

Efficacy of second line treatments in patients with metastatic hormone refractory prostate cancer (mhrpc) is not demonstrated by published evidence from non-randomised trials

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Background

- Docetaxel-based chemotherapy is the currently standard 1st line treatment for patients with mHRPC.
- Few randomised clinical trials of 2nd line treatments after Docetaxel have been published to draw definitive conclusions on survival and clinical benefits.
- At the time of this literature review, there were no recommended second-line treatments for docetaxel pre-treated patients

Objective

- The primary objective of this review was to determine survival and clinical benefits of interventions in the treatment of second line metastatic hormone resistant prostate cancer (mHRPC) in patients that have been previously treated with docetaxel as reported in observational non-comparative or comparative prospective and retrospective studies

Results

- Studies selection:** 825 records were retrieved, and 30 studies were included in the review. (Figure 1).

- Ten trials assessed the efficacy and safety of docetaxel re-challenge, either as monotherapy or combination therapy, in the second-line treatment of mHRPC. Next to docetaxel, the maximum number of studies evaluated mitoxantrone (seven studies). The 13 remaining studies evaluated other included interventions.

Figure 1 • PRISMA Diagram for Study Inclusion and Exclusion

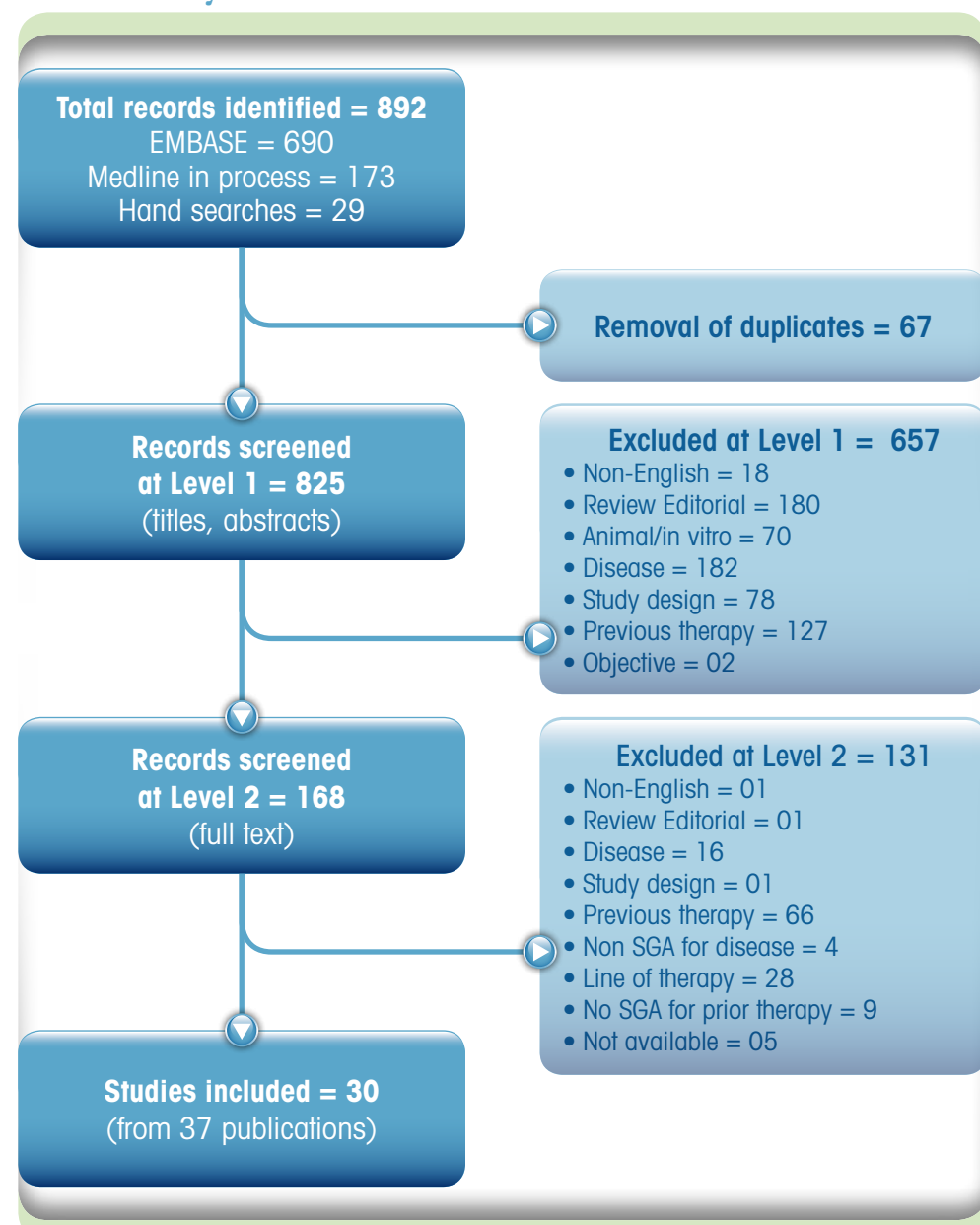


Table 1 • Docetaxel regimen based trials

| Study (linked publications) | N | Intervention/ comparators | Study type |
|--------------------------------|-----|---|--|
| Loriot 2008 | 30 | Docetaxel | Single-arm study |
| Firek 2010 | 35 | | Hospital records and database studies |
| Jankovic 2008 | 25 | Docetaxel + prednisone | Single-arm study |
| Di Lorenzo 2010 | 22 | | Hospital records and database studies |
| Gernone 2010 | 120 | Docetaxel + carboplatin | Retrospective cohort study |
| Ansari 2008 (Ansari 2008b) | 10 | | Single-arm study |
| Gruenwald 2008 | 17 | Docetaxel + estramustine + prednisolone | Single-arm study |
| Reuter 2009 | 38 | | Non-randomised controlled trial (nRCT) |
| Caffo 2010 | 27 | Docetaxel + bevacizumab | Single-arm study |
