a blue discolouration of skin and urine and lymphopaenia, at the highest dose explored (447 mg/m^2) tumour concentrations of AQ4 exceded IC50 values for sensitive cell lines.
Aminoflavone (NSC 686288), a synthetic material related to plant derived flavonoids, has demonstrated cytotoxic activity in a wide range of cell lines and xenografts, with marked activity seen in renal cancer xenografts. This agent requires activation by CYP1A1 and the selectivity toward particular cell lines is related to the ability to induce CYP1A1 expression. A lysine derivative pro-drug of aminoflavone (AFP464) has entered phase I clinical trials exploring dosing on days 1, 8 and 15 every 4 weeks.
Phortress is the L-lysylamide prodrug of the fluorinated benzothiazole 5F 203, which causes cell cytotoxicity via a novel mechanism of action. 5F 203 is translocated into the nucleus by the aryl hydrocarbon receptor where it induces CYP 1A1 which in turn activates 5F 203, causing covalent DNA binding and DNA adducts. This induction of the activating enzyme within cells theoretically could confer selectivity in CYP 1A1 overexpressing tumours, however the known potential for induction of this enzyme in liver or lung led to a cautious trial design for entry of this agent into the clinic. The initial schedule explored, 1 and 8 dosing every 4 weeks, caused dose limiting liver toxicity at the first dose level and a once every 3 weeks schedule is currently being investigated.
Conclusions: The results of the published and available data from ongoing studies of these 3 agents will be summarised and discussed.

References

[1] Steward et al, 2007 Ann Oncology 18 1098–1103.
[2] Albertella et al, 2008 Clin Cancer Research 14 1096–1104.

26 INVITED

Selective CYP17 inhibition with abiraterone acetate (AA) in castration resistant prostate cancer (CRPC): the Royal Marsden Hospital experience

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Background: Studies in CRPC indicate high intra-tumoral androgen levels and continued androgen receptor (AR) signaling, despite androgen deprivation therapy (ADT). The source of these androgens may be adrenal or 'de-novo' intratumoral synthesis. CYP17 is a key enzyme for androgen biosynthesis, catalysing two reactions (C17,20 lyase; 17α hydroxylase). AA, an oral, selective, irreversible inhibitor of CYP17, was discovered at the Institute of Cancer Research and is a >10-fold more potent CYP17 inhibitor than ketoconazole.
Methods: Two parallel trials have been conducted in CRPC pts who have failed ADT: (1) a phase I/II in chemotherapy-naive pts, (2) a phase II in post-docetaxel pts. The phase I study of once-daily, continuous AA, escalating through 5 doses (250 mg – 2000 mg) in three-patient cohorts moved seamlessly into Phase II with expansion at the recommended dose. The primary objective of the Phase II studies was to evaluate AA anti-tumor activity with rejection of the null hypothesis if $\geqslant$7 pts from a maximum of 35 had a PSA decline by $\geqslant$50% (Ho: PSA RR < 10%, Ha: PSA RR > 30%, power 86%, alpha 5%). Measurable disease responses and circulating tumor cells (CTC) were also evaluated.
Results: 21 pts were recruited to the Phase I study. AA was well-tolerated with no DLTs. 1000 mg od was selected as Phase II dose based on PK-PD data. Proof of concept hormonal testing has demonstrated significant testosterone suppression, beyond that achieved by conventional ADT. The null hypothesis was rejected in both Phase II studies with $\geqslant$50% PSA decline rate exceeding 60% in chemotherapy-naive pts and 40% in post-docetaxel pts. 54 pts received AA in the chemo-naive Phase II (median baseline PSA: 75, range: 8.8–964). 38/54 (70%) had a $\geqslant$50% PSA decline and 43/54 (80%) had $\geqslant$30% PSA decline. 29/54 pts had measurable disease on baseline CT; best RECIST response was 15/29 (52%) confirmed partial response (PR). 8/29 (28%) had stable disease (SD) >3 mnths. Median time-to-progression (TTP) is 231 days (95%CI 168–308). 34 post-docetaxel pts received AA (median baseline PSA: 536, range: 26.4–10325). 16/34 (47%) had a $\geqslant$50% PSA decline, and 22/34 had a $\geqslant$30% decline in PSA respectively. 20/34 pts had measurable disease on baseline CT; best RECIST response was 5/20 (25%) confirmed PR; 10/20 SD > 3 mnths. Median TTP is 161 days (95%CI 111–224) days. PSA declines and measurable disease responses have been supported by symptom improvements, reductions in analgesics and CTC. Expected mechanism-based toxicities owing to secondary mineralocorticoid excess (hypertension, hypokalaemia, fluid retention) were ablated with a mineralocorticoid receptor antagonist or low dose corticosteroids.
Conclusion: AA is well-tolerated and demonstrates significant anti-tumor activity. These results support pre-clinical data suggesting that CRPC frequently remains hormone driven. Randomized phase III trials of AA are now open for accrual.

