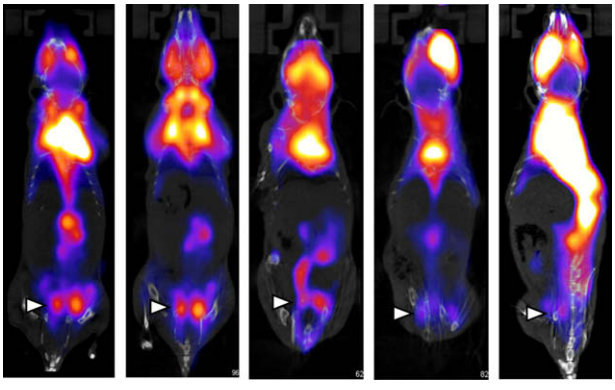
administered at 3 mg/kg by daily oral gavage for 3 weeks with serial 18FDG-PET and T2-weighted MRI imaging at 2 days, 1 week, 2 weeks and 3 weeks post-treatment respectively, followed by sacrifice, prostate harvest and standard hisopathologic and immunohistochemical staining. GSK458 treatment of PTEN/p53 and PTEN mice results in adequate target inhibition, based on pharmacodynamic assessment by 18FDG-PET uptake. There was a significant reduction in tumor burden in both intraepithelial and poorly differentiated atypical components within stroma and partial stromal collapse following 3 weeks of GSK458 treatment, as assessed by MRI and histopathology. MRI assessment suggests that there may be partial regrowth of tumor at the end of 3 weeks of treatment with GSK458, suggesting acquired resistance. These data demonstrate that GSK458 treatment of prostate-specific PTEN/p53 double knockout and PTEN knockout mice, respectively, results in a pharmacodynamic and antitumor response with potential development of acquired resistance. The results underscore the utility of genetically engineered mouse models to predict response to targeted therapies in genetically stratified human clinical trials, and elucidate mechanisms of acquired resistance early in clinical development. The design of rational combinations to overcome resistance to PI3K-directed targeted therapies are also being explored in these genetically engineered mouse models systems.



Day 0	Day 1	Day 2	Day 8	Day 16
	20h after treatment	3h after treatment	22h after treatment	22h after treatment
100% (baseline)	121% (baseline)	34% (baseline)	57% (baseline)	59% (baseline)

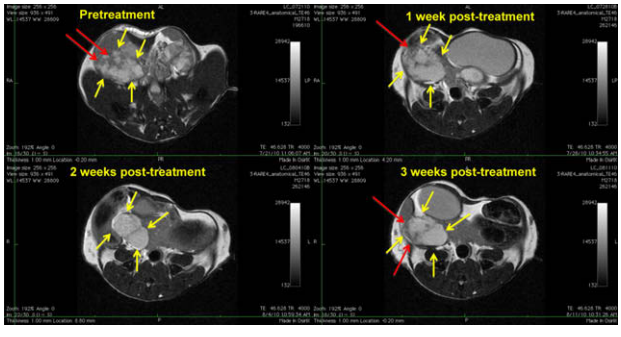


Figure: Impact of GSK458 (PI3K/mTOR inhibitor) on prostate tumor 18FDG-PET uptake and antitumor response in prostate-specific PTEN-p53 double knockout mice. The mice were treated with GSK458 (3 mg/kg) by continuous daily dosing for 3 weeks. Baseline pre-treatment (day 0) and indicated post-treatment (A) PET-CT and (B) MRI scans, respectively, were obtained to serially assess for target inhibition and antitumor response

Wednesday, 17 November 2010 10:15–12:00

WORKSHOP 6

New drug development in the 21st century: Do we need to break from tradition?

28 INVITED

The point of view of academia

M. Piccart[1]. [1]*Institut Jules Bordet, Medicine, Brussels, Belgium*

Owing to the explosive progress in biomedical and pharmaceutical research in the area of cancer biology and a better understanding of the different molecular pathways that drive tumorigenesis, the number of new molecular entities that enter into the development process has increased significantly. However, the rate of approval for marketing of anticancer agents is very low; estimated to be less than 10%.

One of the main limitations of the current drug development paradigm is the lack of a clear target population. This underlines the need to identify biomarkers that can define more precisely which patients will truly benefit from which drugs. Only few biomarkers have attained the level of validation needed for routine clinical use so far, probably due to the current very suboptimal process of biomarker discovery and validation.

Early clinical trials represent a crucial bridge between preclinical drug discovery and the resource-intense randomized phase III trial-the definitive regulatory hurdle for drug approval. High attrition rates and rising costs, when coupled with the extraordinary opportunities opened up by cancer genomics and the promise of personalized medicine call for new approaches in the conduct and design of clinical trials. The key challenges lie in increasing the odds for successful and efficient transition of a compound through the drug development pipeline, as well as in better identifying subsets of patients who truly benefit.

