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G4 ASCO ABSTRACT

First results of a phase III multicenter randomized controlled trial of intensity modulated (IMRT) versus conventional radiotherapy (RT) in head and neck cancer (PARSPORT: ISRCTN48243537; CRUK/03/005)

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Background: Xerostomia is the most common late toxicity of RT to the head and neck. IMRT dose distributions reduce the dose delivered to parotid gland. PARSPORT investigated the role of IMRT in reducing xerostomia in patients with head and neck cancer.
Methods: The PARSPORT trial compared two radiotherapy delivery methods in the treatment of patients with pharyngeal tumors (T1-4, N0-3, M0). Patients received 65 Gy in 30 fractions over 6 weeks delivered using either CT planned parallel opposed lateral fields or parotid-sparing IMRT. Stratification was by site of tumor and center. The primary endpoint was incidence of LENT-SOMA $\geqslant$G2 xerostomia one year after treatment. Secondary endpoints included acute toxicities (CTCAE v3) and other late RTOG and LENT-SOMA radiation toxicities. Proportions of patients with $\geqslant$G2 toxicity were compared using exact tests. For secondary endpoints a significance level of 1% was used.
Results: 94 patients (47 RT; 47 IMRT) were randomized between 2003 and 2007 from six UK centers. 80 patients had oropharyngeal tumors and 14 hypopharyngeal. Radiotherapy was given as primary treatment in 71 patients and post-operatively in 23. 22 patients had AJCC stage I/II disease. Median follow-up was 31.9 months (IQR: 26.6−38.8). Twelve month LENT-SOMA $\geqslant$G2 xerostomia scores were observed in 74% (25/34) of RT and 40% (15/38) of IMRT patients ($p = 0.005$). Corresponding values at 18 months were 71% (15/21) and 29% (9/31) ($p = 0.004$). On the RTOG scale, 12 month $\geqslant$G2 xerostomia was reported in 64% (21/33) RT vs 41% (15/37) IMRT patients ($p = 0.06$). The 18 month incidence was 81% 17/21 RT vs 20% (6/30) IMRT ($p < 0.001$). Acute radiotherapy related $\geqslant$G2 fatigue was more prevalent in the IMRT group (76% vs 41% $p = 0.001$). No differences in acute mucositis or pain scores were seen. At 12 months, no statistically significant differences were seen in other late toxicities. No differences were observed between overall survival and locoregional control rates.
Conclusions: Sparing the salivary glands through use of IMRT significantly reduces the incidence of xerostomia in patients with pharyngeal tumors.

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G5 ASCO ABSTRACT

Ulceration of primary melanoma and responsiveness to adjuvant interferon therapy: Analysis of the adjuvant trials EORTC18952 and EORTC18991 in 2,644 patients

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Background: Ulcerated (Ulc) melanomas have a worse prognosis than non-ulcerated (N-Ulc) melanomas. Ulc and N-Ulc primaries have different stromal characteristics and gene profiles reflecting differences in biology. We analyzed outcome after adjuvant interferon (IFN) therapy in the 2 largest phase III trials (EORTC18952 and 18991) ever conducted in stage IIB-III melanoma patients (pts).
Methods: EORTC18952 compared IFNα-2b (10 MIU, sc, qd, 5 days/wk, for 4 wks) followed by either 10MIU, sc, tiw for 12 mts, or 5MIU for 24 mts) with observation in 1,388 stage IIB-III pts (Lancet 2005;366). EORTC18991 evaluated pegylated IFNα-2b (6 μg/kg, 1$\times$/wk, for 8 wks followed by 3 μg/kg, 1$\times$/wk for up to 5 yrs) versus observation in 1,256 stage III pts (Lancet 2008;372). Using meta-analytical methods, predictive value for Ulc on the value of IFN on relapse-free survival (RFS), distant metastasis-free survival (DMFS), and overall survival (OS) was assessed, overall, and according to stage (IIB, III-N1 or N2 = microscopic or macroscopic-nodal disease).
Results: Overall, the comparison (PEG-)IFNα-2b versus observation regarding RFS, DMFS, and OS led to a reduction in the hazard ratio (HR) of −16% (SE = 5%), −13% (5%), and −8% (5%). Among 2,644 pts randomized, 849 had Ulc primaries, 1,336 N-Ulc primaries, and 459 Ulc unknown. In Ulc group the impact was much greater than in N-Ulc group for RFS (Test For Interaction: $p = 0.02$), DMFS ($p < 0.001$), and OS ($p < 0.001$). The greatest reductions occurred in pts with Ulc and stages IIB/III-N1 In N-Ulc pts reduction was absent. Consistency in the treatment impact was seen in both trials.
Conclusions: The post hoc analyses of EORTC1892 and EORTC18991 indicate strongly that pts with an Ulc primary are far more sensitive to IFN than pts with N-Ulc primaries. This hypothesis will now be tested in the EORTC18081 trial, which compares PEG-IFNα-2b versus observation in pts with Ulc primaries $\geqslant$1 mm.

