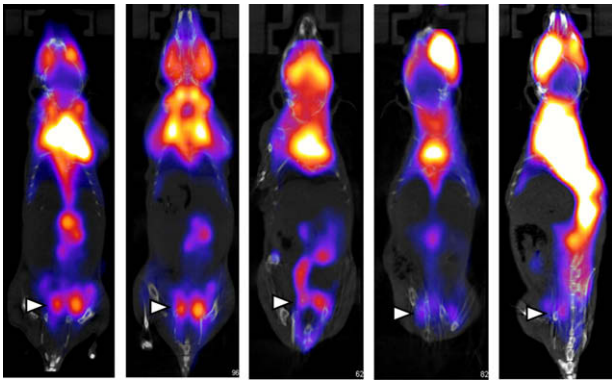
administered at 3 mg/kg by daily oral gavage for 3 weeks with serial 18FDG-PET and T2-weighted MRI imaging at 2 days, 1 week, 2 weeks and 3 weeks post-treatment respectively, followed by sacrifice, prostate harvest and standard hisopathologic and immunohistochemical staining. GSK458 treatment of PTEN/p53 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)

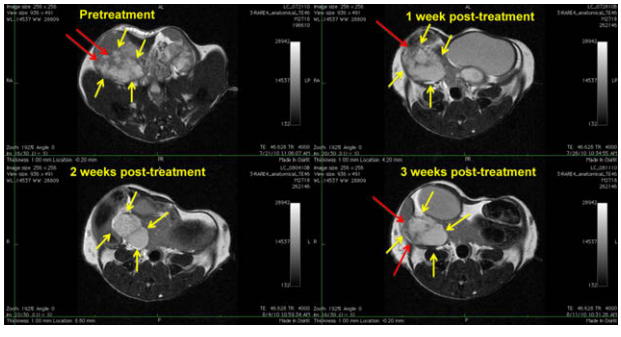


Figure: Impact of GSK458 (PI3K/mTOR inhibitor) on prostate tumor 18FDG-PET uptake and antitumor response in prostate-specific PTEN-p53 double knockout mice. The mice were treated with GSK458 (3 mg/kg) by continuous daily dosing for 3 weeks. Baseline pre-treatment (day 0) and indicated post-treatment (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