BMJ Oncology

NISCAHN: a phase II trial of nivolumab in patients with salivary gland carcinoma (Unicancer ORL-08)

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To cite: Fayette J, Even C, Digue L, *et al*. NISCAHN: a phase II trial of nivolumab in patients with salivary gland carcinoma (Unicancer ORL-08). *BMJ Oncology* 2023;**2**:e000065. doi:10.1136/bmjonc-2023-000065

Received 15 March 2023
Accepted 05 October 2023

Linked

► http://dx.doi.org/10.1136/bmjonc-2023-000214

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ABSTRACT

Objective Salivary gland cancers (SGC) are rare cancers with currently no standard treatment for recurrent/metastatic disease. Based on checkpoint inhibitors benefit in a broad range of tumours, NIvolumab in Salivary gland CArcinoma of the Head and Neck (NISCAHN) evaluated nivolumab efficacy in SGC.

Methods and analysis In this phase II single-stage Fleming design, patients with SGC with a progressive disease progression within 6 months prior to entering the study, were divided into ACC (adenoid cytic carcinoma) and non-ACC. All received nivolumab for a maximum of 12 months. The primary endpoint was the non-progression rate at 6 months (NPR_{6m}) according to Response Evaluation Criteria in Solid Tumors V.1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), overall response rate (ORR), tumour growth rate, safety and quality of life (health-related quality of life).

Results 46 patients with ACC and 52 patients without ACC were enrolled over 1 year. Median follow-up was respectively 29.2 months and 16.9 months for patients with ACC and non-ACC. In the ACC cohort, with 15/45 patients non-progressive at 6 months, the primary endpoint was met (33.3%; 95% CI 21.8 to NE). Nivolumab failed to demonstrate efficacy in the non-ACC cohort (NPR_{6m}: 14.0%; 7/50 patients). ORR, PFS and OS were 8.7% (95% CI 2.4 to 20.8), 5.3 (95% CI 3.2 to 5.6) and 17.2 months (95% CI 12.5-NE) in the ACC cohort, and 3.8% (95% CI 0.5 to 13.2), 1.8 (95% CI 1.7 to 3.5) and 11.5 months (95% CI 7.5 to 14.8) in the non-ACC cohort. Nivolumab safety profile was consistent with previous reports.

Conclusion Nivolumab has limited efficacy in SGC. Differential results were observed in the two cohorts. The primary endpoint was met in the ACC cohort and no new safety signals were identified.

Trial registration number EudraCT number: 2016-001794-32/NCT03132038.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Salivary gland cancers (SGC) are rare forms of head and neck cancers with various histological subtypes.
⇒ No standard treatment has been established for recurrent/metastatic disease.

WHAT THIS STUDY ADDS

⇒ In the NISCAHN study, the efficacy of nivolumab was evaluated in metastatic SGC.
⇒ The safety profile of nivolumab in SGC was consistent with previous reports.
⇒ The primary endpoint was met in the adenoid cystic carcinoma (ACC) cohort but not in the non-ACC cohort.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Nivolumab good tolerability was confirmed and its combination with other agents could be of great interest in patients with ACC.

INTRODUCTION

Salivary gland carcinomas (SGC) are rare cancers accounting for less than 5% of head and neck cancers. At the histological level, a very diverse range of 22 SGC subtypes were listed in the 2017 classification of the WHO,[1 2] the three major being mucoepidermoid carcinoma, adenocarcinoma not otherwise specified and adenoid cystic carcinoma (ACC). SGC can then be classified into two groups: ACC, which represents 60% of the malignant histotypes, and non-ACC. ACC are aggressive tumours characterised by frequent local recurrences and distant metastases and more than half of patients with ACC present locally advanced or metastatic disease.[3] Growth is slow but relentless, and progression poses a challenge to clinicians. Unlike ACC, non-ACC SGC are a heterogeneous group with distinct histologies and variable biological behaviour.

