Abiraterone Acetate in Patients With Castration-Resistant, Androgen Receptor–Expressing Salivary Gland Cancer: A Phase II Trial

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PURPOSE The activity of androgen-deprivation therapy (ADT) in androgen receptor–positive (AR+) salivary gland carcinomas (SGCs) has been established in the past few years. Second-line treatment in castration-resistant patients is still unknown. We investigated the activity of abiraterone acetate as second-line treatment in ADT-resistant, AR+ patients with SGC.

METHODS This was a single-institution phase II trial. A two-stage Simon's design was applied. The primary end point was confirmed objective response rate. Secondary end points were disease control rate, safety, progression-free survival, and overall survival. Patients were eligible when the following criteria were met: histologic diagnosis of AR-overexpressing SGC, measurable disease according to RECIST 1.1, clinical and/or radiologic progression on ADT, suppressed serum testosterone, and no limits for the number of previous chemotherapy lines. All patients received abiraterone 1 g daily plus prednisone 10 mg and luteinizing hormone-releasing hormone agonist until progression or unacceptable toxicities.

RESULTS From 2015 to 2019, 24 AR+ patients with SGC (23 men; median age 65.8 years) were treated within the study. The overall response rate was 21% (5 partial responses), with a disease control rate of 62.5%. The median duration of response was 5.82 months. Median progression-free survival was 3.65 months (95% CI, 1.94 to 5.89), and median overall survival was 22.47 months (95% CI, 6.74 to not reached). Objective response to previous ADT did not correlate with the activity of abiraterone. Adverse events (AEs) were recorded in 22 cases (92%) with grade 3 AEs in six patients (25%): fatigue (two), flushing (one), supraventricular tachycardia (one), and two non–drug-related AEs. No drug-related grade 4 or 5 AEs were recorded.

CONCLUSION Abiraterone plus luteinizing hormone-releasing hormone agonist is active and safe as a second-line option in AR-expressing, castration-resistant SGC.

INTRODUCTION

Salivary duct carcinoma (SDC) has a remarkable morphologic resemblance and similar molecular profiling (eg, androgen receptor [AR] expression; mutations in *TP53* [55%], *HRAS* [23%], and *PIK3CA* [23%]; and amplification of *ERBB2* [35%]) to high-grade breast ductal carcinoma.[1] AR and human epidermal growth factor receptor 2 (HER2) expression can be inhibited successfully by tailored treatments. AR expression is present in more than 90% of SDC cases[2] and 20%-30% of adenocarcinoma, not otherwise specified (NOS).[3] The co-expression of HER2 and AR has been reported in 20%-60% of breast cancers,[4,5] and the rate of co-expression varies between 35%[6] and 58%[7] in SDC. The biologic significance of concomitant HER2 and AR expression in SDC remains to be elucidated, although HER2-enriched cases seem to have a worse outcome.[6,7] Evaluation of AR or HER2 status is currently recommended in SDC by the National Comprehensive Cancer Network and ASCO guidelines.[8,9] However, in the presence of both receptors, there is insufficient evidence supporting the use of androgen blockade over anti-HER2 treatment or vice versa as first-line treatment.

The activity of androgen-deprivation therapy (ADT) in AR-positive salivary gland carcinomas (SGCs) has been established in recent years.[10-12] Responses have been reported with ADT, including some cases of complete remission,[10,11] which mitigate in favor of this

CONTEXT

Key Objective

Androgen receptor–positive (AR+) patients with salivary gland carcinoma (SGC) can benefit from androgen-deprivation therapy (ADT). The best approach after failure of ADT is still unknown. In this setting, therapeutic options include targeting specific molecular pathways (eg, human epidermal growth factor receptor 2), when present, or cytotoxic chemotherapy. No second-line hormone treatments have been successfully tested in this context.

Knowledge Generated

The objective response rate (21%) and survival observed with abiraterone are clinically meaningful for a second-line chemotherapy-free approach. No serious safety issues were observed with this drug in patients with SGC.

