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Original Research

Effect of crossover from placebo to darolutamide on overall survival in men with non-metastatic prostate cancer: sensitivity analyses from the randomised phase 3 ARAMIS study

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ABSTRACT

Background: In the phase 3 ARAMIS study (NCT02200614), darolutamide significantly improved metastasis-free survival in patients with non-metastatic castration-resistant prostate cancer (nmCRPC). Following the primary analysis, the study was unblinded, and placebo recipients were permitted to cross over to open-label darolutamide. Despite crossover, darolutamide significantly improved overall survival (OS). We conducted sensitivity analyses to estimate the effect of placebo–darolutamide crossover on OS.

Methods: Patients with nmCRPC were randomised to oral darolutamide 600 mg twice daily ($n = 955$) or placebo ($n = 554$). Prespecified (rank-preserving structural failure time [RPSFT] and iterative parameter estimation [IPE]) and post hoc (OS-adjusted censoring and inverse probability of censoring weighting [IPCW], with weightings for baseline testosterone and prostate-specific antigen) sensitivity analyses were conducted.

Results: After unblinding, 170 of 554 placebo recipients (30.7%) crossed over to darolutamide. At the final OS intention-to-treat analysis (median 11.2 months after unblinding), darolutamide significantly improved OS by 31% versus placebo (hazard ratio [HR] 0.69, 95% confidence interval [CI] 0.53–0.88; $P = 0.003$). The benefit increased in the analyses adjusting for crossover is as follows: RPSFT HR 0.68, 95% CI 0.51–0.90; $P = 0.007$; IPE HR 0.66, 95% CI 0.51–0.84; $P < 0.001$; OS-adjusted censoring HR 0.59, 95% CI 0.45–0.76; IPCW HR 0.63, 95% CI 0.48–0.81. The favourable safety profile of darolutamide was maintained, including in crossover patients.

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Conclusions: After adjusting for crossover, darolutamide reduced the risk of death by up to 41% in patients with nmCRPC. The effect of darolutamide on OS may have been underestimated in the original intention-to-treat analysis.

1. Introduction

Darolutamide is a structurally distinct and highly potent androgen receptor inhibitor approved for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) based on the results from the phase 3 Androgen Receptor Antagonizing Agent for Metastasis-free Survival (ARAMIS) study [1–4]. At the primary ARAMIS analysis, which was conducted after a median follow-up of 17.9 months, the median metastasis-free survival (MFS) was 40.4 months in the darolutamide group and 18.4 months in the placebo group (hazard ratio [HR] 0.41, 95% confidence interval [CI] 0.34–0.50; $P < 0.001$) [3]. The study was unblinded after darolutamide was found to be superior to placebo in the primary analysis. Patients in the placebo group who were still taking study treatment at that point were permitted to cross over to treatment with darolutamide [4]. Subsequently, the final overall survival (OS) analysis showed that darolutamide reduced the risk of death by 31% relative to placebo (HR 0.69, 95% CI 0.53–0.88; $P = 0.003$) [4].

In clinical trials in oncology, crossover allowance is a common feature that permits patients to switch from the control group to an experimental treatment group if clinical superiority is established in the experimental group [5]. A comprehensive analysis of clinical trials in oncology showed that, between 1 January 1990 and 1 January 2019, 30 randomised phase 3 clinical trials incorporating crossover allowance were published [5]. This total included five interventional clinical trials involving patients with prostate cancer, in which 8–66% of patients crossed over to the superior therapy when permitted [5].

By granting all patients prompt access to the superior therapy, crossover allowance fulfils ethical requirements; however, it confounds subsequent analyses of long-term endpoints, such as OS, because the patients who crossed over will have received both the inferior and the superior treatments [5]. Thus, crossover leads to statistical challenges with intention-to-treat (ITT) analyses because it effectively results in an estimate of an immediate experimental treatment compared with a deferred experimental treatment rather than immediate experimental treatment versus no treatment [6]. Estimates of efficacy and cost-effectiveness based on these studies may be imprecise if the crossover is not corrected for [7]. For this reason, sensitivity analyses are performed to compensate for crossover bias. The present analysis aims to address the impact of placebo–darolutamide crossover on OS estimates in the ARAMIS study.

