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Darolutamide Alone and in Combination With Goserelin in Androgen Receptor–Positive Salivary Gland Carcinoma: Results From the Phase II DISCOVARY Trial

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ABSTRACT

PURPOSE Salivary gland carcinoma (SGC), particularly salivary duct carcinoma (SDC), is a rare and aggressive malignancy with no standard systemic treatment. Androgen receptor (AR) expression is frequently detected in SDC, which suggests inhibition of the AR pathway as a therapeutic strategy. We conducted a prospective phase II trial of the efficacy and safety of darolutamide, a second-generation AR signaling inhibitor, as monotherapy or in combination with goserelin, in patients with AR-positive unresectable locally advanced (LA) or recurrent/metastatic (R/M) SGC.

METHODS DISCOVARY was a multicenter, single-arm, phase II trial conducted in Japan. Patients with unresectable LA or R/M AR-positive SGC were enrolled into two sequential cohorts, a monotherapy cohort (darolutamide 600 mg orally twice daily) and a combination cohort (darolutamide plus goserelin 3.6 mg subcutaneously once every 28 days). The primary end point was objective response rate (ORR). Secondary end points included progression-free survival (PFS), overall survival (OS), safety, and health-related quality of life.

RESULTS Fifty-seven patients were enrolled (monotherapy, n = 24; combination, n = 33). In the monotherapy cohort, the confirmed ORR was 8.3% (90% CI, 1.5 to 24.0) and the median PFS was 5.7 months. In the combination cohort, ORR was 45.2% (90% CI, 29.7 to 61.3) and the median PFS was 13.1 months. Twelve-month OS rates were 91.3% and 87.0%, respectively. Most adverse events were grade 1 or 2 in severity, with no treatment-related deaths. Quality of life was preserved. No clear association between AR expression level or Ki-67 index and treatment response was evident in exploratory analysis.

CONCLUSION Darolutamide demonstrated antitumor activity in AR-positive SGC, with numerically more favorable outcomes with goserelin. Darolutamide plus goserelin may represent a chemotherapy-sparing option in this rare malignancy.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

Salivary gland carcinomas (SGCs) are rare and heterogeneous epithelial malignancies which account for approximately 5%-7% of head and neck cancers.[1,2] Salivary duct carcinoma (SDC) is an aggressive subtype.[3,4] Patients with unresectable locally advanced (LA) or recurrent/metastatic (R/M) SDC have a poor prognosis, with median overall survival (OS) typically under 2 years.[5,6] In the absence of approved systemic therapies, cytotoxic chemotherapy remains a mainstay of treatment, although efficacy is modest and toxicity is substantial.[7] Human epidermal growth factor receptor 2 (HER2) overexpression or amplification is also present in a clinically relevant subset of SDC, and HER2-directed therapy, including HER2-targeted regimens and antibody-drug conjugates, is an important option in eligible patients and an important consideration in treatment sequencing.[8-10]

Androgen receptor (AR) expression is observed in approximately 70%-90% of SDCs.[11] However, AR-targeted monotherapy has shown limited efficacy. First-generation antiandrogens and second-generation AR signaling inhibitors, including enzalutamide, have shown low response rates and modest progression-free survival (PFS), whereas luteinizing hormone–releasing hormone (LHRH) agonist monotherapy has also yielded suboptimal outcomes.[12,13] In

CONTEXT

Key Objective

Can combined androgen blockade with darolutamide plus goserelin address an unmet need in advanced androgen receptor–positive salivary gland carcinoma?

Knowledge Generated

Darolutamide plus goserelin produced clinically meaningful and durable antitumor activity while maintaining a favorable safety profile and preserving health-related quality of life.

Relevance *(J.W. Friedberg)*

With the limitations of the phase II design and inherent challenges with cross-trial comparisons, these promising results expand the therapeutic armamentarium for this rare disease.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.

contrast, combined androgen blockade (CAB) using an AR antagonist plus an LHRH agonist has shown more favorable activity in phase II studies[7,14,15] Nonetheless, first-generation antiandrogens provide incomplete AR pathway inhibition, supporting evaluation of more potent AR signaling inhibitors.[16]

Darolutamide is a second-generation nonsteroidal AR signaling inhibitor with high AR-binding affinity and minimal blood-brain barrier penetration.[17] Phase III trials in prostate cancer have demonstrated its efficacy and tolerability in combination with androgen-deprivation therapy[7,18,19] CAB using darolutamide may therefore achieve more comprehensive suppression of both ligand-dependent and ligand-independent AR signaling.[20]

Despite these favorable characteristics, darolutamide has not been prospectively evaluated in SGC and its clinical activity remains unclear, either alone or in combination with androgen deprivation. To address this unmet need, we conducted the DISCOVARY trial, a prospective, multicenter, phase II study that evaluated darolutamide as monotherapy and in combination with goserelin in patients with AR-positive unresectable LA or R/M SGC. This two-cohort design enabled prospective evaluation of two AR-targeted approaches developed sequentially rather than as a single comparative study, and cross-cohort comparisons were not prespecified for formal inference.

METHODS

Study Design and Patients

DISCOVARY was a prospective, open-label, multicenter, phase II study conducted at 12 institutions in Japan to evaluate the efficacy and safety of darolutamide, administered either as monotherapy or as CAB with goserelin, in patients with AR-positive SGC.

The trial used a sequential, nonrandomized two-cohort design: a darolutamide monotherapy cohort (April 2020-February 2021) and a darolutamide plus goserelin cohort (October 2022-August 2023). The cohorts were developed sequentially rather than as a single comparative design; therefore, cross-cohort comparisons were descriptive and exploratory only (Data Supplement, Fig S1, online only). Additional details on the cohort design and end point assessment are provided in the Data Supplement.

