Clinical Cancer Research

A Journal of the American Association for Cancer Research

May 12, 2003

Ian Judson
CRC Centre for Cancer Therapeutics
Clinical Pharmacology
Institute of Cancer Research
E-Block, 15 Cotswold Road
Sutton, Surrey SM2 5NG
United Kingdom

RE: Manuscript # 030579, Hormonal impact of the 17a-hydroxylase/C17,20-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer

Dear Dr. Judson:

Thank you for submitting the above-mentioned manuscript to *Clinical Cancer Research*. I regret to inform you that we will be unable to publish this paper. This decision was based not only on the enclosed reviewer comments, which we hope will be helpful to you, but also upon the editors ' evaluation of the merits and amount of novel information in your manuscript compared with those of many others we receive. Many worthwhile papers must be declined simply for lack of space, and yours is one of these.

We are returning the file copies of your manuscript along with our reviewer comments. Thank you again for giving us the opportunity to review your work. We encourage you to submit future manuscripts to *Clinical Cancer Research*, and I hope you will do so.

Sincerely,

Waun Ki Hong, M.D.
Deputy Editor
Clinical Cancer Research

Need fax No
for Anne O D

enclosures

Waun Ki Hong, M.D., Deputy Editor • Thoracic/Head & Neck Medical Oncology • Box 432
The University of Texas M.D. Anderson Cancer Center • 1515 Holcombe Boulevard • Houston, TX 77030-4009
Phone: (713) 792-6363 • Fax: (713) 563-9798

Clinical Cancer Research

REVIEWER'S RECOMMENDATIONS (please type)

Manuscript no. and title: 030579/Hormonal impact of the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer

O'Donnell and colleagues describe a "first in human" trial of CB7630 in prostate cancer. The authors should consider:

1. In this reviewer's opinion, the authors over-emphasize the role of androgens in stimulating prostate cancer growth in castrate men. Much work in this area and little persuasive data that residual androgens are important. A more balanced view would be preferable.
2. How important would it be to have another drug that suppresses testosterone to castrate levels? (specific aims of study B and study C).
3. It is unclear why the target testosterone for studies B and C is <0.7 nmol/L "based on local unpublished data". There are hundreds of patients published. If the authors chose to use local controls … they should at least provide the data and describe the populations and their quality controls on medication adherence. Three patients in study A did not adhere to LHRH it appears. Why do authors think their unpublished controls did?
4. How was starting dose chosen? How was dose escalation plan established?
5. The authors should define what Synacthen test is. Presumably it is a low dose ACTH stimulation test. This description is preferred because it is direct, easily understood, and not a proprietary name.
6. The conclusions the authors draw are unclear. It seems it will take > 800 mg, there is LH "override", but only 3 patients were treated so conclusions – short of saying it is safe – are tenuous.
7. The 10 fold variation in AUC at a dose is much higher than with most drugs; not common as the authors imply.
8. How important is another drug to antagonize extragonadal androgen production in conjunction with LHRH analogues? The role of antiandrogens in this setting is controversial – at best. 5 alpha reductase inhibitors also could work in a similar way, but do not clearly help. Why would this drug that suppresses adrenal corticoids be useful?
9. What is the plan for the drug/class?

Clinical Cancer Research

REVIEWER'S RECOMMENDATIONS (please type)

Manuscript no. and title: 030579/Hormonal impact of the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor abiraterone acetate (CB763) in patients with prostate cancer

General Comments:

Abiraterone Acetate is a very interesting drug that appears to have some potential for the treatment of advanced prostate cancer. However, the manuscript is not clearly written and there is concern on how the doses that the authors chose for each study were selected and what is the appropriate dose to bring forward. Many details of the studies were excluded and need to be included.

Specific Comments:

1. Introduction, page 1, second paragraph: Castration does produce objective , biochemical and palliative effects but rarely if ever produces "remission" of the tumor. This needs to be clarified.

2. Methods: Investigational agents, page 8: Please provide additional information on the formulation of the capsules and the stability of the formulation at room temperature. Any data on bio-availability in animals?

3. Dosage and Administration: Eliminate the following sentence: "Dealing with each study in turn:".

4. Dosage and administration: The dose escalation schemes used in Study A, B and C were not traditional , but presumed each study built upon the other and provided the starting dose. This is needs to be clarified in the text. In study B please provide explanation why the starting dose was 200 mg was used. The author needs to clearly define maximum tolerated dose and dose limiting toxicities for all three studies. A standard dose escalation scheme was not utilized in this study (3 patients initially and expand to 6 if DLT). Please provide a description and rationale for the schema that the authors used.

5. Pre-treatment Assessment and Follow-up Investigations: Authors need to clarify the exact blood test that were obtained pre and post-therapy.

6. Endocrine Assessment: Please provide all manufacture and normal ranges for the testosterone, cortisol, 17 α-hydroxyprogesterone, androstenedione, LH and FSH. Information on the preparation and storage of these samples needs to be provide. Were these samples batched?

7. Pharmacokinetics- Analytic method, Assays and Sampling: What is the lower detection limit of the assay for the drug?

8. Results: The Authors should provide more baseline information for each study. This should include median testosterone level, HGB, alkaline phosphatase, LDH and PSA. In addition, the prior treatment history; extent of disease; patients with testosterone level < 0.6 nmol/L, $\geq$ 0.6 nmol/L or non-castrate level. How many patients had orchiectomy or GnRH analog? This could be provided in table.

9. Results, page 15: In part A, the authors escalated the dose from 100 mg to 500 mg after only one patient was treated at 200 mg due to the lack of pharamcodynamic effect. This is a safety study and please provide a better rationale why you would skip the dose level? Three patients treated at 500 mg dose level had a reduction in Testosterone. Please provide the breakdown of the decline (ie how many were not detectable verses > 75% decline). The authors need to provide details on duration of suppression in days. Please explain why three additional patients were added at the 500 mg dose level if not DLTs were encountered and why dose escalation did not continue over 500 mg?

10. Results, page 17: In study B, why was the dose not escalated above 500 mg as written? In addition, table for each study with all the endocrine results would be useful.

11. Overall Toxicity: The description of adverse events needs to be detailed further using common toxicity criteria and placed in a table.

12. The authors should include outcome data for the patients. Any changes in biochemical markers such as PSA?