Matching-Adjusted Indirect Comparison of the Efficacy and Tolerability of Apalutamide and Darolutamide for the Treatment of Nonmetastatic Castration-Resistant Prostate Cancer

Simon Chowdhury,[1] Stéphane Oudard,[2] Hiroji Uemura,[3] Steven Joniau,[4] Jinan Liu,[5] Lindsay Dearden,[6] Jan Sermon,[7] Suzy Van Sanden,[7] Joris Diels,[7] Boris A. Hadaschik[8]

[1]Guy's, King's, and St. Thomas' Hospitals, London, United Kingdom; [2]Georges Pompidou Hospital, Paris, France; [3]Yokohama City University Medical Center, Yokohama, Japan; [4]University Hospitals Leuven, Leuven, Belgium; [5]Janssen Scientific Affairs, LLC, Horsham, PA, USA; [6]Janssen Global Services, Raritan, NJ, USA; [7]Janssen EMEA, Beerse, Belgium; [8]University of Duisburg-Essen, and German Cancer Consortium (DKTK), partner site University Hospital Essen, Essen, Germany

Background

- Nonmetastatic castration-resistant prostate cancer (nmCRPC) is a prostate cancer disease stage defined by progression on ADT without radiographic evidence of distant tumors with conventional imaging techniques
- Apalutamide and darolutamide are both treatments for nmCRPC

Phase 3, randomized, PBO-controlled studies:	SPARTAN[1]:	APA + ADT	vs	PBO + ADT
	ARAMIS[2]:	DARO + ADT	vs	PBO + ADT

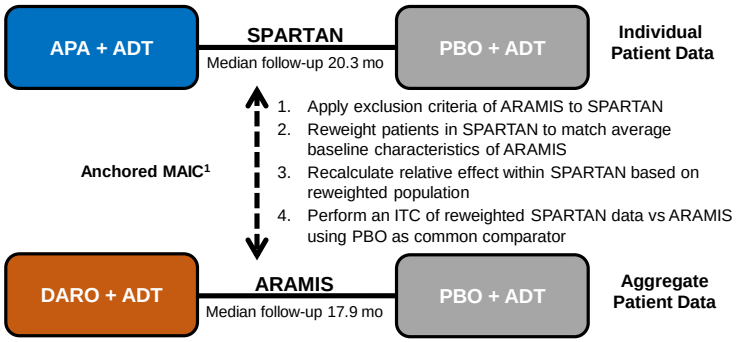
- A head-to-head study of APA + ADT vs DARO + ADT has not been conducted

ADT, androgen deprivation therapy; APA, apalutamide; DARO, darolutamide; PBO, placebo.
Clinical trials: SPARTAN, NCT01946204; ARAMIS, NCT02200614.
1. Smith MR. et al. *N Engl J Med*. 2018;378:1408-1418. 2. Fizazi K, et al. *N Engl J Med*. 2019;380:1235-1246.

Study Objective

- Anchored matching-adjusted indirect comparison (MAIC):
  - To compare the efficacy and tolerability of APA + ADT and DARO + ADT based on results of SPARTAN and ARAMIS:
    - Using an indirect treatment comparison (ITC)
    - While adjusting for potential treatment effect modification

Methods



1. Signorovitch JE, et al. *Pharmacoeconomics*. 2010;28:935-945.

Outcomes of Interest

Efficacy end points (time to event, HR)

- Metastasis-free survival (MFS; primary end point)
- Prostate-specific antigen (PSA) progression
- Progression-free survival (PFS)
- Overall survival (OS)

Tolerability end points (binary events, OR)

- Any adverse events (AEs)
- Any serious AEs (SAEs)

HR: hazard ratio; OR: odds ratio.

ITC After Matching

- Compare the HR/OR based on the reweighted SPARTAN population with the reported HR/OR from ARAMIS in a Bayesian framework
- Noninformative priors
- Major advantage of Bayesian approach: naturally leads to decision framework that supports decision-making[1]
- Answers a question directly relevant to health care decision-makers

"Given the available evidence, how likely is it that one treatment is more beneficial than the other?" [1]

1. Jansen JP, et al. *Value Health*. 2011;14:417-428.

Comparability of the Trials: Key Inclusion Criteria

SPARTAN

Eligibility
- nmCRPC
- PSADT ≤ 10 months
- ECOG PS = 0 or 1

On-Study Requirement
- Continuous ADT

ARAMIS

Eligibility
- nmCRPC
- PSADT ≤ 10 months
- ECOG PS = 0 or 1
- Baseline PSA > 2 ng/mL

On-Study Requirement
- Continuous ADT

ECOG PS, Eastern Cooperative Oncology Group performance status; PSADT, PSA doubling time.

