 204 deaths (420 pts including the 101 randomized in the II part of the study comparing CT/RT with or w/o induction TPF) were required to detect a HR of death of 0.675 (A1 + A2 vs. B1 + B2: 2-sided a = 0.05, b = 0.20) and a 10% difference in G3-4 in-field mucosal toxicity (A1 + B1 vs. A2 + B2). Results: Accrual was completed (421 pts) in April 2012. By May 2012, 348 patients were evaluable for toxicity during the planned concomitant treatments. 82% of pts were male; median age was 60y; PS of 0 (77.8%) or 1 (22.2%). Stage was III (31%).

| In-field mucositis Grade 3 Grade 4 | 37% 4% | 35% 2% | 0.79 0.45 |
| In-field skin reaction Grade 3 Grade 4 | 13% 1% | 20% 1% | 0.07 0.05 |
| RT median dose, Gy (range) | 70 (8-70) | 70 (14-70) | 0.32 |
| RT median duration, weeks (range) | 7 (1-11) | 8 (1-14) | >0.01 |
| Pts with RT interruption >3days | 32% | 38% | 0.22 |
| RT modification due to acute toxicity | 37% | 40% | 0.58 |

Conclusions: No advantage for CET/RT over CT/RT were observed regarding G3-4 in-field toxicities and feasibility. Pts were therefore followed-up to assess OS. Table 1: Disclosure: All authors have declared no conflicts of interest.

1023PD TEMSIROLIMUS IS ACTIVE IN REFRACTORY SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (SCCHN) FAILING PLATINUM-BASED CHEMOTHERAPY AND CETUXIMAB: EFFICACY AND TOXICITY DATA FROM THE PHASE II TEMHEAD STUDY

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Background: Prognosis of patients with failure of cisplatin-based 1st line chemotherapy for recurrent or metastatic SCCHN remains poor. We therefore evaluated temsirolimus after failure of cisplatin and cetuximab in SCCHN.

In-field mucositis Grade 3 Grade 4 13% 1% 20% 1% 0.05 0.06
Methods: Patients with progressive SCCHN and failure of platinum-based chemotherapy and cetuximab were eligible. Patients with loco-regional recurrence as the sole lesion had to have a progression free survival (PFS) of at least 6 months from last therapy. 18 years of age, ECOG 0-2, life expectancy of at least 3 months, and adequate organ function are key inclusion criteria. Brain metastases were allowed, provided local therapy has been completed successfully. Tumor assessment was performed every 6 weeks and assessed according to RECIST 1.0. Primary endpoint was the progression free survival rate (PFS) at 12 weeks. Secondary endpoints were time to progression (TTP), objective response rate (ORR), overall survival and toxicity (according to CTCAE 3.0). 25 mg temsirolimus was given iv. weekly until progression or toxicity precluded. PFS, PFR, and OS estimates were calculated by Kaplan-Meier-Curves. Results: A total of 42 patients entered the trial, of whom 40 were eligible. TTP/median progression status of 0/12 was found in 72/95 pts and missing in 1 patient. Mean age was 61.6y (range: 42-79y) with male predominance (31 pts; 74%). Progression free survival rate at 12 weeks was 40% (C395% 36-113d), and OS 152d (C95% 76-256d). Stable disease (SD) was obtained in 19 pts (56%), progressive disease (PD) in 10 pts (29%), 1 pts was not evaluable for response, and 10 pts had missing scans. Treatment with temsirolimus was well tolerated. Safety data will be presented at the meeting.

Conclusions: Temsirolimus reaches its prespecified endpoint with a PFR at 1.2weeks of 40%. Future data is encouraging and comparing to single agent cetuximab activity in platinum-refractory SCCHN. Further studies with this drug in SCCHN are warranted.

Disclosure: V. Grünwald: research funding: Pfizer Advisory Board: Merck KGU. Khililol: Research support and honorarium Whyeth / Pfizer.T.C. Gauler: ADVISORY BOARD: MERCK KG, Pfizer HONORARIA: Pfizer. All other authors have declared no conflicts of interest.

Background: Outcomes for locoregionally advanced nasopharyngeal carcinoma (NPC) patients have certainly improved with chemoradiation but eventually local and distant failure remains a very important clinical problem. An earlier study showed increased c-Met and VEGF expression in NPC sample compared to normal nasopharyngeal tissue. XL880 (Fosun Innovent, Shanghai) is an oral, ATP-competitive small molecular inhibitor against multiple kinases, in particular c-Met and VEGFR2 which are involved in tumor cell growth, migration, and angiogenesis. The objective of this study was to investigate the therapeutic potential of XL880 in NPC.

Methods: Expressions of total and phosphorylated c-Met, VEGFR2, PDGFR, AXL and Tie-2 were evaluated by western blot in a panel of six NPC cell lines. The effect of XL880 on NPC cell proliferation was evaluated by Titer-Glo luminescent Cell Viability Assay. We further studied the effect of XL880 on NPC cell cycle and apoptosis. In vivo activities of XL880 as single agent and in combination with Cetuximab were investigated in NPC xenografts.

Results: In vitro study showed that XL880 inhibited phosphorylation of both c-Met and VEGFR2. XL880 repressed the growth of both c-Met amplified tumor cells and endothelial cells stimulated with HGF or FGF. For the most XL880 sensitive NPC cell line (H1K-LMP1), which harbored the highest levels of both c-Met and VEGFR2, inhibition of cell growth was associated G0/G1 cell cycle arrest as well as significant downregulation of FAK, Mcl-1 and cyclin D1. XL880 eliminated ~70% of tumor vasculature in xenograft models, inhibited tumor growth, and slowed regrowth of the tumor vasculature after drug withdrawal. Importantly, XL880 decreased invasiveness of primary tumors and reduced metastasis. XL880 in combination with Cetuximab achieved greater antitumor responses than treatment with either agent alone in NPC xenograft models. Additionally, miRNA levels of EGFR ligands TGF alpha and Epirulin were significantly downregulated by XL880 in vivo.

Conclusions: This is the first report of preclinical activity of c-Met/VEGFR2 inhibitor XL880 in NPC. LMP1 (latent membrane protein 1)-positive NPC shows a higher sensitivity to XL880. Further clinical investigation of XL880 is warranted in NPC patients.

Disclosure: All authors have declared no conflicts of interest.

Additional data not available.
The aim of this retrospective review is to evaluate the effect of induction chemotherapy and to correlate between EBV-DNA concentration and tumor response by PET-CT.

**Methods:** Patients with stage III-IVB, WHO II/III received induction chemotherapy with 2 cycles of TPF: Docetaxel 75 mg/m², cisplatin 75 mg/m², 5-fluorouracil 750 mg/m² CI for 96 hours followed 3-4 weeks later by concurrent weekly cisplatin (40 mg/m²) and IMRT (GTV/70 Gy over 35 fractions). EBV-DNA quantification was performed at baseline and repeated before each cycle of TPF. PET scans were performed at baseline and repeated before IMRT. The max standard uptake values (SUV) were recorded in the primary tumors. Metabolic response was defined as a decrease in maximum SUV of 35% or more.

**Results:** 20 patients with LA-NPC (75%Stage IVA/IVB) were reviewed. All but one completed therapy. Objective response, according to RECIST criteria: CR: 4, PR: 14 NE: 2. Median concentration of EBV-DNA was 11,300 copies/ml (range: 1,184 - 43,000). Post TPF, reduction of EBV-DNA copies by >50% was observed in 83% pts and 66% achieved complete biochemical response. In the FDG-avid tumor pts, the median SUV at baseline was 12 (range: 10.5 - 17.4); post TPF metabolic response was observed in 100% and was complete in 33%. All patients with complete biochemical response had a also complete metabolic response by PET. At 2-year loco-regional progression free rate is 95% and 2 year overall survival rate is 85%. No recurrence was seen in complete (biochemical / metabolic) responders.

