What are the optimal systemic treatments for men with metastatic, hormone-sensitive prostate cancer? A STOPCaP systematic review and network meta-analysis

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Abstract

Background
Our prior STOPCaP systematic reviews showed improved survival for men with metastatic hormone-sensitive prostate cancer (mHSPC) 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 performed based on aggregate data (AD) from all available studies.

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

Results
We identified 10 completed trials and one ongoing trial 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 (HR=0.61, 95% CI 0.53-0.71); Doc (HR=0.77, 95% CI 0.68-0.87); Cel+ZA (HR=0.78 95%CI 0.62-0.97) and Doc+ZA (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 Cel+ZA 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 FFS (100% probability). Doc was the second best treatment for overall survival (35% probability).

Conclusions
Uniquely, we have included all available results and appropriately accounted for inclusion of MAMS trials in this AD-NMA. Our results support the use of AAP or Doc with ADT in men with mHSPC. AAP appears to be the most effective treatment. 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**.**

Introduction

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-sensitive prostate cancer (mHSPC). To determine reliably which are most effective, we are conducting a series of systematic reviews under the auspices of the Systemic Treatment Options for Prostate Cancer (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). There is an obvious need to determine reliably which are the most effective in terms of improving survival and reducing progression for men with mHSPC to establish the optimal treatment(s) and so to inform patients, clinicians and policy makers.

However, only the completed arms of the STAMPEDE multi-arm, multi stage platform and the ongoing PEACE -1 trial (NCT01957436) compare any of these therapies head-to head. Network meta-analysis(4, 5) takes advantage of both direct and indirect comparisons in order to rank the efficacy of multiple interventions. Making use of existing STOPCAP reviews (refs) and up-to-date results from individual trials, and also taking account of the multi-arm, multi-stage nature of STAMPEDE, we have conducted a systematic review network meta-analysis of aggregate-data (AD) to assess the optimal systemic treatments for men with mHSPC.

Methods

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

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 should have been diagnosed with mHSPC, and either starting or responding to first-line ADT for metastatic disease (they may have received prior treatments for early, localised disease). Trials were also considered 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 failed first line hormone therapy for metastatic prostate cancer, or had castrate-refractory prostate cancer or if they had included additional first-line treatments on the control arm only.

Trial Identification

As part of the wider STOPCaP project, we regularly and systematically searched a number of trial sources to identify all published, unpublished and ongoing trials in mHSPC. This provides a comprehensive and up-to-date database of all RCTs eligible for all of our STOPCaP systematic reviews. We also requested regular updates from relevant trial teams on the status and reporting plans. Thus, all trials included in our previous STOPCAP review (1, 2) and any additional RCTs meeting the eligibility criteria were included.

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In summary, we searched MEDLINE, EMBASE, clinicaltrials.gov and the Cochrane Central Register of Controlled Trials (CENTRAL), using database-specific search strategies. We also searched proceedings from relevant conferences. In addition, reference lists of review articles and bibliographies of identified trial reports were screened for further eligible trials. Full search strategies are included in Appendix 1 (online only).

Outcomes

The primary outcome is overall survival (OS), with failure-free survival (FFS) the secondary outcome.

Data extraction

The principal data extracted or derived from included studies was the log hazard ratio and standard error, or information to estimate the hazard ratio (e.g. a hazard ratio and confidence interval or p-value(6)) for overall survival (OS) and failure-free survival (FFS). Outcome definitions were also extracted for each trial to ensure their consistency and the appropriateness of combining results in a formal meta-analysis. Additional summary data including start and end dates of recruitment, details of treatment schedules on the control and experimental arms, numbers of patients and their demographics were also extracted, either directly from the trial publications or from prior systematic reviews.

Assessing the risk of bias of included trials

Assessment of study quality for all trials included in the prior STOPCAP reviews had already been performed in the individual reviews, using the Cochrane risk of bias tool(7) and all studies were assessed as having low risk of bias based on reported information and study protocols(8). Risk of bias assessments for additional eligible studies identified for inclusion in the network meta-analysis were also carried out using the Cochrane tool.