Relevance

Abiraterone acetate plus prednisone and luteinizing hormone-releasing hormone analog can be considered as a valid and safe therapeutic option for androgen receptor–positive patients with SGC in second line after failure of ADT.

latter treatment compared with the 20%-30% response rate reported with chemotherapy.[13] A randomized, prospective, multicenter trial is currently ongoing to demonstrate the efficacy of ADT over chemotherapy in patients with relapsed and/or metastatic AR+ SGCs in the first-line setting (NCT01969578).[14] The optimal second-line treatment in castration-resistant patients is still unknown. Abiraterone has been approved for the treatment of metastatic castration-resistant prostate cancer (Pca) in men who are asymptomatic or mildly symptomatic after failure of ADT. Two case reports on patients with SDC progressing to ADT and responding to abiraterone have been published,[15,16] suggesting it may be effective as second-line hormonal treatment.

Herein, we present the final data of a phase II trial in ADT-resistant, AR-expressing patients with SGC undergoing second-line treatment with abiraterone.

METHODS

Study Protocol and Design

This was a single-institution phase II trial. The primary end point was confirmed objective response rate (ORR), defined as the sum of complete response and partial response (PR) according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST1.1).[17] Secondary end points were disease control rate (DCR, the sum of ORR and stable disease); safety in terms of incidence of adverse events (AEs), according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.0; progression-free survival (PFS); and overall survival (OS).

Inclusion criteria were as follows: histologic diagnosis of AR-overexpressing SGC, measurable disease according to RECIST 1.1, clinical and/or radiologic progression on ADT with no limits for the number of previous chemotherapy lines, ongoing androgen deprivation with a serum testosterone level of < 50 ng/dL, and Eastern Cooperative Oncology Group performance status of ≤ 2. Patients with treated brain metastases stable within the last 3 months were eligible. The definition of AR overexpression was based on immunohistochemistry, as described previously.[10] In particular, AR staining intensity was scored from 0 (negative) to 3 (strong) and AR staining extent from 0 (< 10% positive nuclei) to 3 (≥ 70% nuclei expressing AR). A combined expression score was obtained by summing the scores of staining intensity and extent, with a score of 6 defining a tumor as AR-overexpressing. This trial was registered at EUDRACT (2014-001274-34) and ClinicalTrials.gov (NCT02867852). The study was approved by the Institutional Ethical Committee on May 27, 2014 (local study identifier INT 71/14). All patients provided written informed consent. Per the Protocol (online only), genomic tissue analysis was not required; however, in case of tumor sample availability, targeted next-generation technique using Hot Spot Cancer Panel (through PGM, Personal Genome Machine, with Ion Torrent technology—Thermo Fisher Scientific, Life-Technologies, Waltham, MA) was performed. Further details about the Protocol are provided in the Data Supplement (online only).

Study Treatment and Assessments

Abiraterone acetate 1 g/day was taken as four 250-mg tablets daily with oral prednisone 5 mg twice a day. If dose reduction was used for AE management, one dose reduction was allowed to 500 mg daily of abiraterone. The study drug was administered until disease progression (PD) or unacceptable toxicity. During treatment with abiraterone, luteinizing hormone-releasing hormone (LHRH) analogs were administered to suppress testosterone levels to < 50 ng/dL.

Whole-body computed tomography scans were performed at baseline and every 2 months during treatment. Further radiologic scans (eg, magnetic resonance imaging, ultrasound, bone scans, and whole-body fluorodeoxyglucose positron emission tomography scans) were carried out as clinically indicated.

Sample Size and Statistical Analysis

The drug would be considered effective and warrant further evaluation if the response rate was at least 20%. Such a

relatively low rate was deemed justified in this setting, considering the lack of established treatments for this rare tumor, especially when progressing on ADT. The null hypothesis was ORR 5% versus the alternative ORR 20%. This is consistent with literature data, where 5% is the response rate observed with second-line chemotherapy in patients with SGC.[18]

A two-stage Simon design, optimal version, was applied. Type I and type II error rates were set at 10% and 20%, respectively.[19] In the first step, nine patients were enrolled, and the first evaluation took place after the last patient had completed 2 months of study treatment. If at least 1 of 9 responses was observed, the second phase of enrollment was opened to reach a final overall sample size of 24 patients. If at least 3 of 24 responses were recorded, the null hypothesis would be rejected in favor of the alternative and the drug considered promising and worthy of further investigation.

