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Overall survival (OS) results of phase III ARAMIS study of darolutamide (DARO) added to androgen deprivation therapy (ADT) for nonmetastatic castration-resistant prostate cancer (nmCRPC).

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J Clin Oncol 38: 2020 (suppl; abstr 5514)

Background:

DARO is a structurally distinct androgen receptor inhibitor with a favorable safety profile, approved for treating men with nmCRPC after demonstrating significantly prolonged metastasis-free survival, compared with placebo (PBO), in the phase III ARAMIS trial: median 40.4 vs 18.4 months, respectively (HR 0.41; 95% CI 0.34–0.50; P<0.0001). We report final analyses of OS and prospectively collected, patient-relevant secondary endpoints, and updated safety results. Methods: 1509 patients (pts) with nmCRPC were randomized 2:1 to DARO 600 mg twice daily (n=955) or PBO (n=554) while continuing ADT. Secondary endpoints included OS, and times to pain progression, first cytotoxic chemotherapy, and first symptomatic skeletal event. The OS analysis was planned to occur after approximately 240 deaths. Secondary endpoints were evaluated in a hierarchical order.

Results: Final analysis was conducted after 254 deaths were observed (15.5% of DARO and 19.1% of PBO patients). After unblinding at the primary analysis, 170 pts crossed over from PBO to DARO. DARO showed a statistically significant OS benefit corresponding to a 31% reduction in the risk of death compared with placebo. All other secondary endpoints were significantly prolonged by DARO (Table), regardless of the effect of crossover and subsequent therapies on survival benefit. Incidences of treatment-emergent adverse events (AEs) with ≥5% frequency were generally comparable between DARO and PBO, similar to the safety profile observed at the primary analysis. Incidences of AEs of interest (including falls, CNS effects, and hypertension) were not increased with DARO compared with PBO when adjusted for treatment exposure. AEs in the crossover group were consistent with those for the DARO treatment arm. Conclusions: DARO showed a statistically significant OS benefit for men with nmCRPC. In addition, DARO delayed onset of cancer-related symptoms and subsequent chemotherapy, compared with PBO. With extended follow-up, safety and tolerability were favorable and consistent with the primary ARAMIS analysis (Fizazi et al, N Engl J Med 2019;380:1235-46). Clinical trial information: NCT02200614.

Endpoint (median, months)	DARO + ADT (n=955)	PBO + ADT (n=554)	HR (95% CI)	P-value
OS	NR	NR	0.69 (0.53–0.88)	0.003
Time to				
Pain progression	40.3	25.4	0.65 (0.53–0.79)	<0.001
First cytotoxic chemotherapy	NR	NR	0.58 (0.44–0.76)	<0.001
First SSE	NR	NR	0.48 (0.29–0.82)	0.005

Abstract Disclosures: https://coi.asco.org/Report/ViewAbstractCOI?id=295301

Overall Survival Results of the Phase III ARAMIS Study of Darolutamide Added to Androgen Deprivation Therapy for Non-metastatic Castration-Resistant Prostate Cancer

Abstract Number: 5514

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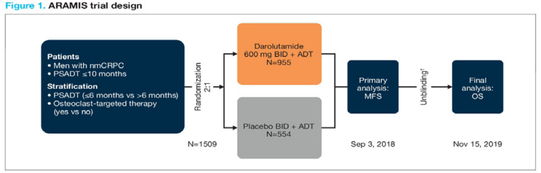
BACKGROUND