Analysis

In order to appropriately include trials that use a MAMS design in a network meta-analysis, we estimated relevant correlations between the effect estimates obtained during periods of overlap between the common control arm and comparator arms using control-arm event-count within the periods of overlap directly from the STAMPEDE investigators.

The primary analysis was carried out using a frequentist contrast-based network meta-analysis model and the `network` suite of commands(5) in Stata v14.1, in which a common heterogeneity variance across all contrasts and consistent network effects are assumed. .

In the primary analysis, all treatment comparisons (e.g. ADT+ZA+Doc vs ADT) were

assumed to be independent, such that no assumptions were made about the interactions between the effects of combined treatments (e.g. ZA and Doc). Sensitivity analyses were carried out to assess robustness of the modelling assumptions applied.

A network map was constructed to display all of the available relationships, with distinct treatments represented by nodes and trials (or separate trial comparisons within the single MAMS design trial) by lines joining appropriate nodes. The thickness of the lines, representing the extent of available data for each comparison, was estimated from the combined number of events for all trials contributing to each individual comparison. Borrowing of strength statistics were calculated using the score decomposition method(9), and represent the proportion of the information on each treatment comparison due to indirect evidence from the network model, as opposed to from direct evidence.

Estimates of relative effect for each pairwise treatment comparison from the primary consistency model were estimated on the hazard ratio scale along with corresponding 95% confidence limits and displayed in a network forest plot(5). Treatment rankings were also calculated using both cumulative probabilities (i.e. the probability of each treatment being a particular rank) and as a surface under the cumulative rank (SUCRA) value, representing 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)

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Finally, we aimed to conduct an indirect comparison of the two most effective treatments to estimate the relative difference in the size of the effects. We then aimed to estimate the absolute benefit of treatment on overall survival at 3 years by applying the HR estimate to the approximate baseline survival at 3 years.

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. However, two trials that together randomised 72

men to receive ADT or ADT plus doc and two trials that 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 presented results for survival outcomes (online table only). One further trial, comparing AAP with standard of care, which aims to recruit 1126 men, is ongoing therefore no results are currently available for inclusion.

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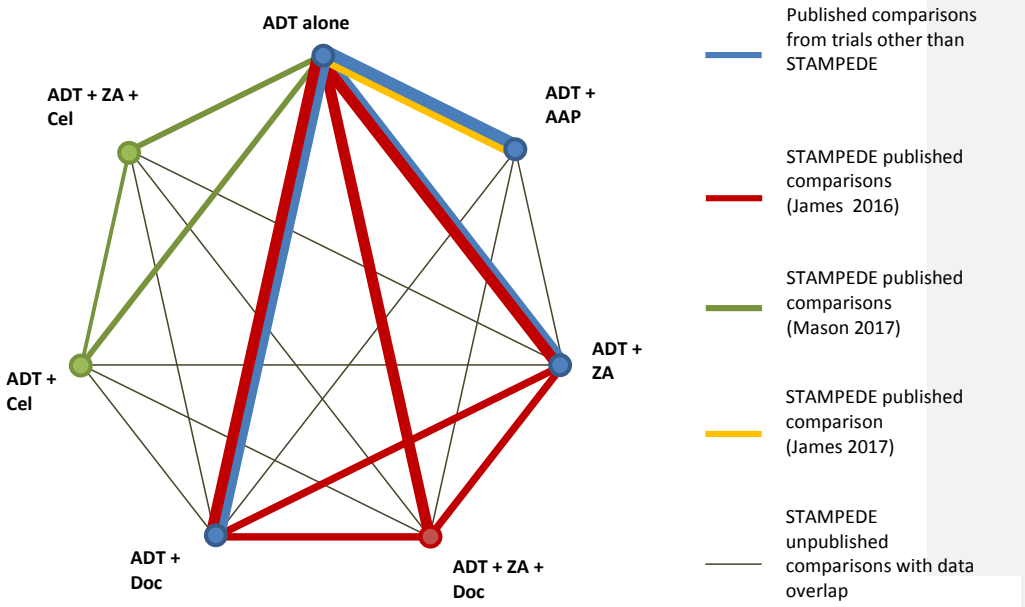
Therefore, six RCTs were identified as eligible for inclusion in the network meta-analysis (Figure 1, Table 1). Two trials compared ADT with ADT plus ZA; two compared ADT with ADT plus doc and one trial compared ADT with ADT plus AAP. The final trial, STAMPEDE(11), contributed 6 separate treatment comparisons(3, 12, 13) to the network. Four comparisons were of ADT with Cel, ZA, Doc or AAP and two further 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 across the 10 completed eligible trials (at least 83% of men randomised in all 11 eligible trials). 2615 men were randomised to receive ADT alone (accounting for the shared control arm patients in the STAMPEDE trial), 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; however definitions of FFS varied between the trials. Notably, the definition of FFS included PSA failure in all trials except LATITUDE(14), whereas all except CHAARTED(15) included death in the outcome definition. Further details of the trials including the definitions used for FFS are given in Table 1.