The study was approved by the institutional review boards of all participating centers and conducted in accordance with the Declaration of Helsinki and Japanese Good Clinical Practice guidelines. All patients provided written informed consent. The trial was registered at ClinicalTrials.gov (identifier: NCT05694819).

Eligibility Criteria

Eligible patients were adults (≥20 years) with histologically confirmed SGC. In the monotherapy cohort, eligible histologic subtypes were limited to SDC, adenocarcinoma not otherwise specified, or carcinoma ex pleomorphic adenoma, confirmed by institutional histopathologic review; cytologic or frozen-section diagnoses were not permitted. For patients diagnosed externally, pathology reports and available slides were reviewed at participating institutions. In the combination cohort, patients with AR-positive tumors determined by local immunohistochemistry (IHC) were eligible regardless of the histologic subtype; subsequent central AR assessment did not affect enrollment.

All patients were required to have unresectable LA or R/M disease not amenable to curative treatment, at least one measurable lesion per RECIST v1.1, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2, and adequate organ function. Prior treatment with AR inhibitors,

CYP17 inhibitors, or GnRH analogs or other ADT was not permitted.

For the monotherapy cohort, AR positivity was centrally confirmed before enrollment using IHC with a predefined cutoff of ≥1% nuclear staining. In contrast, AR status in the combination cohort was assessed locally without a uniform cutoff, reflecting routine clinical practice. Available tumor specimens, including primary tumors and R/M lesions, were eligible for AR assessment. All combination cohort samples subsequently underwent retrospective central AR testing using the same IHC methodology and cutoff as part of a preplanned concordance analysis.

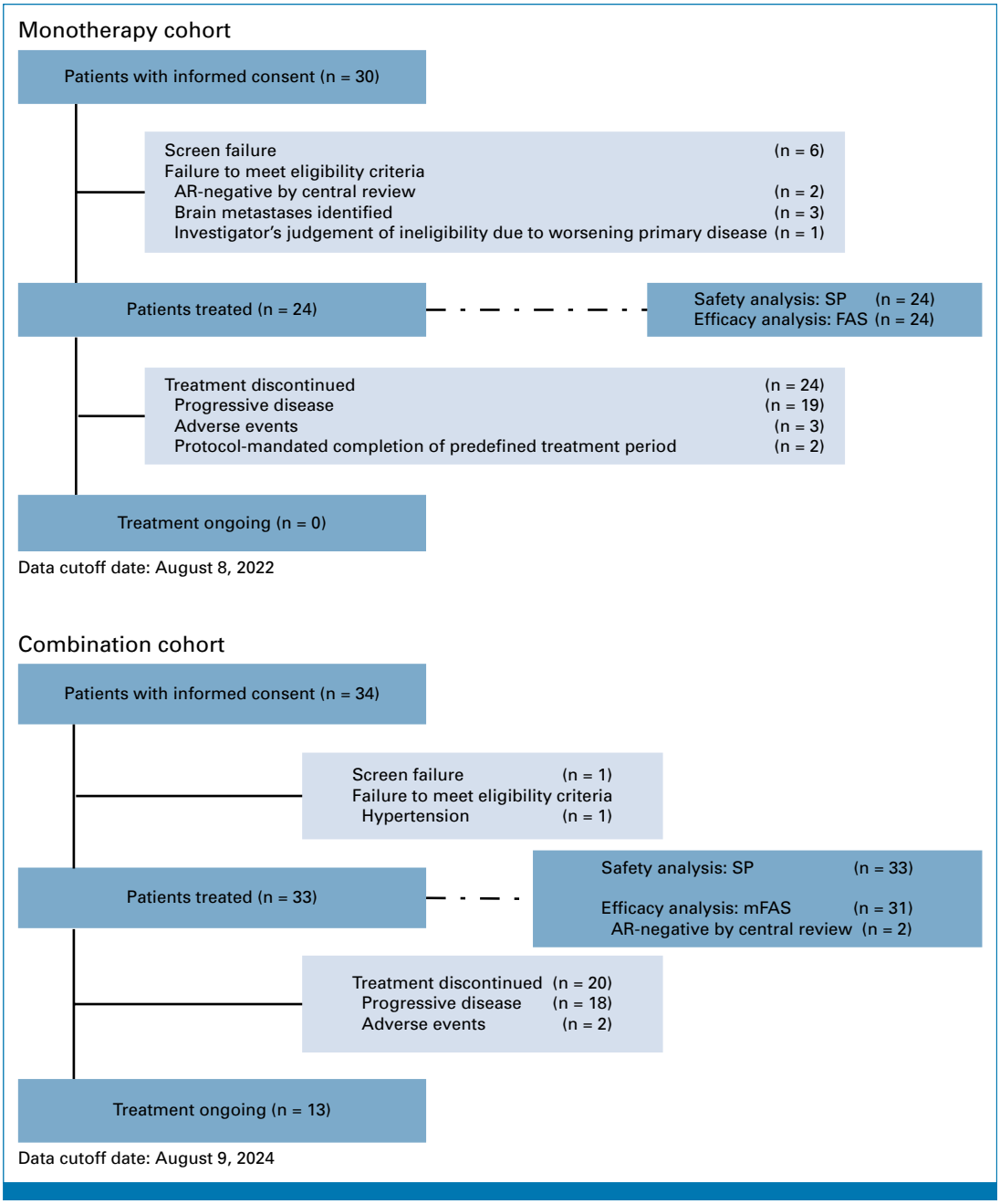

FIG 1. Flow diagram of patient enrollment and disposition. Of the 57 patients enrolled, 24 received darolutamide monotherapy and 33 received CAB. Two CAB patients were AR-negative by central review and excluded from the mFAS. Data cutoff: August 8, 2022, for the monotherapy cohort, and August 9, 2024, for the combination cohort. Two patients in the monotherapy cohort discontinued protocol treatment because of protocol-mandated completion of the predefined treatment period; both were censored in the PFS analysis. AR, androgen receptor; CAB, combined androgen blockade; mFAS, modified full analysis set; PFS, progression-free survival; SP, safety population.

