TO NICE; Comment from NHS QIS nominated expert on:
NICE Technology Appraisal Assessment Report:
Docetaxel for the Treatment of Hormone-refractory Metastatic Prostate Cancer

<u>COMMENTS</u>

<u>General Comments</u>

- This is a comprehensive, well researched and well written report on what is essentially a single randomised controlled trial, with additional evidence and comparisons from other sources. There is little to disagree with the facts or conclusions.

- A definition of hormone-refractory prostate cancer [HRPC] is given on page 30, para. 4, lines 4-6 (although I would have used the original reference). How it is interpreted varies. In particular, some trials only allow one previous hormonal treatment [generally an LHRH analogue], others insist on combined androgen blockade or anti-androgen addition and withdrawal, while many are quite imprecise in the definition of HRPC. This often has a confounding factor when corticosteroids are the control group in such a trial.

- At regular intervals in the report it is stated that corticosteroids are part of best supportive care [e.g. Page 13, paragraph 3, line 6/7, or Page 15, paragraph 2, line 1/2]. In HRPC, corticosteroids represent a recognised standard hormonal treatment, unlike in many other malignancies, where they are only a form of best supportive care. For some patients in the control arms, therefore, corticosteroids will have produced a response either in terms of symptoms or on imaging, etc. This confounding factor is not mentioned at any point in the report. This does not detract from the conclusions, but should be stated clearly at some point. Part of the difficulty relates to the definition of HRPC as noted above.

- Sanofi Aventis, in supporting the main trials with Docetaxel, have tried to allow for the main alternative treatment strategies and future use in the US, Europe, and the UK. To the best of my knowledge, Estramustine [Page 36] is not used a great deal in the UK, as the toxicity is unacceptable to oncologists and patients alike, for the fairly poor response rates seen.

- The economic appraisal makes the stated assumption that patients receiving Docetaxel plus Prednisolone will not receive Mitozantrone plus Prednisolone as second line treatment, which is not included in the overall costing of the strategy. While there is as yet no evidence relating to the use of second line Mitozantrone plus Prednisolone, I believe that such trials are in progress, and would be surprised if this assumption can realistically be made without comment to support it.

- Prior to reading the report, I anticipated that most UK oncologists would have stated the position to be that Docetaxel plus Prednisolone showed a clear if limited clinical effectiveness, is expensive, and may not be ultimately

economically justifiable. The results would have been seen as interesting but needing corroborative evidence from a further similar trial.

This report has largely given the data and credence to this impression, but I am surprised that in section 7.3, recommendations for research [Page 167] that there is no suggestion that a further confirmatory trial was required.

Specific Comments

- Page 30, paragraph 2, line 6. I was surprised by this statement. The most important prognostic factor in prostate cancer is the stage of disease, and even in mHRPC the extent of metastatic disease may be more important than the Gleason score. I get the impression that this paragraph applies more generally to prostate cancer than to mHRPC alone.

- Page 32, paragraph 2, line 3. The reference given is incorrect – the one required is indeed the BAUS guidelines for prostate cancer or metastatic prostate cancer, not the COIN/BAUS guidelines of 1999. I am not sure that it is widely available other than to members of BAUS.

- Page 36, line 1. I appreciate that this has been lifted *verbatim* from the relevant document, but am surprised at the statement that severe neutropenia is very common with Mitozantrone, as well as mild to moderate nausea and vomiting. In the normally recommended doses neither statements are correct.

- Page 81, table 12. The figures for progression free survival are confusing. They actually relate to the patients who failed, rather than survived progression-free. [Page 77, paragraph 3]. The same point applies to table 14 and Page 82, paragraph 3.

- Page 85, table 13. The term 'granulocytes/bands' is confusing.

- Page 51, paragraph 1, line 1-43. Given earlier comments regarding the side effects of Estramustine, this potential limitation of the current analysis is certainly true.

Minor Stylistic/Grammatical Issues

- The definition of terms [Pages 20-28] look as if they have been taken from an equivalent report on ovarian cancer. In particular evaluable disease in prostatic cancer would very rarely include malignant ascites or pleural effusions [I have virtually seen neither] and the level of CA125 would be irrelevant. The section on first line therapy also relates to ovarian cancer. Similarly the definition of staging is that for ovarian cancer, and I would suggest should be updated for prostate cancer.

- Page 22. Dyspnoea 'laboured'.

- A number of abbreviations have slipped into the text without being defined, and sometimes without appearing in the list of abbreviations on Page 19. These include TARs [Page 2, paragraph 3, line 2], ICER [Page 17, paragraph 1, line 9 and Page 148, paragraph 1, line 10], TTO [Page 137, paragraph 2, line 5 and paragraph 3, line 5, but presumably mentioned in line 3] and EVPI [Page 157, paragraph 1, line 8].

- Minor grammatical mistake – exemplified in Page 56, paragraph 2, lines 4-7. The word 'Giving' should not be the start of a new sentence but follow a comma or semicolon. This applies also in paragraph 3, line 7, Page 63, paragraph 1, line 5, and Page 89, paragraph 1, line 7 and paragraph 2, line 3.

- Page 159, second paragraph, line 4 should read 'Prednisone/Prednisolone' as in lines 4 and 7.

- Page 159, second paragraph, line 5, the term 'upper bound' was a new one to me.

- Page 162, paragraph 1, line 13 'this is' should be deleted.

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