The data cutoff date was May 21, 2020. Median follow-up was estimated with the reverse Kaplan-Meier method. Response to abiraterone was compared with previous ADT duration with Kruskal-Wallis test or Mann-Whitney test (as appropriate). For correlation with response to previous ADT, contingency tables were analyzed with χ^2 test or Fisher's exact test, as appropriate, using GraphPad Prism v5.02.

The disease-free interval was defined as the interval from the diagnosis of primary nonmetastatic SGC to the occurrence of metastatic or locoregionally recurrent disease not amenable to curative treatments. Survival curves (PFS and OS) were measured from the start of study treatment. OS was measured from the primary SGC as well. In patients achieving an objective response, duration of response (DoR) was calculated from the first occurrence of response to PD or last follow-up. Disease-free interval, PFS, OS, and DoR were estimated with the Kaplan-Meier method. Survival analyses were performed using SAS University Edition, and statistical significance was set at 0.05.

RESULTS

Patient Characteristics

Twenty-four patients (23 men) entered the trial from March 2015 to November 2019. Median follow-up was 9.47 months (95% CI, 5.66 to 20.56). The median age was 65.8 years (range, 44-77), and Eastern Cooperative Oncology Group performance status was 0-1 in all cases. Pathologic diagnosis according to WHO Classification of Head and Neck Cancer[20] was SDC in 19 patients (79%) and adenocarcinoma NOS in the remaining five cases. AR was overexpressed in all cases (combined score expression level = 6).[17] HER2 was amplified in four cases (three SDC and one adenocarcinoma NOS).

At study entry, serum testosterone was suppressed in all cases. None of the study patients were on any other

treatment for their disease, with the exclusion of LHRH agonists (triptorelin 11.25 mg delivered once every 3 months in two patients, monthly leuprorelin and monthly goserelin in two cases, and triptorelin 3.75 mg in the remaining 20 cases) that were administered to maintain testosterone suppression (< 50 ng/dL as per inclusion criteria) during treatment with abiraterone. Twelve patients received previous systemic chemotherapy (excluding ADT) for recurrent and/or metastatic disease, and more than two lines of chemotherapy had been administered in five patients. All patients had received combined ADT (bicalutamide + LHRH analog in all cases) before study entry (23 as palliative treatments and one patient had received ADT in both adjuvant and palliative settings). Three patients (13%) had a RECIST objective response to previous ADT, with an overall DCR of 96%. The median duration of previous ADT was 10.5 months (range, 2.3-44.3).

All patients had radiologic disease progression according to RECIST v1.1 at study entry with metastatic disease in all cases, and 12 had locoregional disease. The most frequent metastatic sites at study entry were bone and lung (both 67%), followed by nonlocoregional lymph nodes (38%) and liver (33%). Further details on patient characteristics are reported in Table 1.

Response and Survival

Two PRs were observed of the nine cases entering the first Simon's step. After completing the whole study patient accrual, ORR was 21% (five PRs, confirmed in all cases; Fig 1 and Appendix Figs A1 and A2, online only). Median DoR was 5.82 months (95% CI, 4.24 to 10.76). DCR was 62.5% (five PRs + 10 SDs), and PD was the best response in nine cases (37.5%). Three patients were still on active treatment. All the remaining 21 patients discontinued abiraterone because of PD. The median duration of treatment was 3.93 months (range, 1.15-18.88).

Median PFS was 3.65 months (95% CI, 1.94 to 5.89), and median OS was 22.47 months (95% CI, 6.74 to not reached [NR]; Fig 2) from study entry. Twelve-month OS was 66.59% (74.48% in 19 patients with SDC v 50% in five patients with adenocarcinoma NOS, P = .334). Median OS from diagnosis of primary SGC was 94.31 months (95% CI, 46.61 to NR). Further descriptive analyses about clinical and biologic characteristics are available in the Data Supplement (Appendix Fig A3, online only).

