

planned ( $p=0.001$ ). Of pts who required UHA, only 27% resumed their trial drug after recovery. The main statistically significant risk factors for UHA include  $>2$  metastatic sites, (RR 2.6 [1.64–4.38],  $p=0.001$ ), poor performance status (RR 2.47 [1.48–3.72]  $p=0.003$ ), low albumin (RR 2.17 [1.36–3.52]  $p=0.001$ ) and cytotoxic combination trials (RR 1.7 [1.09–2.86]  $p=0.025$ ).

**Conclusions:** Unplanned admissions constitute 20.6% of Phase I inpatients, with the majority being disease rather than treatment-related. Regardless of length of stay, UHA portend poor outcomes for patients who are on treatment, with a risk profile underscoring the importance of pt and trial selection.

## 1258

## POSTER

### Changing perceptions of oncologists referring advanced colorectal (ACRC) patients (pts) to phase 1 trials: an evidence based approach

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**Introduction:** After failure of conventional treatment pts with ACRC who remain well may receive phase 1 therapy. Pts rely on referring physicians opinion when considering treatment and a change in perception may increase number of referrals.

**Methods:** Analyze the outcome for 78 ACRC pts treated in 23 phase I trials at the Royal Marsden Hospital (RMH), between Jan 04–08. Apply newly developed RMH prognostic score (0–3, comprising high LDH, albumin  $<35$  mg/dl and  $\geq 2$  number of metastatic sites; In addition, survey 64 colorectal oncologists who referred pts to our unit aiming to understand the reasons for referral and knowledge regarding experimental therapy. Describe whether after reading audit results their approach to phase 1 changed.

**Results:** *Audit:* Median age: 62 yrs [range (r): 26–79]. PFS and OS were 8.6 (95% CI: 6.4–10.7) and 29.1 weeks (95% CI: 15.7–42.5), respectively. 28.8 and 8.2% of the pts were assessed as having SD at 3 and 6 months, respectively. In the multivariate analysis, a high RMH prognostic score (2–3) was associated with poor OS [HR: 1.42 (1.09–1.85),  $p=0.007$ ]; median OS was 19.4 weeks (95% CI 11.7–27.1) compared to 47.4 weeks for those pts with RMH prognosis score of 0–1 (95% CI 41.3–53.6,  $p=0.029$ ).

*Survey:* 28/64 (44%) questionnaires were returned from medical and clinical oncologists (14/14). The median length of oncology experience was 10 yrs (r: 2–25); 64% had previous phase 1 experience and  $>85\%$  were familiar with logistics and eligibility criteria. The most common reason for referral was lack of treatment options (64%); and the main reason for referral to our unit was proximity to pts (32%) and known centre of excellence (29%). The most common characteristic analyzed in pts before referral was performance status (93%). Median time spent with pts to discuss phase 1 was 10 min (r: 5–45) and possibility of any clinical benefit (43%) the main point. The median predicted PFS and OS was 2 (r: 2–4) and 5 (r: 4–8) months, respectively. 39% predicted that the prognostic factors in RMH score would be associated with outcome. 68% felt the audit results met their expectations although 42% would change their approach in some way. Moreover 21% would increase the number of referrals and 81% would be keen to answer similar questionnaires in the future.

**Conclusion:** Colorectal oncologists have a good knowledge regarding general outcomes of phase 1 trials in ACRC. The most common reason for referral was lack of treatment options, 42% of oncologist surveyed would change their approach in some way after reading audit results and 1/5 would increase their number of referrals.

## 1259

## POSTER

### Trabedersen (AP 12009) in the treatment of pancreatic carcinoma and other malignant tumors: interim results of the Phase I/II study

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**Background:** TGF- $\beta 2$  stimulates metastasis of various malignant tumors and suppresses antitumor responses of the immune system.