Possible therapies are scarce for patients who suffers from SCG. Surgery followed by radiotherapy is the curative treatment

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of choice, and for inoperable recurrent or metastatic disease, treatments are only systemic and palliative. Prognosis is poor with an overall response rate (ORR)<10% under chemotherapy.[4] Due to the rarity of these tumours, it is very difficult to obtain clear data on SGC. However, overall survival (OS) was estimated at 32.3 months after apparition of lung metastases and 20.6 months for metastases elsewhere. The median doubling time of pulmonary metastasis of ACC was estimated at 393 days.[1 2] Patients with recurrent or metastatic non-ACC SGC may achieve ORR ranging from 15% to 50% with conventional cytotoxic chemotherapy but duration of response is typically limited to 6–9 months.[1 2 5]

When the NISCAHN study was designed, no randomised study were realised and only small trials were published. Most efficient drugs were cisplatin, fluorouracil, anthracyclines, taxanes or vinorelbine, but only disappointing results were obtained.[1 2 6 7] Molecular dismemberment made it possible to better classify SGC and highlighted targetable molecular abnormalities[8 9] such as *HER2* amplification that allowed the use of HER2 inhibitors alone or in combination with taxanes,[10 11] or fusion *ETV6-NTRK3* in secretory carcinoma treated with larotrectinib.[12] Several targeted therapies like EGFR or KIT inhibitors[2 13 14] were also tested but only treatments using multitarget tyrosine kinase inhibitors (TKIs), in particular VEGFR inhibitors, seemed promising.[15–18] In that regard, a non-blinded randomised phase II trial comparing axitinib to placebo recently demonstrated a 6-month progression-free survival (PFS) rate of 73.2% vs 23.2% (p<0.001) and a median PFS of 10.8 months versus 2.8 months.[19]

As they have proven to play a pivotal role in the outcome of various types of cancers, the immune checkpoint programmed death-1 (PD-1) receptor and its corresponding ligands (PD-L1 and PD-L2) offer a scientific interest for the treatment of SGC. Indeed, if the effectiveness of anti-PD-1 antibodies is correlated with the tumour mutation burden and SGC often harbour no or few mutations,[20] the usual slow disease progression could allow efficacy of checkpoint inhibitors. Moreover, high PD-L1 expression was reported in high-grade SGC subtypes previously shown to be associated with aggressive behaviour (eg, salivary duct carcinoma and squamous cell carcinoma) and linked to an inferior disease-free survival,[21] and both cytoplasmic and membranous PD-L2 expression were observed in ACC tumour cells.[22 23]

In the multicentre phase II NISCAHN trial, we assessed the efficacy of nivolumab, an anti-PD-1 monoclonal antibody, in patients with SGC. As response rate was probably not a relevant objective to evaluate a new drug in the ACC cohort, non-progression rate at 6 months became the primary objective of this study. Interestingly, this primary endpoint was also presumably more adapted to test immune checkpoint inhibitors.[24] Furthermore, since ACC progression is generally slow, a proof of progression according to Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1 criteria in the 6 months period prior to entering the study, was mandatory to confidently evaluate NISCAHN main objective. Finally, in the NISCAHN study, ACC and non-ACC cohorts were conducted and analysed in parallel as their natural history is quite different.

MATERIALS AND METHODS

Study design

The NISCAHN study was a multicenter single-arm phase II trial. Eligible patients were men and women aged≥18 years with histologically confirmed SGC (ACC or non-ACC), recurrent or metastatic, not eligible for local treatment. Eligible patients had ECOG performance status 0–1, documented evidence of progression based on a central radiological reviewed assessment (baseline radiological evaluation should demonstrate disease progression according to RECIST V.1·1[25] when compared with a prior disease assessment done within a 6-month period prior to study entry). The number of previous therapies was unlimited with a 28 days wash-out period before starting nivolumab.

Patient involvement

Patients were not involved in the design and conduct of this research. The information notice, consent form and lay summary have been submitted to the Patients' Committee for Clinical Research in Cancerology of the Ligue Nationale contre le Cancer for review, opinion and advice. We intend to disseminate the main results of the trial to public and participants.