Safety

At least one AE was reported in 92% of patients (22). The most frequent drug-related AEs (all grades; Table 2) were fatigue (38%), flushing (29%), and hypokalemia (17%). Grade 3 AEs were observed in six cases (25%): four were drug-related (two fatigue, one flushing, and one supraventricular tachycardia) and two non–drug-related (one cancer-related pain and one xerostomia; Table 2 and Data Supplement). The median number of AEs per patient was 3 (range, 0-5). No drug-related grade 4 and 5 AEs were

TABLE 1. Patient Characteristics

Characteristic	N = 24
Sex, No. (%)	
Male	23 (96)
Female	1 (4)
Median age, years (range)	65.8 (44-77)
ECOG PS, No. (%)	
0	10 (42)
1	14 (58)
Primary tumor site, No. (%)	
Parotid gland	19 (79)
Submandibular gland	2 (8)
Minor salivary gland	3 (13)
Histology, No. (%)	
SDC	19 (79)
AR+ adenocarcinoma NOS	5 (21)
HER2 status at IHC, No. (%)	
3+	4 (17)
2+	7 (29)
1+	7 (29)
Negative	1 (4)
NA	5 (21)
Previous systemic treatments for R/M disease, No. (%)	
Chemotherapy	12 (50)
Lines of chemotherapy	
1	7 (58)
2	3 (25)
≥ 3	2 (17)
ADT	24 (100)
Median duration of previous ADT, months (range)	10.5 (2.3-44.3)
Best response to previous ADT, No. (%)	
PR	3 (13)
SD	20 (83)
PD	1 (4)
Sites of disease at study entry, No. (%)	
Distant metastases	24 (100)
Distant metastases and LR disease	12 (50)
Distant metastases only (without LR disease)	12 (50)
No. of distant metastatic sites, No. (%)	
1	4 (17)
2	11 (46)
3	5 (21)
4	1 (4)
5	3 (12)

(continued in next column)

TABLE 1. Patient Characteristics (continued)

Characteristic	N = 24
Site of distant metastases at study entry, No. (%)	
Lung	16 (67)
Bone	16 (67)
Distant (nonregional) lymph nodes	9 (38)
Liver	8 (33)
Pleura	6 (25)
Brain	5 (21)
Soft tissue	1 (4)

Abbreviations: ADT, androgen-deprivation therapy; AR+, androgen receptor–positive; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; LR, locoregional; NA, not available; NOS, not otherwise specified; PD, disease progression; PR, partial response; R/M, recurrent and/or metastatic; SD, stable disease; SDC, salivary duct carcinoma.

observed. No dose reduction was needed, and none of the patients discontinued the trial for toxicity.

DISCUSSION

The primary aim of the trial was reached, demonstrating for the first time to our knowledge that abiraterone acetate combined with LHRH analog is active in castration-resistant, AR-positive patients with SGC. We observed an ORR of 21% with a median PFS and OS of 3.65 months (95% CI, 1.94 to 5.89) and 22.47 months (95% CI, 6.74 to NR), respectively. The extension of these positive results in ADT-resistant patients highlights the value of this approach in AR-overexpressing patients with SGC. This trial started in 2014 and, at that time since it was for Pca, ADT followed by abiraterone at progression was believed to be a valid option for castration-resistant, AR-positive patients with SGC. In the past few years, the treatment landscape of advanced Pca has evolved[21-27] and, as expected, some successful paradigms have been adopted in clinical trials on AR-positive SGCs, including enzalutamide[28] and abiraterone.