Figure 1. Network meta-analysis structure



Control-arm (ADT) events and patients that contribute to more than one treatment comparison within the network analysis were used to derive estimates of correlations between effect estimates for the network analysis.

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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.

Trial	Recruitment period	Median Follow up (months))	Treatment	Treatment (N)	Control (N)	Definition of Failure-free Survival (FFS)
CALGB 90202 (16)	June 2004 – April 2012	unknown	ADT + ZA	323	322	Time to first bone progression, PSA progression, or death.
GETUG 15 (17)	Oct 2004-Dec 2008	84	ADT + Doc	192	193	Time to PSA progression, radiographic progression or death
STAMPEDE(D) (3)	Oct 2005 – Jan 2011	69	ADT + Cel	188	377	Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer
STAMPEDE (F) (3)	Oct 2005 – Jan 2011	69	ADT + ZA + Cel	190	377	Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer
STAMPEDE (B) (13)	Oct 2005 – March 2013	43	ADT +ZA	366	724	Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer
STAMPEDE (C) (13)	Oct 2005 – March 2013	43	ADT + Doc	362	724	Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer
STAMPEDE (E) (13)	Oct 2005 – March 2013	43	ADT + ZA + Doc	365	724	Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer
CHAARTED (18)	July 2006 – Dec 2012	54	ADT + Doc	397	393	***Time to PSA rise or clinical progression***
ZAPCA (KYUH TRIG0705) (19)	May 2008 – Dec 2010	42	ADT +ZA	109	110	Time to earliest date of PSA progression, clinical progression, first SRE, death for any reason, or cessation of protocol treatment for any reason
STAMPEDE (G) (12)	Nov 2011- Jan 2014	40	ADT + AAP	500	502	Time to PSA failure, progression of local, lymph-node, or distant metastases; or death from prostate cancer
LATITUDE (14)	Feb 2013 – Dec 2014	30	ADT + AAP	597	602	***Time to radiographic progression or death from any cause***

Borrowing of strength from the network

Inclusion in the network led to a gain in information for each of the pairwise treatment comparisons. For OS, this ranged from 0.9% (AAP) to 9.2% (ZA+Doc) and for FFS the gains were generally greater and ranged from 6.7% (Doc) to 21.7% (ZA + Doc, Table 2)

Table 2. Borrowing of strength statistics

Comparison	OS	FFS
ADT vs ADT +Cel	5.4%	17.3%
ADT vs ADT + ZA + Cel	5.2%	17.1%
ADT vs ADT + ZA	3.9%	7.7%
ADT vs ADT + ZA + Doc	9.2%	21.7%
ADT vs ADT + Doc	2.0%	6.7%
ADT vs ADT + ABI	0.9%	7.4%

Overall Survival

The network-meta-analysis HR estimates suggested that compared to ADT alone each of AAP (HR=0.61 95% CI 0.530.71); 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) improved survival. There was no survival advantage observed with ZA (HR=0.90 95% CI 0.79 – 1.03) or Cel (0.94 95% CI 0.75 – 1.17) over ADT alone. It should be noted that for the comparisons of ADT versus ADT + Cel; ADT + ZA + Cel and ADT + ZA + Doc, the only data available was from a single comparison from STAMPEDE trial(3, 13). There was no evidence of variation or inconsistency 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).