2. Methods

ARAMIS (ClinicalTrials.gov number NCT02200614) was a randomised, double-blind, placebo-controlled, phase 3 clinical study in which patients with nmCRPC and a prostate-specific antigen (PSA) doubling time of 10 months or less were randomised in the ratio of 2:1 to receive oral darolutamide 600 mg twice daily or matching placebo while continuing standard androgen-deprivation therapy. The study design, baseline characteristics, primary MFS results and final OS results have been published previously [3,4]. The trial protocol is available at https://clinicaltrials.gov/ProvidedDocs/14/NCT02200614/Prot_002.pdf.

The primary analysis of MFS was conducted in September 2018 when metastasis or death had been documented in 437 patients, after which the study was unblinded. All patients still receiving darolutamide or placebo were offered the opportunity to receive open-label treatment with darolutamide. The final analysis of OS was conducted in November 2019.

Four sensitivity analyses were conducted to estimate and potentially adjust for the bias introduced by crossover, two of which were prespecified in the protocol. Prespecified crossover adjustment methods were rank-preserving structural failure time (RPSFT) [8] and iterative parametric estimation (IPE) [9]. Both methods involve construction of a Kaplan–Meier curve that is intended to resemble the curve for the placebo group if crossover to darolutamide had not occurred. RPSFT uses a grid search, whereas IPE iteratively determines the model parameter describing the treatment effect size.

In addition, two post hoc sensitivity analyses were conducted. These involved censoring placebo-randomised patients at crossover and inverse probability of censoring weighting (IPCW). With IPCW, patients are censored at the time of switching, and data from patients with similar prognoses (based on baseline characteristics, in this case, PSA and testosterone levels) who were not censored are given a higher weighting to replace the information loss from censoring in the overall data set. This method rests on the assumption that there are no unmeasured confounders [7].

3. Results

In total, 1509 men who were randomised to receive darolutamide ($n = 955$) or placebo ($n = 554$) were included in the primary analysis. The study was unblinded in November 2018 after the primary analysis. At that time, 170 patients who were still receiving placebo (30.7%) elected to cross over to receive treatment with open-label darolutamide (Fig. 1). At the time of the final analysis of OS (data cutoff date of 15 November 2019), the median duration of follow-up was 29.0 months overall and 11.2 months from unblinding.

By the final OS analysis, 254 patients had died, including 148 patients (15.5%) randomised to darolutamide and 106 patients (19.1%) randomised to placebo. In the ITT analysis, which included data from the double-blind and crossover phases of the trial, darolutamide treatment was associated with significant improvement in OS compared with placebo: HR 0.69, 95% CI 0.53–0.88; $P = 0.003$. This survival benefit was achieved even though 307 patients (55%) randomised to placebo compared with 141 patients (15%) randomised to darolutamide received subsequent life-prolonging therapy for castration-resistant prostate cancer. In the group randomised to placebo, as well as the 170 patients (31%) who crossed over to receive darolutamide, 75 (14%) received docetaxel, 33 (6%) received abiraterone acetate + prednisone , 29 (5%) received enzalutamide and two (<1%) received sipuleucel-T [4]. Subsequent therapies in patients randomised to darolutamide included docetaxel in 82 (9%), abiraterone acetate + prednisone in 29 (3%), enzalutamide in 28 (3%), sipuleucel-T in one (<1%) and cabazitaxel in one (<1%) [4].

3.1. Sensitivity analyses

The four sensitivity analyses indicate that crossing over to placebo may have affected the final estimate of OS (Fig. 2). The protocol-specified analyses suggest that the reduction in the risk of death attributable to darolutamide would be slightly larger if crossover had not occurred: 32% risk reduction in the RPSFT analysis (HR 0.68, 95% CI 0.51–0.90) and 34% risk reduction in the IPE analysis (HR 0.66, 95% CI 0.51–0.84).