Unlike abiraterone, enzalutamide has been unsuccessfully tested in advanced and/or unresectable metastatic AR-positive patients with SGC, first-line and beyond, with a short-lived ORR of 4% (95% CI, 0.5 to 15) in first line and one response of 11 ADT-pretreated patients.[28] Although no direct comparisons can be made between the two trials, median PFS was longer in the enzalutamide study (5.5 months) than in the current one (3.65 months). The majority (76%) of patients included in the Alliance A091404 trial received the study drug as first-line hormone therapy. On the contrary, in the present study, all patients started abiraterone after progressing on prior ADT. This might have led to a negative patient selection that, in turn,
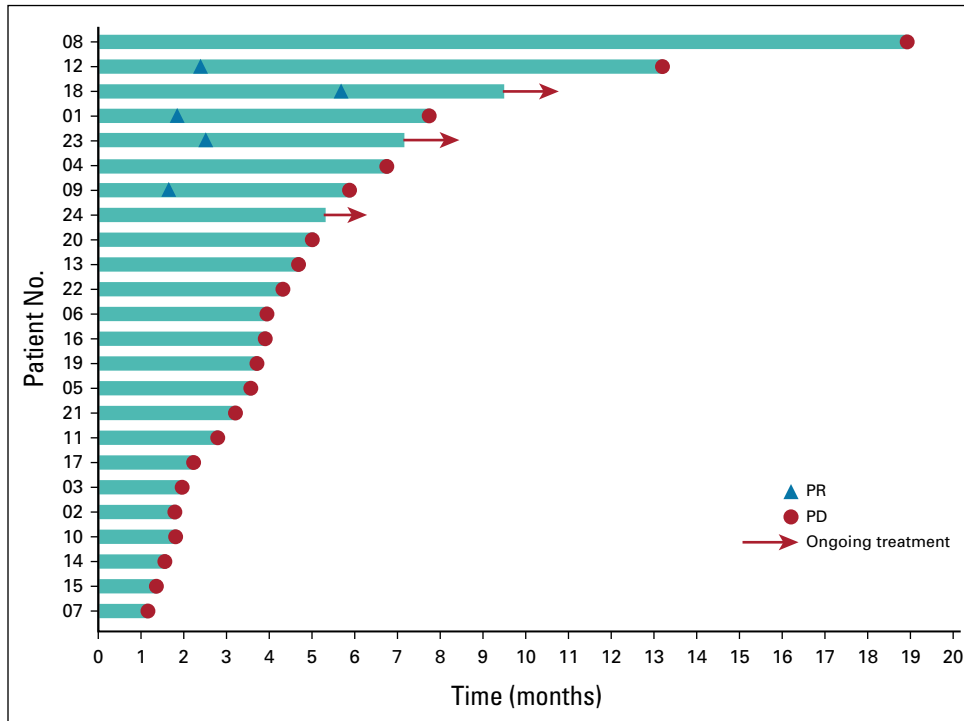
FIG 1. Swimmer plot showing the duration of treatment with abiraterone. PD, disease progression; PR, partial response.

might help to explain the shorter PFS compared with enzalutamide. On the basis of their mechanisms of action, different activity of these two agents cannot be ruled out in AR-expressing SGCs. Enzalutamide is a direct antagonist of AR and exerts its activity even by blocking the intracellular AR pathway, thus requiring AR overexpression. Abiraterone inhibits the biosynthesis of androgens by blocking the action of CYP17A1 expressed in cancer cells (eg, prostate and breast cancer) and normal testicular and adrenal tissue. However, in a series of 30 recurrent and/or metastatic patients with SDC, mRNA expression of *CYP17A1* was negative,[29] suggesting that in AR-positive SGCs, tumor inhibition could be the result of tumor CYP-independent androgen deprivation.

