NSCLC tumor samples were 100% matching the data of DNA sequencing. In those 340 cases of unknown phenotype tumor samples, 28 cases were stained positive by L858R antibody and 24 cases were stained positive by exon 19 deletion antibody. The positive rate by both antibodies is 15.3%. The DNA of all positive samples and all staining negative adenocarcinoma samples were sent to do DNA sequencing, which showed the sensitivity of the IHC with the antibodies is 92.5% and the specificity is 95.8%. Some tumor samples carrying the mutations with low percentage of cancer cells were missed by direct sequencing, but detected by IHC with mutant EGFR antibodies.
Conclusions: The IHC combined mutant EGFR specific antibodies and wtEGFR antibody can be used to detect the EGFR mutations and measure the expression level of total EGFR protein in tumors. In addition, this assay enables us to examine paraffin blocks from small biopsy samples, which are difficult to extract enough high quality DNA for sequencing. The assay has the potential to be used to screen lung cancer patients for the treatment with EGFR kinase inhibitors in a clinical setting.

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Comparison of phase I trial (P1T) abstract quality between the EORTC-NCI-AACR and ASCO meetings

J. Ho[1], E. Strevel[1], N. Chau[1], G.R. Pond[1], A. Murgo[2], P. Ivy[2], L.L. Siu[1]. *[1]Princess Margaret Hospital, Division of Medical Oncology and Haematology, Toronto, Ontario, Canada; [2]National Cancer Institute, Cancer Therapy Evaluation Program, Bethesda-Maryland, USA*

Background: Conference abstracts of P1T communicate important information on anti-cancer drug development. Based on an electronic survey of 27 experts in oncology developmental therapeutics, our group recently reported a scoring system which assessed the quality of P1T abstract reporting (Strevel et al. Clin Cancer Res 14:1782–1787, 2008). For instance, the top three items deemed absolutely essential in phase I abstract reporting were description of dose-limiting toxicity, recommended dose, and grade 3 or greater toxicity at least possibly attributable to the study drug.
Methods: A scoring system for evaluating the quality of P1T abstracts based on a survey of experts was previously developed. This system was applied to all P1T abstracts presented at the EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics from 2003 to 2007. The results were compared to quality scores of 1,683 P1T abstracts published in the ASCO Annual Proceedings from 1997 to 2006, previously reviewed and reported by Strevel et al.
Results: 304 EORTC-NCI-AACR P1T abstracts were reviewed. Characteristics of these abstracts are as follows: oral proffered paper vs poster presentations = 2.3% vs 97.7%; governmental or academic vs industry funding = 18.4% vs 81.6%; US vs Europe vs international vs others = 58% vs 27% vs 10% vs 5%; multi-centre vs single-centre trials = 71% vs 29%. The mean quality score for the 229 EORTC-NCI-AACR P1T abstracts was 69.6%, as compared to 64.5% for the 713 ASCO P1T abstracts published in the same overlapping time period from 2003 to 2006. A strong correlation was observed between the two conferences in whether the abstracts contained the information of interest (Spearman correlation coefficient = 0.78). Multivariate analysis of combined conference abstracts indicates that predictors of increased quality score include a more recent year of presentation ($p < 0.001$), combination therapy trials ($p < 0.001$), non-North American trial centers ($p < 0.001$), and industry-sponsor trials ($p = 0.05$).
Conclusions: P1T abstracts presented at the EORTC-NCI-AACR have slightly higher quality scores than those presented at ASCO. This is likely due to higher character limits (2,500 vs 2,000), allowance for updating previously presented data, and the more sub-specialized anti-cancer drug development focus of the EORTC-NCI-AACR conference. There remains room in both conferences for improving abstract quality, which may be achieved by adopting P1T reporting guidelines.

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A phase 1 study of XL281, a potent and selective inhibitor of RAF kinases, administered orally to patients (pts) with advanced solid tumors

G.K. Schwartz[1], S. Yazji[2], D.S. Mendelson[3], M.A. Dickson[4], S.H. Johnston[5], E.W. Wang[6], P. Shannon[7], L. Pace[4], M.S. Gordon[7]. *[1]Memorial Sloan-Kettering Cancer Center, Oncology, New York, USA; [2]Exelixis, Clinical Development, San Francisco, CA, USA; [3]Premier Oncology, Oncology, Scottsdale, AZ, USA; [4]Memorial-Sloan Kettering Cancer Center, Oncology, New York, USA; [5]Exelixis, Clinical Operations, San Francisco, CA, USA; [6]Exelixis, Translational Medicine, San Francisco, CA, USA; [7]Premier Oncology, Oncology, Scottsdale, AZ, USA*