TABLE 1. Baseline Patient Characteristics

Characteristic	Monotherapy (n = 24)	Combination (n = 33)
Age, median (range)	67.0 (35-79)	63.0 (40-84)
Sex, No. (%)		
Male	23 (95.8)	26 (78.8)
Female	1 (4.2)	7 (21.2)
PS, No. (%)		
0	18 (75.0)	28 (84.8)
1	6 (25.0)	4 (12.1)
2	0 (0.0)	1 (3.0)
Histology, No. (%)		
SDC	16 (66.7)	32 (97.0)
AC, NOS	4 (16.7)	1 (3.0)
Carcinoma ex PA	4 (16.7)	0 (0.0)
AR positivity, No. (%)		
<70%	1 (4.2)	4 (12.1)
≥70%	23 (95.8)	29 (87.9)
Locoregional, No. (%)		
−	20 (83.3)	27 (81.8)
+	4 (16.7)	6 (18.2)
Metastasis, No. (%)		
−	1 (4.2)	3 (9.1)
+	23 (95.8)	30 (90.9)
Metastatic site, No. (%)		
Lung	18 (75.0)	25 (75.8)
Liver	4 (16.7)	6 (18.2)
Bone	5 (20.8)	7 (21.2)
Skin	1 (4.2)	1 (3.0)
Proximal LN	16 (66.7)	23 (69.7)
Distal LN	10 (41.7)	14 (42.4)
Others	5 (20.8)	6 (18.2)
Primary site, No. (%)		
Parotid gland	16 (66.7)	22 (66.7)
Submandibular gland	7 (29.2)	10 (30.3)
Minor salivary gland	1 (4.2)	1 (3.0)
Previous treatment, No. (%)		
Surgery	20 (83.3)	23 (69.7)
Radiation	17 (70.8)	22 (66.7)
Systemic therapy[a]	15 (62.5)	14 (42.4)

NOTE. Demographic and clinical characteristics of patients in the monotherapy (n = 24) and combination (n = 33) cohorts. Variables included age, sex, ECOG PS, histology, AR positivity, locoregional recurrence, distant metastasis, metastatic sites, primary tumor site, and previous treatment. Baseline characteristics are presented descriptively; no formal between-cohort statistical testing was planned.

Abbreviations: AC, adenocarcinoma; AR, Androgen receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; LA, locally advanced; LN, lymph node; NOS, not otherwise specified; PA, pleomorphic adenoma; R/M, recurrent/metastatic; SDC, salivary duct carcinoma.

[a]Systemic therapy includes prior systemic treatment for unresectable LA or R/M disease, but also systemic therapy administered as part of curative-intent treatment.

Treatment

Treatment was initiated within 28 days of provisional registration. Darolutamide was administered orally at 600 mg twice daily in continuous 28-day cycles. In the combination cohort, goserelin 3.6 mg was administered subcutaneously once every 28 days starting on day 1.

Treatment was continued until disease progression, unacceptable toxicity, withdrawal of consent, or investigator decision. Supportive care was permitted as clinically indicated. Darolutamide dose modifications were allowed according to protocol-defined criteria, whereas goserelin dose reduction was not permitted.

Assessments

Baseline assessments included clinical evaluation, laboratory tests, electrocardiography, and imaging. Tumor assessments using computed tomography or magnetic resonance imaging were performed every 8 weeks. Tumor response was evaluated by investigators and by blinded independent central review in accordance with RECIST v1.1.

Adverse events (AEs) were monitored throughout treatment and for 28 days after the last dose and graded using National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. Serious AEs, treatment discontinuations, and dose modifications were recorded. Health-related quality of life (HRQoL) was assessed using EQ-5D-5L and the EuroQol visual analog scale (EQ-VAS) at baseline, each treatment cycle, and at the end of treatment.

End Points

The primary end point was objective response rate (ORR), assessed by investigators in the monotherapy cohort and by independent central review in the combination cohort.

Secondary end points included reciprocal ORR assessments (central review in the monotherapy cohort and investigator assessment in the combination cohort), best overall response (BOR), duration of response (DOR), clinical benefit rate (CBR), and clinical benefit duration (CBD). CBR was defined as complete response (CR), partial response (PR), or stable disease (SD) lasting at least 24 weeks. Disease control rate (DCR) was defined as CR, PR, or SD maintained for ≥6 weeks. Additional secondary end points included PFS, OS, safety, and HRQoL assessed using EQ-5D-5L and EQ-VAS. In the combination cohort, concordance between local and central AR assessment (≥1% nuclear staining) and exploratory analyses of the association between centrally assessed Ki-67 labeling index and clinical outcomes were also evaluated.

Statistical Analysis

The planned sample size was 24 patients in the monotherapy cohort and 32 in the combination cohort, based on exact tests

for single proportions. A null ORR of 15% was selected as the minimum level of antitumor activity considered clinically meaningful in this single-arm phase II setting. Assuming a null ORR of 15%, 21 evaluable patients were required in the monotherapy cohort for 90% power at a one-sided alpha of .05 with an expected ORR of 45%, and 27 in the combination cohort with a target ORR of 40%; sample sizes were increased to allow for unevaluable cases. Additional details on the cohort-specific design assumptions are provided in the Data Supplement.