Procedures

Nivolumab was provided by BMS (Rueil-Malmaison, France). It was administered as a 60 min (± 5 min) intravenously infusion at a fixed dose of 3 mg/kg on D1 and D15 of each 28-day cycle. All eligible patients received nivolumab treatment until disease progression or for a maximum of 12 cycles, whichever occurred first. Dose reductions or escalations were not allowed during the course of the study. Treatment delays were implemented in the event of toxicity and patients were withdrawn from the study in case of severe toxicity. Radiographic tumour assessments (Head&Neck area, chest, abdomen and pelvis) were conducted by local sites every 8 weeks during treatment phase and every 3 months during follow-up phase. Beyond the initial 1-year study period, in case of recurrence within the 24-month interval of time following the last infusion, patient could restart nivolumab as part of the protocol for a maximum of 12 months.

Outcomes

The primary endpoint was the 6 months non-progression rate (NPR_{6m}) defined as the proportion of patients with a complete response (CR), partial response (PR) or stable disease (SD) as per RECIST V.1.1 after 6 months of treatment. Secondary endpoints were ORR, PFS, OS, tumour growth rate before and under treatment in all eligible patients, as well as safety and health-related

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quality of life (HRQoL). ORR was defined as the number and percentage of patients with a confirmed CR or PR from nivolumab first dosing to progression according to RECIST V.1.1, or the date of subsequent therapy, whichever occurred first. PFS was defined as the time from nivolumab first dosing to progression, or death (by any cause in the absence of progression). OS was defined as the time from nivolumab first administration to death due to any cause. Tumour growth rate was defined as the percentage of change in the sum of the longest diameter of target lesions before and during treatment. Safety was based on the occurrence of adverse events (AEs) and assessed at each cycle using the National Cancer Institute Common Terminology Criteria for Adverse Events V.4.0. Patient-reported outcomes were evaluated using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and the head and neck cancer-specific supplementary module (QLQ-H&N35) at the onset of treatment, at every cycle and at the end of treatment.

Pathological analysis (exploratory)

Tumour samples were collected at baseline and sent for a centralised review and for PD-L1 staining with the monoclonal mouse anti-PD-L1 antibody (clone 22C3) on Ventana ULTRA platform. The PD-L1 staining was realised at the CRB of Léon Bérard centre. Results were given by Combined Positive Score (CPS). Tumor-infiltrating lymphocytes (TILs) were assessed by pathologists on H&E stained full sections obtained from operative specimen according to the scoring guidelines of the International TILs Working Group 2014.[26]

Statistical analysis

The same hypothesis was selected for both cohorts (ACC and non-ACC) in which 40% NPR_{6m} was expected under treatment. In this setting, a lower limit of 20% NPR_{6m} or less would mean that Nivolumab did not warrant further investigation in this setting. According to a single-stage Fleming design, a sample size of 42 evaluable patients were necessary to provide 90% power to reject the null-hypothesis with a one-sided, type I error of 5%. If 14 or more patients were non-progressive at 6 months, nivolumab was considered promising. To be evaluable for efficacy, a subject had to meet the eligibility criteria and received at least one treatment administration. To account for a non-assessable patient rate of 10%, 46 patients were required per cohort. The safety population included all patients who had received at least one dose of nivolumab.

Descriptive statistics were used to characterise patients at baseline. Qualitative variables were described using frequency and percentage distributions. Quantitative data were described using median, minimum and maximum values.

NPR_{6m} (primary endpoint) was summarised by a proportion together with its unilateral 95% CI. Patients without disease progression who died within the 6 months following treatment initiation from a cause other than neoplastic or toxic death were considered as not evaluable.

PFS and OS were estimated using the Kaplan-Meier method and described in terms of median along with the associated two-sided 95%CIs. Median follow-up was calculated by a reverse Kaplan Meier estimate. Patients who have not progressed or died at the time of analysis were censored at the time of their latest RECIST assessment. ORR was summarised by a proportion together with its 95%CI. Tumour growth rate was calculated from prebaseline until baseline divided by the time between these two visits[27] and from baseline to disease progression. HRQoL data were analysed following the EORTC recommendations. All analyses were conducted with SAS V.9.4 (SAS Institute).

RESULTS

Patients' characteristics and treatment exposure

At data cut-off date (21 July 2020), out of 116 patients who signed the consent form, 98 patients (46 ACC; 52 non-ACC) were included by 12 French centres between March 2017 and March 2018 (online supplemental figure 1). Patients' characteristics are summarised in table 1.