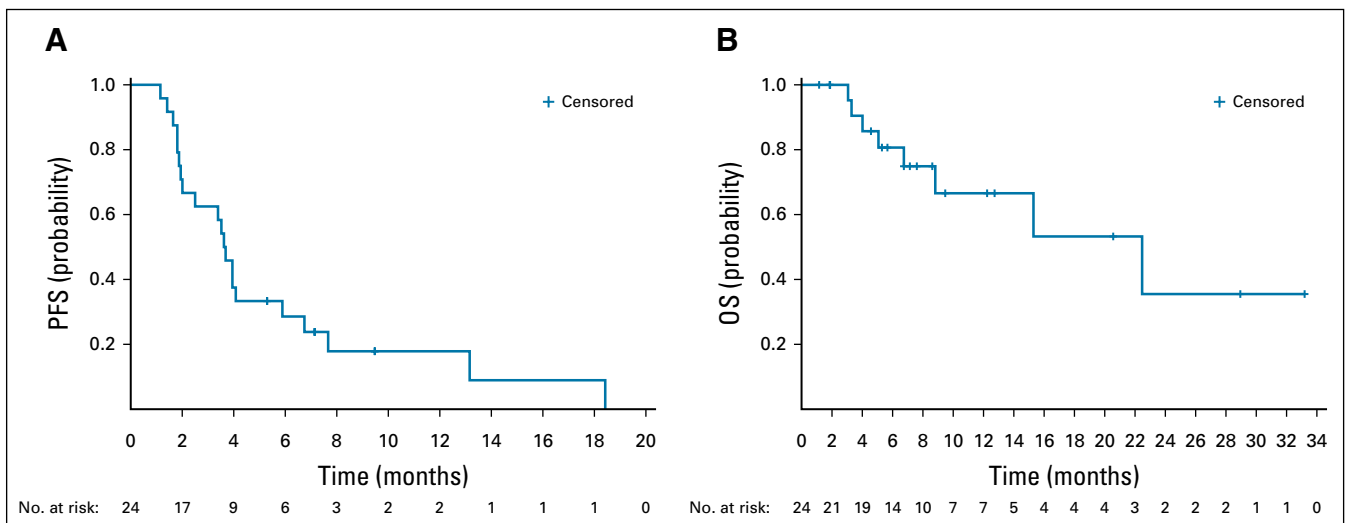In addition, we can speculate on the positive patient selection in our study. In a previous analysis, we observed that

FIG 2. (A) PFS and (B) OS in the study population. OS, overall survival; PFS, progression-free survival.

TABLE 2. Drug-Related AEs

AE	Any Grade, No. (%)	G3, No. (%)
Fatigue	9 (38)	2 (8)
Flushing	7 (29)	1 (4)
Hypokalemia	4 (17)	—
Hypomagnesemia	3 (12)	—
Edema	3 (12)	—
Constipation	3 (12)	—
Hypernatremia	2 (8)	—
Supraventricular tachycardia	1 (4)	1 (4)
QTc prolongation	1 (4)	—
Hypertension	1 (4)	—
ALT/AST increase	1 (4)	—
ALP increase	1 (4)	—
Dyspepsia	1 (4)	—
Abdominal pain	1 (4)	—
Nocturia	1 (4)	—
Sweating	1 (4)	—
Anorexia	1 (4)	—
Myalgia	1 (4)	—

Abbreviations: AE, adverse event; ALP, alkaline phosphatase; CTCAE, Common Terminology Criteria for Adverse Events; G3, CTCAE grade 3; QTc, corrected QT interval at electrocardiogram.

the activity of androgen blockade was a function of high AR expression (combined score expression level 6).[10] In the enzalutamide trial, an AR expression in > 5% of tumor cells was considered adequate, thus diluting its potential effect. Moreover, although AR has been reported in histotypes other than SDC or adenocarcinoma NOS, its expression is generally weak[2] and possibly not driving the biology of the tumor.[3] In this context, the enzalutamide study included four patients with nonselected histotypes. Unlike castration-resistant Pca, the AR-V7 variant has been found in naïve patients with SDC,[29] with a nonsignificant trend toward female over male patients,[30] and six female patients were included in the enzalutamide trial compared with one female in our study.

We are aware that PFS of the current study is modest (median 3.65 months), but it is consistent with that

reported with second-line cisplatin and vinorelbine (median 3.5 months).[18] However, with the caveats of an indirect comparison and a different histopathologic case mix, the survival benefit (median OS 22.47 months) and the ORR (21%) reported in this study are better than those observed with second-line chemotherapy (median OS 4 months and ORR 5%),[18] highlighting the importance of tackling the AR pathway in these tumors.