The primary end point in both cohorts was evaluated using a two-sided 90% CI, corresponding to a one-sided type I error of 0.05. The monotherapy cohort used investigator-assessed ORR, and the combination cohort used independently centrally reviewed ORR, as prespecified. The monotherapy cohort was analyzed in the full analysis set (FAS), defined as eligible patients who received at least one dose of study treatment and had at least one postbaseline tumor assessment. The combination cohort was analyzed in the modified FAS (mFAS), defined as the FAS excluding patients

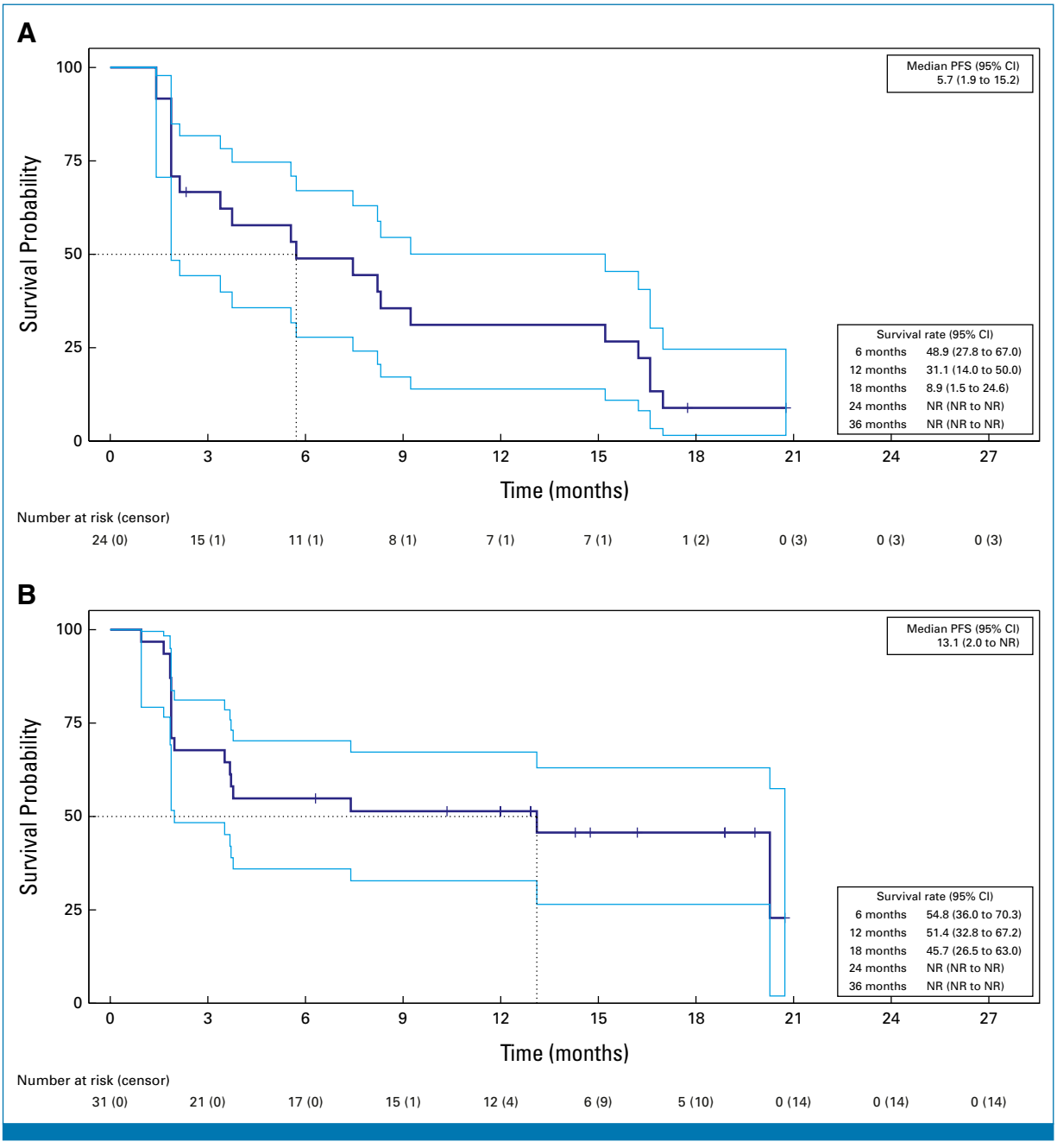

FIG 2. Kaplan-Meier curves for PFS and OS. Kaplan-Meier curves for PFS and OS in the monotherapy and combination cohorts. For PFS, the median PFS was 5.7 months (95% CI, 1.9 to 15.2) in the monotherapy cohort (n = 24; Fig 2A) and 13.1 months (95% CI, 2.0 to NR) in the combination cohort (n = 31, mFAS; Fig 2B). For OS, 12-month OS rates were 91.3% (95% CI, 69.5 to 97.8) in the monotherapy cohort (Fig 2C) and 87.0% (95% CI, 68.9 to 94.9) in the combination cohort (Fig 2D). NR, not reached; OS, overall survival; PFS, progression-free survival. (continued on following page)

determined to be AR-negative by central review. Safety analyses included all treated patients.