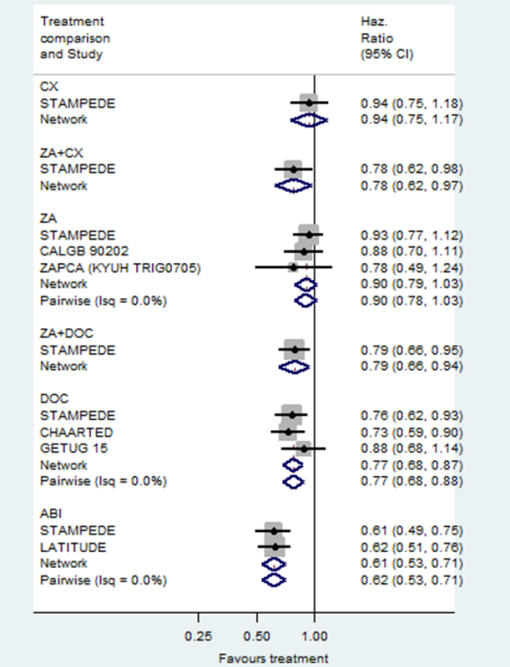


Figure 2. Overall Survival. Forest plot of network and pairwise estimates of treatment effects (all treatments compared with ADT alone)

Treatment rankings

Based on the treatment rankings, 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).

	AAP	Doc	Doc + ZA	ZA + Cel	ZA	Cel	ADT
Best	**94.2**	0.7	1.3	3.8	0.0	0.0	0.0
2nd best	5.3	**34.9**	25.5	33.0	0.3	1.0	0.0
3rd best	0.4	36.8	**30.3**	27.0	2.4	3.1	0.0
4th best	0.1	23.6	30.8	**23.9**	12.2	9.3	0.1
5th best	0.0	3.8	9.3	9.3	**48.7**	26.0	2.9
6th best	0.0	0.2	2.6	2.5	31.3	**33.6**	29.8
Worst	0.0	0.0	0.2	0.5	5.1	27.0	**67.2**
SUCRA	**1.0**	**0.7**	**0.6**	**0.6**	**0.3**	**0.2**	**0.1**

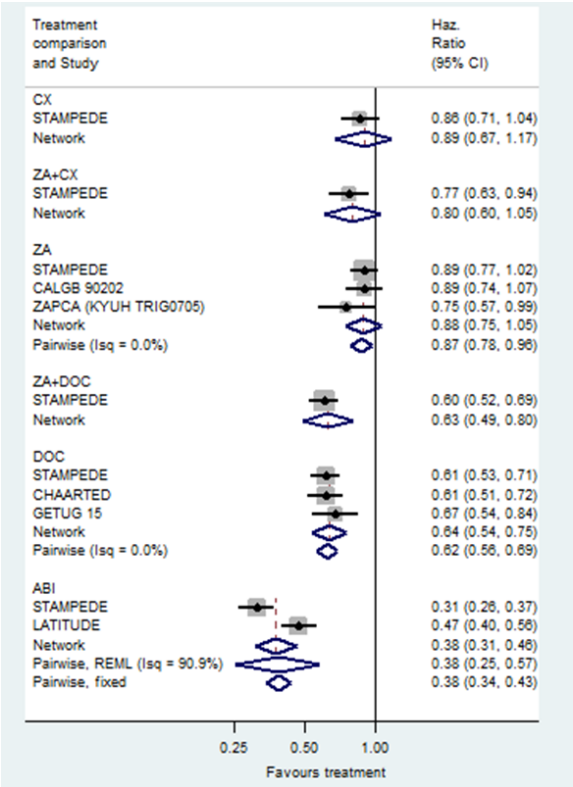
Table 3. Treatment ranking (% probability) and SUCRA values based on OS results

Failure-free survival

There was a failure-free survival benefit associated with the addition to ADT with 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 such benefit was 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 are 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 comparison (I^2=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).