- Non-metastatic castration-resistant prostate cancer (nmCRPC) is defined as rising prostate-specific antigen (PSA) despite castrate levels of testosterone with ongoing androgen deprivation therapy (ADT), and no detectable metastases by conventional imaging.[1]
- Patients with nmCRPC are at risk of metastatic progression and cancer-specific mortality and morbidity.[2,3]
- The nmCRPC patient population is largely asymptomatic from their disease and still active in their daily life. They would benefit from treatments that prolong survival and delay disease progression, with minimal treatment-related adverse events (AEs), and that do not interfere with their quality of life.[4]
- Darolutamide is a structurally distinct androgen receptor inhibitor (ARI) approved for the treatment of men with nmCRPC.[5–7]
  - Darolutamide significantly prolonged metastasis-free survival (MFS) versus placebo by 22 months at the time of the primary analysis in the ARAMIS study (median MFS of 40.4 months with darolutamide vs 18.4 months with placebo; hazard ratio [HR] 0.41; 95% confidence interval [CI] 0.34–0.50; *P*<0.0001).[8]
  - Darolutamide had a favorable safety profile and was not associated with an increased incidence of most ARI-associated AEs (eg, falls, hypertension, and central nervous system [CNS]-related events).[8]
- Darolutamide shows low blood–brain barrier penetration in rodents, supported by a neuroimaging study in humans, which may be associated with a low risk of CNS adverse effects.[9–10]
- Darolutamide has a low potential for drug–drug interactions with medications commonly used to treat comorbidities in the nmCRPC patient population, such as calcium channel blockers, statins, and anticoagulants.[11]
  - Minimizing risks from drug interactions with polypharmacy is an important component of optimal management for patients with nmCRPC.
- We report here the pre-specified final analysis of the ARAMIS trial for overall survival (OS), all other secondary endpoints, and long-term safety.

METHODS

- ARAMIS was a double-blind, randomized, multicenter, global phase III trial to evaluate the efficacy and safety of darolutamide versus placebo in addition to ADT in men with nmCRPC (**Figure 1**).
- MFS was the primary endpoint.
- Secondary endpoints were OS, time to pain progression, time to first cytotoxic chemotherapy, and time to first symptomatic skeletal event (SSE).
  - The two-sided significance level of 0.05 for secondary endpoints was split between primary and final analysis, which were tested hierarchically based on OS (interim α=0.0002; final α=0.0498).
- Treatment-emergent AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
- The study was unblinded on November 30, 2018, following the positive results from the primary analysis for MFS.

Figure 1. ARAMIS trial design



[†]At unblinding, all patients in the placebo group discontinued study treatment. 170 of these patients then opted to receive open-label darolutamide.
ADT, androgen deprivation therapy; BID, twice daily; MFS, metastasis-free survival; nmCRPC, non-metastatic castration-resistant prostate cancer; OS, overall survival; PSADT, prostate-specific antigen doubling time.

RESULTS

- At data cut-off for final analysis (November 15, 2019), median follow-up was 29.1 months.
- 170 patients (31% of 554 randomized to placebo) crossed over from the placebo group to open-label darolutamide treatment after unblinding.
- 466 patients of 591 with ongoing darolutamide treatment at unblinding continued treatment with darolutamide during the open-label period.
- Median treatment duration was 25.8 months for patients randomized to darolutamide (double-blind and open-label periods), 11.0 months for crossover patients receiving darolutamide (open-label period), and 11.6 months for the patients receiving placebo during the double-blind period.
- More than half the patients in the placebo group received subsequent life-prolonging therapy as compared with 15% of patients randomized to darolutamide (**Table 1**).
  - This represents 29% of the patients who discontinued darolutamide and 56% of those who discontinued placebo treatment.

Table 1. First life-prolonging therapy in patients who discontinued study treatment

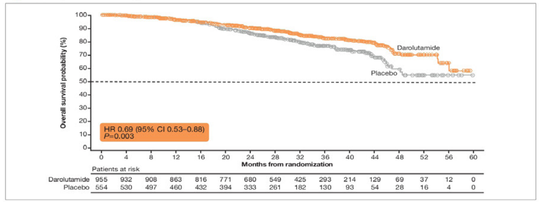
Patients, n (%)	Darolutamide (double-blind and open-label) (N=955)[†]	Placebo (double-blind and open-label) (N=554)
Discontinued study treatment	488 (51)	554 (100)
Ongoing with darolutamide treatment	466 (49)	147 (86)[‡]
Received subsequent life-prolonging therapy	141 (15)	309 (56)
Received life-prolonging therapy for CRPC		
Darolutamide	NA	170 (31)
Docetaxel	82 (9)	75 (14)
Abiraterone, abiraterone acetate	29 (3)	33 (6)
Enzalutamide	28 (3)	29 (5)
Sipuleucel-T	1 (0.1)	2 (0.4)
Cabazitaxel	1 (0.1)	0 (0)