Time-to-event end points were estimated using the Kaplan-Meier method. For PFS, progression or death was counted as an event. Patients without an event were censored on the date of their last progression-free tumor assessment or at the start of subsequent therapy if initiated before documented progression. DOR and CBD were analyzed using analogous censoring rules. HRQoL analyses were descriptive and based on observed data only, without imputation of missing data. Additional statistical details are provided in the Data Supplement. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

A total of 57 patients with AR-positive SGC were enrolled, including 24 in the monotherapy cohort and 33 in the combination cohort (Fig 1). The two patients excluded from the mFAS because of central AR negativity had progressive disease (PD) as their BOR; the discordance likely reflected tumor heterogeneity or interpretive differences, and case-

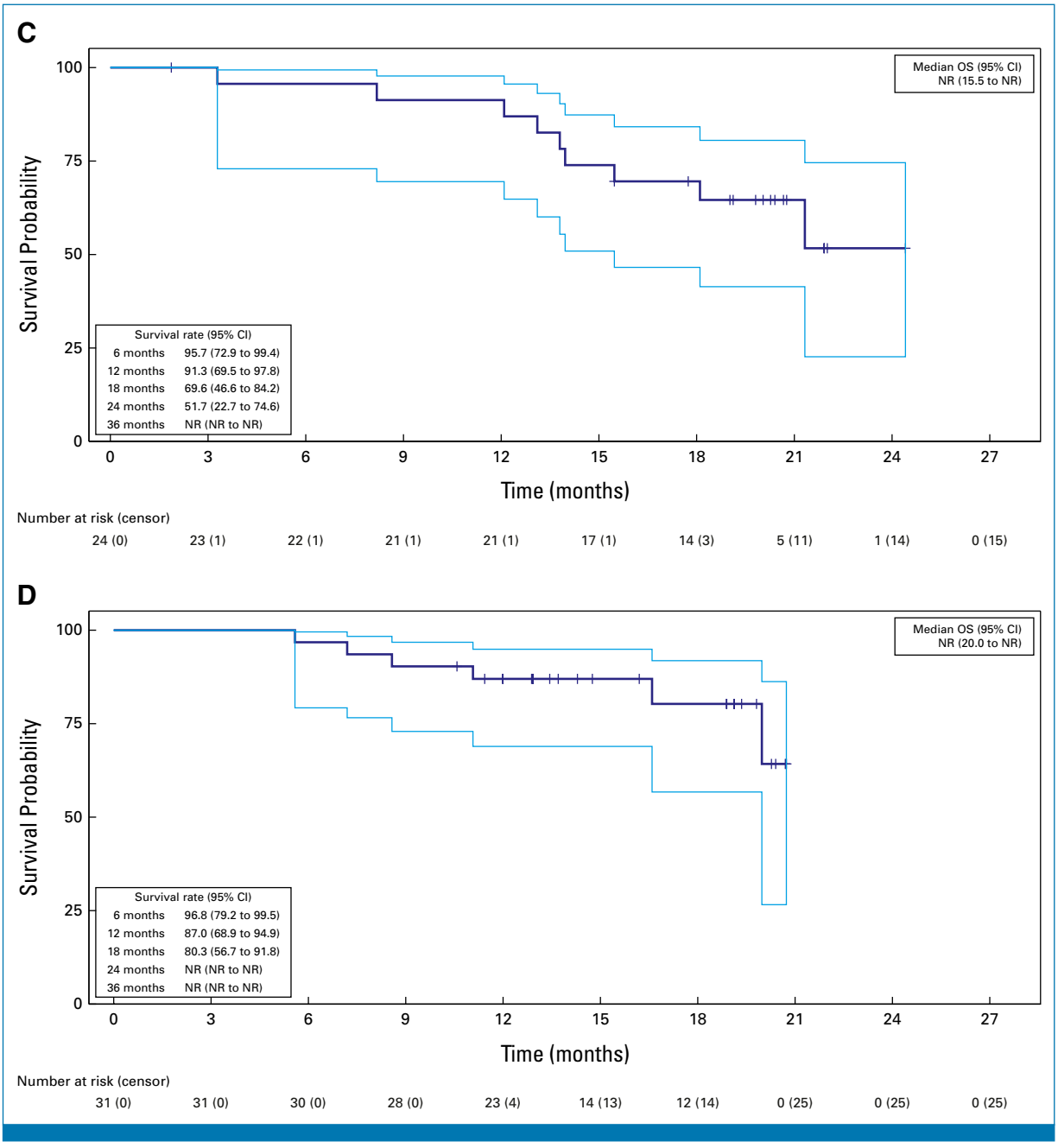

FIG 2. (Continued).

level details are provided in the Data Supplement (Table S4). All patients were included in the safety analysis.

Baseline characteristics are summarized in Table 1. Prior systemic therapies in the combination cohort are detailed in the Data Supplement (Table S1). The combination cohort included a higher proportion of SDC and fewer male patients than the monotherapy cohort. Most patients in both cohorts were male, had an ECOG PS of 0, and had distant metastases, most commonly in the lungs, distant lymph nodes, and bone. The parotid gland was the most common primary site. Approximately half of the patients had received prior systemic therapy, mainly platinum-based chemotherapy.

Efficacy

In the monotherapy cohort (n = 24), the investigator-assessed ORR was 8.3% (90% CI, 1.5 to 24.0), with two PRs and no CRs. The CBR was 41.7%, and the DCR was 54.2%. The median PFS was 5.7 months (95% CI, 1.9 to 15.2). The median OS was not reached at a median follow-up of