27 INVITED

Novel atypical retinoic acid metabolism blocking agents (RAMBAs)/ CYP26 inhibitors for breast cancer therapy

L.K. Gediya[1], P. Purushottamachar[1], A. Khandelwal[1], J. Mehta[1], A. Godbole[1], V.C.O. Njar[1]. *[1]University of Maryland School of, Department of Pharmacology and Experimental Therapeutics, Baltimore, USA*

Despite the success of all-trans-retinoic acid (ATRA)-based differentiation therapy in acute promyelocytic leukemia (APL), the broad promise of ATRA and other retinoids in the clinic has not yet been realized. Translation of retinoid activities from the laboratory to the clinic has met with intrinsic or acquired retinoid resistance. An important mechanism of acquired ATRA resistance involves increased ATRA metabolism. Therefore, retinoic acid metabolism blocking agents (RAMBAs) may be valuable in the treatment of a variety of diseases, including cancers.
The talk will focus on the development of VN/14−1, a novel atypical retinoic acid metabolism blocking agent (RAMBA) via inhibition of CYP26 and a novel aromatase (CYP19) inhibitor that also possess multiple desirable anti-cancer activities. Based on its unique characteristics as a multi-targeting anti-cancer agent, it has enormous potential to be a very promising drug for breast cancer therapy. VN/14−1 is an extremely potent inhibitor of CYP26 and of aromatase (CYP19), key enzymes implicated in breast cancer progression. Although the mechanisms underlying the actions of VN/14−1 are still not fully understood, several molecular effects have been observed. In vitro and in vivo, VN/14−1 treatment leads to: (i) down-regulation of ERα, AIB1, pMAPK, HER-2, cyclin D1, cdk4, Bcl2; (ii) up-regulation of cytokeratins 8/18, E-cadherin, BAD and BAX; (iii) cell cycle arrest in G1 and G2/M phases; (iv) induction of differentiation; and v. induction of apotosis. These properties appear to be responsible for VN/14-1's extremely potent inhibition of a variety of endocrine-sensitive and -resistant breast cancer cells and tumor xenografts. VN/14−1 and related RAMBAs are currently undergoing further preclinical studies under the auspices of Cancer Research UK in view of clinical trials in breast cancer patients.

Wednesday, 22 October 2008 10:15–12:00

WORKSHOP 6

Design and conduct of phase II trials for targeted agents

28 INVITED

Adaptive phase II trials

D. Berry. *USA*

Abstract not received

29 INVITED

Parallel phase II trials – European perspective

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The ultimate objective in oncology drug development is to establish new standard of care which may result in significant therapeutic benefit for patients. This aim is achieved through the development of new agents which need to be optimally integrated in existing therapeutic strategies.
There have been an increasing number of new targeted agents addressing molecular pathways. A major challenge is to first identify early signs of activity for this plethora of new agents and second to take the decision to embark in large phase III trials which will eventually position new candidates within the therapeutic armaterium. As new approaches may be needed to reach this goal, parallel phase II may be an option to address these issues. In early phase of development, parallel phase II testing for activity of new agents in various tumor types bearing a certain target may be considered for early sign of activity. Subsequently randomized phase II should be considered specifically for combination approaches once potential preliminary efficacy has been demonstrated. These approaches have methodological limitations and may not necessarily apply to all agents and/or tumor types. The role and place of phase II in the decision process

should be evaluated as methodological improvement is needed for go/no go decision. Phase II should also be envisaged as a critical part of drug development to obtain better insight on the biology of the disease and/or mechanism of action of tested agents. To achieve this goal, companion biological and imaging studies should be considered for optimized phase III designs.

30 INVITED

Patient enrichment strategy in phase II

J. De Bono. *United Kingdom*

Abstract not received

31 INVITED

Using biomarkers in phase II studies

J. Tabernero[1], A. Cervantes[2], J. Baselga[1]. *[1]Vall d'Hebron University Hospital, Medical Oncology Department, Barcelona, Spain; [2]Clinic University Hospital, Medical Oncology Department, Valencia, Spain*