Trabedersen (AP 12009) is a TGF- $\beta 2$ -specific antisense oligonucleotide. Trabedersen was safe and effective in high-grade glioma patients, as shown in a randomized, active-controlled Phase IIb study. In patients

with anaplastic astrocytoma the median survival benefit was 17.4 months compared to standard therapy. A Phase III study (SAPPHIRE) is ongoing. In this study we evaluate the maximum tolerated dose (MTD), safety, tolerability, pharmacokinetics, and efficacy of intravenous treatment with trabedersen in patients with other advanced tumors.

**Methods:** In the open label, multicenter, dose-escalation Phase I/II study (AP 12009-P001; NCT00844064; sponsor: Antisense Pharma, GER), 33 patients with advanced pancreatic carcinoma (stage IVA/IVB, N=23), malignant melanoma (stage III/IV, N=5), or colorectal carcinoma (stage III/IV, N=5) were enrolled in several cohorts. Patients were treated intravenously with trabedersen as 2nd to 4th-line therapy as monotherapy with escalating doses in two treatment schedules (1st schedule: 7 d on, 7 d off; 2nd schedule: 4 d on, 10 d off; up to 10 cycles).

**Results:** Treatment with trabedersen was safe and well tolerated. Within the 1st treatment schedule MTD was established at 160 mg/m<sup>2</sup>/d, after NCI-CTC grade 3 dose limiting toxicities (2 self-limiting and transient thrombocytopenias, 1 exanthema) had occurred. One patient with metastatic pancreatic carcinoma had a complete response of liver metastasis and is alive 41 months after enrollment.

In the 2nd treatment schedule dose escalation was stopped after the 4th cohort, before MTD had been reached, as a dose was identified, which was well tolerated and had very promising efficacy data. The median overall survival for patients with pancreatic carcinoma treated with the defined dose (N=5) was 13.4 months. One patient of this cohort shows stable disease 14.8 months after enrollment in the study.

First efficacy results were also seen in advanced malignant melanoma, as one patient treated within the 1st schedule survived 13.8 months.

**Conclusions:** Trabedersen is a promising treatment option for patients with advanced solid tumors. Currently the study continues with recruitment of 24 patients with either pancreatic carcinoma or malignant melanoma.

## 1260

## POSTER

### Multicenter parallel phase II trials of the polo-like kinase 1 inhibitor BI-2536 in patients with advanced head and neck cancer, breast cancer, ovarian cancer, soft tissue sarcoma and melanoma. The first protocol of the European Organisation for Research and Treatment of Cancer (EORTC) Network Of Core Institutes (NOCI)

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**Background:** BI-2536 inhibits Polo-like kinase 1 (Plk1), resulting in mitotic arrest, disruption of cytokinesis, and apoptosis in susceptible tumor cell populations. Plk1, a serine/threonine-protein kinase, is a key regulator of multiple processes fundamental to mitosis and cell division. EORTC 90061 assessed the efficacy and safety of BI-2536 in five different cohorts of patients with advanced solid tumors.

**Materials and Methods:** Patients with head and neck cancer (no prior chemotherapy [CTX] for recurrent or metastatic disease), breast cancer (after a maximum of two lines of prior CTX), ovarian cancer (progressive within 6 months after completion of platinum based CTX), soft tissue sarcoma (after no more than one combination or two single agent CTX) or CTX-naïve melanoma with documented progression, adequate performance status, and good organ function were eligible. BI-2536 was given by i.v. infusion of 200 mg on day 1 every three weeks until intolerance or disease progression. Primary end point was the objective response rate (OR) according to RECIST. Secondary end points included safety (CTCAE version 3.0) and overall survival. For each tumour type a Simon optimal 2-stage design for OR was applied (type 1 and type 2 error 10%, null hypothesis 5% OR, alternative hypothesis 20% OR; stage 1 and 2: 12 and an additional 25 patients, respectively). If no OR were observed among the first 12 patients the tumour type was closed for further accrual.