**Conclusion:** A negative post induction FDG-PET and complete biochemical response after TPF are of significant value in LA-NPC and are useful determinant to predict outcome.

**Disclosure:** All authors have declared no conflicts of interest.

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**Annals of Oncology**

**1030P**

**INSULIN GROWTH FACTOR RECEPTOR AS A PROGNOSTIC MARKER IN OPERABLE SQUAMOUS-CELL LARYNGEAL CANCER**

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**Introduction:** Prognosis of patients with operable squamous-cell laryngeal cancer is highly variable and therefore potent prognostic biomarkers are warranted. The Insulin-Growth Factor Receptor (IGFR)-mediated signaling pathway plays a critical role in laryngeal carcinogenesis.

**Patients and methods:** We identified all patients with localised TNM stage I-III laryngeal cancer managed with potentially curative intent between May 1985 and June 2008. Immunohistochemical (IHC) expression of IGFR-alpha, IGFR-beta and IGFR2 was evaluated using the Histo-score (H-score) climax and mRNA levels of important effectors of the IGFR-mediated pathway were assessed, including IGFR1, IGF-binding protein 3 (IGFBP3), suppressor of cytokine signaling 2 (SOCS2) and members of the MAP kinase (MAPK1, MAPK9) and phosphatidylinositol-3 kinase (PIK3CA, PIK3R1) families. Cox-regression models were applied to assess the predictive value of the components of the IGFR-mediated pathway on disease-free survival (DFS) and overall survival (OS).

**Results:** Among 289 eligible patients, 95.8% were male, 95.2% were current or ex smokers, 75.4% were alcohol abusers, 15.6% had node-positive disease and 32.2% had received post-operative irradiation. After a median follow-up of 74.5 months, median DFS was 94.5 months and median OS was 106.3 months. Using the median H-score as the pre-defined cut-off value, IGFR-alpha overexpression was associated with decreased DFS (p = 0.0538) and OS (p = 0.0157). Increased mRNA levels of MAPK9 were associated with prolonged DFS (p = 0.0209) and OS (p = 0.0108), as were increased mRNA levels of PIK3CA, albeit not significantly (p = 0.0723 and 0.0726 for DFS and OS respectively). In multivariate analysis, IGFR-alpha overexpression was associated with a 46.6% increase in the probability for relapse (p = 0.0374). Independent predictors for poor OS included node-positive disease (HR = 2.569, 95%CI: 1.610-4.100, p = 0.0001); subglotic or transglotic location (HR = 1.756, 95%CI: 1.016-3.036, p = 0.0438) and IGFR1-alpha IHC overexpression (HR = 1.475, 95%CI: 1.000-2.178, p = 0.05).

**Conclusion:** IGFR-alpha IHC overexpression may serve as an independent predictor of relapse and survival in operable laryngeal cancer. Prospective evaluation of IGFR-alpha prognostic utility is warranted.

**Disclosure:** All authors have declared no conflicts of interest.
Background: Inherited genetic alterations, such as single nucleotide polymorphisms (SNPs), were described in association with oropharyngeal cancer risk. However, existing studies have analyzed a limited number of genetic variants. Base of tongue (BT) squamous cell carcinoma (SCC) is a common tumor of oropharynx; however, the association of SNPs and BTSCC risk is still not clarified and, therefore, this was the aim of the present study.

Methods: Genomic DNA of 49 BTSCC patients and 49 controls was extracted from peripheral blood samples using the QIamp kit (Qiagen®). Each sample was genotyped individually using DNA high-resolution microarrays containing 500,568 SNPs array 5.0 (Affymetrix®). Further sample processing, including digestion, adaptor ligation, amplification, fragmentation, labeling, hybridization, washing and scanning was assayed according to the standard protocol. Genotype data were acquired by genotyping calling of samples using the clarm algorithm provided by Bioconductor software. The differences between groups were analyzed by the logistic regression model. The SNPs localized in genes of interest were selected by the base analysis in DAVID and NCBI websites. The validation of selected SNPs was performed by RT-PCR, using TaqMan® SNP Genotyping Assays (Applied Biosystems) in all samples studied.

Results: We observed 6.609 SNPs with distinct frequencies between BTSCC patients and controls. Fifty-two SNPs (0.8%) were located in coding sequence (CDS), 51 (0.8%) in 3’ and 5’-untranslated regions (UTR), 3,461 (52.4%) in up or downstream regions (DWS) and 3,045 (46.0%) in introns. Ten SNPs were selected for validation and eight of them were validated, evidencing those localized in genes related to cell regions (DWS) and 3,045 (46.0%) in introns. Ten SNPs were selected for validation and eight of them were validated, evidencing those localized in genes related to cell regions (DWS) and 3,045 (46.0%) in introns. Ten SNPs were selected for validation and eight of them were validated, evidencing those localized in genes related to cell regions (DWS) and 3,045 (46.0%) in introns.

Conclusions: In laryngeal cancer, an interaction of high mTOR and cyclin D1 mRNA interaction, were independent predictors of relapse, while node-positive status and subglottic-translational localization were associated with higher risk of death.

Disclosure: All authors have declared no conflicts of interest.

103P STUDY ON ASSOCIATION OF POLYMORPHISM OF CYP P 450 2D6 WITH HEAD AND NECK CANCER AND TREATMENT RESPONSE IN PATIENTS RECEIVING NEOADJUVANT CHEMOTHERAPY (TPF) FOLLOWED BY CHEMORADIATION

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Aim of study: 1.To study the association of genetic polymorphism in CYP 2D6 in patients of locally advanced head and neck cancer. 2. Try to assess a correlation between this polymorphism & response to treatment. Need of the study: To find out a possible genetic level explanation for the different response achieved in patients with similar histopathology, stage, exposure to carcinogen & ethnicity undergoing similar treatment.

Material & method: A study comprising of 150 patients & 150 controls was done to analyse the association between polymorphs of Cyp 450 2D6 with Head & neck cancer and treatment response (TPF- > CTRT). Two cycles of TPF(paclitaxel-175 mg/m2 D1, cisplatin 35 mg/m2 D2-D3 and 5Fu 1gm/m2 D1-D3 ) were given followed by radiotherapy with concurrent cisplatin (40 mg/m2).The response to the treatment was assessed clinically, radiologically & by laryngoscopy- post treatment. Genotyping of the blood samples was done. Analysis of the association between genetic polymorphisms and risk of HNSCC was estimated by calculating crude odds ratio (OR). A p-value of <0.05 was considered statistically significant. The statistical analysis was performed with the SPSS software package (version 11.0 for Windows; SPSS Chicago, IL).

Results: 1. Patients with Cyp 2D6*1 showed good response to the therapy given, while Cyp 2D6*4 and “10 were poor responders.

Conclusion: 1. There is a strong association of polymorphs of Cyp 2D6 (*4 &*10) with occurrence of head and neck cancer. 2. Response to treatment (TPF- > CT + RT) is polymorph graded. Our study, thus provides an insight in to the concept of “Right therapy to the right patient” & may also explain to the fact that why, only some people are more prone to develop head and neck cancer despite the usage of tobacco/alcohol by so many people. Disclosure: All authors have declared no conflicts of interest.
patients. We have developed a randomized trial comparing the efficacy and toxicities of CCRT versus NAC-RT for locally advanced nasopharyngeal cancer.

Patients and methods: A total of 175 patients were included in the study. The 87 patients received concurrent radio-chemotherapy daily 70 Gy/7 weeks with cisplatin 100 mg/m² 3 weeks then followed by adjuvant chemotherapy for 3 cycles (q 3 weeks), consisting of cisplatin 80 mg/m² on day 1 and 5-FU 1,000 mg/m² on day 1-4. The 88 patients received neoadjuvant chemotherapy for 3 cycles (q 3 weeks) consisting of docetaxel 75 mg/m² on day 1, cisplatin 75 mg/m² on day 1, and 5-FU 750 mg/m² on days 1-4 followed by concurrent radiotherapy daily 70 Gy/7 weeks with carboplatin AUC 1.5 weekly for 6 weeks.