Coexpression of HER2 (3+) and AR was observed in 17% of patients. Promising results have been described in phase II trial with the combination of trastuzumab plus docetaxel in 57 HER2-overexpressing metastatic patients with SDC.[31] These findings were confirmed by an impressive 90% ORR with ado-trastuzumab emtansine in 10 heavily pretreated, HER2-amplified patients with SDC.[32] These results open the discussion on the optimal therapeutic sequence in patients co-expressing AR and HER2. In breast cancer, cross talk between AR and HER2 pathway has been reported.[33] HER2 promotes AR transcription and leads to *ERK* activation, which, in turn, regulates both HER2 and AR, resulting in a positive feedback loop,[34] suggesting that inhibition of AR could be successfully used as an alternative treatment strategy to block HER2-positive cancers.[33] In our series, two of four HER2 3+ cases were pretreated with trastuzumab, only one of which responded to abiraterone. With the caveat of the limitation of the low number of patients, we might assume that, in SGC, an AR-mediated response could be independent of HER2 blockade.

Since next-generation sequencing was performed in 15 cases only, a limitation of this study is the lack of extensive biologic characterization of AR-overexpressing cancer patients treated with abiraterone. The biologic profile of these tumors could deepen the knowledge about the role of genomic alterations in determining ADT sensitivity or resistance.

In conclusion, abiraterone in association with LHRH analog is active as second-line in AR-expressing, castrate-resistant SGCs. The assessment of the molecular phenotype in these patients could provide further biologic details on mechanisms of response and ADT resistance. Patient selection might contribute to improve the treatment efficacy especially for PFS, which currently is still unsatisfactory.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Abiraterone Acetate in Patients With Castration-Resistant, Androgen Receptor–Expressing Salivary Gland Cancer: A Phase II Trial

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Consulting or Advisory Role: Merck Serono, Bristol Myers Squibb, Sanofi/Regeneron, Angelini Pharma, MSD Oncology, Sun Pharma, GlaxoSmithKline
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Consulting or Advisory Role: Eisai, Boehringer Ingelheim, AstraZeneca, SOBI, Novartis, Bayer, MSD, Merck Serono, Roche, Bristol Myers Squibb, Incyte, Doxapharma, GlaxoSmithKline, Nanobiotix, Debiopharm Group, Amgen, Ipsen, Roche
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Travel, Accommodations, Expenses: Merck Serono, Bristol Myers Squibb, MSD, Eisai, AstraZeneca

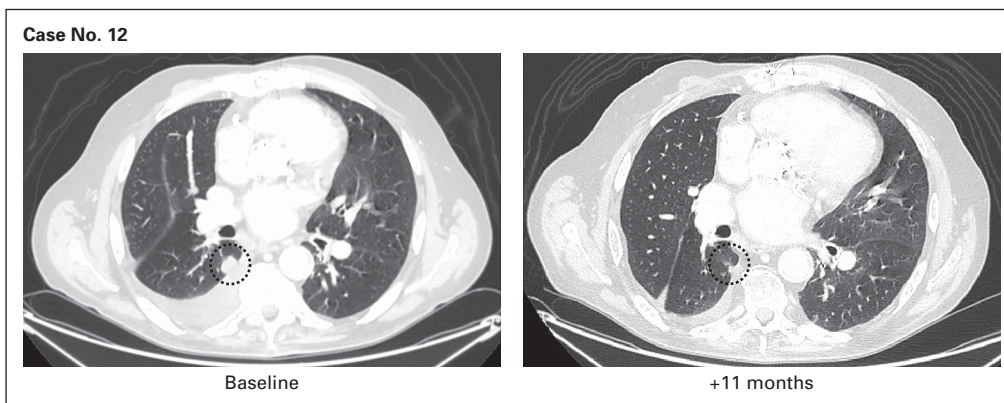No other potential conflicts of interest were reported.