In the ACC cohort, median age was 59 years old (range: 36–80) and 43.5% patients were women. In the non-ACC cohort, median age was 63 (range: 29–81) and 44.2% were women. All but seven patients (4 ACC; 3 non-ACC) were metastatic. The majority (45 ACC; 51 non-ACC) had received prior anti-cancer therapy and 55 patients (21 ACC; 34 non-ACC) were treated with one or more lines of chemotherapy in metastatic settings (online supplemental tables 3A,B). Median duration of nivolumab was 5.6 months (range: 0.5–11.5) and 3.2 months (range: 0.3–12.3) in the ACC and non-ACC cohorts, respectively (online supplemental table 2). In total, 14 patients received the first 12 cycles of treatment (10 ACC; 4 non-ACC). At data cut-off, 58 deaths (26 ACC; 32 non-ACC) were reported due to progressive disease (16 ACC; 21 non-ACC), cancer-related reasons (10 ACC; 9 non-ACC), intercurrent disease (1 non-ACC), and myocardial infarction (1 non-ACC), 10 patients were still followed (7 ACC; 3 non-ACC), among which 5 (3 ACC; 2 non-ACC) were rechallenged after relapse: 2 patients with ACC were still followed and one was dead while the 2 patients without ACC were still under treatment at the time of the analysis. Median follow-up was 29.2 months (range: 14.5–36.2) and 16.9 months (range: 6.6–31.4) for the ACC and non-ACC cohorts, respectively.

Efficacy

Efficacy data are summarised in table 2 and Consolidated Standards of Reporting Trials flow diagram is presented in online supplemental figure 1.

Three patients were not evaluable for NPR_{6m} (one ACC without 6-month RECIST evaluation and two non-ACC, one consent withdrawal and one death of intercurrent disease before 6-month evaluation). In the ACC cohort,

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Table 1 Patients' demographics and baseline characteristics

	ACC (n=46)	Non-ACC (n=52)
Sex		
M (%)	26 (56.5%)	29 (55.8%)
F (%)	20 (43.5%)	23 (44.2%)
Median age (range)	59 (36–80)	63 (29–81)
ECOG		
0	23 (50.0%)	19 (36.5%)
1	23 (50.0%)	32 (61.5%)
2	0 (0.0%)	1 (1.9%)
Classification at initial diagnosis; n (%)		
T		
0	1 (2.2)	1 (1.9)
1	4 (8.7)	6 (11.5)
2	11 (23.9)	7 (13.5)
3	10 (21.7)	12 (23.1)
4	9 (19.6)	12 (23.1)
X	11 (23.9)	14 (26.9)
N		
0	24 (52.2)	15 (28.8)
1	2 (4.3)	9 (17.3)
2	7 (15.2)	14 (26.9)
3	1 (2.2)	0 (0)
X	12 (26.1)	14 (26.9)
M		
0	33 (71.7)	43 (82.7)
1	13 (28.3)	9 (17.3)
Primary site of cancer		
Major glands; n (%)	32 (69.6)	44 (84.6)
Parotid	12 (26.1)	34 (65.4)
Sublingual*	3 (6.5)	2 (3.8)
Submandibular*	18 (39.1)	8 (15.4)
Minor glands; n (%)	14 (30.4)	8 (15.4)
Base of tongue†	2 (4.3)	3 (5.8)
Floor of mouth‡	2 (4.3)	0 (0)
Lacrimal gland	1 (2.2)	0 (0)
Larynx	2 (4.3)	1 (1.9)
Paranasal sinuses‡	6 (13.0)	1 (1.9)
Peritonsillar area†	0 (0)	1 (1.9)
Posterior pharyngeal walls	0 (0)	0 (0)
Retromolar trigone	0 (0)	0 (0)
Soft palate	2 (4.3)	3 (5.8)
Metastatic disease at inclusion		
Yes§	42 (91.3%)	49 (94.2%)
No	4 (8.7%)	3 (5.8%)
Locoregional relapse at inclusion		
Yes	11 (23.9%)	16 (30.8%)
No	35 (76.1%)	36 (69.2%)
Prior treatments	45 (97.8%)	51 (98.1%)
Surgery	39 (84.8%)	47 (90.4%)
Radiotherapy	42 (91.3%)	47 (90.4%)
Prior chemotherapy	21 (45.7%)	34 (65.4%)
1 line	13	12
2 lines	2	9
>2 lines	6	13
Histology for non-ACC (as per local review¶)		
Mucoepidermoid carcinoma		6 (11.5%)
Adenocarcinoma, NOS**		28 (53.8%)
Salivary duct carcinoma		2 (3.8%)
Other		16 (30.8%)
Acinic cell carcinoma		3
Carcinoma ex-pleomorphic adenoma		1
Epidermoid carcinoma		3
Hyalinising clear cell carcinoma		2
Myoepithelial carcinoma		4
Myoepithelioma††		1
Oncocytic carcinoma		1
Undifferentiated carcinoma		1