Results: The number of patients who completed the treatment for the CCRT group was 34 (39.1%) and for the NAC-RT group was 54 (61.4%). The most common reasons for study discontinuation were adverse events and patient’s willingness. The grade 3 and 4 treatment-related adverse events were two times higher in the CCRT group (p < 0.06), mostly mucositis / stomatitis and nausea / vomiting. There was no difference in hematologic adverse events between groups. The 1-year progression-free survival rate was 91.8% and 89.3% in the CCRT and NAC-RT group, respectively. No evidence of disease at the time of this interim analysis was found in 76.5% in the CCRT group and 85.2% in the NAC-RT group.

Conclusion: Induction chemotherapy with docetaxel / cisplatin and 5-fluoro-uracil followed by concurrent radio-chemotherapy was tolerable and provided well control of disease. These interim results early revealed no difference in PFS but less side effects and increase number of the patients with no evidence of disease in the NAC-RT arm.

Disclosure: All authors have declared no conflicts of interest.

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reduction and 38 patients received RT at the full dose. Three months after therapy completion tumor response was observed in 33 patients and after 2 years, 25 patients were in complete remission. Although treatment was accompanied with a rate of grade 3 and 4 toxicity of 30% during induction chemotherapy and up to 68% during radiotherapy with cetuximab, our treatment seems feasible. Toxicities resolved within 3 months after end of treatment and only two patients became dependent on gastric feeding tubes after two years, compared to 21 patients during treatment. We lost one patient because of treatment related toxicity and 73% of the 49 included patients finished treatment without dose reduction or delay of treatment. 2-year progression-free survival rate was 59% and 2-year overall survival rate was 63%, respectively.

Conclusion: Concurrent radiotherapy plus cetuximab after three courses of induction chemotherapy was feasible and associated with promising complete remission, progression-free and overall survival rates. Further optimization of dose and sequence is warranted.

Disclosure: All authors have declared no conflicts of interest.

1039P
INDUCTION CHEMOTHERAPY USING DOCETAXEL, CISPLATIN AND FLUOROURACIL (TPF) FOLLOWED BY CONCURRENT CHEMORADIOThERAPY VS THE SAME CONCOMITANT CHEMORADIOTHERAPY IN PATIENTS WITH LOWLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (LASSCHN)

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Background: Concomitant chemoradiotherapy (CCRT) with cisplatin is considered a standard treatment of LASSCHN. The role of induction chemotherapy (IC) followed by CCRT remains controversial. Our aim was to compare neoadjuvant chemotherapy with 3 cycles of TPF followed by CCRT to CCRT alone. The 1ry objective of the study was ORR and the 2ry objectives were toxicity, PPS and OS.

Patients and methods: Between 2006 & 2008, 100 patients with histologically proven SCC of the Head & Neck (stage IB-IVA) were enrolled. WHO PS 0-1, with a bone marrow, liver and kidney functions. Fifty patients received 3 cycles of IC including docetaxel 75 mg/m2 IV over 1h D1, cisplatin 75mg/m2 IV over 3h D1 and 5-FU 750 mg/m2 IV continuous infusion over 24 h D5 (repeated every 3 wks). Premedications before and after docetaxel and cisplatin with prophylactic antibiotic on D5 and G-CSF on D6. This was followed by CCRT in the form of radiotherapy using conventional fractionation (2 Gy/day, 5 f/wk, total dose of 76Gy) with concurrent weekly cisplatin 20 mg/m2 IV (Gp A). In gp B, patients received CCRT alone. Response was assessed by physical examination, CT scan and endoscopy after 2 cycles, after completion of IC, and 6-8 wks after completion of CCRT.

Results: All patients in both gps had completed the treatment schedule and were evaluable for response, toxicity and survival. The median age was 44.5 years in both gps (range 27-62). Seventy percent of patients had PS 0, 65 patients had cervical LN evaluable for response, toxicity and survival. The median age was 44.5 years in both groups. Severe side effects in both groups were mucositis and weight loss. The 2-year PFS and OS rates were 70%, 86% and 75%, 80% respectively.

Conclusion: Induction chemotherapy using TPF followed by CCRT is safe, tolerable and effective treatment and can significantly improve survival in patients with LASSCHN.

Disclosure: All authors have declared no conflicts of interest.

1040P
THE IMPACT OF INDUCTION CHEMOTHERAPY ON CISPLATIN ULTRALOW-DOSE INTERLEUKIN-2 THERAPY IN CARRIERS OF A 379T Mutation in the interleukin-2 (IL-2) RECEPTOR (CTRT) IN OPHRAPHYGICAL SQUAMOUS CELL CANCER (OPC)

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Background: Induction (IC) with TPF (Taxotere, Cisplatin, 5-FU) has been associated with improved outcome in advanced head and neck squamous cell cancer patients (pts). Full dose of cisplatin (300 mg/m2) during CTRT has been demonstrated to impair patients’ outcome. The aim of the current study is to investigate whether the IC could impact on cisplatin dose intensity during CTRT in a homogeneous population of OPC.

Materials and methods: The study population consisted of 101 pts with stage III-IV OPC treated from 07/2004 to 12/2011 with IC (n = 53) plus CTRT or CTRT alone (n = 48). IC consisted of TPF, while weekly 50 mg/m2 or 3-weekly 100 mg/m2 cisplatin was administered concurrently with RT (planned chemotherapy dose = 300 mg/m2); planned RT dose = 66-70 Gy, 3DRT or IMRT with a conventional or accelerated fractionation). Carboplatin substituted cisplatin in case of creatinine clearance less than 60 mL/min. HPV status, concurrent cisplatin dose intensity and RT overall treatment time (OTT) were analyzed.

Results: Stage IV pts were 100% in the IC group and 83% in CTRT, while HPV-positive OPCs were detected in 58% and 63% of the cases respectively. TPF median number of cycles was 3, with a mean cisplatin median dose administered of 200 mg/m2; RT median total dose administered was 70 Gy in both group. Accelerated fractionated RT was adopted in 65% of CTRT alone group and in 21% of IC group. Two pts (1 in each group) did not complete CTRT because of cardiovascular events. Median cisplatin dose intensity was 77.7% and 75% (35%-100%) while in CTRT group was 86% and 91.7% (33%-100%), with a p value = 0.014. In 11 pts (21%) treated with IC and only in 1 pts (2%) treated with CTRT alone cisplatin was substituted with carboplatin. No different cisplatin dose intensity was identified in HPV positive versus HPV negative cases. Prolonged OTT (longer than 5 days) was observed in two patients in IC group due to sepsis and severe mucositis as well as in one patient in CTRT group due to machine failure.

Conclusions: Concurrent cisplatin dose intensity was significantly reduced in pts receiving IC compared to CTRT alone, irrespective of HPV status. Whether this has an impact on the results of IC followed by full dose CT/RT has to be clarified.

Disclosure: All authors have declared no conflicts of interest.

1041P
THE TOLERANCE OF TPF CHEMOTHERAPY REGIME STANDARD OR MODIFIED IN HEAD NECK CANCER PATIENTS OVER 65 YEARS OLD

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Background: Docetaxel, cisplatin, 5FU regimen (TPF) has became a standard for induction chemotherapy in locally advanced squamous cell cancer of head and neck (SCCHN). However, little is known about tolerance and efficacy of TPF in older patients. Objective of the study was to evaluate the tolerance of induction chemotherapy with TPF regimen in SCCHN patients over 65 years, looking for side effects especially degree 3 and 4.