Background: Mutations in K-RAS or B-RAF are found in a large proportion of human tumors, and lead to RAF/MEK/ERK pathway activation. Preclinical models containing K-RAS or B-RAF mutations are sensitive to RAF kinase inhibitors. XL281 is a potent and selective inhibitor of wild type and mutant RAF kinases, and shows anti-tumor activity in multiple xenograft models.
Methods: Pts with advanced solid tumors are enrolled in successive cohorts and receive XL281 orally once daily on a 28-day cycle. Tumor response is assessed every 2 cycles. Pharmacokinetic (PK) samples from plasma and pharmacodynamic (PD) samples from hair, buccal mucosa, peripheral blood mononuclear cells (PBMC) and optional tumor biopsies are collected for biomarker analyses and B-RAF and K-RAS genotyping.
Results: Of twenty-one pts enrolled in 6 cohorts, dosed at10, 20, 40, 60, 100 or 150 mg daily; 16 pts are evaluable to date. Tumor types include colorectal (CRC) (n = 5), papillary thyroid (PTC) (5), ovarian (1), prostate (1), carcinoid (2) and melanoma (2). No dose-limiting toxicities were observed; the most frequent treatment-related adverse events are grade 1or 2 nausea, vomiting, diarrhea and fatigue. Three CRC pts have stable disease (SD) for 20 weeks, with one showing a ~20% reduction in target lesions. Five PTC pts, 2 with a confirmed B-Raf V600E mutation, have SD (36+, 32+, 20+, 8+, 8+ wks, respectively). Three pts (1 prostate, 1 carcinoid, 1 melanoma) have SD (19, 24+, and 22+ wks, respectively). XL281 is rapidly absorbed (median tmax = 2 hrs), has a median t1/2 of ~8 hrs, and shows minimal accumulation after repeat dosing. XL281 exposure generally increases with increasing dose and appears dose proportional. Administration of XL281 modulates RAF target activity as assessed by reduction in the stimulation of phosphorylated ERK in PBMCs post-treatment.
Conclusions: XL281 is generally well tolerated, with early signs of clinical activity. In 15 evaluable pts, 11 have SD of which 9 pts exceeded 16 weeks on study. Reduced pERK is observed in PBMCs, indicative of target modulation. The MTD has not yet been defined and dose escalation continues.

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Effect of selection of QTc formula on eligibility of patients for phase I cancer clinical trials

M. Benjamin[1], D. Casa[1], W. Tembe[2], B. Piper[1], S. Anthony[1], R. Ramanathan[1], R. Tibes[1], G. Jameson[1], D. Von Hoff[1], M. Borad[3]. *[1]Scottsdale Clinical Research Institute/TGen, Clinical Research, Scottsdale, AZ, USA; [2]TGen/Translational Genomics Research Institute, Research, Phoenix, AZ, USA; [3]Mayo Clinic of Arizona, Clinical Research, Scottsdale, AZ, USA*

Background: The corrected QT interval (QTc) is often utilized as an eligibility criterion in Phase I cancer clinical trials. Numerous formulae have been utilized in the conduct of these trials to calculate the QTc to correct for values based on the ventricular rate, characterized by the RR interval. The primary objective of this pilot study was to ascertain if selection of a particular formula (e.g. Bazzett) could affect the eligibility rate for patients enrolling on Phase I trials. Secondary objectives were to determine the proportion of patients who were on medications that could potentially prolong QTc, the proportion of concomitant medications that could potentially prolong QTc and if factors such as underlying cardiovascular disease, electrolyte imbalances (e.g. hypokalemia) or age were correlated with QTc prolongation.
Materials and Methods: A retrospective chart review was conducted in the setting of a Phase I clinic and 130 patient charts were reviewed. Absolute QT values were obtained from screening ECGs. Concomitant medications and co-morbidities of interest (underlying cardiovascular disease, history of arrythmias) were tabulated. QTc values for each patient were calculated using seven different formulae (Bazzett [B], Fridericia [F], Framingham [FR], Hodges [H], Mayeda [M], Van de Water [V] and Wohlfart [W]). Generally used values (>470 ms in females and >450 ms in males) were used for purposes of QTc prolongation. Concomitant medication potential for QTc prolongation was ascertained using a publicly available database, AzCert (www.qtdrugs.org). Statistical significance of the association between QTc and factors of interest were calculated using Fisher's exact test.
Results: Ineligibility rates ranged from 3.1% to 17.7% (FR:3.1%, V:3.1%, H:3.1%, W:3.1%, F:3.9%, B:10.8% and M:17.7%). We also found that a consistent ineligibility rate (3.1%) could be achieved by using formulae appropriate QTc thresholds as opposed to generally used values. The proportion of patients taking medications with potential to prolong QTc was 51% while the proportion of concomitant medications with the potential to prolong QTc was 12%. No correlation was found between QTc prolongation and age, gender, underlying cardiovascular conditions, primary site or electrolyte imbalances ($p > 0.05$ in all cases).
Conclusions: Uniform criteria and guidelines for selection of QTc formulae need to be developed. Formulae specific QTc thresholds also need to be specified.