The results of the post hoc sensitivity analyses are consistent with the protocol-specified analyses, although the estimates differ by varying degrees towards lower HRs compared with the primary analysis. The censoring at crossover analysis suggests that the risk of death would have been 41% lower in darolutamide recipients compared with placebo

recipients if crossover had not occurred (HR 0.59, 95% CI 0.45–0.76). The IPCW analysis, which included weightings of patients based on baseline testosterone and PSA levels, suggests that the risk of death would have been 37% lower (HR 0.63, 95% CI 0.48–0.81).

3.2. Safety

Given the shorter treatment exposure, the incidence of adverse events (AEs) during darolutamide treatment in patients who crossed over from placebo was lower than in patients randomised to darolutamide during the double-blind treatment phase (Table 1). Of note, the incidence of AEs commonly associated with androgen receptor inhibitor therapy remained lower in patients who crossed over to darolutamide than in the overall placebo group.

4. Discussion

We conducted sensitivity analyses to assess the impact of placebo–darolutamide crossover on OS in 170 (30.7%) of the 554 patients assigned to placebo at the beginning of the study. In the unadjusted ITT analysis of OS, in which these individuals were analysed as if they had never received darolutamide, the risk of death was significantly reduced by 31% (HR 0.69) in the darolutamide group relative to the placebo group. All four sensitivity analyses showed that crossover from placebo to darolutamide affected the estimate of the treatment effect, with lower HRs for OS, ranging from 0.59 to 0.68 (32–41% risk reduction). The protocol-specified, time-to-failure model-based methods yielded results (HR 0.68, 95% CI 0.51–0.90, with RPSFT; HR 0.66, 95% CI 0.51–0.84, with IPE) that were closer to those of the unadjusted analysis than were the results from the post hoc censoring-based methods (HR 0.59, 95% CI 0.45–0.76, with naive censoring; HR 0.63, 95% CI 0.48–0.81, with IPCW censoring).

At the final ARAMIS analysis, the safety profile of darolutamide remained favourable, and AE incidences in patients who switched were consistent with those in the original treatment groups. Lower AE incidences observed in the crossover group compared with the group randomised to darolutamide reflect the shorter exposure to darolutamide in the crossover group. No unexpected findings were observed in patients who crossed over from placebo to darolutamide.

Other randomised, placebo-controlled, phase 3 studies of androgen receptor inhibitors in nmCRPC allowed crossover from placebo after the primary MFS endpoint was met. Therefore, OS analyses of the placebo arms also included some patients who received open-label active drug [10–13]. In the PROSPER study, treatment with enzalutamide reduced the risk of death by 27% compared with placebo (HR 0.73, 95% CI 0.61–0.89; $P = 0.001$) [13]. In the placebo group, 87 of 465 patients (19%) crossed over to receive enzalutamide for a median of 14.5 months before the survival analysis [13]. To account for crossover, a sensitivity analysis of PROSPER data was carried out using RPSFT modelling, which indicated minimal difference from the base case (HR 0.72, 95% CI 0.60–0.87) [14]. In contrast, in the SPARTAN study, in which treatment with apalutamide reduced the risk of death by 25% compared with placebo in the unadjusted ITT analysis (HR 0.75, 95% CI 0.59–0.96; $P = 0.0197$), the benefit was greater in sensitivity analyses accounting for 76 of 398 patients (19%) who crossed over from placebo to apalutamide using naive censoring (HR 0.68, 95% CI 0.54–0.87) and IPCW censoring methods (HR 0.68, 95% CI 0.53–0.87) [12]. Similar to our findings, naive censoring and IPCW censoring resulted in lower HRs compared with RPSFT and IPE analyses.