[†]1 patient in the darolutamide group never received study treatment.
[‡]Percentage based on the number of patients who crossed over to receive darolutamide after the end of the double-blind period (n=170).
CRPC, castration-resistant prostate cancer; NA, not applicable.

Efficacy

- Final analysis was conducted after 254 deaths were observed (148/955=15.5% of patients receiving darolutamide and 106/554=19.1% of patients receiving placebo).
- Darolutamide was associated with a statistically significant 31% reduction in the risk of death compared with placebo (HR 0.69; 95% CI 0.53–0.88; two-sided *P*=0.003; **Figure 2**).
  - The OS rate at 3 years was 83% (95% CI 80–86%) in the darolutamide group and 77% (95% CI 72–81%) in the placebo group.
  - OS benefit was observed despite more than half of patients in the placebo group receiving subsequent darolutamide or other life-prolonging therapy.
- The treatment effect for OS consistently favored darolutamide in prespecified subgroups, although the confidence intervals in some subgroups with smaller sample size did cross 1.

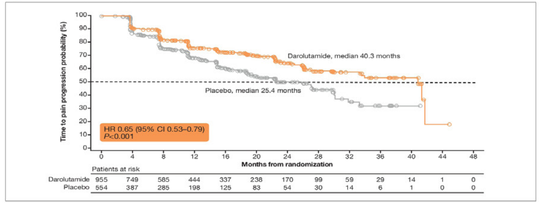
Figure 2. Kaplan–Meier analysis of overall survival



CI, confidence interval; HR, hazard ratio.

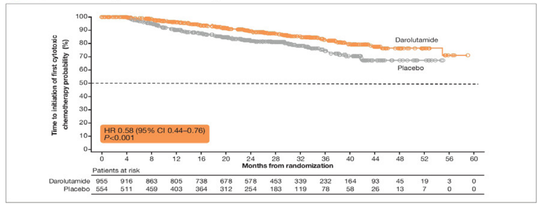
- Darolutamide also significantly delayed time to pain progression, time to first cytotoxic chemotherapy, and time to first SSE (**Figures 3–5**).
- All exploratory endpoints tested at this analysis favored darolutamide for delaying disease progression and additional treatment.
  - Time to first prostate cancer-related invasive procedure: HR 0.42 (95% CI 0.28–0.62); *P*<0.001.
  - Time to initiation of subsequent antineoplastic therapy: HR 0.36 (95% CI 0.27–0.48); *P*<0.001.

Figure 3. Time to pain progression†



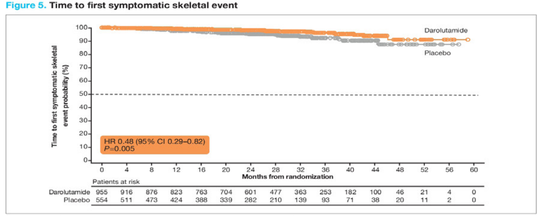
[†]Time to pain progression was evaluated using data from the primary analysis cut-off date of September 3, 2018.
All analyses for the placebo group include the 170 patients who crossed over to darolutamide treatment during the open-label study period.
CI, confidence interval; HR, hazard ratio.

Figure 4. Time to first cytotoxic chemotherapy



All analyses for the placebo group include the 170 patients who crossed over to darolutamide treatment during the open-label study period.
CI, confidence interval; HR, hazard ratio.