Materials and methods: Retrospective study of the database of Head and Neck Cancer Department of Gustave Roussy Institute between 2006 and 2009: all patients over 65 years who received a TPF induction chemotherapy were included.

Results: Among 300 patients treated with TPF induction chemotherapy, we found 57 pts over 65 years : 41 (70%)between 65 - 70, 9 (15%)between 70 - 75 and 7 (12%) over 75. Most of patients received an organ preservation treatment for T3N0-1M0 hypopharynx and larynx cancer (52%). 30 pts had an impaired nutritional status and 37(64%) an ACE 27 index superior of 2. 40 pts (70%) accomplished their planed cycles but only 37(65%) received the planned doses. 23 pts (41%) presented a grade 3 or 4 hematological or gastrointestinal adverse events and 5 toxic deaths were observed.

Conclusion: This retrospective study confirms the high risk of toxicity of induction chemotherapy with TPF combination in elderly SCCHN patients that may compromise the postoperative outcome in patients over 65 years presenting at least one comorbidity and demnitrity. Geriatric assessment is probably useful in this population to better select candidates to induction chemotherapy.

Disclosure: All authors have declared no conflicts of interest.

1042P
SERIAL COMPREHENSIVE GERIATRIC EVALUATION IN ELDERLY HEAD AND NECK CANCER PATIENTS UNDERGOING RADIOTHERAPY

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Background: Elderly head and neck (H&N) cancer patients can present with significant co-morbidities whilst treatment induces additional morbidity. Comprehensive geriatric assessment (CGA) has been proposed as a key treatment approach in elderly cancer patients. We studied the feasibility of serial CGA during radiotherapy in this population.

Material and methods: Patients aged ≥ 65 years with primary H&N cancer undergoing curative radiotherapy (with or without systemic treatment), were
evaluated by the screening instruments Vulnerable Elders Survey-13 (VES-13) and G8, and CGA, at baseline and in the 4th week of their treatment at General Hospital Groeninge or Ghent University Hospital.

Results: Ninety eligible patients with a median age of 72 (range 65-87) consented. Patients mostly presented with an advanced stage tumour (67.8%, stage III-IV) of the larynx (46.7%) and pharynx (32.2%). Thirteen patients declined assessment in the 4th week of therapy. Of those patients, one withdrew from further study participation, one died and in two patients, a change of therapeutic intent was indicated. Nine patients declined because they felt too ill. At baseline, 40.3%, 64.9% and 71.4% of patients were defined vulnerable, based on respectively VES-13 (cut-off ≥3), G8 (cut-off ≤14) and CGA (defined as impairments in two or more domains).

Significantly more patients were considered vulnerable at week 4 by VES-13 (55.8%, P < 0.0001), G8 (90.9%, P < 0.0001) and CGA (81.8%, P < 0.05). Patients presented with deficits in the following domains: co-morbidity (CIRS-G), nutrition (MNA), community functioning (IADL), physical status (Tinetti), self-care (ADL), emotional wellbeing (GDS) and cognition (MMSE) at both points in time. In addition, the incidence of vulnerability in all health domains increased during treatment, with especially deterioration of nutritional (P < 0.0001), functional (P < 0.0001), mental (P < 0.0001) and emotional (P < 0.001) status.

Conclusion: Serial CGA identifies multidimensional health problems and their evolution during therapy. It indicates the need for re-evaluation of a patient’s health status and could guide intensive supportive care in elderly patients treated for HN& cancer. Acknowledgement: Our work is supported by a grant from the Belgian Government, National Cancer Plan (NKp_024_018).

Disclosure: All authors have declared no conflicts of interest.

PHASE II STUDY OF BIWEEKLY DOSE-INTENSE PACITAXEL PLUS GEMCITABINE (GEM/TAX) IN PATIENTS WITH RECURRENT LOCOREGIONAL OR METASTATIC HEAD AND NECK SQUAMOUS CELL CARCINOMA

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Background: Patients with metastatic head and neck squamous cell carcinoma (HNSCC) have a poor prognosis, limited treatment options, and median survival of 6 to 9 months. Paclitaxel (TAX) and gemcitabine (GEM) have both shown activity in HNSCC. The optimal combination, dosing, and scheduling of both drugs is, however, unknown. Thus, we investigated the efficacy and safety of biweekly dose-intense GEM/TAX in patients with recurrent locoregional or metastatic HNSCC.

Methods: An open-label, single-institution, single-arm, phase II study was conducted for patients (pts) who were previously treated with no more than two cytorexicotic regimens. The pts received paclitaxel (150 mg/m² IV) and gemcitabine (3000 mg/m² IV) on day 1 and 15. The treatments were repeated every 28 days (one cycle), until disease progression or unacceptable toxicity. The primary end point was response rate. RECIST-defined response was evaluated every 2 cycles (8 weeks) and toxicities were evaluated after each cycle (4 weeks).

Results: Fifty-five pts were enrolled into the trial (M: F 42:13, median age (range): 56 (23-84), performance status 0-2, 48 pts had previous radiation therapy and 39 had previous surgery), 41 of whom were response evaluable. Of these 41 patients, two pts (4.8%) achieved complete response (CR) and 17 (41.4%) demonstrated a partial response (PR). Thus, the overall response rate was 46%. Thirteen pts (31.7%) had stable disease (SD), resulting in tumor control in 32 of 41 pts (78% with CR, PR or SD), whereas 9 pts (21.1%) had disease progression (PD). Among those pts who achieved objective response or stable disease, the median response duration was 5 months and median time to progression was 4 months. Median overall survival (OS) was 15 months. Myelosuppression was the most common adverse event. Grade 3-4 neutropenia and anemia were observed in 5 (12%) and 11 (26%) pts, respectively. Eight (19%) pts developed grade 3 infection. None of these pts, however, had febrile neutropenia and there were no treatment-related deaths.

Conclusions: The combination of biweekly dose intense GEM/TAX was tolerable and active regimen in patients with recurrent locoregional or metastatic HNSCC. Our findings warrant further investigation in a larger patient population.

Disclosure: All authors have declared no conflicts of interest.

PHASE IB TRIAL OF IMO-2055 IN COMBINATION WITH 5-FU, CISPLATIN AND CETUXIMAB IN 1-LINSTE PPTS WITH RECURRENT/METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (R/M SCCHN)


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Purpose: IMO-2055 is a toll-like receptor 9 agonist with potential to enhance the efficacy of antitumor agents through immune stimulation.

Methods: IMO-2055 was administered to 1-line pts with R/M SCCHN on days 1, 8 and 15 of each 3-wk cycle in combination with 5-FU, cisplatin and cetuximab. IMO-2055 doses were to be escalated (3 + 3 design) from dose level (DL) 1 (0.16 mg/kg) to DL2 (0.32 mg/kg) and DL3 (0.48 mg/kg) if ≤3 pts or ≤2 pts in the previous DL had dose-limiting toxicities (DLTs). DLTs were defined as any Gr3/4 treatment-related toxicity in cycle 1 confirmed by the safety monitoring committee (SMC). Expansion cohorts were planned at DL1 and at the maximum tolerated dose (MTD) level. A maximum of 6 cycles of combined treatment was planned; pts were to continue cetuximab and IMO-2055 until disease progression. Primary objective was to determine the MTD; other objectives included evaluation of safety profile, PK and tumour effects.

Results: 13 pts (1 F, 12 M) with a median age of 59 (range 42-67) yr received IMO-2055. No DLTs occurred at DL1 (n = 3); at DL2 (n = 4), 2/4 pts experienced DLTs. Although during the DL1 expansion cohort (n = 6), only 1 pt experienced DLTs, the overall safety profile of the combined treatment led to early trial termination. Formally, DL1 (0.16 mg/kg IMO-2055) can be considered as the MTD although it was not confirmed by the SMC, as the trial was prematurely stopped. 12 (92%) pts experienced Gr ≥3 treatment-emergent adverse events (TEAEs) with 4 pts having Gr ≥3 TEAEs related to IMO-2055. 1 patient died during the trial with serious AEs related to IMO-2055. Most frequently reported Gr ≥3 TEAEs were neutropenia (DL1 = 78%; DL2 = 50%), hypokalemia (DL1 = 22%; DL2 = 75%) and hypomagnesaemia (DL1 = 11%; DL2 = 75%). PK assessment was very limited; partial responses were observed in 3/13 pts.