Sensitivity analyses such as those used in the present analyses have limitations. The assumption of a common treatment effect for earlier and later start of treatment is a potential limitation of RPSFT and IPE, which this study cannot verify [15]. Censoring at crossover can remove a significant duration of survival time from placebo recipients who crossed over, thereby introducing an unfavourable bias to the placebo arm. This may be concluded from the HR estimates obtained with the sensitivity analysis methods in the present analysis. The assumption that there are no unmeasured confounders is a limitation of IPCW; if all relevant confounders have not been considered, OS estimates will likely be biased. In addition, bias may be introduced if there are not enough uncensored patients in the placebo group similar to those who crossed over.

Regardless of the method for assessing sensitivity, any analysis of crossover is subject to selection bias. Only a limited number of patients

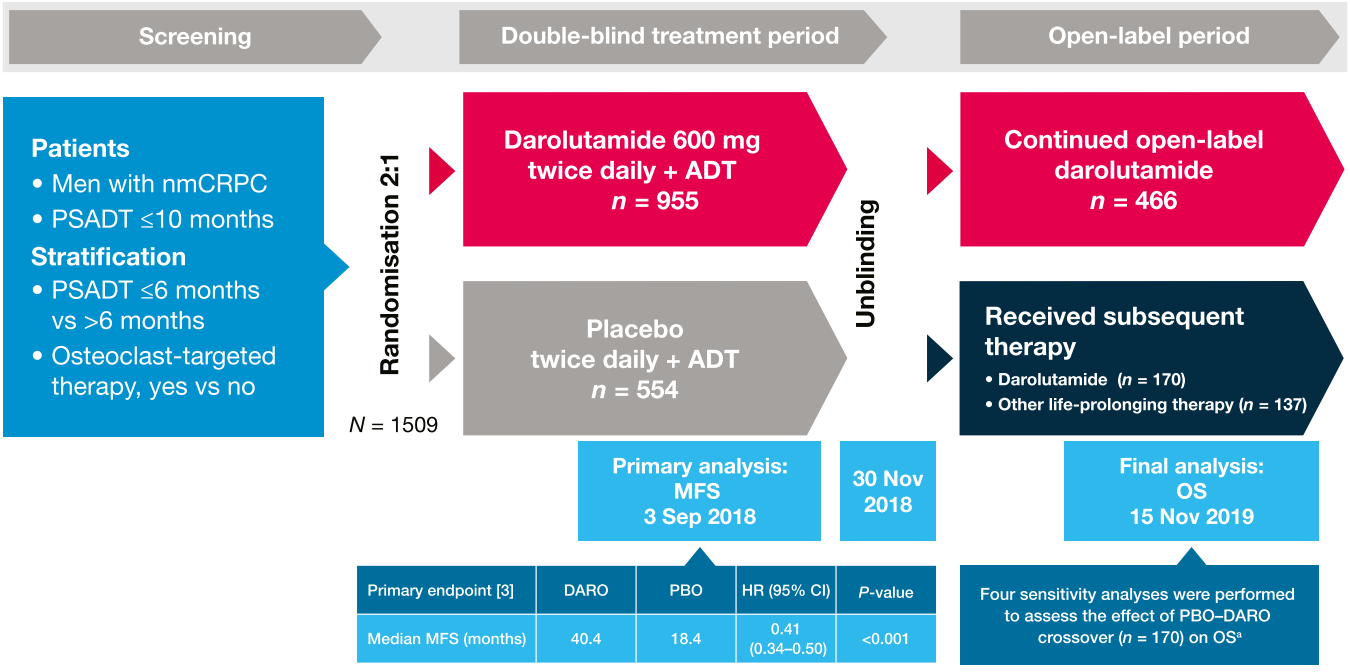

Fig. 1. Study design and patient flow. [a] The median treatment duration from unblinding to final data cutoff was 11 months. ADT, androgen-deprivation therapy; CI, confidence interval; DARO, darolutamide; HR, hazard ratio; MFS, metastasis-free survival; nmCRPC, non-metastatic castration-resistant prostate cancer; OS, overall survival; PBO, placebo; PSADT, prostate-specific antigen doubling time.

