298 POSTER

Oxaliplatin induces the expression of genes involved in capecitabine activation: preliminary results of a pharmacodynamic study in esophageal cancer

L. Pendyala[1], G. Wilding[2], P. Smith[3], R. Iyer[4], H. Nava[5], C. Nwogu[6], M. Javle[7]. *[1]Roswell Park Cancer Institute, Medicine, Buffalo, USA; [2]Roswell Park Cancer Institute, Biostatistics, Buffalo, USA; [3]Roswell Park Cancer Institute, Pharmacology, Buffalo, USA; [4]Roswell Park Cancer Institute, Medicine, Buffalo, USA; [5]Roswell Park Cancer Institute, Surgery, Buffalo, USA; [6]Roswell Park Cancer Institute, Surgery, Buffalo, USA; [7]Roswell Park Cancer Institute, Medicine, Buffalo, USA*

Background: Capecitabine (CAP) is activated to 5-fluorouracil (5FU) in 3 enzymatic steps involving carboxylesterase (CE), cytidine deaminase (CDA) and thymidine phosphorylase (TP). Our *in vitro* studies indicate that Oxaliplatin (OXP) induces CE gene expression. 5FU, OXP and radiation (XRT) is an effective neoadjuvant regimen for esophageal cancer (EC) (J Clin Oncol 20: 2844, 2002). Study aims: Explore if OXP induces expression of genes related to CAP activation in tumor biopsies (TB) and peripheral blood mononuclear cells (PMN) and correlate these changes with OXP pharmacokinetics (PK) and response in a phase I neoadjuvant study of OXP, CAP and XRT for EC.
Materials and Methods: OXP (85 mg/m^2) administered on days (D) 1, 15 and 29. CAP dose levels (DL) I: 1000, II: 1250 or III: 1500 mg/m^2 in 2 divided doses, Mon-Fri, weekly with XRT (1.8 Gy daily $\times$28). CAP + XRT started on D3. Expression of CE, CDA and TP genes in TB and PMN was evaluated before treatment and on D2 (24 hrs post-OXP) using real time QRT-PCR with comparative C_T method. After chemoradiation, patients (pts) underwent esophagectomy. Platinum in plasma ultrafiltrate was measured using Atomic Absorption Spectrophotometry and PK parameters were derived using WINNONLIN. Statistical techniques included were the signed rank test and the Spearman rank correlation.
Results: 16 pts were treated (3 at DLI, 6 at DLII and 7 at DLIII). 8 underwent esophagectomy: 3 complete responses, 2 microscopic residual disease (<1 cm), 3 downstaged. 3 pts progressed. TB and PMN gene expression data were available for 15 pts. CDA and TP had similar level of expression in TB and PMN; CE had lower expression in PMN ($p < 0.01$). No correlation noted between TB and PMN gene expression. Induction of one or more of the 3 genes was noted in TB in several pts. The changes in gene expression did not correlate with the PK of oxaliplatin. PMN did not show the same trend in expression changes as the TB. CE expression in D2 TB and the fold increase in its expression from the pretreatment showed significant correlation to response ($p \leqslant 0.03$). TP expression in D2 TB was also related to response ($p = 0.03$). Induction of one or more genes by OXP appears to be associated with response and lack of induction with PD.
Conclusions: OXP induces the expression of genes involved in CAP activation to 5FU in EC and this induction may be related to response. PMN do not serve as a surrogate tissue for studying expression changes for these genes.

299 POSTER

Randomized phase II trial of irofulven/prednisone, irofulven/capecitabine/prednisone, or mitoxantrone/prednisone in hormone refractory prostate cancer (HRPC) patients failing first-line docetaxel: preliminary results

L. Hart[1], J. Hainsworth[2], T. Ciuleanu[3], S. Oudard[4], E. Berger[5], J. Alexandre[6], K. Chi[7], D. Ruether[8], C. Kahatt[9], J. MacDonald[10]. *[1]Florida Cancer Specialists, Florida, USA; [2]Sarah Cannon Cancer Center, Nashville, USA; [3]Ion Chiricuta Institute of Oncology, Cluj, Romania; [4]Hôpital Européen Georges Pompidou, Paris, France; [5]North Shore Hematology/Oncology, East Setauket, USA; [6]Hôpital Cochin, Paris, France; [7]British Columbia Cancer Agency, Vancouver, Canada; [8]Tom Baker Cancer Centre, Calgary, Canada; [9]CAC Oncology, Le Kremlin-Bicêtre, France; [10]MGI PHARMA, Inc, Bloomington, USA*

