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Accessibility
What is the optimal systemic treatment of men with metastatic, hormone-naive prostate cancer? A STOPCAP systematic review and network meta-analysis

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Background: Our prior Systemic Treatment Options for Cancer of the Prostate systematic reviews showed improved survival for men with metastatic hormone-naive prostate cancer when abiraterone acetate plus prednisolone/prednisone (AAP) or docetaxel (Doc), but not zoledronic acid (ZA), were added to androgen-deprivation therapy (ADT). Trial evidence also suggests a benefit of combining celecoxib (Cel) with ZA and ADT. To establish the optimal treatments, a network meta-analysis (NMA) was carried out based on aggregate data (AD) from all available studies.

Methods: Overall survival (OS) and failure-free survival data from completed Systemic Treatment Options for Cancer of the Prostate reviews of Doc, ZA and AAP and from recent trials of ZA and Cel contributed to this comprehensive AD-NMA. The primary outcome was OS. Correlations between treatment comparisons within one multi-arm, multi-stage trial were estimated from control-arm event counts. Network consistency and a common heterogeneity variance were assumed.

Results: We identified 10 completed trials which had closed to recruitment, and one trial in which recruitment was ongoing, as eligible for inclusion. Results are based on six trials including 6204 men (97% of men randomised in all completed trials). Network estimates of effects on OS were consistent with reported comparisons with ADT alone for AAP [hazard ratio (HR) = 0.61, 95% confidence interval (CI) 0.53–0.71], Doc (HR = 0.77, 95% CI 0.68–0.87), ZA + Cel (HR = 0.78, 95% CI 0.62–0.97), ZA + Doc (HR = 0.79, 95% CI 0.66–0.94), Cel (HR = 0.94 95% CI 0.75–1.17) and ZA (HR = 0.90 95% CI 0.79–1.03). The effect of ZA + Cel is consistent with the additive effects of the individual treatments. Results suggest that AAP has the highest probability of being the most effective treatment both for OS (94% probability) and failure-free survival (100% probability). Doc was the second-best treatment of OS (35% probability).

Conclusions: Uniquely, we have included all available results and appropriately accounted for inclusion of multi-arm, multi-stage trials in this AD-NMA. Our results support the use of AAP or Doc with ADT in men with metastatic hormone-naive prostate cancer. AAP appears to be the most effective treatment, but it is not clear to what extent and whether this is due to a true increased benefit with AAP or the variable features of the individual trials. To fully account for patient variability across trials, changes in prognosis or treatment effects over time and the potential impact of treatment on progression, a network meta-analysis based on individual participant data is in development.

Key words: prostate cancer, abiraterone, docetaxel, systematic review, network meta-analysis, androgen-deprivation therapy

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Numerous randomised controlled trials (RCTs) have evaluated or are currently evaluating, the addition of other therapies to androgen-deprivation therapy (ADT) in men with metastatic hormone-naive prostate cancer (mHNPC). To determine reliably which are effective, we are conducting a series of systematic reviews under the auspices of the Systemic Treatment Options for Cancer of the Prostate (STOPCAP) collaboration. Our prior STOPCAP systematic reviews showed improved survival when abiraterone acetate plus prednisolone/prednisone (AAP) or docetaxel (Doc), but not zoledronic acid (ZA), were added to ADT [1, 2]. Trial evidence also suggests a benefit of combining celecoxib (Cel) with ZA and ADT [3].

However, only the reported comparisons of the STAMPEDE multi-arm, multi-stage (MAMS) platform and the ongoing Prostate Cancer Consortium in Europe (PEACE)-1 trial (NCT01957436) will be able to provide head-to-head results comparing these therapies. Network meta-analysis [4, 5], which takes advantage of both direct and indirect comparisons, is therefore needed to determine reliably which is the optimal treatment(s), and so to inform patients, clinicians and policy makers. We have therefore conducted a systematic review and network meta-analysis of aggregate data (AD) to assess the optimal systemic treatments for men with mHNPC, making use of existing STOPCAP reviews [1, 2] and up-to-date results from individual trials, and also taking account of the MAMS platform design of the STAMPEDE trial protocol.

### Methods

The full protocol for this review was registered in July 2017 (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017071811, 1 March 2018, date last accessed).