**Results:** 76 patients were included between 07/2007 and 04/2008. Five patients never received study drug because of ineligibility. The median number of cycles was 2 in all organ types, except for a median of 4 in ovarian cancer. Main drug-related toxicities were febrile neutropenia (gr 3/4: 19.7%), and fatigue (gr 2/3: 31.0%). Most frequent grade 3–4 toxicities were neutropenia (81.6%), thrombocytopenia (19.7%) and anemia (15.5%). Most frequent non-hematologic toxicities were fatigue (gr 2/3: 31.0%), alopecia (26.7%), anorexia (14.1%), and nausea (12.7%), mostly grade 1–2. An

unconfirmed partial response was observed in a melanoma patient. The five strata were closed after 12 eligible patients had been entered without responding.

**Conclusions:** BI-2536 showed limited or no anti-tumour activity based on the Simon optimal design. These data however do not compromise further exploration of this class of agents with optimal documentation of dose, schedule and adequate translational research to optimize the development of polo-kinase 1 inhibitors.

## Diagnostic/Biomarkers

Poster presentations (Tue, 22 Sep, 09:00–12:00)

### Diagnostic/Biomarkers

1300

POSTER

**Immunohistochemical evaluation of PI3K/p-Akt pathways alterations in combination with conventional biomarkers in early stage breast cancer patients treated with cyclophosphamide/methotrexate/5-fluorouracil based chemotherapy: identification of an Unfavorable Biologic Profile**

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**Background:** Akt activation through PI3K, leads to the phosphorylation of p27 protein thus avoiding nuclear entry and inducing mislocation to the cytoplasm of the protein with consequent inhibition of p27 cell cycle inhibitory function. The prognostic role of PI3K/Akt pathway alterations correlating phenotypic profiles with bio-pathologic variables of known clinical importance have been investigated in a retrospective series of early stage breast cancer patients (BC pts) treated with cyclophosphamide/methotrexate/5-fluorouracil based chemotherapy (CMF). **Materials and Methods:** p-Akt, PI3K and p27 expression were evaluated by immunohistochemistry in a series of stage I/II BC pts who underwent conservative surgery and were candidates to receive CMF adjuvant therapy plus radiotherapy. Multiple Correspondence Analysis (MCA) was used to identify sub-groups of pts with different prognosis, while uni- and multivariate Cox regression analyses were applied to determine the impact of parameters identified by MCA on 10-yr Disease Free Survival (DFS), together with clinico-pathological features. Receiver Operative Curve (ROC) analysis was adopted for optimal cut-off values.

**Results:** In a series of 133 pts, with a median follow-up of 107 months (range 40 to 141), those pts characterized by high Ki67 index, p53+, p-Akt+, PI3K+ and HER2+ (Adverse Biologic Factors, ABF) were associated with tumor relapse at the MCA analysis. ROC analysis dicotomized between pts with a Favourable Biological Profile (FBP, <3 ABF) and Unfavorable Biologic Profile (UBP ≥3 ABF). UBPs showed a significantly shorter 10-yr DFS than FBP pts at Kaplan-Meier analysis (67.0% vs 91.3%, p=0.0006). According to the multivariate analysis, the biologic profile was the only significant prognostic indicator for longer DFS (p=0.002). Significant factors at uni- and multivariate analysis are shown in the table.

| Factors | Univariate (HR, 95% CI) | p-value | Multivariate (HR, 95% CI) | p-value |
|---------|-------------------------|---------|---------------------------|---------|
| Grading | 3.32 (1.31–8.43)        | 0.012   | –                         | –       |
| PgR     | 2.37 (1.03–5.48)        | 0.043   | –                         | –       |
| UBP     | 4.24 (1.73–10.40)       | 0.002   | 4.24 (1.73–10.40)         | 0.002   |

**Conclusions:** These data suggest that the activation of Akt may contribute together with high Ki67 index, p53+, p-Akt+, PI3K+ and HER2+ in predicting recurrence in early stage BC pts homogeneously treated with CMF based therapy.