Conclusion: High rates of Gr ≥3 neutropenia and electrolyte disturbances were observed. Based on the overall safety data, regimens combining IMO-2055, cetuximab, 5-FU and platinum-containing chemotherapy cannot be recommended for phase II trials.

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OUTCOME OF OROPHARYNGEAL CANCER ACCORDING TO TREATMENT IN DIFFERENT RISK-PROFILE GROUPS: AN ANALYSIS OF A RETROSPECTIVE SERIES OF PATIENTS TREATED IN A TERTIARY CANCER CENTRE

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Background: Epidemiology and outcome of oropharyngeal cancer (OPC) are changing in the last decades, due to the role of HPV infection. No different treatment modality has been identified as more effective in treating OPC according to HPV or smoking status.

Material and methods: Two series of locally advanced (stage III-IV) squamous cell OPC patients (pts) treated at our Institution were considered1) treated with surgery followed by radiotherapy (dose 50-66 Gy), from 1/1991 to 7/2000 ("surgical series"), 2) receiving concurrent chemoradiation (CTRT) (RT dose = 66-70 Gy), with/without induction docetaxel, cisplatin, 5-fluorouracil (TPF) chemotherapy (CT), from 7/2004 to 3/2011 ("CTRT series")Smokkis L, et al. Expression of HPV16 integrated in order to stratify each series according to Ang risk profile (low, intermediate, high risk). Overall survival (OS) and disease free survival (DFS) were calculated with Kaplan-Meier method.
Results: Globally, 171 pts were considered, 56 in surgical and 115 in CRTT series. In CRTT series, 40% of the pts received induction TPF chemotherapy; in surgical series 57% of the pts had extracapsular extension and/or microscopically involved surgical margins.

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<tr>
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<th>Surgical series</th>
<th>CRTT series</th>
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<tr>
<td>p16 expression</td>
<td>39%</td>
<td>59%</td>
</tr>
<tr>
<td>Stage III</td>
<td>13%</td>
<td>7%</td>
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<tr>
<td>Stage IV</td>
<td>87%</td>
<td>93%</td>
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<tr>
<td>Low risk</td>
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<td>Intermediate risk</td>
<td>23%</td>
<td>41%</td>
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<tr>
<td>High risk</td>
<td>57%</td>
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Five-year (yr) OS for p16 positive pts was 50% in surgical and 88% in CRTT series, while for p16 negative was 38% and 49% respectively (p < 0.001). When stratifying for risk profile, 5-yr OS of low risk CRTT pts was 100% vs 54% of surgical pts (p = 0.0042) and 5-yr DFS was 93% vs 53% (p = 0.0079); 5-yr OS of intermediate risk CRTT pts was 76% vs 46% of surgical pts (p = 0.0141) and 5-yr DFS was 79% vs 38% (p = 0.0359). High risk CRTT pts had a 5-yr OS of 51% vs 36% of surgical pts (p = 0.1902) and a 5-yr DFS of 24% vs 36% (p = 0.6411).

Discussion: In this retrospective analysis, low and intermediate risk OPC pts had a greater survival benefit when treated with CRTRT compared with surgery followed by RT. Although with the limits of different RT techniques and lack of CT in adjacent to postoperative RT, these data should be considered as hypothesis generating for new trials design.

Disclosure: All authors have declared no conflicts of interest.

Disclosure: All authors have declared no conflicts of interest.

EDT 1046P ELECTROCHEMOTHERAPY (ECT) WITH BLEOMYCIN AS A PALLIATIVE TREATMENT OF REGIONAL RELAPSE IN HEAD AND NECK CANCER (H&NC) PATIENTS (PTS). A PILOT STUDY

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Background: ECT is the administration of electrical pulses in the tumour during perfusion of chemotherapy allowing the introduction of the drug in neoplastic cell. H&N regional relapse no suitable for local or systemic treatment has a median survival of 3 months causing local pain and anxiety to the pts. We prospectively analysed antitumoral activity of ECT in regional relapse of H&Nc not suitable for other therapies.

Methods: Pts with local-regional relapse of H&Nc from mucosa (squamous carcinoma), thyroid gland, salivary gland, cutaneous squamous or cutaneous melanoma were included. Other inclusion criteria were good general condition, no history of reaction to Bleomycin, life spectancy of 3 or more months and no other therapies.

Results: Between 2009-2011, 26 ECT courses were performed in 18 consecutive pts and systemic chemotherapy. All authors have declared no conflicts of interest.

Discussion: ECT has a high antitumoral activity in regional relapse of H&Nc of different histologies. This local therapy may have a place in the future as palliative treatment of H&Nc.

Disclosure: All authors have declared no conflicts of interest.

EDT 1047P PSYCHOLOGICAL DISTRESS AND QUALITY OF LIFE EVALUATION IN HEAD AND NECK CANCER: THE ROLE OF FAMILY CAREGIVER

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Background: Recently the figure of family caregiver (FCG) has become a hot topic, and is still largely un-investigated among head and neck cancer patients. Our aim of our study was to describe a more detailed way the role of FCG, to evaluate quality of life (QoL) and psychological distress of FCGs and patients, and to investigate relationships between FCG’s wellbeing and patient’s QoL and emotional pattern.

Methods: Sixty couples of patients and their caregivers were enrolled in this observational cross-sectional study between April 2007 and May 2011 at 1st ENT Division, 2nd Medical Oncology Division and 2nd Radiotherapy Division of San Giovanni Battista Hospital of Turin. Inclusion criteria were: histological diagnosis of SCC, advanced stage (III-IV), completion of curative treatment and no evidence of disease at the enrolment. Psycho- oncological assessment was performed using Distress Thermometer (DT), Stay-Trait Anxiety Inventory Manual in Y1 and Y2 form (STAI Y1-Y2), Beck Depression Inventory (BDI), Montgomery-Asberg Depression Rating Scale (MDRS), EORTC-QLQ-C30 and Head and Neck-35 module and Caregiver Quality of Life Index-Cancer (QQLC).

Results: Patients state and trait anxiety are 46.7% (STAI Y1 mean value 40.2 ± 10.2; cut-off 40) and 36.7% (STAI Y2 mean value 36.7 ± 8.2; cut-off 40) respectively; self reported and clinician rated depression are 31.6% (BDI mean value 8.2 ± 5.3; cut-off 9) and 48.3% (MDRS mean value 7.9 ± 5.9; cut-off 6) respectively. FCGs state and trait anxiety are 50% (STAI Y1 mean value 42.5 ± 9.9; cut-off 40) and 41.7% (STAI Y2 mean value 39.1 ± 8.7; cut-off 40) respectively; self reported and clinician rated depression are 28.3% (BDE mean value 7.3 ± 4.7; cut-off 9) and 41.7% (MDRS mean value 7.6 ± 5.8; cut-off 6) respectively. Data analysis underlined a positive association among emotional scales of patients and caregivers. Patients’ psychological aspects are negatively associated with caregivers’ QoL and viceversa.

Conclusions: Anxiety and depression are often present in FCGs and cured HNC. Patients long term Patient’s QoL is the result of a frail balance between FCG and patient emotional and psychological distress. A psychological support for FGG could improve patient well being.

Disclosure: All authors have declared no conflicts of interest.