#### Eligibility criteria

The eligibility criteria for inclusion in this network meta-analysis mirror those in prior systematic reviews [1, 2]. In brief, eligible trials should have been randomised in a way which precluded prior knowledge of the treatment assigned and compared ADT alone with ADT in combination with any of the agents (or combinations of agents) under consideration, namely celecoxib (Cel), zoledronic acid (ZA), celecoxib and zoledronic acid (ZA + Cel), docetaxel (Doc), zoledronic acid + docetaxel (ZA + Doc) or abiraterone acetate plus prednisolone (AAP). The men randomised were diagnosed with mHNPC, and either starting or responding to the first-line ADT for metastatic disease (they may have received prior treatments for early, localised disease). Trials were also eligible if they met the above criteria but additionally co-administered supportive treatments on the experimental arm only. Trials were excluded if they had randomised men who had castration-resistant prostate cancer or if they had included additional first-line treatments only on the control arm only.

#### Trial identification

As part of the wider STOPCAP project, we regularly and systematically search a number of sources to identify all published, unpublished and ongoing trials in mHNPC, providing a comprehensive and up-to-date database of all RCTs eligible for all of our STOPCAP systematic reviews. We also request regular updates from relevant trial teams on the status and reporting plans. Thus, all trials included in our previous STOPCAP reviews [1, 2] and any additional RCTs meeting the eligibility criteria were included.
the proportion of the information for each treatment comparison that
the indirect evidence from the network model has contributed, were
calculated using the score decomposition method [9].

Estimates of relative effect for each pairwise treatment comparison
from the primary consistency model were estimated on the HR scale
along with corresponding 95% confidence limits and displayed in a
network forest plot [5]. Treatment rankings were also calculated and
summarised as a surface under the cumulative rank (SUCRA) value, rep-
resenting the re-scaled mean ranking [10]. Further detailed methods
relating to all the planned analyses may be found in the Statistical
Analysis Plan (available on request).

Finally, we conducted an indirect comparison of the two most effective
treatments to estimate the relative difference in the size of the effects. We
estimated the absolute benefit of treatment on OS at 3 years by applying
the HR estimates to the approximate survival at 3 years.

Role of the funding source

The funders of the study (Medical Research Council and Prostate Cancer
UK) had no role in study design, data collection, data analysis, data inter-
pretation or writing of the report. The corresponding author had full ac-
cess to all the data in the study and had final responsibility for the
decision to submit for publication.

Results

Description of the included trials

Searches undertaken for the STOPCAP project identified 11 trials
that were eligible for inclusion in the network meta-analysis. Five
of these 11 eligible trials could not be included in the network
meta-analysis. Of these five, two trials that together randomised
72 men to receive ADT or ADT plus doc and two trials that to-
gether randomised 102 men to receive ADT versus ADT plus ZA
identified as eligible for a previous STOPCAP review [2] could
not be included here as they had not yet presented results for sur-
vival outcomes. The fifth trial, PEACE-1 (NCT01957436),

-comparing standard of care with or without AAP continues to re-
cruit towards a target of 1168 men and no results are currently
available for inclusion.

Therefore, six RCTs that had reported results were included in
the network meta-analysis (Figure 1, Table 1). Two trials
compared ADT with ADT plus ZA; two compared ADT with
ADT plus Doc and one trial compared ADT with ADT plus
AAP. The final trial, STAMPEDE [11], contributed six separate
treatment comparisons [3, 12, 13] to the network. Four com-
parisons were of ADT with Cel, ZA, Doc or AAP and two fur-
ther comparisons were of ADT with combinations of ZA
plus Cel or ZA plus Doc. Importantly, although each of the six
comparisons shared a common control arm, there was some
non-contemporaneous recruitment to individual treatment
comparisons. In total, 6204 men were included in the network
meta-analysis, representing 97% of men randomised in all com-
pleted eligible trials (at least 83% of men randomised in all 11
eligible trials). Accounting for the shared control arm patients
in the STAMPEDE trial, 2615 m en were randomised to receive
ADT alone, and 3589 men were randomised to receive ADT in
combination with one of the treatments being considered in the
network.

OS and FFS were reported for all of the treatment comparisons.
The definition of FFS included time to prostate specific antigen
(PSA) or clinical progressionor death for all of the trials, except
LATITUDE [14], which did not include time to PSA progression
and CHAARTED [15], which did not include time to death.
Further details of the trials, including the definitions used for
FFS, are given in Table 1.