1301

POSTER

**The transcription factor p53 enhances the long-term survival effect of survivin in T4 breast cancer patients – 10-year results from a single institution**

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**Background:** A large proportion of human tumors, including breast cancer, show deregulated expression of a variety of proteins such as survivin or p53, but the prognostic significance of most of them remains controversial. We analysed the expression and the association with survival of survivin (S) in T4 breast cancer pts. In addition we have attempted to correlate whether other molecular markers including p53 may influence the long-term predictive value of S.

**Materials and Methods:** from 1992 to 2001 53 consecutive T4 breast cancer pts. were included in this study. The median follow up was 125 mth. All 53 pts received primary chemotherapy, surgery, RT, adjuvant chemotherapy and hormone therapy if indicated. The median age was 51 yrs. Pathological characteristics: 28 pts (53%) were ER+ and 25 (47%) ER-; 17 pts (32%) were PR+ and 36 (68%) PR-; 24 pts (45%) were both ER and PR-, 16 (30%) both ER and PR+, 12 (23%) ER+ PR-; 10 pts (19%) HER2+, 43 (81%) HER2-; 18 pts (34%) HER2, ER and PR negative (Triple Negative; TN), and 35 (66%) non-TN. 17 pts (32%) were Ki 67 positive; 13 (24%) were p53 positive and 21 (40%) S positive (SP), 11 pts (21%) were both S and p53 positive.

**Results:** In the entire group of 53 pts the 5-year and 10-year OS was 60.4% and 43.4% respectively. The 5-year and 10-year OS in the S negative (SN) pts was 75% and 56.3% respectively. The 5-year and 10-year OS in SP pts was 38% and 23.8% respectively (p=0.009). The overall 5-year and 10 year DFS was 45% and 32.1% respectively. The 5-year and 10-year DFS in 32 SN pts was 59.4 and 37.5% respectively. The 5-year and 10-year DFS in 21 SP pts was 23.8% (p=0.095). Among pts with p53 positive or negative no statistically significant differences were observed in terms of 5-year and 10-year DFS and OS. A multivariate analysis in SP pts showed an Hazard Ratio (HR) of 2.6 (CI 1.2 to 5.5; p=0.012). When SP was associated with several prognostic variables (age, ER, PR, G2/3, Ki 67, stage T4 d and HER2) the HR ranged between 2.3 and 2.6, whereas when SP was associated with p53 the HR was 3.27 (CI 1.5 to 7.2).

**Conclusions:** In our study SP pts had a worse outcome compared to SN in terms of both DFS and OS. Among the prognostic variables evaluated only p53 enhances negatively the effect of S on survival.

1302

POSTER

**Assessment of the precursors of heme biosynthesis in patients with breast tumour**

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**Background:** Regulation and control of heme/porphyrin biosynthesis is very important for therapy of cancer. Some experimental studies found an increased level of protoporphyrin IX in human breast cancer cells. We tried to assess the precursors of heme biosynthesis in biological media of breast cancer and benign tumour patients.

**Materials and Methods:** Delta-aminolevulinic acid (delta-ALA) in urine and delta-aminolevulinic acid dehydratase (delta-ALAD) activity in blood of 264 breast cancer patients and 73 benign breast tumour patients were measured by spectrophotometry.

**Results:** The mean delta-ALA concentration in urine was 16.10 μmol/g creatinine (95% CI = (14.92–17.27) for cancer patients and 14.28 μmol/g creatinine (95% CI = 12.25–16.30) for benign tumour patients (p<0.05). The figures for delta-ALAD were 38.89 U/L (95% CI = 36.73–41.05), and 41.01 U/L (95% CI = 37.72–44.30), respectively (p>0.05).

**Conclusion:** Our findings show that heme/porphyrin biosynthesis in breast cancer patients is affected more than in benign tumour patients. The mean concentration of delta-aminolevulinic acid in urine of cancer patients is significantly higher than that in benign tumour patients.