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

A. Reid[1], G. Attard[1], N. Babu Oommen[1], D. Olmos[1], P. Fong[1], R. Molife[1], M. Dowsett[2], G. Lee[3], A. Molina[3], J.S. De-Bono[1]. *[1]Royal Marsden NHS Foundation Trust, Drug Development Unit, London, United Kingdom; [2]Royal Marsden NHS Foundation Trust, Academic Departmentt of Biochemistry, London, United Kingdom; [3]Cougar Biotechnology, Inc, Los Angeles, CA, USA*

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

D. Lacombe[1]. *[1]European Organisation for Research and Treatment of Cancer (EORTC), Scientific Strategy, Brussels, Belgium*

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