Borrowing of strength from the network

Inclusion in the network led to a gain in information for each of
the pairwise treatment comparisons (Table 2). For OS, this
ranged from 0.9% (AAP) to 9.2% (ZA + Doc). For FFS, the gains
Overall survival

The network meta-analysis HR estimates suggested that compared with ADT alone each of AAP (HR = 0.61, 95% CI 0.53–0.71), Doc (HR = 0.77, 95% CI 0.68–0.87), ZA + Doc (HR = 0.79, 95% CI 0.66–0.94) and ZA + Cel (HR = 0.78, 95% CI 0.62–0.97) in combination with ADT improved survival. There was no survival advantage observed with ADT in combination with either ZA (HR = 0.90, 95% CI 0.79–1.03) or Cel (0.94, 95% CI 0.75–1.17) over ADT alone. For the comparisons of ADT versus ADT + Cel, ADT + ZA + Cel and ADT + ZA + Doc, the only data available were from single comparisons within the STAMPEDE trial [3, 13]. There was no evidence of heterogeneity between the effects of treatment within any of the individual treatment comparisons and all of the estimates from the network analysis were in keeping with those obtained in the previously reported pairwise meta-analyses where available (Figure 2).

Treatment rankings

When used in combination with ADT, AAP has the highest probability (94%) of being the most effective treatment, Doc has a 35% probability of being the second-best treatment and ADT alone has the highest probability of being the least effective treatment (67%, Table 3).

Failure-free survival

There was an FFS benefit associated with adding ADT to each of AAP (HR = 0.38 95% CI 0.31–0.46), Doc (HR = 0.64 95% CI 0.54–0.75) and ZA + Doc (HR = 0.63 95% CI 0.49–0.80) compared with ADT alone. No statistically significant benefit was

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**Table 1. Description of included trials (or treatment comparisons from the STAMPEDE trial) and FFS definition used in the trial. All trials had a control arm of ADT**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Recruitment period</th>
<th>Median follow-up (months)</th>
<th>Treatment</th>
<th>Treatment (N)</th>
<th>Control (N)</th>
<th>Definition of FFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 90202 [21]</td>
<td>June 2004 to April 2012</td>
<td>Unknown</td>
<td>ADT + ZA</td>
<td>323</td>
<td>322</td>
<td>Time to first bone progression, PSA progression, or death</td>
</tr>
<tr>
<td>GETUG 15 [22]</td>
<td>Oct 2004 to Dec 2008</td>
<td>84</td>
<td>ADT + Doc</td>
<td>192</td>
<td>193</td>
<td>Time to PSA progression, clinical progression or death</td>
</tr>
<tr>
<td>STAMPEDE (Arms A versus D) [3]</td>
<td>Oct 2005 to Apr 2011</td>
<td>69</td>
<td>ADT + Cel</td>
<td>188</td>
<td>377</td>
<td>Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer</td>
</tr>
<tr>
<td>STAMPEDE (Arms A versus F) [3]</td>
<td>Oct 2005 to Apr 2011</td>
<td>69</td>
<td>ADT + ZA + Cel</td>
<td>190</td>
<td>377</td>
<td>Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer</td>
</tr>
<tr>
<td>STAMPEDE (Arms A versus B) [13]</td>
<td>Oct 2005 to March 2013</td>
<td>43</td>
<td>ADT + ZA</td>
<td>366</td>
<td>724</td>
<td>Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer</td>
</tr>
<tr>
<td>STAMPEDE (Arms A versus C) [13]</td>
<td>Oct 2005 to March 2013</td>
<td>43</td>
<td>ADT + Doc</td>
<td>362</td>
<td>724</td>
<td>Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer</td>
</tr>
<tr>
<td>STAMPEDE (Arms A versus E) [13]</td>
<td>Oct 2005 to March 2013</td>
<td>43</td>
<td>ADT + ZA + Doc</td>
<td>365</td>
<td>724</td>
<td>Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer</td>
</tr>
<tr>
<td>CHAARTED [23]</td>
<td>July 2006 to Dec 2012</td>
<td>54</td>
<td>ADT + Doc</td>
<td>397</td>
<td>393</td>
<td>Time to PSA rise or clinical progression</td>
</tr>
<tr>
<td>ZAPCA (KYUH TRIG0705) [24]</td>
<td>May 2008 to Dec 2010</td>
<td>42</td>
<td>ADT + ZA</td>
<td>109</td>
<td>110</td>
<td>Time to earliest date of PSA progression, clinical progression, first SRE, death for any reason, or cessation of protocol treatment for any reason</td>
</tr>
<tr>
<td>STAMPEDE (Arms A versus G) [12]</td>
<td>Nov 2011- Jan 2014</td>
<td>40</td>
<td>ADT + AAP</td>
<td>500</td>
<td>502</td>
<td>Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer</td>
</tr>
<tr>
<td>LATITUDE [14]</td>
<td>Feb 2013 to Dec 2014</td>
<td>30</td>
<td>ADT + AAP</td>
<td>597</td>
<td>602</td>
<td>Time to radiographic progression or death from any cause</td>
</tr>
</tbody>
</table>

