The ethical dimension of first-in-human studies has always been carefully considered. In the standard Phase One study, there is therapeutic intent, although the probability is unfortunately low. In the phase zero setting, no therapeutic benefit is expected. Thus, the motivation of the volunteer patients is primarily altruism. Differences between Phase Zero and Phase One, including the relative risks and benefits of biopsies, will be discussed.

22 INVITED

Implementation of phase 0 trials

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An increase in the number of identified therapeutic cancer targets achieved through recent biomedical research has resulted in the generation of a large number of molecules that need to be tested further. Current development of (anticancer) drugs is a rather inefficient process that for an average new molecule takes around 10−15 years. It is also a challenging process as it is associated with high costs and a low rate of approval. It is known that less than 10% of new molecular entities entering clinical phase I testing progress beyond the investigational program and reach the market; this probability is even lower for anticancer agents. In 2003 the US FDA declared the urgent need for new toolkits to improve the critical development path that leads from scientific discovery to the patient.

In this scenario, Phase 0 (zero) trials should allow an early evaluation in humans of pharmacokinetic and pharmacodynamic profiles of test compounds through administration of sub-pharmacological doses to a low number of humans. Phase 0 trials are clinical studies conducted early in Phase I, before the traditional dose escalation, safety and tolerance studies. These first-in-man trials should involve a very limited number of normal volunteers or patients, exposed to a novel compound at a reduced dose compared to starting doses in Phase I and for a short time-period. Typically, Phase 0 studies have no therapeutic neither diagnostic intent. Due to the low doses administered and the low risk of toxicity, shorter preclinical packages to support these studies are required. Phase 0 trials have been proposed to help in making an early selection of promising candidates for further evaluation in Phase I/II/III trials, providing a potentially useful instrument for drug discovery, particularly in the field of oncology. Phase 0 studies are expected to reduce costs of drug development, and to limit preclinical in vitro and in vivo testing and the time-period of drug development. However, there are also concerns about the utility and feasibility of Phase 0 studies.

In January 2006 guidelines on exploratory investigational new drug studies in humans have been published by the US FDA, and currently a Phase 0 program is ongoing at the National Cancer Institute in order to evaluate the real impact (feasibility and utility) of Phase 0 studies on drug development. In Europe a Position Paper produced by the EMEA in 2004 raised the possibility of a reduced preclinical safety package to support early microdose clinical studies, and, as announced by a recent Concept Paper on medicinal products published by the CHMP of EMEA, EMEA's guidelines on Phase 0 studies are expected shortly. There are a number of relevant practical issues to be considerd prior to execution of Phase 0 trials.

Execution of Phase 0 trials may be hampered by ethical reasons as well as by the willingness of patients to take part in these trials that will have no therapeutic benefit to them.

Despite the opportunities provided by Phase 0 trials, it is expected that more efficient, faster and less costly drug development is achieved especially by better preclinical selection of clinical candidates based in more stringent assessment of proof of concept as well as by selection of clinical candidates with better pharmacological profiles and by better definition of the target population of patients. However, the true impact on the drug development process and especially the safety of Phase 0 studies need to be carefully explored.

References

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23 INVITED

Industry perspective

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Abstract not received

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

WORKSHOP 5

Targeting the CYP pathway

24 INVITED

The evolution of CYPs from metabolising enzymes to potential targets in cancer therapy development

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Cytochromes P450 (CYP) are a superfamily of haemothiolate monoxygenases comprising at least 57 functional proteins in humans. Selective CYP subfamily members are responsible for the biosynthesis of ecosanoids and steroids. As such inhibitors of these endogenous pathways are identified as a route to therapy. Exemestane, Letrozole and Anastrozole are inhibitors of CYP19 key to the aromatisation of androgens to produce oestrogens that drive hormone dependent cancers. Inhibitors of CYP24A1 extends the half life of endogenous calcitriol and Vitamin D analogues with potential benefit in cancer treatment. Inhibitors of CYP26 could prevent deactivation of All-Trans-Retinoic-Acid used in the treatment of PML. CYPs also function to metabolise xenobiotics and conventionally are regarded as detoxification enzymes that promote the elimination and diminish the pharmacology of drugs. At least fifteen members of CYP1, 2, 3 and 4 subfamilies contribute to the fate of drugs by increasing their polarity with often profound changes to their pharmacokinetic and pharmacodynamic properties. There is growing evidence that such pathways can contribute to the deactivation of anticancer drugs and hence the presence or even over expression of drug metabolising CYPs in tumours could be considered as a resistance mechanism.

The high expression of selected CYPs in tumours creates the potential for tumour selective activation to generate either pan-cytotoxic or molecularly targeted agents. As a consequence CYPs can now be recognised as potential therapeutic targets. The activation of several classes of clinically important alkylating agent notably the oxazaphosphorines (e.g. cyclophosphamide), and nitrosoureas is known to involve selective CYPs although the liver is generally acknowledged to contribute significantly to their clinical utility. The potential for design of agents that are substratess for extrahepatic CYPs offers the promise of tumour selective prodrugs. AQ4N (banoxantrone), currently in Phase IIa trials, is a prodrug topoisomerase II inhibitor activated by CYP1A1, 2B6 and 3A4 specifically under hypoxic conditions and for which clinical proof of concept as a hypoxia targeted agent is shown. Other agents, including Prodrax, based on the concept of N-oxide reduction pioneered by the discovery of AQ4N are also under development. Other developments include, the aminobenzothioazole, Phortress, a CYP1A1 inducer effective in AhR competent tumours. The design of chloromethylpyrolloindolines as prodrugs of ultrapotent minor groove alkylating agents that are specifically activated by selective CYP isoforms is also currently underway. The increasing interest in the CYP expression of clinical tumours alongside the development of relevant preclinical models should provide a rich seam of opportunity for the discovery CYP-activated drugs.

25 INVITED

CYP-activated prodrugs as chemotherapeutics

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Background: Increasing tumour specificity and reducing toxicity by the use of inactive systemic prodrugs which are preferentially metabolised within the tumour cells to cytotoxic agents is an attractive therapeutic strategy. Many drugs in clinical use induce, inhibit or are metabolised by the cytochrome P450 group of enzymes (CYPs), which are present in many tissues, including tumour cells.

Three agents are being investigated in early clinical trials which attempt to utilise tumour CYPs to convert prodrugs to active metabolites within the target tissue.

Methods/Results: The first agent to enter the clinic, AQ4N, is selectively activated within hypoxic tissues by CYPs 3A4, 1A1 and 2B6 to AQ4, a topoisomerase II inhibitor and DNA intercalator. This agent has completed phase I evaluation in a dose escalation study with fractionated radiotherapy in oesophageal cancer [1]. Additionally a proof of principle study where a single of AQ4N was given prior to surgery demonstrated that tumour levels of AQ4 were higher than adjacent tissues with selective activation in hypoxic regions of the tumour [2]. Drug related adverse events include

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

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[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

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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.

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WORKSHOP 6

Design and conduct of phase II trials for targeted agents

28 INVITED

Adaptive phase II trials

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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