Figure 5. Time to first symptomatic skeletal event



All analyses for the placebo group include the 170 patients who crossed over to darolutamide treatment during the open-label study period.
CI, confidence interval; HR, hazard ratio.

Safety

- The safety profile of darolutamide at final analysis is consistent with the primary analysis reported previously (**Table 2**).
  - AEs of patients who received darolutamide after crossover from placebo were consistent with those in the darolutamide treatment arm.
- Incidences of AEs of interest known to be associated with ARIs continued to show small or no differences between the darolutamide and placebo groups (**Tables 3** and **4**).

Table 2. Overview of adverse events

Adverse event, n (%)	Darolutamide (double-blind) (N=954)	Placebo (double-blind) (N=554)	Placebo–darolutamide crossover (N=170)
Any grade adverse event	818 (85.7)	439 (79.2)	119 (70.0)
Grade 3 or 4 adverse event	251 (26.3)	120 (21.7)	27 (15.9)
Grade 5 adverse event	38 (4.0)	19 (3.4)	2 (1.2)
Serious adverse event	249 (26.1)	121 (21.8)	26 (15.3)
Adverse event leading to study drug discontinuation			
Any grade adverse event	85 (8.9)	48 (8.7)	8 (4.7)
Grade 3 or 4 adverse event	5 (0.5)	9 (1.6)	0

References

1. Gillessen S, et al. *Eur Urol*. 2020: Epub ahead of print.
2. Smith MR, et al. *J Clin Oncol*. 2013;31:3800–3806.
3. McKay R, et al. *Prostate Cancer Prostatic Dis*. 2017;20:276–282.
4. Mateo J, et al. *Eur Urol*. 2019;75:285–293.
5. Bayer HealthCare Pharmaceuticals, Inc. 2019. Nubeqa (darolutamide) US prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212099Orig1s000lbl.pdf. Accessed December 13, 2019.
6. Moilanen AM, et al. *Sci Rep*. 2015;5:12007.
7. Fizazi K, et al. *Lancet Oncol*. 2014;15:975–985.
8. Fizazi K, et al. *N Engl J Med*. 2019;380:1235–1246.
9. Williams S, et al. *J Clin Oncol*. 2020;38(suppl 6):abstr 326.
10. Zurth C, et al. *J Clin Oncol*. 2019;37(7_suppl):156.
11. Shore N, et al. *Targ Oncol*. 2019;14:527–539.

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Table 3. Incidence of adverse events of interest in the safety population during the double-blind study period

	Darolutamide (double-blind) (N=954)		Placebo (double-blind) (N=554)	
Adverse event	Any grade, n (%)	Grade 3 or 4, n (%)	Any grade, n (%)	Grade 3 or 4, n (%)
Fatigue	126 (13.2)	4 (0.4)	46 (8.3)	5 (0.9)
Bone fracture[†]	52 (5.5)	10 (1.0)	20 (3.6)	5 (0.9)
Falls (including accident)	50 (5.2)	9 (0.9)	27 (4.9)	4 (0.7)
Weight decreased (any event)	40 (4.2)	0	14 (2.5)	0
Asthenic conditions[‡]	38 (4.0)	2 (0.2)	17 (3.1)	2 (0.4)
Rash[§]	30 (3.1)	2 (0.2)	6 (1.1)	1 (0.2)
Seizure (any event)[‖]	2 (0.2)[‖]	0	1 (0.2)	0
Mental impairment disorders[¶]	19 (2.0)	3 (0.3)	10 (1.8)	0
Depressed mood disorders[¶]	21 (2.2)	1 (0.1)	10 (1.8)	0
Hypertension	74 (7.8)	33 (3.5)	36 (6.5)	13 (2.3)
Hot flush	57 (6.0)	0	25 (4.5)	0
Cardiac arrhythmias[5, #]	70 (7.3)	17 (1.8)	24 (4.3)	4 (0.7)
Coronary artery disorders[¶]	38 (4.0)	19 (2.0)	15 (2.7)	2 (0.4)
Heart failure[¶]	18 (1.9)	4 (0.4)	5 (0.9)	0