AAP, abiraterone acetate plus prednisolone/prednisone; ADT, androgen-deprivation therapy; Cel, celecoxib; Doc, docetaxel; FFS, failure-free survival; SRE, skeletal related events; ZA, zoledronic acid.
seen with the addition of Cel (HR = 0.89 95% CI 0.67–1.17); ZA + Cel (HR = 0.80 95% CI 0.60–1.05) or ZA alone (HR = 0.88 95% CI 0.75–1.05). In all cases, the HR estimates obtained through the network were very similar to those obtained using a standard pairwise meta-analysis, providing confirmation that the network model is behaving as expected. There was evidence of variation or inconsistency between the effects of treatment within the individual treatment comparisons of ADT versus ADT plus AAP (I² = 91%, heterogeneity P = 0.001) where there was a large variation between the size of the relative effects (but not the direction of the effect) observed between the two included trial comparisons. However, there was no evidence of variation or inconsistency between the effects of treatment within the remaining treatment comparisons, and all of the estimates from the network analysis were in keeping with those obtained in the previously reported pairwise meta-analyses where available (Figure 3).

Therefore, we carried out a sensitivity analysis using the outcome of time to PSA failure as reported in LATITUDE to assess the robustness of our primary analysis. This analysis, whilst not changing our interpretation, did result in an HR estimate from the network analysis was slightly more in favour of treatment (HR = 0.30, 95% CI 0.27–0.34) with no evidence of variation of inconsistency (I² = 0, heterogeneity P = 0.78).

Based on the treatment rankings, when combined with ADT, AAP has the highest probability (100%) of being the most effective treatment in terms of FFS, whilst either Doc alone (45% probability) or in combination with ZA (52% probability) is most likely to be the second–best treatment. ADT alone has the highest probability of being the least effective treatment (73%, Table 4).

### Indirect comparison of the two most effective treatments

When used in combination with ADT, two treatments, AAP and Doc, emerged as being effective in terms of improving both OS and FFS relative to ADT alone, and with the greatest probabilities of being the top two most effective treatments; therefore, they were compared indirectly in a pairwise comparison. The HR estimate for the effect of ADT + AAP relative to the effect of ADT + Doc on OS is 0.80 (95% CI 0.66–0.96). Assuming a baseline OS of 60% at 3 years with ADT + Doc, this translates to an absolute survival benefit associated with AAP of 6% (95% CI = 1% to 11%), that is, to 66% at 3 years (95% CI 61% to 71%). For FFS, the HR for the effect of ADT + AAP relative to ADT + Doc is 0.59 (95% CI 0.46–0.75) (Figure 4).

### Discussion

#### Summary of results

Based on the current data, either AAP or Doc alongside ADT improves the survival of men with mHNPC. Although AAP has the highest probability of being the most effective treatment, with Doc + ADT the second most effective treatment, uncertainty remains about the difference in absolute magnitude of survival benefit between these two treatments (between 1% and 9% at 3 years). Adding ZA + Doc or ZA + Cel to ADT also improved survival relative to ADT alone.

#### Strengths

This is the first network meta-analysis to comprehensively assess and rank the effects of all the systemic treatments for mHNPC recently tested in RCTs. By working with trial investigators, we have been able to make use of the most up-to-date, and consistent AD from six trials and 6204 men, representing 97% of those randomised in reported, eligible trials. Thus, it provides the most reliable assessment of the relative effects of these agents to date. In particular, our analysis has been able to shed light on the comparison of AAP and Doc in conjunction with ADT and has also reinforced the observed survival benefit associated with the combination of Cel and ZA, although not with either of these agents given individually [3]. Furthermore, to the best of our knowledge, this is the first example of a network meta-analysis that has taken account of the complexities of including a MAMS platform trial, appropriately adjusting the analysis for the proportion of the control-arm patients common to different pairwise comparisons. Obtaining limited unpublished information direct from the investigators made this possible.