Comparability of the Trials: Baseline Characteristics

	ARAMIS	SPARTAN
	N = 1509	N = 1207
PSADT (months), median	4.5	4.4
PSADT ≤ 6 months, %	69	71
Age (years), median	74	74
PSA at baseline (ng/mL), median	9.2	7.8
ECOG PS = 1, %	31	23
Use of bone-targeted agent, %	4	10
Time from initial diagnosis (months), median	86	95
Testosterone level (nmol/L), median	0.6	0.8
No. of previous hormonal therapy = 1, %	19	20
No. of previous hormonal therapy > 1, %	76	80
Pts from North America, %	12	35
Pts from Europe, %	64	50

Comparability of the Trials: Baseline Characteristics

	ARAMIS		SPARTAN
	N = 1509		N = 1207
PSADT (months), median	4.5		4.4
PSADT ≤ 6 months, %	69		71
Age (years), median	74		74
PSA at baseline (ng/mL), median	**9.2**	**>**	**7.8**
ECOG PS = 1, %	**31**	**>**	**23**
Use of bone-targeted agent, %	**4**	**<**	**10**
Time from initial diagnosis (months), median	**86**	**<**	**95**
Testosterone level (nmol/L), median	**0.6**	**<**	**0.8**
No. of previous hormonal therapy = 1, %	19		20
No. of previous hormonal therapy > 1, %	76		80
Pts from North America, %	**12**	**≠**	**35**
Pts from Europe, %	**64**	**≠**	**50**

Baseline Characteristics Were, on Average, Comparable After Matching

	ARAMIS	SPARTAN	
	N = 1509	N = 1207	Matched N = 1150[a] N_{eff} = 455
PSADT (months), median	**4.5**	4.4	**4.5**
PSADT ≤ 6 months, %	**69**	71	**69**
Age (years), median	**74**	74	**74**
PSA at baseline (ng/mL), median	**9.2**	7.8	**9.2**
ECOG PS = 1, %	**31**	23	**31**
Use of bone-targeted agent, %	**4**	10	**4**
Time from initial diagnosis (months), median	**86**	95	**85**
Testosterone level (nmol/L), median	**0.6**	0.8	**0.6**
No. of previous hormonal therapy = 1, %	**19**	20	**19**
No. of previous hormonal therapy > 1, %	**76**	80	**76**
Pts from North America, %	**12**	35	**12**
Pts from Europe, %	**64**	50	**64**

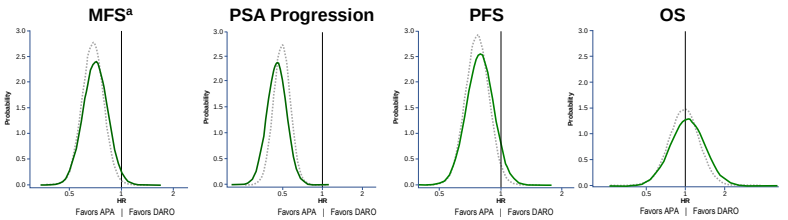
[a]Patients with PSA at baseline < 2 ng/mL were excluded.
N_{eff}, effective sample size.

Efficacy Results Before and After Matching (HR, 95% CI)

	ARAMIS[1]	SPARTAN[2] (before matching)	SPARTAN (after matching)
Metastasis-free survival	0.41 (0.34-0.50)	0.28 (0.23-0.35)	0.29 (0.22-0.38)
PSA progression	0.13 (0.11-0.16)	0.06 (0.05-0.08)	0.06 (0.05-0.08)
Progression-free survival	0.38 (0.32-0.45)	0.29 (0.24-0.36)	0.30 (0.23-0.39)
Overall survival	0.71 (0.50-0.99)	0.70 (0.47-1.04)	0.75 (0.45-1.23)

1. Fizazi K, et al. *N Engl J Med*. 2019;380:1235-1246. 2. Smith MR, et al. *N Engl J Med*. 2018;378:1408-1418.

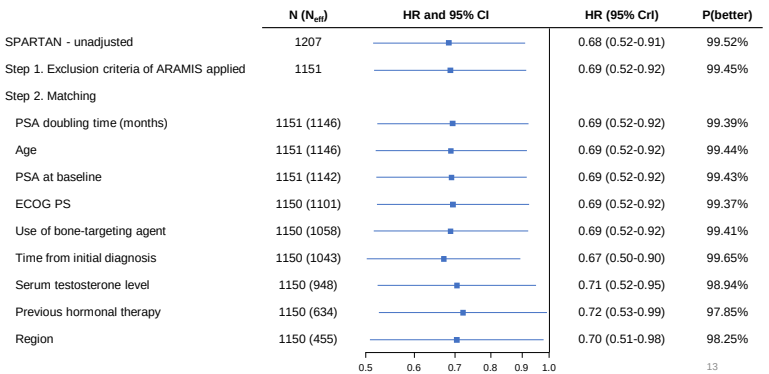
APA + ADT Compared With DARO + ADT After Matching



MFS[a]	PSA Progression	PFS	OS
HR (95% CrI) 0.70 (0.51-0.98)	**HR (95% CrI) 0.46 (0.33-0.64)**	**HR (95% CrI) 0.79 (0.59-1.08)**	**HR (95% CrI) 1.05 (0.58-1.93)**
Probability HR < 1 98.3%	**Probability HR < 1 ~100%**	**Probability HR < 1 93.2%**	**Probability HR < 1 43.5%**

CrI, credible interval.
[a]MFS was the primary end point for the SPARTAN and ARAMIS studies.
Solid green line = weighted; dashed gray line = unweighted.

