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Indirect Comparison of Abiraterone Acetate Plus Prednisone and Docetaxel for the Treatment of Metastatic "Hormone-Sensitive" Prostate Cancer

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INTRODUCTION

- Abiraterone acetate (AA) is a prodrug of abiraterone, a specific inhibitor of CYP17 that potently inhibits persistent adrenal and intratumoral androgen synthesis.[1]
- Docetaxel (DOC) is an antineoplastic agent in the taxane class. Its mechanism of action includes disrupting the microtubular network that is essential for cellular functions, leading to inhibition of cell division and cell death.[2]
- When DOC was used in combination with androgen deprivation therapy (ADT), a statistically significant improvement in overall survival ([OS] 10-15 months) was seen in patients with metastatic hormone-sensitive prostate cancer (mHSPC).[2]
- LATITUDE is a randomized phase 3 clinical trial, evaluating ADT+AA+prednisone (P) versus ADT in a population of patients with newly diagnosed high-risk (NDx HRD) mHSPC (Table 1).[3] ADT+AA+P demonstrated significant OS benefit in patients with mHSPC compared with ADT in both phase 3 trials in which this combination was assessed (LATITUDE[3] and STAMPEDE[4]).
- We conducted an indirect comparison to determine the relative efficacy of AA+P versus DOC in mHSPC patients.

METHODS

- A systematic literature review (SLR) was performed to identify randomized controlled trials (RCTs) involving patients with mHSPC.
- The feasibility of conducting an indirect comparison with data from the identified RCTs was assessed on the grounds of:
  - Population: patients with NDx HRD and/or high-volume disease (HRD/HVD) mHSPC (definitions are presented in Table 1);
  - Intervention: ADT+AA+P or ADT+DOC;
  - Comparator: ADT;
  - Outcomes and time points: outcome definitions and time points of outcome collection had to be comparable.
- To estimate the relative treatment effects for ADT+AA+P versus ADT+DOC on OS and radiographic progression-free survival (rPFS) outcomes, a fixed-effects Bayesian network meta-analysis was performed. Results are presented as:
  - Hazard ratios (HRs) for rPFS and OS with 95% credibility intervals (CrIs), and
  - Bayesian pairwise probability for a treatment to perform better than a comparator (presented as probability of the HR < 1).

Table 1. Definition of HVD and HRD

Trial	Definition of HVD	Definition of HRD
GETUG-AFU 15	Presence of visceral metastases and/or 4 or more bone metastases with at least 1 outside of the vertebral column and pelvis	NA
CHAARTED		
LATITUDE		At least 2 of the following high-risk prognostic factors: Gleason score of ≥ 8; presence of 3 or more lesions on bone scan; presence of measurable visceral (excluding lymph node disease) metastasis on CT or MRI RECIST Version 1.1 scan

CT, computed tomography; MRI, magnetic resonance imaging; NA, not applicable; RECIST, Response Evaluation Criteria In Solid Tumors.

RESULTS

- 22 RCTs, published in 51 publications and assessed on grounds of study design, interventions, population and outcomes, were included in the SLR (Figure 1).
  - 2 RCTs, CHAARTED[5-7] and GETUG-AFU 15,[8,9] provided data in a population closely matched to that of LATITUDE and were therefore included in the primary network with LATITUDE (Figure 2).
  - To identify more recently published data from RCTs included in the indirect comparison network, publications of CHAARTED, GETUG-AFU 15, and STAMPEDE published after the SLR cut-off date were identified manually.
- CHAARTED and GETUG-AFU 15 reported outcomes for patients with NDx HVD. As the intent-to-treat (ITT) population in LATITUDE was patients with NDx HRD, a post hoc analysis of LATITUDE data provided results for a subgroup of patients with NDx HRD&HVD, which were used in the main analysis; the LATITUDE NDx HRD population was tested in SA.
- STAMPEDE[4,10] was only explored in SA as it reported on a broader mHSPC population, without specific data in the HVD/HRD subgroups (Figure 2).
- Treatment with ADT+AA+P showed improvement versus ADT+DOC in OS (HR: 0.85; CrI: 0.63, 1.14) (Figure 3) as well as in rPFS (HR: 0.71; CrI: 0.49, 1.02) (Figure 4), with Bayesian probabilities for ADT+AA+P being more effective compared with ADT+DOC (86.7% and 96.8%, for OS and rPFS, respectively) (Table 2).
- Results from the SA were consistent with those of the main analysis (Table 2).