#### Limitations

Whilst we have been comprehensive in our approach to this review, relying on AD inevitably has limitations. For example, whilst most trials include PSA progression as part of the definition of FFS, the LATITUDE trial [14] presented results for PSA failure and clinical or radiological progression separately. Whilst our pre-specified primary analysis used time to clinical or radiological progression for the LATITUDE trial, a sensitivity analysis which used time to PSA failure data from LATITUDE showed that our results are robust to these different definitions. In hindsight, although this might have been the preferable primary analysis, it would have made little difference to our interpretation and conclusions.

There are differences in the patient characteristics, which may influence the effects of the various treatments either within or across trials. Despite these differences, however, there has been no clear evidence of heterogeneity in the effects of zoledronic acid, docetaxel or abiraterone across trials in the individual STOPCAP systematic reviews [1, 2]. Nevertheless, some of the

### Table 2. Borrowing of strength statistics (% of information gained per pairwise analysis through inclusion in the network)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>OS, %</th>
<th>FFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADT versus ADT + Cel</td>
<td>5.4</td>
<td>17.3</td>
</tr>
<tr>
<td>ADT versus ADT + ZA</td>
<td>3.9</td>
<td>7.7</td>
</tr>
<tr>
<td>ADT versus ADT + ZA + Cel</td>
<td>5.2</td>
<td>17.1</td>
</tr>
<tr>
<td>ADT versus ADT + Doc</td>
<td>2.0</td>
<td>6.7</td>
</tr>
<tr>
<td>ADT versus ADT + ZA + Doc</td>
<td>9.2</td>
<td>21.7</td>
</tr>
<tr>
<td>ADT versus ADT + AAP</td>
<td>0.9</td>
<td>7.4</td>
</tr>
</tbody>
</table>

AAP, abiraterone acetate plus prednisolone/prednisone; ADT, androgen-deprivation therapy; Cel, celecoxib; Doc, docetaxel; FFS, failure-free survival; OS, overall survival; ZA, zoledronic acid.
individual trials have suggested treatment–covariate interactions, notably that the effects of Doc may be moderated by the extent of metastatic disease volume and that the effects of AAP may be associated with age [1, 12]. There are no well-defined methods to appropriately assess such interactions in an AD network meta-analysis. Therefore, they will be best investigated through the collection and re-analysis of individual participant data from all of the eligible trials, which the STOPCAP collaborators are currently working to undertake.

**Context**

Previously, both Doc and AAP have been shown to improve survival and delay progression in men with mHNPC [2, 16]. However, as no trials have set out to directly compare ADT plus docetaxel with ADT plus AAP, network meta-analysis provides the only comprehensive approach to this treatment comparison. However, the design of the STAMPEDE trial, in which treatments were simultaneously compared against ADT alone, has enabled an opportunistic analysis in which outcomes for men randomised within the same time frame to receive ADT plus Doc or ADT plus AAP were compared [17]. Whilst not a fully powered analysis, the results demonstrated an advantage of AAP over Doc with respect to FFS (HR = 0.51, 95% CI 0.39–0.67, P < 0.001), which did not translate to a survival benefit (HR = 1.16, 95% CI 0.82–1.65, P = 0.40). It is not clear why the findings of the STAMPEDE analysis differ with respect to OS from the findings of the network meta-analysis. The STAMPEDE analysis is a direct comparison of men who were randomised contemporaneously to receive either AAP or Doc in addition to ADT. The network meta-analysis has considerably more power to detect differences in treatment effects, due to both the inclusion of more trials and more men, and the additional strength that other treatment comparisons lend within the network. However, the inclusion of more trials, that randomised men to receive a variety of treatments over a longer time period inevitably brings with it greater variability, due to the broader case mix of patients, with different prognoses, and with differing access to treatments after progression of disease. It has not been possible in this analysis to account for changes in care over time, particularly

![Figure 2. Overall survival. Forest plot of network and pairwise estimates of treatment effects [all treatments compared with androgen-deprivation therapy (ADT) alone]. AAP, abiraterone acetate plus prednisolone/prednisone; CI, confidence interval; Cel, celecoxib; Doc, docetaxel; ZA, zoledronic acid.](image-url)
whilst the number of new treatments available at relapse has rapidly increased, and once again this is best achieved through the collection and analysis of individual participant data.