APPENDIX
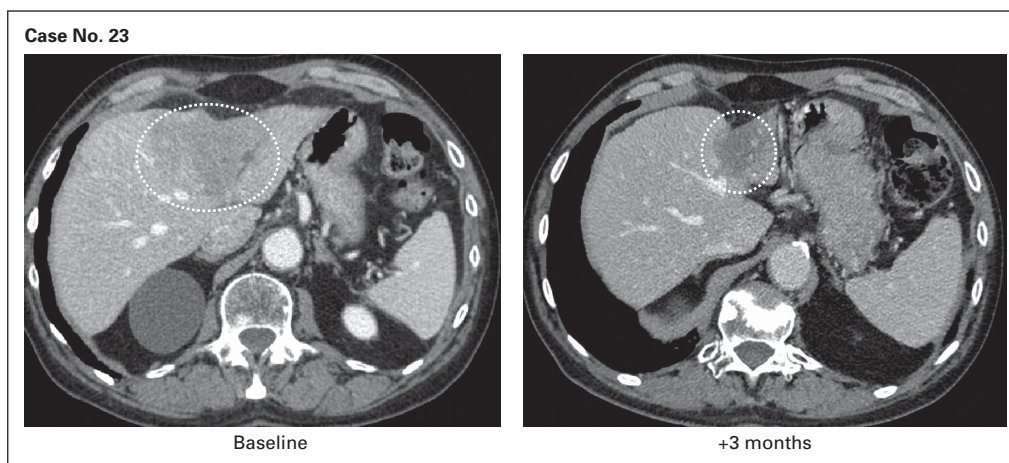

FIG A1. Case of a responding lung metastasis.

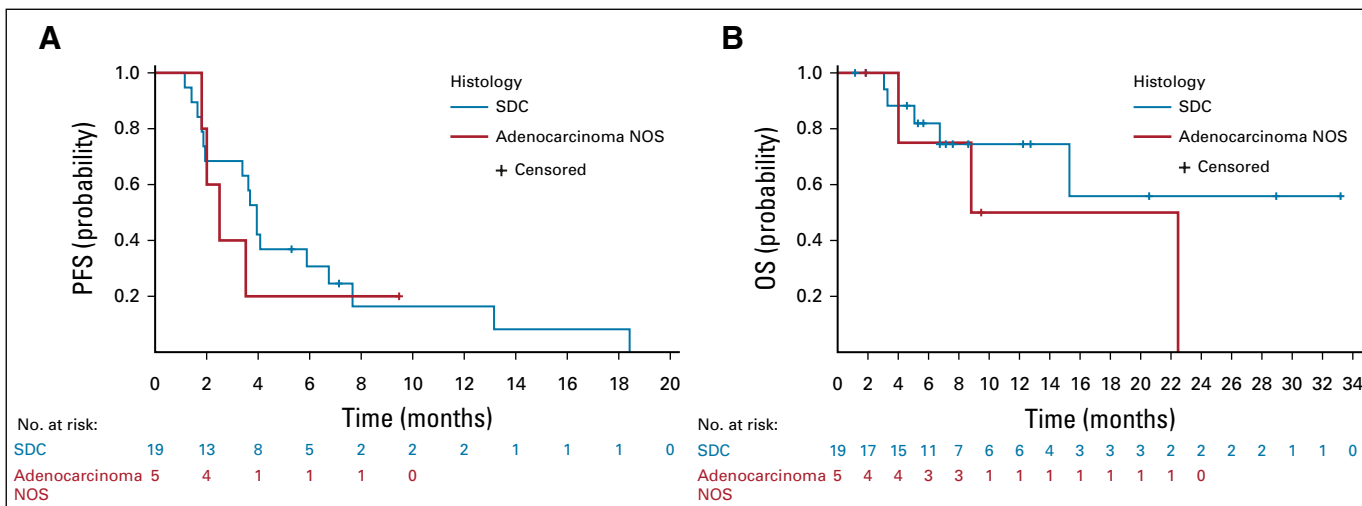**FIG A2.** Case of a responding liver metastasis.

FIG A3. PFS and OS stratified according to histology (SDC v adenocarcinoma NOS): product-limit survival estimate of (A) PFS and (B) OS. NOS, not otherwise specified; OS, overall survival; PFS, progression-free survival; SDC, salivary duct carcinoma.