Current attrition rate of new oncology drugs is very high, this leading not only to an unsustainable budget in the pharmaceutical industry but a sense of great disappointment in the oncology community level. To curtail this rate of attrition, investigation leaders need to make confident decisions as early as possible during the drug development process and to ensure that only those drugs with an optimal safety/efficacy profile move to phase III development and only patients most likely to benefit from the drug are enrolled into the pivotal regulatory trials. A greater understanding of the biology of cancer coupled with major advances in biotechnology has resulted in the identification of rationally-designed targeted agents. Proof of principle and robust antitumour activity may be most efficiently demonstrated in phase II studies involving patients bearing tumours that are principally driven by aberrations of the specific target or dysregulation of related signal transduction pathways. The hope is that by identifying tumours that are dependent upon the targeted pathway and by demonstrating that the drug modulates the pathway (either abrogating or promoting the signal) it will be possible to identify the right population of patients for the pivotal trials and hence significantly increase the probability of success. Once a biomarker has been identified, the assay validated and its intended use defined, the challenge becomes how to incorporate the biomarker assay into the drug development program and design of the phase II and phase III development. At this time point several decisions have to be made regarding whether to evaluate the biomarker prospectively or retrospectively, whether to collect tumour or a surrogate tissue, whether to retrieve archival tumour samples from pathology laboratories or obtain recent fresh biopsies, how best to design and power the trial to test both the effect of the drug and the possible predictive value of the biomarker. Surrogate samples, such as blood and serum, while being much more accessible carry more risk because the tissue may be representative of tumour exposure but not of the tumour biology. In this sense, some biomarkers are present from the very early tumorigenic process (like K-Ras mutations in colon cancer) but some others are closely related in time to late-stage changes (like PI3K and p53 mutations and PTEN deletions in colon cancer, c-MET mutations in NSCLC and secondary c-KIT mutations in GIST). The latter examples would definitely favour the acquisition of a recent tumour sample in order to guarantee that the possible findings in the tumour correlate with the current dysregulated situation of the disease. On the other hand, retrospective biomarker analysis has the advantage that patient enrolment is not compromised, the assay does not need to be ready prior to study commencement, and multiple biomarkers can be evaluated. Additionally the quality and volume of tissue in the archival sample may limit the success of a selected biomarker analyses. Therefore, the decision on whether archival tissue – usually coming from the primary tumour resection – or recently fresh biopsied tissue is needed for the consecution and success of the biomarker should be made taking in consideration all the previously mentioned aspects. The development of biomarkers in phase II development holds great promise but also creates new challenges. Further actions are needed in order to implement the development of tumour biomarkers in this setting. These include among others the need for greater information among patients, patients' coalitions and advocate groups, institutional review boards, local Health Administrations, Regulatory Agencies, clinicians, pathologists and other physicians involved in the acquisition of good quality tumour samples. The ultimate goal of this biomarker development process from tumour biopsies will be to facilitate oncology drugs development and to identify which patients are most likely to benefit.

Wednesday, 22 October 2008 14:00–15:00

Keynote Lecture

32 INVITED

New response evaluation criteria in solid tumors: revised RECIST guideline version 1.1

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Background: Assessment of the change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics: both tumor shrinkage (objective response) and disease progression are useful endpoints in clinical trials. Since RECIST was published in 2000, many investigators, cooperative groups, industry and government authorities have adopted these in criteria in the assessment of treatment outcomes. However, a number of questions and issues have arisen which have led to the development of a revised RECIST guideline, due for release in a special issue of the European Journal of Cancer in January 2009.
Highlights of Revised RECIST 1.1: Changes include: *Number of lesions to be assessed*: based on evidence from numerous trial databases merged into a data warehouse for analysis purposes, the number of lesions required to assess tumor burden has been reduced from a maximum of 10 to a maximum of 5 total (and from 5 to 2 per organ, maximum). *Assessment of pathological lymph nodes is now incorporated*: nodes with a short axis of <15 mm are considered measurable. The short axis measurement should be included in the sum of lesions in calculation of tumor response. Nodes that shrink to <10 mm short axis are considered normal. *Confirmation of response* is no longer required since evaluation of a large amount of clinical data showed that the probability of measurement error is so small that this extra evaluation is not needed. This will also make it easier to deploy RECIST criteria in phase III settings. *Disease progression* is clarified in several aspects: in addition to the previous definition of progression in target disease of 20% increase in sum, a 5 mm absolute increase is now required as well to guard against over calling PD when the total sum is very small. Furthermore, there is guidance offered on what constitutes "unequivocal progression" of non-measurable/non target disease, a source of confusion in the original RECIST guideline. Finally a section on detection of new lesions, including the interpretation of PET scan assessment is included. *Imaging Guidance*: the revised RECIST includes a new imaging appendix with updated recommendations on the optimal anatomical assessment of lesions
Supporting Articles and Future Work: In addition to the guideline itself, the special issue in which it appears will include several other articles from members of the RECIST Working Group, including a paper summarizing the data warehouse analyses, as well as papers on independent radiology review, challenges in response and progression assessment in phase III trials, design implications of using non-response endpoints in phase II trials, and a paper describing the evidence to support the lymph node proposal. A key question considered by the working group in developing the revision to RECIST was whether it was "time" to move from anatomic unidimensional assessment of tumor burden to either volumetric anatomical assessment or to functional assessment with PET or MRI. The Working Group did not believe there is at present sufficient standardization and wide-spread availability to integrate these alternative assessment methods into all aspects of RECIST. The only exception to this is in the use of FDG-PET imaging as an adjunct to determination of progression. As will be detailed in the final paper in this special issue, the use of these promising newer approaches (which could either add to or substitute for anatomical assessment as described in RECIST) requires appropriate and rigorous clinical validation studies. The RECIST Working Group looks forward to such data emerging in the next few years to allow the appropriate changes to the next iteration of the RECIST criteria.