Other network meta-analyses have been reported. Feyerabend et al. [18] presented the results of an indirect comparison of AAP and Doc based on the results of just two trials. Wallis et al. [19]  

<table>
<thead>
<tr>
<th>Treatment comparison and study</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cel+ADT vs ADT</td>
<td></td>
</tr>
<tr>
<td>Network</td>
<td>0.86 (0.71, 1.04)</td>
</tr>
<tr>
<td></td>
<td>0.89 (0.67, 1.17)</td>
</tr>
<tr>
<td>ZA+ADT vs ADT</td>
<td></td>
</tr>
<tr>
<td>CALGB 90202</td>
<td>0.89 (0.74, 1.07)</td>
</tr>
<tr>
<td>STAMPEDE</td>
<td>0.89 (0.77, 1.02)</td>
</tr>
<tr>
<td>ZAPCA (KYUH TRIG0705)</td>
<td>0.75 (0.57, 0.99)</td>
</tr>
<tr>
<td>Network</td>
<td>0.88 (0.75, 1.05)</td>
</tr>
<tr>
<td>Pairwise (I²=0%; Heterogeneity p=0.54)</td>
<td>0.87 (0.78, 0.96)</td>
</tr>
<tr>
<td>ZA+Cel+ADT vs ADT</td>
<td></td>
</tr>
<tr>
<td>STAMPEDE</td>
<td>0.77 (0.63, 0.94)</td>
</tr>
<tr>
<td>Network</td>
<td>0.80 (0.60, 1.05)</td>
</tr>
<tr>
<td>Doc+ADT vs ADT</td>
<td></td>
</tr>
<tr>
<td>CHAARTED</td>
<td>0.61 (0.51, 0.72)</td>
</tr>
<tr>
<td>GETUG 15</td>
<td>0.67 (0.54, 0.84)</td>
</tr>
<tr>
<td>STAMPEDE</td>
<td>0.61 (0.53, 0.71)</td>
</tr>
<tr>
<td>Network</td>
<td>0.64 (0.54, 0.75)</td>
</tr>
<tr>
<td>Pairwise (I²=0%; Heterogeneity p=0.76)</td>
<td>0.62 (0.56, 0.69)</td>
</tr>
<tr>
<td>ZA+Doc+ADT vs ADT</td>
<td></td>
</tr>
<tr>
<td>STAMPEDE</td>
<td>0.60 (0.52, 0.69)</td>
</tr>
<tr>
<td>Network</td>
<td>0.63 (0.49, 0.80)</td>
</tr>
<tr>
<td>AAP+ADT vs ADT</td>
<td></td>
</tr>
<tr>
<td>LATITUDE</td>
<td>0.47 (0.40, 0.56)</td>
</tr>
<tr>
<td>STAMPEDE</td>
<td>0.31 (0.26, 0.37)</td>
</tr>
<tr>
<td>Network</td>
<td>0.38 (0.31, 0.46)</td>
</tr>
<tr>
<td>Pairwise, fixed</td>
<td>0.38 (0.34, 0.43)</td>
</tr>
<tr>
<td>Pairwise, REML (I²&gt;91%; Heterogeneity p=0.001)</td>
<td>0.38 (0.25, 0.57)</td>
</tr>
</tbody>
</table>

Figure 3. Failure-free survival. Forest plot of network and pairwise estimates of treatment effects [all treatments compared with androgen-deprivation therapy (ADT) alone]. AAP, abiraterone acetate plus prednisolone/prednisone; CI, confidence interval; Cel, celecoxib; Doc, docetaxel; ZA, zoledronic acid.
have also reported indirect comparisons of ADT plus AAP with ADT plus Doc. However, we have concerns regarding the methodological approaches used by the authors, in particular, the inclusion of patients with and without metastases; the double-counting of shared control arm patients, and therefore correlations, from the STAMPEDE trial and the use of flawed subgroup analysis methodology [20].