| Heidenreich 2010 (Epplen 2010) | 59 | | Non-randomised controlled trial (nRCT) |

Discussion

- No published systematic literature review on observational trials in mHRPC was identified prior to this review.
- Limited non-randomized evidence was published in the ten year period studied.
- Most data was non-comparative and included small sample size. Only one study out of 30 was comparative.
- In addition, different definitions for PFS and PSA response were used.
- Results appear to confirm clinical benefit of docetaxel re-challenge vs. mitoxantrone. However, results should be treated cautiously.
- Based on the literature results, it is difficult to draw conclusions about the clinical efficacy of mHRPC second line chemotherapy.

References: See poster handout.
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Methods

- Method:** A systematic literature review (SLR) was performed.
- Databases and additional sources:** Sources included PUBMED (including Medline in process) and EMBASE databases from 2000 to March 2010. The following conference proceedings were hand searched: ASCO, ASCO-GU, ESMO, AUA and AACR and selected conference abstracts from 2000 to March 2010.
- Screening:** A two-level screening process was performed. Level 1 screened titles and abstracts, and Level 2 screened full-text sources.
- Language:** No language restrictions were applied in the search strategy.
- Identification and selection of studies:**
 - The search strategy included combinations of free text and Medical Subject Headings. Separate sets of terms were used for the health condition of interest (mHRPC) and the study type (observational non-comparative or comparative

prospective and retrospective studies).

- To be included in the review trials had to meet pre-defined eligibility criteria; observational non-comparative or comparative prospective and retrospective studies, in metastatic HRPC among docetaxel pre-treated patients now receiving second-line therapy.
- Quality assessment:** Inclusion or exclusion of studies was performed in parallel by two researchers; disagreements were resolved by consensus.
- Data extraction:** Data extracted included the study design, country, population size and characteristics, and results (i.e., overall survival (OS) Progression Free Survival (PFS), PSA response).