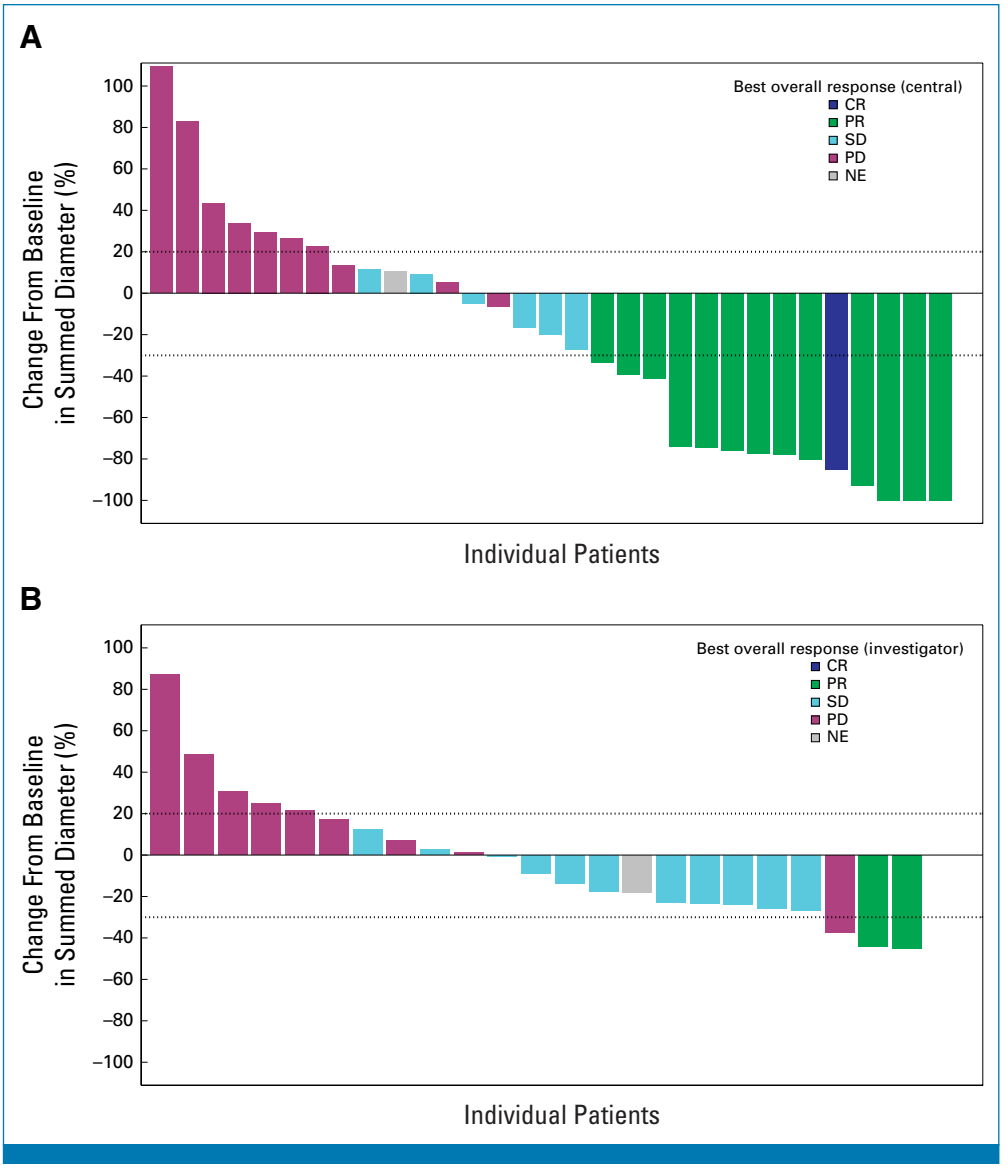

FIG 3. Waterfall plot of best percentage change in tumor size in the combination and monotherapy cohorts. Maximum percentage change in target lesions from baseline by central review in the combination cohort (Fig 3A; n = 31, mFAS) and by investigator assessment in the monotherapy cohort (Fig 3B; n = 24, FAS). Bars represent individual patients, and dashed lines indicate RECIST thresholds for PR (−30%) and PD (+20%). CR in lymph node lesions may not appear as 100% regression in the waterfall plot because, under RECIST v1.1, CR can be assigned when the short axis decreases to <10 mm even if the sum of target lesion diameters does not reach 0 mm. CR, complete response; FAS, full analysis set; mFAS, modified full analysis set; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

19.1 months, with a 12-month OS rate of 91.3% (95% CI, 69.5 to 97.8). The median CBD and DOR were 16.4 months (95% CI, 7.5 to 17.0) and 14.7 months (95% CI, 14.4 to 15.1), respectively. At data cutoff, all patients had discontinued treatment, mainly due to disease progression (n = 19). After discontinuation of protocol treatment, three patients subsequently received ADT with bicalutamide plus leuprorelin.

In the combination cohort (n = 31), the centrally assessed ORR was 45.2% (90% CI, 29.7 to 61.3), including one CR and 13 PRs, thereby meeting the primary end point. The two patients excluded from the mFAS because of central AR negativity had PD as their BOR. The discordance likely reflected tumor heterogeneity or interpretive differences. Centrally assessed AR positivity in the mFAS ranged from 5% to 100% (Data Supplement Table S4). The CBR and DCR were 51.6% and 64.5%, respectively. The median PFS was 13.1 months (95% CI, 2.0 to not reached [NR]), and the 12-month OS rate was 87.0% (95% CI, 68.9 to 94.9). The median CBD was 20.3 months (95% CI, 13.1 to NR), and the median DOR was 18.2 months (95% CI, 11.3 to NR). At data cutoff, 13 patients (39.4%) remained on treatment, whereas 20 (60.6%) had discontinued, primarily because of disease progression (n = 18).

Antitumor activity in the combination cohort was observed regardless of prior systemic therapy. Among five patients previously treated with HER2-targeted therapy, BOR to study treatment was PR in three patients, SD in one, and PD in one. Exploratory subgroup analyses did not identify a clear association between ORR and prior systemic therapy, AR expression level, or Ki-67 labeling index. Corresponding subgroup-specific results are provided in the Data Supplement (Table S2). No objective response was observed among evaluable patients with AR positivity <70%; however, the number of such patients was small. Concordance between local and central AR assessment was 93.9% (31/33; 95% CI, 79.8 to 99.3). Detailed efficacy data are shown in Figures 2 and 3, Table 2, and the Data Supplement (Figs S2 and S3 and Table S2).