There was some inconsistency between the definitions of FFS used in the individual trials (Table 1), notably all except the LATITUDE trial included PSA failure in the definition. 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 (5% CI 0.27-0.34) with no evidence of variation of inconsistency (I^2=0, heterogeneity p=0.78).

Figure 3. Failure Free survival. Forest plot of network and pairwise estimates of treatment effects (all treatments compared with ADT alone)



Based on the treatment rankings, 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).

Table 4. Treatment raking (% probability) and SUCRA values based on FFS results

	ABI	ZA+Doc	Doc	ZA+CX	ZA	CX	ADT
Best	**100.0**	0.0	0.0	0.0	0.0	0.0	0.0
2nd best	0.0	**52.0**	**45.1**	2.6	0.0	0.3	0.0
3rd best	0.0	**41.3**	**47.9**	9.5	0.1	1.2	0.0
4th best	0.0	5.7	6.7	**53.3**	14.7	19.1	0.5
5th best	0.0	1.0	0.3	21.5	**42.0**	31.4	3.8
6th best	0.0	0.0	0.0	10.4	37.6	**29.1**	22.9
Worst	0.0	0.0	0.0	2.7	5.6	18.9	**72.8**
SUCRA	**1.0**	**0.7**	**0.7**	**0.4**	**0.3**	**0.3**	**0.1**

Indirect comparison of the two most effective treatments

Two treatments, AAP and Doc, emerged as being effective in terms of improving both OS and FFS relative to ADP alone, and having the greatest probabilities of being the top two most effective treatments and were therefore compared indirectly in a pairwise comparison. The HR estimate for the effect of ADT + AAP relative to the effect of ADT + Doc on overall survival is HR=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%), i.e. to 66% at 3 years (range 61% to 71%). For FFS, the HR for the relative effect of ADT + AAP to ADT + Doc is 0.59, 95% CI 0.46-0.75 (Figure 4).

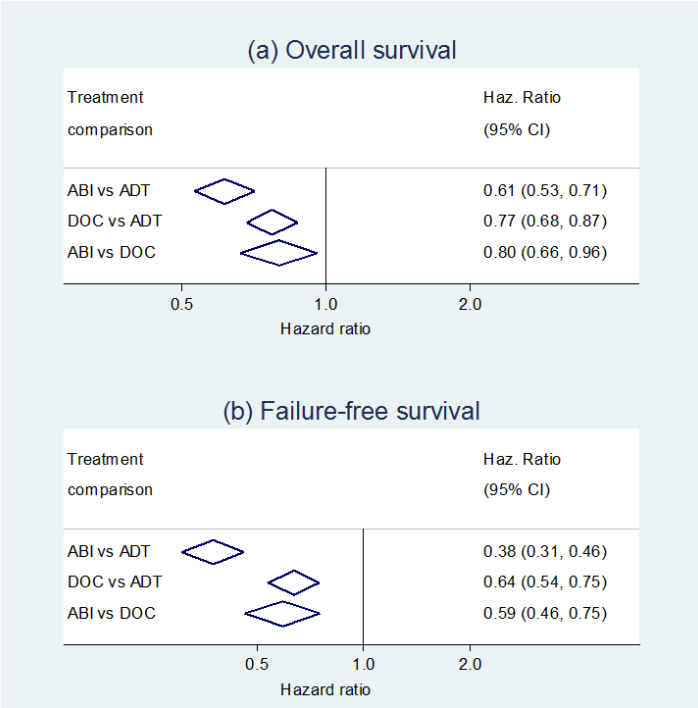


Figure 4. Indirect comparison of the two most effective treatments (a) OS and (b) FFS