Figure 2 • Median OS reported (weeks) in the docetaxel re-challenge studies

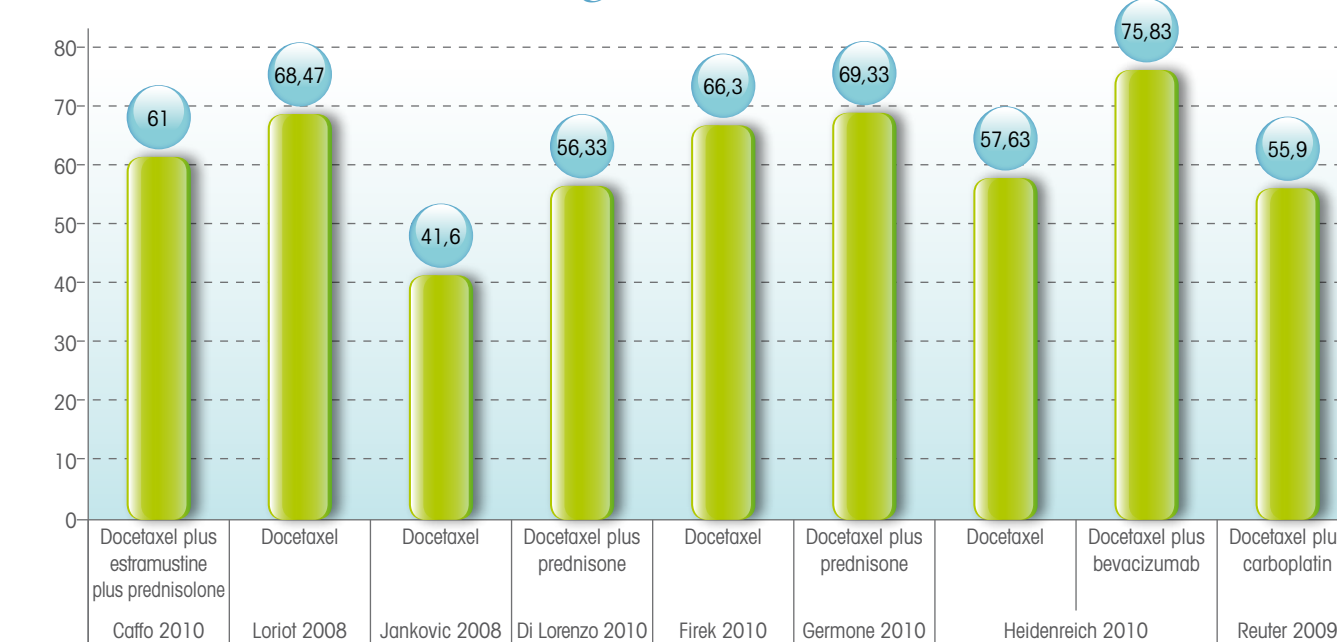


Figure 3 • Median OS reported (weeks) in Mitoxantrone and other treatment studies



Table 2 • Mitoxantrone and others regimen based trials

| Study (linked publications) | N | Intervention/ comparators | Study type |
|--|-----|---|---------------------------------------|
| Michels 2006 | 68 | Mitoxantrone | Hospital records and database studies |
| Thomas 2009 | 10 | Mitoxantrone + prednisone | Retrospective cohort study |
| Berthold 2008 | 232 | Mitoxantrone (I and II) | |
| El Demery 2006 | 43 | Mitoxantrone Other treatments | Single-arm study |
| Rosenberg 2009 (Harzstark 2008) | 36 | Mitoxantrone + prednisone + ixabepilone | |
| Small 2009 (Harzstark 2009) | 43 | Mitoxantrone + prednisone + ixabepilone | Single-arm study |
| Doshi 2009 | 31 | GM-CSF + ketoconazole + mitoxantrone | |
| Hahn 2009 | 49 | Pemetrexed | Single-arm study |
| Caffo 2010b | 20 | Pemetrexed | |
| Bradley 2009 | 27 | Vorinostat | Single-arm study |
| Dahut 2008 | 22 | Sorafenib | |
| Aragan-Ching 2008 | 24 | Sunitinib | Single-arm study |
| Smith 2009 | 36 | Sunitinib | |
| Loriot 2009 | 40 | Carboplatin + etoposide | Single-arm study |
| Sella 2009 | 15 | Paclitaxel + carboplatin + estramustine | |
| Nelius 2009 | 17 | Cyclophosphamide + dexamethasone | Single-arm study |
| Vaishampayan 2009 (Vaishampayan 2009b) | 19 | Bevacizumab + satraplatin + prednisone | |
| Blesa 2009 | 17 | Oxaliplatin + capecitabine | Single-arm study |
| Lainakis 2008 | 37 | Ketoconazole + doxorubicin | |
| Gross 2008 | 9 | TPI 287 | Single-arm study |

| Study (linked publications) | N | Intervention | Median PFS (weeks) (range or 95% CI) |
|--|----|---|--------------------------------------|
| Docetaxel re-challenge | | | |
| Loriot 2008 | 30 | Docetaxel | 18.63 (3.9 – 56.33) |
| Jankovic 2008 | 25 | | 34.67 (95% CI, 16.47 – 52.43) |
| Firek 2010 | 35 | Docetaxel plus prednisone | 26.87* (4.33 – 65.0) |
| Di Lorenzo 2010 | 45 | | 21.67 (8.67 – 34.67) |
| Caffo 2010 | 27 | Docetaxel plus estramustine plus prednisolone | 15.0* (NA) |
| Heidenreich 2010 | 27 | Docetaxel | 26.87 (NA) |
| | 32 | Docetaxel plus bevacizumab | 38.57 (13.0 – 147.33) |
| Mitoxantrone and other treatments | | | |
| Caffo 2010 ^a | 20 | Pemetrexed | 9.0 (3.0 – 26.0) |
| Loriot 2009 | 40 | Carboplatin plus etoposide | 9.1 (2.6 – 41.6) |
| Sella 2009 | 15 | Paclitaxel plus carboplatin plus estramustine | 17.33 (4.77 – 56.33) |
| Berthold 2008 ^a | 89 | Mitoxantrone | 13.87* (9.53 – 19.07) |
| | 76 | Mitoxantrone 1 | 16.03* (9.1 – 40.3) |

CI: Confidence Interval
^a N=25 ^b N=43 ^c N=28
^d TAX 327 study who crossed over to receive docetaxel after mitoxantrone or vice versa
 NA: Non available

CONCLUSIONS

- The SLR showed a lack of available non-randomised evidence and among the selected studies evidence was not strong enough due to small sample sizes, non-comparative nature and variable PFS and PSA response definitions. This literature review demonstrates that it is difficult to infer the clinical efficacy of mHRPC 2nd line chemotherapy.