Finally, a key question that remains for both clinicians and patients is whether the two most effective treatments, AAP and Doc, could be safely combined and if so, what the impact of the combination may be on OS. This question will only be resolved when results from the ongoing PEACE-1 trial are available.

**Conclusions**

Our results support the use of either AAP or Doc alongside ADT in men with mHNPC. AAP appears to be the most effective treatment, but it is not clear to what extent and whether this is due to a true increased benefit with AAP or to the variable features of the individual trials. To fully account for patient variability across trials, changes in prognosis or treatment effects over time, and the potential impact of treatment on progression, a network meta-analysis based on individual participant data is currently in development.

**Acknowledgements**

The STOPCAP Collaborators thank all patients who participated in the trials and contributed to this research. The meta-analysis would not have been possible without their participation or without the institutions and collaborative groups that carried out the trials, including a great many trial sites. We thank STAMPEDE trial team for supplying additional data to facilitate the network meta-analysis.

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### Table 4. Treatment ranking (% probability) and SUCRA values based on failure-free survival results

<table>
<thead>
<tr>
<th>AAP</th>
<th>ZA + Doc</th>
<th>Doc</th>
<th>ZA + Cel</th>
<th>ZA</th>
<th>Cel</th>
<th>ADT alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best</td>
<td>100.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Second best</td>
<td>0.0</td>
<td>52.0</td>
<td>45.1</td>
<td>2.6</td>
<td>0.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Third best</td>
<td>0.0</td>
<td>41.3</td>
<td>47.9</td>
<td>9.5</td>
<td>0.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Fourth best</td>
<td>0.0</td>
<td>5.7</td>
<td>6.7</td>
<td>53.3</td>
<td>14.7</td>
<td>19.1</td>
</tr>
<tr>
<td>Fifth best</td>
<td>0.0</td>
<td>1.0</td>
<td>0.3</td>
<td>21.5</td>
<td>42.0</td>
<td>31.4</td>
</tr>
<tr>
<td>Sixth best</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>10.4</td>
<td>37.6</td>
<td>29.1</td>
</tr>
<tr>
<td>Worst</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>2.7</td>
<td>5.6</td>
<td>18.9</td>
</tr>
<tr>
<td>SUCRA</td>
<td>1.0</td>
<td>0.7</td>
<td>0.7</td>
<td>0.4</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

AAP, abiraterone acetate plus prednisolone/prednisone; ADT, androgen-deprivation therapy; Cel, celecoxib; Doc, docetaxel; SUCRA, surface under the cumulative rank; ZA, zoledronic acid.

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**Figure 4.** Indirect comparison of the two most effective treatment combinations (A) overall survival and (B) failure-free survival. AAP, abiraterone acetate plus prednisolone/prednisone; ADT, androgen-deprivation therapy; CI, confidence interval; Cel, celecoxib; Doc, docetaxel; ZA, zoledronic acid.
UK Medical Research Council (MC_UU_12023/25); Prostate Cancer UK Research Innovation Award (RIA16-ST2-020).

Disclosure

CLV, DJF, IWW, JFT, LHMR, SB and GG declare no competing interests. MKBP, MSp and MSy report grants from Astellas, Janssen, Novartis, Pfizer, Sanofi and Clovis Oncology outside the submitted work. JC reports grants from MRC as well as personal fees from Pfizer and GSK, and grants from Novartis outside the submitted work. NWC reports participation on advisory boards for Astellas, Janssen, Ferring, Bayer, AstraZeneca and corporate-sponsored Research for AstraZeneca. KE reports participation on advisory boards for Janssen and Sanofi outside the submitted work. MDM receives personal fees from Sanofi, Bayer and Janssen, outside the submitted work. NDJ reports participation on advisory boards for Sanofi and Novartis, and grants, personal fees and non-financial support from Janssen, outside the submitted work. CJS reports Ownership BIND; Advisory board personal fees and non-financial support from Janssen, outside the submitted work. NDJ reports participation on advisory boards for Janssen and Novartis, outside the submitted work. MKBP, MSp and MSy report grants from Astellas, Janssen, Biomedicine, Astra Zeneca, Sanofi, Janssen, BIND, Bayer; Grants from Janssen, Astellas/Medivation, Sanofi, Janssen, Soci, Exelixis, and consultancy for Astellas/Medivation, Pfizer, Sanofi, Janssen, BIND, Bayer, Genentech.

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