EDT 1048P RADIATION-INDUCED MALIGNANCY FOLLOWING DEFINITIVE RADIOTHERAPY FOR NASOPHARYNGEAL CARCINOMA

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Purpose: To analyze the clinicopathological characteristics, treatment modalities, and potential prognostic factors of radiation-induced malignancy (RIM) in patients with nasopharyngeal carcinoma (NPC).

Methods: We reviewed institutional electronic medical records of 39.118 patients with NPC treated by definitive radiotherapy between February 1984 and 2003. A total of 224 patients with confirmed RIM were included in this study.

Results: The median latency between radiotherapy for NPC and the diagnosis of RIM was 9.5 years (range, 3.1 to 30.2 years). Squamous cell carcinoma was the most common histologic type, followed by fibrosarcoma, osteosarcoma, and adenocarcinoma. Median progression-free survival and overall survival (OS) of the 216 patients who underwent treatment were 18.7 months (95% CI, 12.8 to 24.5) and 32.0 months (95% CI, 23.8 to 40.1), respectively. Five-year OS rates were 36.9% and 20.2% for carcinoma and sarcoma, respectively (P = 0.004). The 5-year OS rates were 45.4%, 21.8%, and 0% for the surgery (140 patients), radiotherapy (44 patients), and chemotherapy (32 patients) groups, respectively (P = 0.000). The independent prognostic factors associated with improved OS were histologic diagnosis of carcinoma and complete surgical resection.

Conclusion: Histologic type and treatment modality were the significant prognostic factors for patients with RIM. Complete resection apparently offers the best chance for long-term survival. In select patients with locally advanced and unresectable RIM, reirradiation should be strongly considered as a curative option.

Disclosure: All authors have declared no conflicts of interest.

EDT 1049P THE CHANGING ORAL MICROBIAL ECOSYSTEM IN OSCC FROM DIAGNOSIS TO RADIOTHERAPY

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Purpose: Multiple factors influence the oral microflora (OMF) in oral squamous cell carcinoma (OSCC). This could range from tobacco habits to radiotherapy administered. A preliminary study performed in our hospital revealed the differential support offered by each of these factors on various microbial groups - aerobes, anaerobes, gram negative anaerobes (GNAB) and Candida.

Method: The study attempts to analyse the microbial alteration so as to improve the possible impact that OMF could create on mucositis and other...
morbidities that radiation would leave behind. Microbial analysis of saliva samples were done from healthy volunteers (n = 35), tobacco chewers (n = 37) (Age & Sex matched), OSCC (n = 32) and during radiotherapy (n = 31) of these patients (n = 50 study samples). Frequency of isolation and mean colony forming units obtained were subjected to Kruscal – Wallis, Mann - Whitney (unpaired values) and Wilcoxon - signed rank test (paired values) for comparison.

Results: No isolation of Citrobacter, Enterobacter, Proteus in normal samples and Corynebacteria, Staphylococcus epidermidis in study samples. Tobacco – induced change: Among aerobes, E. coli, Citrobacter, Proteus, Klebsiella pneumonia and Enterobacter increased (p < 0.05), whereas, Streptococcus pneumoniae, Corynebacteria, Staphylococcus epidermidis, aerobic Streptococcus decrease (p > 0.05) significantly. Amongst the anaerobes, anaerobic Streptococcus, Prevotella decreased whereas Fusobacteria, P. gingivalis increased, but, all non - significantly (p > 0.05). Tumor - induced change: E. coli, Enterobacter and anaerobic Streptococci, Fusobacteria, Prevotella (anaerobes & GNAB) significantly increased (p < 0.05). Radiation – induced change: Among aerobes, Streptococcus pneumoniae, Staphylococcus epidermidis decreased. Proteus, Klebsiella pneumoniae, Enterobacter, and amongst anaerobes, Streptococcus increased (p < 0.05) significantly. A non-significant increase was noted in Fusobacteria and P. gingivalis.

Conclusions: The study impresses on the rapidly modifying nature of OMF that accommodates non – residents and increasing proportions of more pathogenic microorganisms that may contribute to the enhanced morbidity.

Disclosure: All authors have declared no conflicts of interest.

1050P WHOLE-BODY DIFFUSION MRI AND SKELETAL LESIONS IN THYROID CANCER: DIAGNOSTIC AND THERAPEUTIC IMPLICATIONATIONS

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Background: Forty-fifty percent of the patients with metastatic TC suffer from bone metastases.1050P-CT is employed to assess bone metastases although it lacks of specificity, mostly in lytic lesions of differentiated thyroid cancer (DTC). Whole body MRI (WB) and whole-body diffusion MRI captures both bone and bone marrow involvement, more common in medullary metastases. 99mTc scintigraphy is employed to assess bone lesions although it lacks of accuracy, mostly in lytic lesions of differentiated thyroid cancer (DTC). CT scan has demonstrated promising clinical activity for patients with recurrent and/or metastatic thyroid cancer (MTC). Whole body MRI (WB-DWI) are emerging as accurate tools for detection and therapy monitoring of thyroid cancer (MTC). Material and methods: Since 2010, nine MTC (5M/4F) and five DTC (3M/2F) patients were included. A false-positive was a bone scan Bone CT

WP-DWI

Bone scan

Bone CT

Number of exams

14

12

12

True positive

10

8

8

True-negative

4

4

4

False-positive

0

(MTC)

0

False-negative

0

1 (MTC)

1 (MTC)

Sensitivity %

100

88

88

Specificity %

100

80

100

Accuracy %

100

86

92

In five (1 MTC/4 DTC) out eight (62%) true-positive bone scan, WB-DWI demonstrated a higher number of bone lesions. In three patients (2 MTC/1 DTC), WB-DWI showed a cystic evolution in the responding lesions during TKI (apart from the histotype).

Conclusions: In our hands WB-DWI is the best imaging method to identify bone lesions from TC. It could potentially address unmet clinical and therapeutic needs for a reliable measure of bone lesion response in this rare tumors.

Disclosure: All authors have declared no conflicts of interest.

1700P ANTI-ANDROGEN THERAPY FOR THE PATIENTS WITH RECURRENT AND/OR METASTATIC SALLIVARY DUCT CARCINOMA EXPRESSING ANDROGEN RECEPTORS: A RETROSPECTIVE STUDY

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Background: Salivary duct carcinoma (SDC) is one of the WHO classified histological types of salivary gland tumors (SGT) and consists of less than 10% among all the SGT. SDC is known as highly malignant with its aggressive clinical course, high rate of recurrence and metastasis and 2-3 years of median survival time. Up-front therapy is surgery, but treatment option is quite limited when it recurs and/or metastasis not being suitable for surgical resection. Androgen receptor (AR) is expressed in about 90% of SDC. Several reports suggest that AR would be a good candidate for treatment target for this entity.

Patients and methods: We conducted a retrospective analysis in patients with AR positive, recurrent and/or metastatic SDC treated anti-androgen therapy in our institution from January 1997 and April 2012. AR positivity was defined by immunohistochemistry (AR441, DAKO). Anti-androgen therapy was given as a single agent LH-RH analogue every four weeks until disease progression or intolerable adverse events. Responses to anti-androgen therapy were assessed according to RECIST.

Results: Eight patients were included. All were male. Median age was 57 years (range 40-76). Primary site was parotid gland in 7 and submandibular gland in 1. Initial clinical stage was II in 2, IVA in 3 and IVC in 1. All patients had received surgery for SDC prior to anti-androgen therapy. The patterns of relapse were locoregional recurrence in 4 and distant metastasis in all. Median number of cycles of anti-androgen therapy was 4 (range 2-10). No serious adverse event was seen. The best responses were PR in 2 and SD in 3, and median time of response duration was 4.6 months. After progression of anti-androgen therapy, all but one received chemotherapy included platinum compounds, taxanes and fluorouracil. Median overall survival time from receiving anti-androgen therapy was 22 months.