Our growing knowledge of the genetic landscape of cancer is providing the basis for a new generation of prognostic and predictive biomarkers. There is tremendous scope for these biomarkers to contribute to the drug development process, with the aim of increasing the success rate, accelerating the timeline of new molecularly targeted therapies to regulatory approval and patient benefit, and ultimately facilitating the implementation of personalized cancer medicine.

Coupling of smaller 'proof of principle' studies with larger registration trials offers the promise of speeding up the time to market of new therapies. Clever new designs can provide valuable insight regarding mechanisms of action of and resistance to novel drugs by identifying patients who are most likely to respond to a novel therapy early in the drug development process. Armed with new omics, prospective translational research, and international collaboration, we are well on our way to break from tradition and open a new chapter of drug development.

The NEOBIG initiative will be summarized as it represents one attempt at a more efficient and targeted drug development in breast cancer.

Finally, the importance of a healthy collaboration between academia and pharma will be emphasized: models for such a collaboration now exist and represent a "win-win" situation for both parties as well as the best way of keeping faith with trial participants.

29 INVITED

In search of intermediate endpoints

E. Eisenhauer[1]. [1]*NCIC Clinical Trials Group, Queen's University, Kingston, Ontario, Canada*

The major goals of cancer drug development are to identify new agents that improve the *quantity* or *quality* of patient survival, with acceptable adverse effects. Furthermore, increasingly in today's environment of molecular targeted treatment, it is expected that, in the course of drug development, criteria for selection of patients most likely to experience benefits or least likely to experience serious adverse effects will be identified.

Endpoints of studies that definitively address these goals include *overall or relapse free survival* as well as *patient reported outcomes* using validated Quality of Life instruments. Studies evaluating these outcomes generally occur at the end of a long road of early phase trials, have large samples sizes and are randomized in design. Some of these randomized trials may also include integration of (putative) selection biomarkers with the aim of validation within the definitive randomized trial.

The cost in terms of time, patients, expectations and funding is high when agents fail in phase III or when there are lost opportunities to identify predictive biomarkers. Early rejection of agents *likely to be inactive* should increase efficiency but requires use of endpoints occurring earlier

in the disease course. Such "intermediate" endpoints should ideally be surrogates for the "real" endpoints of interest, but may still be useful for drug development decision making even in the absence of proven surrogate value. The risks in using intermediate endpoints of uncertain surrogate value is that false positive or negative decisions may be made about drug activity leading to rejection of active drugs or continued study of inactive drugs. Balancing these risks may be increased efficiency in development of agents when true positive and negative decisions are made.
Intermediate endpoints for efficacy to be examined will include: *anatomic measures* of cancer burden (e.g. objective response, progression rates, continuous measures of tumour size, and time to progression), *functional measures* of cancer status (e.g. positron emission tomography based), *circulating measures* of disease activity (e.g. circulating tumour cell numbers or quality, serum markers*), molecular measures* of drug activity (e.g. pharmacodynamic effects of drug in tumour). The strengths and weaknesses of each will be evaluated, designs for their use explored, and suggestions offered regarding how predictive biomarker development can be integrated into studies with these endpoints.

30 INVITED

Innovation, collaboration, and agility: essential characteristics for the biopharmaceutical industry in the 21st century

M.L. Rothenberg. *USA*

Abstract not received

31 INVITED

The point of view of EMEA

F. Pignatti. *USA*

Abstract not received

32 INVITED

The point of view of FDA

R. Justice[1], A. Ibrahim[1], A. Murgo[1], R. Pazdur[1]. *[1]Food and Drug Administration, Office of Oncology Drug Products, Silver Spring, USA*

Most new oncology drug development is currently focused on identifying molecular targets that are responsible for cancer cell growth and survival and on designing therapies that are specific for these targets. For many of these new agents the classical cytotoxic drug development paradigm is no longer appropriate.
In Phase 1 it may be preferable to determine an optimal dose rather than a maximally tolerated dose and to include patients with cancers whose growth and survival is known to be driven by the therapy's target.
Phase 2 study designs shoud be carefully considered. A single-arm Phase 2 trial design with objective response rate as the primary endpoint may fail to identify active agents with a cytostatic mechanism of action. Alternative Phase 2 study designs include randomized active control trials, randomized dose response studies, and randomized discontinuation trials with a primary endpoint of progression-free survival. For therapeutics that are thought to be precisely targeted, Phase 2 trials provide an opportunity to determine whether a companion *in vitro* diagnostic test is necessary to identify patients who are likely to benefit versus those who are not. These Phase 2 trials can also provide data needed to validate the diagnostic.
Phase 3 trials are now international in scope and differences in ethnic factors, medical practice, and available therapies may pose design challenges. For trials designed to support U.S. approval, it is important that the results be applicable to the U.S. population. While there is a trend towards using progression-free survival as the primary endpoint, in many drug and disease settings overall survival may still be the most appropriate primary endpoint. Phase 3 studies using a companion diagnostic as an eligibility criterion should use the to-be-marketed test and the diagnostic should be approved by the time of drug approval.
An accelerated approval strategy based on objective response rates in single-arm trials in patients who have received extensive prior therapy is not recommended. Response rates are likely to be low and difficult to interpret and patients must have received all approved available therapy for the disease. In addition, what constitutes available therapy is determined at the time of regulatory action. Randomized trials designed to demonstrate superiority of a new therapy over available therapy are recommended with confirmation of clinical benefit, e.g., improved survival, in the same studies. A proposal for an accelerated approval development plan should include the design of the confirmatory studies (more than one). These studies should be agreed to by FDA and should be ongoing at the time of marketing approval.
Each new drug development program poses unique challenges and interaction between sponsors and FDA is recommended at each stage of development.