Estimated reduction or increase in hazard ratio (SE%) of (PEG-)IFNα-2b vs observation)

	Non-ulcerated primary (N = 1336)			Ulcerated primary (N = 849)		
	RFS	DMFS	OS	RFS	DMFS	OS
All pts	−4% (7%)	+7% (8%)	+11% (8%)	−27% (7%)	−33% (7%)	−31% (7%)
IIB/III-N1	−14% (11%)	+1% (13%)	+10% (15%)	−31% (7%)	−42% (9%)	−44% (10%)
III-N2	+2% (9%)	+11% (10%)	+12% (11%)	−19% (11%)	−20% (9%)	−13% (12%)

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G6 ASCO ABSTRACT

Clinical activity observed in a phase I dose escalation trial of an oral c-met and ALK inhibitor, PF-02341066

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Background: PF-02341066 (PF) is a selective, ATP-competitive, small molecule oral inhibitor of the c-Met/HGFR and ALK receptor tyrosine kinases that has not previously been tested in humans. A Phase 1 dose-escalation trial evaluating PF as an oral single agent was conducted to investigate safety, PK and PD in patients (pts) with advanced cancer (excluding leukemias).
Methods: PF was administered under fasting conditions QD or BID on a continuous schedule to pts in successive dose-escalating cohorts at doses ranging from 50 mg QD to 300 mg BID. Pts with advanced cancer were enrolled in the study.
Results: Thirty-seven pts were enrolled into the dose escalation part of the study. Tumor types included colorectal, pancreatic, sarcoma, ALCL and NSCLC. The MTD was 250 mg BID. Three DLTs were observed: grade 3 increase in ALT (1 pt at 200 mg QD) and grade 3 fatigue (2 pts at 300 mg BID). The most common AEs were nausea, emesis, fatigue and diarrhea. Nausea and emesis were independent of dose or duration of treatment. Mean AUC (30−57% CV) and Cmax (36−69% CV) increased proportionally with dose from 100 mg QD to 300 mg BID. The median terminal half-life was 46 hours. A 2- to 4-fold increase in the oral midazolam (MDZ) AUC was observed following 28-days of PF dosing at 100 mg QD ($n = 3$) and 300 mg BID ($n = 2$), respectively, suggesting PF to be an inhibitor of CYP3A. Ten pts have entered an enriched RP2D cohort of pts with tumors harboring c-Met amplification/gene mutation or ALK fusion genes. There has been 1 confirmed PR in a sarcoma pt with ALK rearrangement (inflammatory myofibroblastic tumor). Among 10 NSCLC pts whose tumors harbor EML4-ALK rearrangement, 1 pt has had a PR, 2 pts have achieved unconfirmed PR and 4 pts have had SD (3 have experienced reduction in tumor burden by ~20% in measurable lesions and 1 has been treated for 28 weeks).
Conclusions: The MTD of PF is 250 mg BID. The major AEs were fatigue or GI-related, and all AEs were manageable and reversible. There was no evidence of non-linear PK at PF doses >100 QD. Treatment with PF-02341066 resulted in promising clinical activity against tumors carrying activating ALK gene rearrangements. Further study of PF in pts with ALK-dependent tumors is warranted.