remained in the study at the point of unblinding and were eligible to cross over from placebo to darolutamide. Moreover, the mean duration of treatment with darolutamide was shorter in patients who crossed over than were originally randomised to darolutamide. Thus, no conclusions should be drawn regarding preferences for early versus late initiation of treatment with darolutamide. Nevertheless, suboptimal treatment of nmCRPC can result in rising PSA levels and shortened PSA doubling time, which are associated with more rapid metastatic progression [16]. Therefore, early initiation of combination treatment for nmCRPC with androgen-deprivation therapy and an androgen receptor inhibitor could reduce the risk of disease progression. This hypothesis needs to be examined in appropriately designed prospective clinical trials.

In conclusion, compared with placebo, darolutamide significantly improved OS in the ARAMIS ITT analysis, even though 30.7% of patients originally assigned to placebo crossed over to receive darolutamide during the study. The sensitivity analyses adjusting for crossover consistently showed OS HR estimates that were at least as favourable to darolutamide versus placebo as the ITT analysis, suggesting that the original OS analysis may have underestimated the benefit of darolutamide. These findings confirm that darolutamide is an effective and well-tolerated androgen receptor inhibitor when used as an early treatment option in patients with nmCRPC. A plain language summary of this report is available online in the supplementary appendix of this article.

Data sharing statement

Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA 'Principles for responsible clinical trial data sharing. 'This pertains to scope, time point and process of data access.

