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

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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.