Background: First-line docetaxel-based chemotherapy shows a survival benefit for HRPC patients (pts), although little data exist regarding post-docetaxel second-line chemotherapy. Based on evidence of irofulven (IROF) activity in HRPC observed in prior Phase I/II studies, a randomized Phase II study in docetaxel-refractory HRPC pts was initiated using IROF/prednisone (P) or IROF/capecitabine (Cap)/P versus mitoxantrone (M)/P.
Methods: Between Jun-04 and Jan-06, pts with histologically-proven metastatic HRPC who progressed by RECIST or PSAWGR criteria during or within 3 months of completing prior docetaxel treatment were randomized to 1 of 3 treatments in a 2:2:1 ratio: *Arm A*: IROF (0.45 mg/kg, Day [D]1, 8 every [q] 3 weeks [w]) and P (10 mg po daily); *Arm B*: IROF (0.4 mg/kg D1, 15), Cap (2000 mg/m^2 D1−15 q4w) and P; *Arm C*: M (12 mg/m^2 q3w) and P. Pts had adequate hematologic and organ function, Karnofsky performance status (KPS) $\geqslant$70%, and were stratified by baseline pain status. Primary endpoint was time to progression (TTP); secondary endpoints included survival, PSA response, pain response and safety assessment.
Results: As of May-06, 134 pts from 34 centers in 9 countries were randomized and treated (Arm A/B/C: 53/54/27). Median age for each group was 64/67/63 years, KPS $\geqslant$80% for each group was 79%/94%/59% of pts, median baseline PSA (ng/mL) 144/136/243, disease-related pain at baseline 61%/58%/63%; other characteristics, including metastatic site distribution, were comparable among arms. *Efficacy*: With a median follow-up of 9.7 months (range 1.7–22.6), progression was reported in 84% of pts and 49% have died across all treatment groups.
Safety: 129 pts were evaluated. Median cycles/pt (A/B/C) 3/2/3; most common Gr 3–4 toxicities (% pts): asthenia (6%/10%/0%), vomiting (2%/12%/0%) and diarrhea (4%/6%/0%). The most common laboratory Gr 3–4 abnormalities were neutropenia (17%/10%/44%) and thrombocytopenia (15%/14%/4%).

	Arm A, IROF/P N = 53	Arm B, IROF/Cap/P N = 54	Arm C, M/P N = 27
PSA decrease >50% or PR (RECIST)	5 (9%)	11 (20%)	1 (4%)
Stable disease >12 w	11 (21%)	7 (13%)	4 (15%)
TTP (months), Median (95% CI)	1.9 (1.4–2.4)	2.1 (1.8–2.4)	1.0 (0.5–1.6)
Overall survival (months), Median (95% CI)	10.7 (7.6−13.8)	10.2 (6.3−14.1)	7.2 (2.3−12.2)

Conclusion: Preliminary results suggest a longer survival and TTP, a higher PSA response, and an acceptable safety profile for IROF/P and IROF/Cap/P compared to M/P. Based on these data, IROF may have a role in treating docetaxel-resistant HRPC pts.

300 POSTER

Phase I study of an oral isotype-selective histone deacetylase (HDAC) inhibitor in patients (pts) with advanced solid tumors

L.L. Siu[1], M. Carducci[2], E.X. Chen[1], M. Maclean[1], R. Pili[2], S. King[2], T. Patterson[3], Z. Li[3], A. Kalita[3], G.K. Reid[3]. *[1]Princess Margaret Hospital, University Health Network, Medical Oncology and Hematology, Toronto, Canada; [2]Sidney Kimmel Cancer Center at Johns Hopkins, Medical Oncology, Baltimore, USA; [3]MethylGene Inc., Montreal, Canada*

Background: MGCD0103 is a unique non-hydroxamate, orally available inhibitor of human HDACs. Deregulation of HDAC activity is associated with malignant diseases in humans and small molecule inhibitors of HDACs have emerged as a novel therapeutic class of molecules with anticancer potential. Their proposed mechanism of anticancer activity is via regulation of aberrant gene expression at the transcriptional level, leading to inhibition of proliferation, induction of apoptosis and/or cell differentiation in cancer cells.
Methods: A phase I trial of MGCD0103 given intermittently as an oral dose 3$\times$/weekly, 2 weeks out of 3 is being conducted in pts with advanced solid tumors. Objectives included: safety, tolerability, pharmacodynamic (PD) and pharmacokinetic (PK) evaluation of HDAC activity.
Results: Six dose levels have been evaluated: 12.5, 20, 27, 36, 45 and 56 mg/m^2. 34 pts with the following demographics have received MGCD0103: M:F = 22:12, median age (range) = 59 (29−75). From 28 pts the following are known: ECOG 0:1:2=10:17:1; primary tumor sites: colorectal (8), renal (5), lung (4), others (11); prior chemotherapy, radiotherapy and immunotherapy were given to 22, 12 and 2 pts respectively. A total of 65 cycles have been administered (N = 28) mean = 2.3 and range = 1–11. Most common adverse events in pts (N = 27) are: Grade 1–3 fatigue 18 pts (67%), nausea 13 pts (48%); Grade 1–2 vomiting, 8 pts (30%) and anorexia, 6 pts (22%). MTD has been reached. PD evaluations include inhibition of HDAC activity and induction of H3 histone acetylation. The portion of pts with >20% inhibition of HDAC activity increased with dose as compared to baseline levels and induction of histone acetylation exceeded 50% in a majority of pts (3 out of 5) at 45 mg/m^2. Terminal $t_{1/2}$ in plasma was found to be approximately 9 hrs and duration of the PD effects persisted for 72 hrs after dosing, supporting this intermittent dosing regimen. Stable disease beyond 2 cycles has been achieved in 4 pts to date. Serum IL-6 levels may correlate with fatigue encountered on study.
Conclusion: Evaluations indicate MGCD0103 can be safely administered on a 3$\times$/weekly 2 weeks out of 3 schedule to pts with solid tumors.