As such, Bayer commits to sharing upon request from qualified

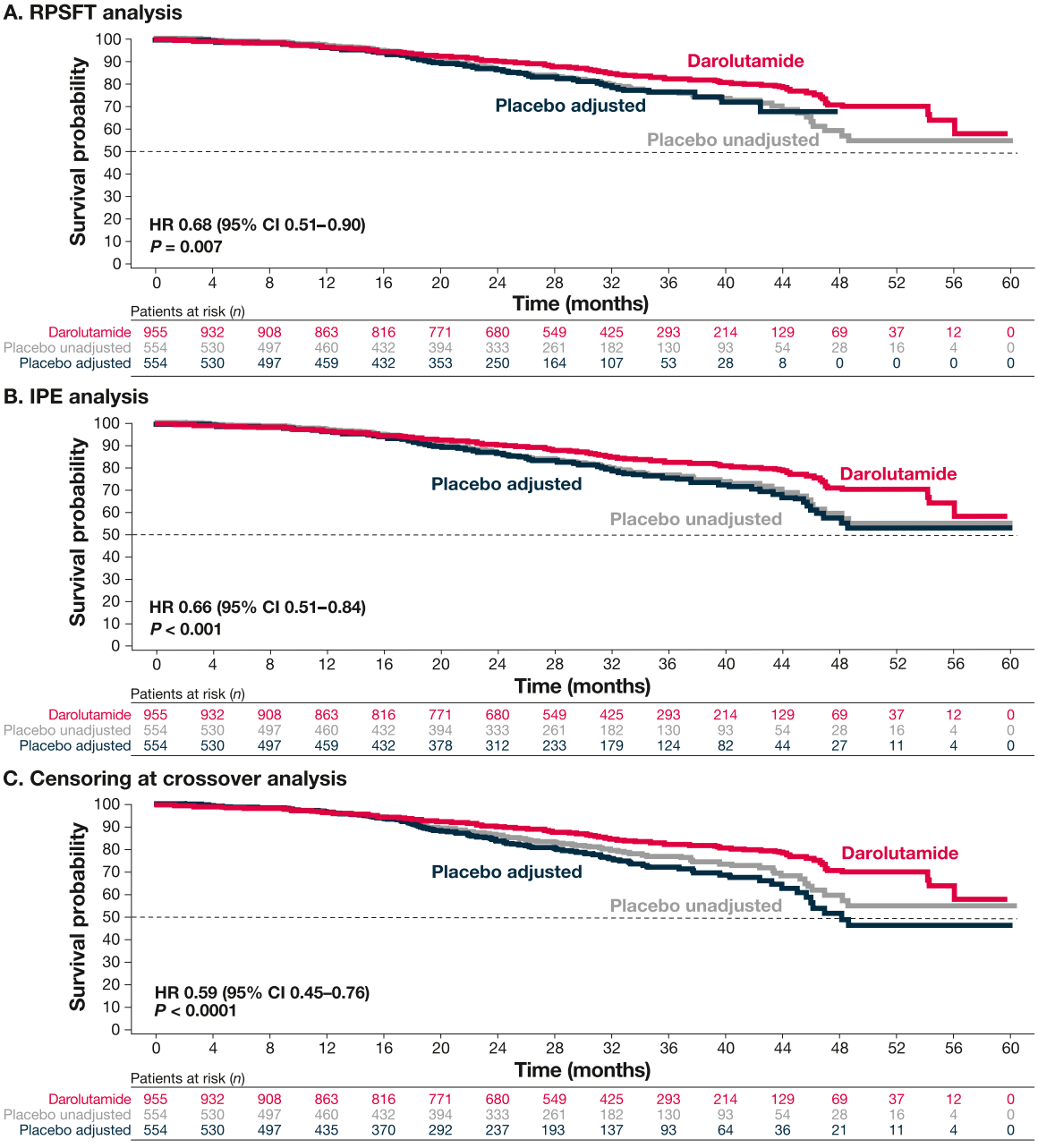

Fig. 2. Overall survival analyses: (A) RPSFT; (B) IPE; (C) censoring at crossover. CI, confidence interval; HR, hazard ratio; IPE, iterative parameter estimation; OS, overall survival; RPSFT, rank-preserving structural failure time.

Table 1
Adverse events (safety analysis set).

AEs, *n* (%)	Double-blind treatment phase		Placebo–darolutamide crossover after unblinding ($n = 170$)
	Darolutamide ($n = 954$[a])	Placebo ($n = 554$)	
Any treatment-emergent AE	818 (85.7)	439 (79.2)	119 (70.0)
Serious AE	249 (26.1)	121 (21.8)	26 (15.3)
CTCAE grade 3/4[b]	251 (26.3)	120 (21.7)	27 (15.9)
AEs leading to permanent discontinuation of treatment	85 (8.9)	48 (8.7)	8 (4.7)
AEs commonly associated with androgen receptor inhibitor therapy			
Fatigue	126 (13.2)	46 (8.3)	7 (4.1)
Falls	50 (5.2)	27 (4.9)	4 (2.4)
Fracture[c]	52 (5.5)	20 (3.6)	5 (2.9)
Rash[d]	30 (3.1)	6 (1.1)	4 (2.4)
Mental impairment disorder[e]	19 (2.0)	10 (1.8)	0
Hypertension	74 (7.8)	36 (6.5)	3 (1.8)

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities.

[a] One patient randomised to darolutamide never received treatment and was therefore not included in the safety analysis set.

[b] Treatment-emergent AEs were graded according to CTCAE v4.03.

[c] This category combines the following MedDRA v20.0 terms: any fractures and dislocations, limb fractures and dislocations, pelvic fractures, skull fractures, facial bone fractures and dislocations, spinal fractures and dislocations, and thoracic cage fractures and dislocations.

[d] This category combines the following MedDRA terms: rash, macular rash, maculopapular rash, papular rash, pustular rash, erythema and dermatitis.

[e] This category is a MedDRA High-Level Group Term.

scientific and medical researchers patient-level clinical trial data, study-level clinical trial data and protocols from clinical trials in patients for medicines and indications approved in the US and EU as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after 1 January 2014.

Interested researchers can use www.vivli.org to request access to anonymised patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the member section of the portal.

Data access will be granted to anonymised patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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CRediT authorship contribution statement

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113342.

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