Discussion and conclusion: Anti-androgen therapy was well tolerated and demonstrated promising clinical activity for patients with recurrent and/or metastatic SDC. This might delay the start of chemotherapy and provide survival benefits, and this approach warrants further investigation.

Disclosure: All authors have declared no conflicts of interest.
Conclusions: This preliminary prospective study demonstrates that G8 score identify frailty in 42% of elderly SCCHN patients older than 65 years. An adapted tool for geriatric assessment in SCCHN patients seems necessary.

Disclosure: All authors have declared no conflicts of interest.

1055 Efficacy of Myofibroblasts as an Indicator for Invasion and Nodal Metastasis in OSCC
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Purpose: Tumour cells work in close coordination with stromal elements from its stage of initiation to metastasis. Oral squamous cell carcinoma (OSCC) is one of the top ten cancers in the world with only survival rate of 56%. Myofibroblasts (MF), a cell that is identified transiently in the wounds, have also been shown in tumor stromogenesis in a variety of malignancies. MFs been highlighted for their proinvasive role in tumors. These cells remain less explored in OSCC in terms of invasion and nodal metastasis – Prognosticators.

Method: The study was aimed towards understanding the possibility of MF being an indicator of invasion and nodal metastasis. This was achieved through assessing the presence and distribution pattern of MF in OSCC using α-SMA. To improve further our understanding a semiquantitative analysis (0= No staining, 1= Focal Positivity, 2= Multifocal Positivity) was performed and compared with that from normal mucosa (NM, number of cases (n) =10), chronic inflammatory lesions (CIL, n= 22), surgical margins (SM, n = 52), and OSCC (n= 84) samples (n= 52).

Results: No MFs were present in NM and SM. 84% and 32% of OSCC and CIL showed MFs respectively. Heterogeneous pattern (Presence/absence in a location, Loose/Syncitial arrangements, and Focal/Multifocal distribution) of MFs was seen in OSCC while they were seen closer to the center of the lesion away from the epithelium in CIL. Lesions reported for longer duration showed MF in CIL. The MFs were not seen in all the invasive fronts. Significant difference in the number of MFs was observed between NM and OSCC (p = 0.00), CIL and SM (p =0.003), CIL and OSCC (p = 0.00), SM and OSCC (p = 0.00).

Conclusion: MF formation and its retention seems to be influenced by duration (reactive lesions), and basement membrane invasion with stressed extracellular matrix (OSCC). Stress-dictated distribution patterns may prove valuable in distinguishing pN0 and pN+ groups. Small incisional biopsies may not be useful in predicting both invasion and nodal metastasis either by quantitation or by distribution pattern analysis owing to the heterogeneity that is displayed.

Disclosure: All authors have declared no conflicts of interest.

1056 Treatment Failure in High-Risk Head and Neck Cancer Treated with Adjuvant Chemoradiation
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Background: Adjuvant chemoradiation (adCRT) is the standard of care in resectable high-risk head and neck squamous cell carcinoma (HNSCC). We select patients (pts) for adCRT if they are physically fit and have at least 1 major (extra-capsular nodal spread or positive resection margins) and/or 2 minor (pT4, pN2, perineural or vascular invasion) high risk pathological factors. Loco-regional control and disease-free survival (DFS) are good and the toxicities manageable. The aim of our study was to evaluate the patterns of treatment (tt) failure with this therapy.

Methods: We reviewed the charts of all pts with resected high-risk HNSCC treated with adCRT, from 2007 to 2011. Pts and disease characteristics, compliance to tt, date and first site of tt failure and disease status at last follow-up (FU) were reviewed. Overall survival (OS) and DFS were estimated using Kaplan-Meier method.

Results: 221 consecutive pts were included, 93.6% male, median age 59 years. The incidence of stage IV, disease (72.8%) and major high risk pathological features such as involved surgical margins (50.6%) and extranodal spread of the disease (52.0%) was high. Compliance to tt was good with 94.5% of pts completing at least 2 cycles of chemotherapy. There were two toxic deaths. With a median FU of 18.8 months, 57 pts (25.8%) experienced disease recurrence. Local or regional recurrence as the first site of tt failure occurred in 25 pts (11.3%) and distant metastasis (mets) occurred in 32 pts (14.5%). The most common site of metastatic disease was the lung (26 pts, 11.7%). Lung recurrence occurred at a median FU of 8 months. Nine pts (4%) recurred with lung mets less than 6 months after the end of adCRT. Five pts were diagnosed of primary lung cancer during FU. At last FU 175 pts (79.2%) were alive; 154 (69.9%) in complete remission. The Kaplan-Meier estimates of 3-year OS and DFS were 68% and 59%, respectively.
Conclusions: Through adequate selection of pts and supportive measures, high it compliance and manageable toxicity of adCRT are achieved. The observed early recurrence in a small number of pts, mainly in the lung, might suggest that more detailed pretreatment staging and FU evaluation for earlier lung disease detection are warranted.

Disclosure: All authors have declared no conflicts of interest.

PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS OF 5-FLUOROURACIL IN CHINESE HEAD AND NECK CANCER (HNC) PATIENTS

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Background: Pharmacokinetic (PK) variability of 5-fluorouracil (5-FU) has been demonstrated for >30 years and a significant link between exposure and therapeutic response has been identified. A maximum tolerated exposure (MTE) has been used to optimize dosing.

Objective: The objective of this study was to characterize the PK variability of 5-FU in the Chinese HNC population and examine the relationship between AUC, toxicity and efficacy. The 5-FU MTE in this population was compared with MTE identified for European HNC patients.

Methods: 89 treatment naive patients with HNC were enrolled. 5-FU was administered with cisplatin (80mg/m² D1) and 5-FU (4g/m², 120h IV). Blood samples were collected at steady state after the first 18h of 5-FU infusion. Plasma was analyzed by a 5-FU immunoassay and AUC was calculated. Relationship between 5-FU AUC and 5-FU related toxicities was examined. Preliminary efficacy results were evaluated for 5-FU related toxicity.

Results: The patient 5-FU AUC values varied widely: from 15 to 103 mg · h/L. 33% of patients were within the target range of 25-35 mg · h/L; 18% were below and 49% were above. Toxicity was recorded for 89 patients. Among the 44 patients with AUC above the target range, severe mucositis or myelosuppression was experienced by 32 patients. By comparison, among the 45 patients within or below target range, only 3 experienced severe toxicities. ROC analysis for 5-FU AUC and severe mucositis identified a cut-point of 36 mg · h/L (p < 0.0001). These results are listed in the table below.

| Incidence of severe mucositis and myelosuppression with 5-FU AUC |
|-------------------|-----------------|
| AUC                | Grade 3         |
| ≤35 mg·h/L        | 3%              |
| >35 mg·h/L        | 3%              |
| Grade 0 - 2       | 47%             |

Conclusion: Results of this study demonstrate wide PK-variability of 5-FU exposure and a significant relationship between severe toxicity and AUC in HNC cancer patients. The study confirms that the MTE in this population is similar to a European HNC population treated with cisplatin/5-FU. TDM using the target range of 25-35 mg · h/L may have benefit in lowering toxicity in HNC patients.

Disclosure: All authors have declared no conflicts of interest.

CISPLATIN + VINORELBINE (DDP + VNB) ADMINISTERED IN 60 CASES OF RECURRENT/METASTATIC SALIVARY GLAND MALIGNANCIES (RMSGM): FINAL REPORT

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Background: RMSGM are not amenable to the usual treatment with surgery and post-operative radiotherapy. The role of chemotherapy (CT) for RMSGM is palliative only. VNB showed moderate activity in our experience (Bull Cancer 85:892; 1998) and in a randomized phase II trial we had demonstrated that the DDP + VNB combination had a better outcome than VNB alone (Cancer 91:541; 2001). In this abstract we report the final results of this combination in 60 cases.