TABLE 2. Efficacy Outcomes

Efficacy Outcome	No.	%	95% CI	90% CI
Monotherapy cohort (n = 24, FAS)				
CR	0	0.0	0.0 to 14.2	—
PR	2	8.3	1.0 to 27.0	—
SD	11	45.8	25.6 to 67.2	—
PD	9	37.5	18.8 to 59.4	—
NE	2	8.3	1.0 to 27.0	—
ORR by investigator[a]	2	8.3	—	1.5 to 24.0
ORR by ICR	5	20.8	7.1 to 42.2	8.6 to 38.9
DCR	13	54.2	32.8 to 74.4	—
CBR	10	41.7	22.1 to 63.4	—
Combination cohort (n = 31, mFAS)				
CR	1	3.2	0.1 to 16.7	—
PR	13	41.9	24.5 to 60.9	—
SD	6	19.4	7.5 to 37.5	—
PD	10	32.3	16.7 to 51.4	—
NE	1	3.2	0.1 to 16.7	—
ORR by investigator	14	45.2	27.3 to 64.0	29.7 to 61.3
ORR by ICR[a]	14	45.2	—	29.7 to 61.3
DCR	20	64.5	45.4 to 80.8	—
CBR	16	51.6	33.1 to 69.8	—

NOTE. Efficacy results of monotherapy and combination cohorts. End points included ORR, CBR, and DCR with 95% or 90% CIs as predefined. Abbreviations: CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; FAS, full analysis set; ICR, independent central review; mFAS, modified full analysis set; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Primary end point in each cohort (investigator-assessed ORR in the monotherapy cohort; centrally reviewed ORR in the combination cohort).

Safety

Darolutamide monotherapy was generally well tolerated. Grade ≥3 AEs occurred in nine (37.5%) of 24 patients. Two patients experienced three serious TRAEs: anaphylaxis, drug eruption, and rhabdomyolysis. No treatment-related deaths occurred. Endocrine-related AEs included gynecomastia (20.8%) and malaise (8.3%), all grade 1 to 2. Darolutamide dose reduction, temporary interruption, and permanent discontinuation were required in four, six, and three patients, respectively, all due to serious TRAEs.

In the combination cohort, grade ≥3 AEs occurred in six (18.2%) of 33 patients. Three patients experienced serious AEs considered possibly related to study treatment: hypersensitivity and pyrexia related to darolutamide, and disseminated intravascular coagulation related to both darolutamide and goserelin; all were manageable, with no grade 4 or 5 AEs. Endocrine-related AEs included malaise (9.1%) and hot flushes (6.1%). Temporary interruption occurred in eight patients for darolutamide and one for goserelin; darolutamide dose reduction was required in one patient. Permanent discontinuation occurred in two patients for darolutamide and one for goserelin, all due to serious TRAEs. Detailed safety data are summarized in Table 3.

Patient-Reported Outcomes

HRQoL assessed by EQ-5D-5L and EQ-VAS was generally preserved during treatment. Using a reported EQ-VAS minimal important difference of 5 points,[21,22] mean EQ-VAS scores improved modestly in the combination cohort but generally remained below this threshold in the monotherapy cohort. No consistent clinically meaningful deterioration was observed in any EQ-5D-5L domain. Questionnaire completion was 100% at baseline in both cohorts and declined over time; detailed completion and missing-data frequencies at each scheduled assessment are shown in

TABLE 3. Adverse Events

AE	Grade 1, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)
Monotherapy cohort (n = 24)				
Gynecomastia	4 (16.7)	1 (4.2)	0	0
Nausea	3 (12.5)	1 (4.2)	0	0
Fever	3 (12.5)	1 (4.2)	0	0
Constipation	0	3 (12.5)	0	0
Eczema	0	3 (12.5)	0	0
Anemia	0	3 (12.5)	0	0
Fatigue	3 (12.5)	0	0	0
AST increase	3 (12.5)	0	0	0
ALT increase	3 (12.5)	0	0	0
Lymphocytopenia	0	0	1 (4.2)	1 (4.2)
Neutropenia	0	1 (4.2)	1 (4.2)	0
Laryngeal edema	0	0	0	1 (4.2)
GGT increase	0	0	1 (4.2)	0
Anaphylactic shock	0	0	1 (4.2)	0
Shingles	0	0	1 (4.2)	0
Urinary tract infection	0	0	1 (4.2)	0
Drug rash	0	0	1 (4.2)	0
Arthritis	0	0	1 (4.2)	0
Rhabdomyolysis	0	0	1 (4.2)	0
Combination cohort (n = 33)				
AST increase	4 (12.1)	2 (6.1)	0	0
ALT increase	4 (12.1)	2 (6.1)	0	0
Nasopharyngitis	4 (12.1)	2 (6.1)	0	0
Malaise	1 (3.0)	2 (6.1)	0	0
Anemia	1 (3.0)	2 (6.1)	0	0
Abnormal liver function	3 (9.1)	0	0	0
Vomiting	3 (9.1)	0	0	0
Fever	3 (9.1)	0	0	0
Weight loss	3 (9.1)	0	0	0
COVID-19	3 (9.1)	0	0	0
Neutropenia	0	1 (3.0)	1 (3.0)	0
Hypercalcemia	0	0	1 (3.0)	0
Infection	0	0	1 (3.0)	0
Hypersensitivity	0	0	1 (3.0)	0
Atrial fibrillation	0	0	1 (3.0)	0
Drug rash	0	0	1 (3.0)	0
Jawbone necrosis	0	0	1 (3.0)	0

NOTE. Summary of AEs in both cohorts. Grade 1 to 2 events were reported if they occurred in ≥3 patients, whereas all grade ≥3 events (≥1 occurrence) were reported. No grade 5 events or treatment-related deaths were observed. Events are categorized by grade.
Abbreviations: AEs, adverse events; GGT, gamma-glutamyl transferase.

the Data Supplement (Table S3), and longitudinal EQ-VAS changes are shown in the Data Supplement (Fig S4).