Impact of Matching on MFS Comparison

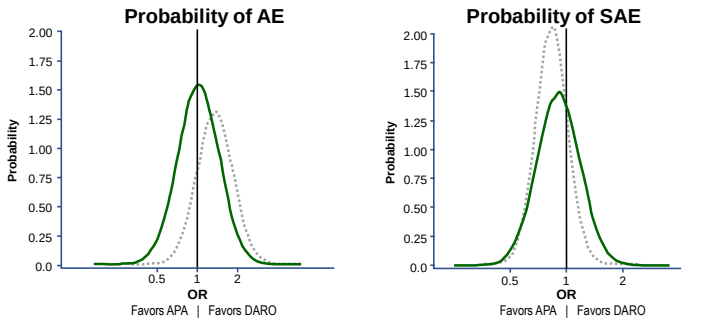


Tolerability Results Before and After Matching (OR, 95% CI)

	ARAMIS[1]	SPARTAN[2] (before matching)	SPARTAN (after matching)
Any AE	1.49 (1.15-1.94)	2.01 (1.17-3.47)	1.52 (0.79-2.91)
Serious AE	1.32 (1.02-1.70)	1.10 (0.83-1.45)	1.20 (0.75-1.90)

1. Fizazi K, et al. *N Engl J Med*. 2019;380:1235-1246. 2. Smith MR, et al. *N Engl J Med*. 2018;378:1408-1418.

Probabilities of AE or SAE Were Comparable Between Treatments



OR (95% CrI), 1.02 (0.50-2.04)	OR (95% CrI), 0.91 (0.53-1.53)
Probability OR < 1, 48.2%	Probability OR < 1, 64.5%

Solid green line = weighted; dashed gray line = unweighted.

Limitations of the Analysis

- Matching could only be performed with characteristics reported in the ARAMIS trial
- Both trials are ongoing, and OS data remain immature, with a limited number of events

Conclusions

- Results suggest that patients with nmCRPC treated with APA + ADT had more favorable MFS, PFS, and PSA progression compared with those treated with DARO + ADT
- Results suggest a similar OS benefit between APA + ADT and DARO + ADT, but data are still immature
- Both treatments have a similar tolerability profile based on incidence of any AE or SAE

Acknowledgments

- The authors would like to thank the patients who participated in these studies and their families, as well as the investigators, study coordinators, study teams, and nurses
- The SPARTAN study was funded by Janssen Research & Development
- Writing assistance was funded by Janssen Global Services, LLC

Disclosures

- **S. Chowdhury** reports advisory roles for Clovis Oncology, Astellas Pharma, Bayer, Pfizer, and Janssen-Cilag; stock in Curve Life; speakers' bureau for Pfizer; honoraria from Clovis Oncology and Novartis; and research funding from Sanofi/Aventis and Clovis Oncology
- **S. Oudard** reports advisory roles for Pfizer, Bayer, Merck, Bristol-Myers Squibb, Novartis, Eisai, Sanofi, Janssen, and Astellas Pharma; travel from Pfizer, Bayer, Merck, Bristol-Myers Squibb, Novartis, and Eisai; honoraria from Pfizer, Bayer, Merck, Bristol-Myers Squibb, Novartis, Eisai, Sanofi, Astellas Pharma, and Janssen; and research funding from Ipsen and Sanofi
- **H. Uemura** reports advisory roles for Janssen Oncology, Bayer, Astellas, Sanofi, Takeda, and AstraZeneca, and honoraria from Daiichi Sankyo, Kyowa Hakko Kirin Co., Ltd., and Fujifilm-Toyama Chemical
- **S. Joniau** reports advisory roles and honoraria from Janssen, Astellas, Ipsen, Pfizer, Sanofi, and Bayer
- **J. Liu**, **L. Dearden**, **J. Sermon**, **S. Van Sanden**, and **J. Diels** are current or former employees of Janssen and hold/held stock in Johnson & Johnson
- **B.A. Hadaschik** reports advisory roles for Bayer, Lightpoint Medical, Inc., Janssen R&D, Bristol-Myers-Squibb, and Astellas; research funding from Profound Medical, German Cancer Aid, German Research Foundation, Janssen R&D, Bristol-Myers-Squibb, and Astellas; and travel from AstraZeneca, Janssen R&D, and Astellas