Methods: From April 2001 to February 2009, 60 cases with RMSGM were enrolled. All patients received the following regimen: DDP 80 mg/m² d 1 + VNB 25 mg/m² d 1, 1.8 every 3 weeks. The study foresees a maximum of 6 cycles.

Results: Patients characteristics were as follows: 35 males (58%) and 25 females (42%); median age: 56 yrs (range 20-68); median ECOG PS: 1 (0-2); histology: adenocarcinoma 15 (25%), adenosquamous 34 (57%), others 11 (18%); site of disease: local 30 (50%), nts +/- local 30 (50%). Forty-two pts received DDP + VNB as first line CT (70%) while 18 pts (30%) had the combination as second-line CT (30%). After a median of 5 cycles of first line DDP + VNB responses were: 3 CR (7%), 10 PR (24%), 14 NC (33%) and 15 PD (36%). After a median of 4 cycles of second line CT responses were: 0 CR; 1 PR (5%), 6 NC (33%) 11 PD (62%). Median survival: 10 months (2-39) for first line CT; 4 months (1-12) for second line CT. G3-4 toxicity: neutropenia (20%), anemia (12%), nausea/vomiting (12%), peripheral toxicity (3%).

Conclusions: DDP + VNB is an effective first line CT in RMSGM; second line CT has a low palliative activity. Toxicity seems acceptable. This regimen could be suitable for an integration with new biologic target agents.

Disclosure: All authors have declared no conflicts of interest.

ANTI OXIDANT CAPACITY OF CALENDULA OFFICINALIS FLOWERS EXTRACT AND PREVENTION OF RADIATION INDUCED OROPHARYNGEAL MUCOSITIS IN PATIENTS WITH HEAD AND NECK CANCERS: A RANDOMIZED CONTROLLED CLINICAL STUDY

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To determine the effect of Calendula officinalis flower extract mouthwash as gel formulation on radiation-induced oropharyngeal mucositis (OM) in patients with head-and-neck cancer. Forty patients with neck and head cancers who were treated with radiotherapy or chemoradiotherapy were randomly assigned to receive either 2% calendula extract mouthwash or placebo (20 patients in each group). The subjects were treated with telecobalt radiotherapy at conventional fractionation (2 Gy/fraction, five fractions weekly, 20–35 fractions within 4–7 weeks). Oropharyngeal mucositis was evaluated by two doctors (a radiation oncologist and a dentist), using the oral mucositis assessment scale (OMAS). The patients also received concurrent chemotherapy. Calendula mouthwash significantly decreased the intensity of OM compared to placebo at week 2 (score: 5.5 vs. 6.8, p = 0.019), week 3 (score: 8.25 vs. 10.95, p < 0.0001) and week 6 (score: 11.4 vs. 13.5, p = 0.031). Total antioxidant, polyphenol and flavonoid contents and quercetin concentration of the 1% extract were 2353.4 ± 56.5 µM, 76.66 ± 23.24, 314.40 ± 6.52 mg/g and 19.41 ± 4.34 mg/l respectively. Calendula extract gel could be effective on decreasing the intensity of radiotherapy-induced OM during the treatment and antioxidant capacity may be partly responsible for the effect.

Disclosure: All authors have declared no conflicts of interest.

HORIZONTAL LATERAL THYROIDECTOMY—THOMAS TECHNIQUE: A NOVEL SURGICAL APPROACH TO THYROID NEOPLASMS

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Background: Kocher’s anterior approach is the universal standard for thyroidectomy but with several complications. Feasibility of horizontal lateral thyroidectomy (Thomas Technique), based on 3 D volumetric anatomy is a novel concept to minimize complications to the superior, Recurrent Laryngeal nerves, Para thyroids and vessels which are posterior and lateral. Unique anatomy of platysma, safeguarding of sub platysmal venous plexus and investing layer of deep fascia in relation to Cosmetic outcome is highlighted.

Methods: Superior results from the pilot study, prompted to extend the study for the next 2 years. Of 283 subjects thus enrolled, 231 were females and 52 males. 118 had benign disease out of which 17 were MNGs, 31 adenomas and 9 cysts. Out of 165 Cancers, 160 were differentiated (96 papillary, 44 follicular, 20 mixed and 5 medullary). 18 had intra thoracic extensions. Using single ipsilateral incision 40 hemi thyroidectomies, 70 total thyroidectomies of benign and 55 total thyroidectomies of malignant disease were performed. Preoperative and postoperative course was uncomplicated and cosmetic outcome was excellent.

Objective: This feasibility study was designed to avoid all the known complications of thyroidectomy and an unesthetic anterior scar.

Methods: Superior results from the pilot study, prompted to extend the study for the next 2 years. Of 283 subjects thus enrolled, 231 were females and 52 males. 118 had benign disease out of which 17 were MNGs, 31 adenomas and 9 cysts. Out of 165 Cancers, 160 were differentiated (96 papillary, 44 follicular, 20 mixed and 5 medullary). 18 had intra thoracic extensions. Using single ipsilateral incision 40 hemi thyroidectomies, 70 total thyroidectomies of benign and 55 total thyroidectomies of malignant disease were performed. Preoperative and postoperative course was uncomplicated and cosmetic outcome was excellent.

Disclosures: All authors have declared no conflicts of interest.
intrathoracic extensions. Complications described in the literature are minimised. Superior cosmetic results compared to Kocher’s technique.

Disclosure: All authors have declared no conflicts of interest.

**FIRST-IN-MAN PHASE I STUDY OF TPCS2A-BASED PHOTOCHEMICAL INTERNALISATION (PCI) OF BLEOMYCIN IN LOCALLY RECURRENT OR ADVANCED/METASTATIC, CUTANEOUS OR SUBCUTANEOUS MALIGNANCIES**

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Objective: PCI is a novel technique in which chemotherapeutic cytotoxicity is enhanced with a photosensitiser and light exposure. This dose-escalation study assessed the safety and tolerance of TPCS2a (tetraphenyl chlorin disulphonic acid, Amphinex®) in bleomycin PCI, pharmacokinetic profiles, and determined the maximum tolerated dose (MTD).

Method: Cohorts of 3 to 6 patients were enrolled and the TPCS2a dose escalated by a pre-specified amount until dose-limiting toxicity (DLT) occurred in at least two patients (≥33%). Patients received TPCS2a at a starting dose of 0.25mg/kg. Four days later they received bleomycin (15,000IU/m² IV) and after 3 hours red light laser (652nm) was applied to target lesions for 600 seconds to initiate a therapeutic response. Patients were followed for 3 months.

Results: Nineteen patients were enrolled: 4 with cutaneous breast cancer, 13 squamous cell carcinoma (SCC) of head and neck and other regions, 2 other cancers. 17/19 patients experienced 94 AEs, most commonly pain, photosensitivity and nausea. Most (83%) were mild or moderate. Fourteen episodes of pain (3 severe) were treatment-related. Mean patient-reported pain using a VAS scale declined from 4.9 to 1.3 24 hours after treatment. Four patients experienced skin photosensitivity reactions; 3 were in the highest dose cohort. 10/19 patients experienced 15 serious adverse events: 3 (swelling, and blistering of hands, tongue oedema) were probably related to treatment. The MTD of TPCS2a was found to be 1.5mg/kg. At day 28, 11/16 patients had a complete response (CR) in target lesions, 2 had a partial response (PR), 2 had stable disease (SD) and 1 had progressive disease (PD). At last visit there were 8 CRs, 2 PRs, 2 SDs and 2 PDs. During the course of the study four patients died (no relation to treatment) and six were withdrawn prematurely.

Conclusion: With appropriate analgesia and anaesthesia TPCS2a-based PCI of bleomycin was well tolerated in these patients with locally advanced cancer. Treatment-related AEs were as expected and can be managed. Preliminary efficacy data are very encouraging and a phase II study in HNSCC has just begun.

Disclosure: All authors have declared no conflicts of interest.