Discussion

Summary of results

Based on the current data, the addition of AAP to ADT has the highest probability of been the most effective treatment and Doc + ADT the second most effective treatment in improving survival in mHSPC. Uncertainty remains about the difference in the magnitude of of survival benefit between these two treatments (1 to 9% at 3 years). Adding Doc + ZA or Cel + ZA to ADT also improved survival relative to ADT alone,

Strengths

This is the first network meta-analysis (ESMO ref) to comprehensively assess and rank the effects of all the current systemic treatments for mHSPC. It includes results from 6 trials and 6204 men, representing 97% of those randomised in all completed eligible trials, and borrows strength from across the network, providing 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, years ahead of direct trial evidence from the ongoing PEACE-1 trial becoming available. Our comprehensive approach also reinforces 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 takes account of the complexities of including a MAMS trial, appropriately adjusting the analysis for the proportion of the control arm patients common to different pairwise comparisons. Obtaining limited unpublished information direct form the investigators made this possible.

Limitations

Whilst we have been comprehensive in our approach to this review, relying on aggregate data inevitably has limitations. For example, while 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 progressions separately. However, a sensitivity analysis that instead includes the PSA-failure data from LATITUDE, suggest that our results are robust to these different definitions. Also, we were not able to assess the potential impact of treatment on progression on estimates of effect overall survival. Some of the individual trials have suggested treatment-covariate interactions, notably that the effects of Doc may be moderated by the extent of metastatic disease volume (ref) and that the effects of AAP may be associated by age (refs). It is always difficult to thoroughly investigate such interactions in aggregate data meta-analysis, and there are no well-defined methods to appropriately assess such interactions within a network. Similarly, we have not been able to assess the impact of changes in underlying prognosis over time and how the extent of follow up may

impact on this. Each of these limitations are best addressed with the collection and reanalysis of individual participant data from all of the eligible trials. Hence, we are currently working together with all of the STOPCAP collaborators to conduct such an analysis. Finally, a key question 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 overall survival. Although the ongoing PEACE-1 trial may shed some light on this, it is unlikely that results will become available for some years yet.

Context

Previously, both docetaxel and AAP have been shown to improve the survival and delay progression in men with mHSPC(2, 20), however, no trials have set out to directly compare docetaxel with AAP, hence the clear need for a network meta-analysis. The design of the STAMPEDE trial has enabled an opportunistic analysis of treatment arms using these two treatments (*insert ref to the STAMEPDE direct comparison*). Whilst not a fully-powered analysis, the trial design, in which a variety of treatments were compared against ADT alone simultaneously, meant that a subset of men were randomised to receive either docetaxel or AAP within the same time frame. Whilst the results of the STAMPEDE analysis demonstrated an advantage of AAP over Doc with respect to FFS (HR=0.56, 95% CI 0.42-0.75, p<0.001) they did not translate to a survival benefit (HR=1.13 95% CI 0.77-1.66, p=0.53). Although we cannot be certain of the reasons for this there are a number of potential sources of discrepancy between the findings from the trial and our aggregate data network meta-analysis. Firstly, whilst the analysis within the STAMPEDE trial is based on a direct comparison of only those men who were randomised contemporaneously to receive AAP or Doc, our indirect analysis is based on results from all men randomised, over a wider timescale, to either treatment, both within STAMPEDE and across the remaining trials. This inevitably gives more power to the network meta-analysis both by including information from the remaining trials and treatment comparisons and also because within the network model, each separate pairwise comparison lends a degree of strength to other treatment

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comparisons within the network, but cannot account for any changes in care over time, particularly while the number of new treatments available at relapse has rapidly increased.

Conclusions

Our results support the use of either AAP or Doc alongside ADT in men with mHSPC. AAP appears to be the most effective treatment, but it is not clear to what extent. 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**.**

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