Figure 1. PRISMA Diagram of Study Attrition

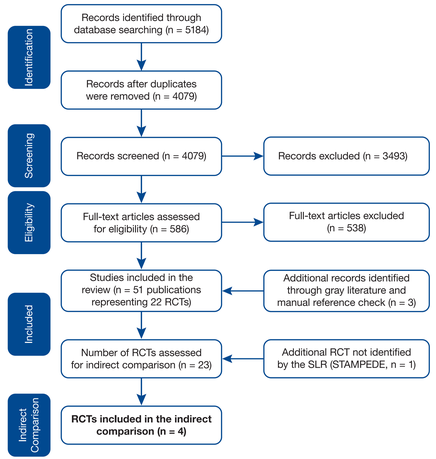
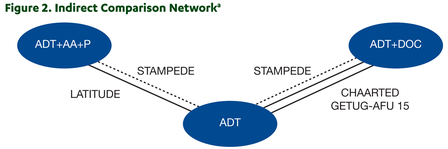


Figure 2. Indirect Comparison Network[a]



[a]Dashed lines indicate sensitivity analyses network.

Figure 3. Posterior Density: OS - Main Analysis, ADT+AA+P vs ADT+DOC

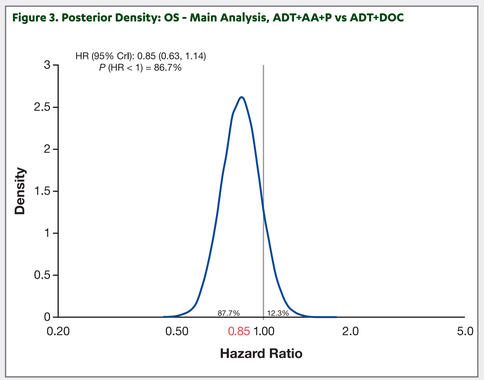


Figure 4. Posterior Density: rPFS - Main Analysis, ADT+AA+P vs ADT+DOC

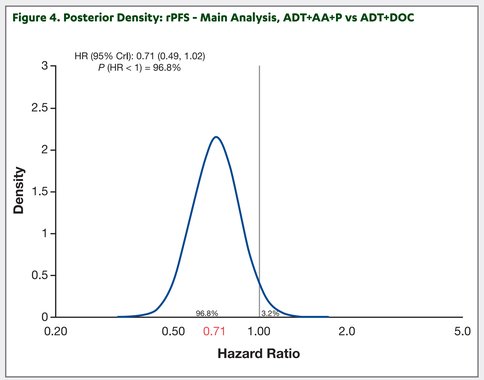


Table 2. Results

		ADT+AA+P vs ADT			ADT+DOC vs ADT			Indirect comparison	
		LATITUDE		STAMPEDE	CHAARTED	GETUG-AFU 15	STAMPEDE	ADT+AA+P vs ADT+DOC	
		HVD&HRD	HRD (ITT)	M1	HVD	HVD	M1	HR	P_{AA-DOC}
OS	Main analysis	0.57 [0.46, 0.71]			De novo HVD 0.63 [0.49, 0.81][5]	De novo HVD 0.78 [0.54, 1.12][9]		**0.85 [0.63, 1.14]**	**86.7%**
	Sensitivity analysis 1		0.62 [0.51, 0.76][3]					**0.92 [0.69, 1.23]**	**71.8%**
	Sensitivity analysis 2			0.61 [0.49, 0.75][4]			0.76 [0.62, 0.92][10]	**0.91 [0.71, 1.18]**	**76.4%**
rPFS	Main analysis	0.43 [0.36, 0.52]				HVD 0.61 [0.44, 0.83][9]		**0.71 [0.49, 1.02]**	**96.8%**
	Sensitivity analysis		0.47 [0.39, 0.55][3]					**0.76 [0.53, 1.10]**	**92.9%**

MI, distant metastasis; P_{AA+DOC}, Bayesian pairwise probability for ADT+AA+P being more effective compared with ADT+DOC.

CONCLUSIONS

- In the absence of head-to-head trials, indirect comparisons based on Bayesian network meta-analysis can provide useful insights to clinicians and reimbursement decision-makers on the relative efficacy of treatment options and help guide choice of therapy for the management of NDx mHSPC.
- Based on the Bayesian indirect comparison, ADT+AA+P is at least as effective as, and possibly superior to, ADT+DOC in reducing the risk of disease progression and death.
- This indirect comparison does present some limitations:
  - Only 1 study was available for any given treatment comparison of rPFS analyses.
  - The population from LATITUDE included only patients with NDx HRD; data on the proportion of patients with HRD were not available from CHAARTED, GETUG-AFU 15, and STAMPEDE.

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ACKNOWLEDGMENTS

This study was supported by funding from Janssen Research & Development. Writing assistance was provided by Shala Thomas, PhD, of PAREXEL, and was funded by Janssen Global Services, LLC.

Poster presented at the Annual Congress of the European Society for Medical Oncology (ESMO), September 8-12, 2017, Madrid, Spain • Supported by funding from Janssen Research & Development