DISCUSSION

The DISCOVARY study is the first prospective, multicenter phase II trial to evaluate darolutamide, given either as monotherapy or as CAB with goserelin, in patients with AR-positive SGC. This rare and aggressive malignancy is associated with early distant metastasis, limited responsiveness to cytotoxic chemotherapy, and limited approved systemic options. Immunotherapy has generally shown modest activity across salivary gland cancers, although responses have been reported in selected populations.[5,7,23,24] The sequential two-cohort design enabled prospective assessment of two AR-targeted strategies.

Numerically higher efficacy outcomes were observed in the combination cohort than in the monotherapy cohort. However, because the study was not designed or powered for formal cross-cohort comparison, these findings should be interpreted as descriptive and exploratory. Although median DOR was similar across cohorts, the small number of responders in the monotherapy cohort precludes firm conclusions regarding a durable benefit in a distinct subgroup. No clear clinical or biologic predictors of such benefit were identified, and these findings should therefore be considered exploratory.

The present results appear favorable relative to prior reports of AR-targeted therapy and some chemotherapy series, although cross-trial comparisons should be interpreted cautiously.[7,8,25-27] Prior studies have suggested that CAB may be more active than AR-targeted monotherapy in AR-positive SGC,[13,15] and the present findings are consistent with the hypothesis that more complete AR pathway suppression may improve antitumor activity.[18,19] However, chemotherapy remains clinically active in SGC, and randomized data have not established superiority of endocrine therapy over chemotherapy in the first-line R/M setting. Accordingly, the present findings should be interpreted as supporting activity rather than establishing superiority over chemotherapy.[6,28]

HER2-directed therapy is also an important real-world comparator in HER2-positive SDC. CAB may therefore be most relevant as a chemotherapy-sparing option, particularly in HER2-negative disease or when HER2-directed therapy is not appropriate. Reported efficacy across phase II studies of CAB has been heterogeneous[14,15] and may have been influenced by cross-trial differences in prior treatment exposure, HER2 distribution, histologic composition, and AR expression. Thus, the present results support the activity of darolutamide plus goserelin rather than superiority over other CAB regimens. Additional comparisons with prior studies are provided in the Data Supplement (Table S5).

The activity observed with CAB is biologically plausible and may reflect more comprehensive AR signaling inhibition.[29] AR signaling inhibitor monotherapy may increase circulating testosterone,[30] whereas goserelin suppresses androgen production and may enhance AR blockade by reducing residual androgen signaling.[31,32] Darolutamide's suitability for this strategy is further supported by its high AR-binding affinity, lack of agonist activity, and minimal central nervous system penetration.[19,33]

Most of our present patients had SDC, which limits conclusions for non-SDC histologies. No clear association was identified between treatment response and AR IHC intensity or Ki-67 labeling index, although the number of patients with lower AR expression was small. These biomarker findings should therefore be considered exploratory.

With respect to safety, both treatment strategies were generally well tolerated, with no treatment-related deaths. Grade ≥3 AEs were more frequent in the monotherapy cohort than in the combination cohort (37.5% *v* 18.2%). Endocrine-related AEs were mostly grade 1 to 2, with gynecomastia observed only in the monotherapy cohort, possibly reflecting suppression of testosterone-related effects by goserelin in the combination cohort.[34] Baseline differences and the sequential, nonrandomized design may also have contributed to these findings.

Several limitations of this study should be acknowledged, including its sequential, nonrandomized design, potential selection bias, and limited sample size. Although the combination cohort showed numerically higher ORR and longer PFS, the study was not designed or powered for formal cross-cohort comparison, and the observed differences between cohorts may have been influenced by differences in enrollment period, histology, HER2 status, AR assessment, and other baseline factors. The time gap between cohort enrollment may also have introduced temporal confounding related to changes in referral patterns, imaging practice, supportive care, access to subsequent therapies, and broader clinical management. Local AR testing in the combination cohort may also have introduced variability. In addition, HER2 status was not prospectively specified for collection, precluding robust HER2-stratified efficacy analyses and limiting assessment of treatment sequencing with HER2-directed therapy. Accordingly, these findings should be interpreted cautiously and considered to support further evaluation of darolutamide plus goserelin rather than any conclusion of superiority.

In summary, the DISCOVARY trial provides the first prospective evidence for darolutamide as monotherapy and in combination with goserelin in AR-positive SGC. The combination cohort showed numerically more favorable efficacy outcomes while maintaining tolerability and quality of life. CAB may represent a promising chemotherapy-sparing option in this rare malignancy.

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CLINICAL TRIAL INFORMATION

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De-identified individual participant data that underlie the results reported in this article will be made available upon reasonable request. Requests will be reviewed jointly by the primary investigator and the study sponsor, and data sharing will be subject to approval, execution of an appropriate data use agreement, and compliance with ethical and legal requirements.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Darolutamide Alone and in Combination With Goserelin in Androgen Receptor–Positive Salivary Gland Carcinoma: Results From the Phase II DISCOVARY Trial

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