Median exposure in the double-blind period was 18.5 months for patients in the darolutamide group and 11.6 months for patients in the placebo group.
[†]Combined term comprising MedDRA terms of any fractures and dislocations, limb fractures and dislocations, skull fractures, facial bone fractures and dislocations, spinal fractures and dislocations, and thoracic cage fractures and dislocations.
[‡]Combined term comprising MedDRA terms of asthenic conditions, disturbances in consciousness, decreased strength and energy, malaise, lethargy, and asthenia.
[§]MedDRA labeling grouping, including preferred terms of rash, rash macular, rash maculo-papular, rash papular, and rash pustular.
[‖]One additional incidence of seizure occurred in the darolutamide group during the open-label period, in a patient with a history of epilepsy.
[¶]MedDRA High Level Group term.
[#]Although the incidence of the adverse event of cardiac arrhythmias was higher with darolutamide than with placebo, medical history of cardiac arrhythmia and electrocardiogram abnormalities were both present to a greater extent in the darolutamide group at baseline, as observed at primary analysis.
MedDRA, Medical Dictionary for Regulatory Activities.

Table 4. Exposure-adjusted incidence rate for adverse events of interest in the safety population during the double-blind study period

	EAIR for any grade (per 100 subject-years)	
Adverse event	Darolutamide (N=954)	Placebo (N=554)
Fatigue	8.3	7.4
Bone fracture[†]	3.4	3.2
Falls (including accident)	3.3	4.3
Weight decreased (any event)	2.6	2.2
Asthenic conditions[‡]	2.5	2.7
Rash[§]	2.0	1.0
Seizure (any event)[‖]	0.1	0.2
Mental impairment disorders[¶]	1.3	1.6
Depressed mood disorders[¶]	1.4	1.6
Hypertension	4.9	5.8
Hot flush	3.8	4.0
Cardiac arrhythmias[5, #]	4.6	3.8
Coronary artery disorders[¶]	2.5	2.4
Heart failure[¶]	1.2	0.8

Median exposure in the double-blind period was 18.5 months for patients in the darolutamide group and 11.6 months for patients in the placebo group.
[†]Combined term comprising MedDRA terms of any fractures and dislocations, limb fractures and dislocations, skull fractures, facial bone fractures and dislocations, spinal fractures and dislocations, and thoracic cage fractures and dislocations.
[‡]Combined term comprising MedDRA terms of asthenic conditions, disturbances in consciousness, decreased strength and energy, malaise, lethargy, and asthenia.
[§]MedDRA labeling grouping, including preferred terms of rash, rash macular, rash maculo-papular, rash papular, and rash pustular.
[‖]One additional incidence of seizure occurred in the darolutamide group during the open-label period, in a patient with a history of epilepsy.
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[#]Although the incidence of the adverse event of cardiac arrhythmias was higher with darolutamide than with placebo, medical history of cardiac arrhythmia and electrocardiogram abnormalities were both present to a greater extent in the darolutamide group at baseline, as observed at primary analysis.
EAIR, exposure-adjusted incidence rate; MedDRA, Medical Dictionary for Regulatory Activities.

CONCLUSIONS

- Darolutamide significantly improved OS versus placebo in men with nmCRPC.
  - 31% reduction in risk of death: HR 0.69 (95% CI 0.53–0.88); *P*=0.003.
- Darolutamide significantly delayed the onset of cancer-associated morbidity and subsequent chemotherapy versus placebo.
  - Time to pain progression, subsequent chemotherapy, and SSE were all significantly prolonged versus placebo.
- With extended follow-up, the safety profile of darolutamide was favorable and consistent with the primary analysis previously reported.
  - Incidences of most ARI-associated AEs were not increased with darolutamide versus placebo, taking treatment exposure into account.
- These results provide further compelling evidence for early darolutamide treatment in men with nmCRPC.

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