Wednesday, 17 November 2010 14:05–14:45

Special Lecture

33 INVITED

Hallmarks of cancer, ten years later: evolving principles, and therapeutic targeting

D. Hanahan. *Switzerland*

Abstract not received

Wednesday, 17 November 2010 14:45–16:15

PLENARY SESSION 2

Proffered paper session

1LB LATE BREAKING ORAL

Development and validation of robust immunohistochemical assays for phospho-histone-H3 and Eg5 as pharmacodynamic biomarkers to support Eg5 inhibitor (LY2523355) clinical trials in patients with advanced malignancies

For full abstract, see p. 3.

34 ORAL

DNA amplifications of kinase inhibitor targets in human cancer

M.J. Anstett[1], P.J. Wyngaard[2], B.A. Steck[3], R.E. Dull[3], D.R. Rhodes[1]. *[1]Compendia Bioscience, Science, Ann Arbor MI, USA; [2]Compendia Bioscience, Technology, Ann Arbor MI, USA; [3]Compendia Bioscience, Data, Ann Arbor MI, USA*

The identification of oncogenic protein kinases in cancer has prompted the development of several novel targeted therapies. In many cases, such therapies have elicited dramatic clinical responses in patients harboring genetic activation of the target kinase. To identify additional opportunities to apply existing targeted therapies, we undertook a systematic DNA copy number analysis of 20 targeted kinases across more than 2,900 cancer patients. Array CGH data were collected from 27 independent studies and processed with standard normalization and segmentation procedures. In total, we identified 391 significant DNA amplifications (5+ copies) of targeted kinases in 324 cancer patients, suggesting that 5–10% of cancer patients harbor a detectable DNA amplification that might indicate benefit from an existing targeted therapy. Seventeen of the twenty targets showed evidence for significant amplification at least once. Notably, significant amplifications of targeted kinases were most common in cancers of the brain (24%) and breast (17%), occurred in small subsets of cancers of the colon (7%), lung (5%) ovary (5%) and pancreas (3%) and were rare or non-existent in liver cancer (1 of 197), leukemia (0 of 221) and myeloma (0 of 192). Within brain cancer, glioblastoma was most exceptional, where frequent amplifications of EGFR (41.6%), PDGFRA (9.7%), KIT (6.7%) and MET (2.7%) occurred, and rare amplifications of 8 other targeted kinases were also observed. ERBB2 amplification was found to be frequent in breast cancer (11.2% frequency), but was also observed in small subsets of colorectal (1.1%) and lung cancer patients (0.8%). In addition to glioblastoma, EGFR amplifications were observed in astrocytoma (18%) and lung adenocarcinoma (2.6%), but not in other solid tumors. Recurrent FGFR1 amplifications were observed in cancers of the breast (4.5%), pancreas (3.5%), ovary (1.6%), colon (0.6%) and lung (0.5%), whereas FGFR2 and FGFR3 amplifications occurred rarely. Other recurrent amplifications of targeted kinases included: JAK2 in ovarian (1.4%) and cervical cancer (2.4%), ALK in neuroblastoma (1.4%), AURKA in breast (1.1%), colon (1.1%) and lung cancer (0.5%), FLT3 in colorectal cancer (2.8%), IGF1R in ovarian cancer (2.1%), and SRC in colorectal cancer (1.1%). To investigate the possibility that the identified target amplifications represent driver amplifications and might thereby confer sensitivity to the appropriate targeted therapy, we performed minimal common region analysis of the genomic regions containing the amplified targets. Importantly, most of the identified target amplifications were highly focal and the targeted kinase was the most frequently amplified gene in the genomic region, suggesting that amplification of the target is likely a driver event. In summary, our analysis demonstrated that many targets of existing therapies are focally amplified in identifiable patient sub-populations spanning multiple cancer types.