*One patient in the ACC cohort had tumour on submandibular and on sublingual.
†One patient in the non-ACC cohort had tumour on base of tongue and on peritonsillar area.
‡One patient in the ACC cohort had tumour on floor of mouth and on paranasal sinuses.
§Metastatic sites at inclusion are described in online supplemental table 1.
¶Local reviews were realised by REFCOR (Réseau d'Expertise Français des Cancers ORL Rares) members.
**Not otherwise specified.
††This patient was first diagnosed with myoepithelioma of the left vocal cord then developed lung metastasis and had locoregional recurrence with the involvement of lymph node.
ACC, adenoid cystic carcinoma; NOS, not otherwise specified.

the primary endpoint was met with 15/45 (33.3%) patients alive without progression at 6 months (one-sided 95% CI 21.8% to -). In the non-ACC cohort, nivolumab demonstrated low level of efficacy with only 7/50 non progressive patients at 6 months, for a NPR_{6m} of 14% (one-sided 95% CI 6.8 to –).

ORR were estimated at 8.7% (95% CI 2.4% to 20.8%) and 3.8% (95% CI 0.5% to 13.2%) in the ACC and non-ACC cohorts, respectively, with only 6/98 objective responses (ACC: 4 PR; non-ACC: 2 PR). Median PFS was 5.3 months (95% CI 3.2 to 5.6) for patients with ACC and

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Table 2 Efficacy data summary

Primary endpoint	ACC n=45	Non-ACC n=50
NPR_{6m}	33.3% (one-sided 95% CI 21.8 to NE)	14.0% (one-sided 95% CI 6.8 to NE)
Pts alive without progression at 6 months	n=15/45 (1 NE)	n=7/50 (2 NE)
Secondary endpoints	**ACC n=46**	**Non-ACC n=52**
Median PFS (in months)	43 PFS events 5.3 (95% CI 3.2 to 5.6)	51 PFS events 1.8 (95% CI 1.7 to 3.5)
Median OS (in months)	26 OS events 17.2 (95% CI 12.5 to NE)	32 OS events 11.5 (95% CI 7.5 to 14.8)
Overall response rate (at best overall response)	8.7% (95% CI 2.4 to 20.8)	3.8% (95% CI 0.5 to 13.2)
CR	0 (0%)	0 (0%)
PR	4 (8.7%)*	2 (3.8%)†
SD	26 (56.5%)	22 (42.3%)
PD	16 (34.8%)	28 (53.8%)

*The histological types of the four ACC responders were soft pelate, larynx, paranasal sinuses and submandibular. Duration of best overall response was 3.2, 20.7, 9.7 and 5.9 months.
†The histological types of the two non-ACC responders were epidermoid and adenocarcinoma.
ACC, adenoid cystic carcinoma; CR, complete response; NPR_{6m}, non-progression rate at 6 months; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

1.8 months (95% CI 1.7 to 3.5) for patients with non-ACC (figure 1). Median OS was longer in the ACC cohort with 17.2 months (95% CI 12.5 to NE) and 11.5 months (95% CI 7.5 to 14.8) (online supplemental figure 2). Tumour growth rate was not decreased after the start of nivolumab (data not shown). Swimmer plots are available in online supplemental figure 3. They describe patient by patient the duration of treatment and clinical endpoints.

Biomarker correlates

In order to assess PD-L1 expression and TILs score, tumour samples were collected at baseline.

As shown in table 3, 20/45 ACC and 27/50 non-ACC were analysed. ACC tumours showed low level of PD-L1 as only 5 out of 20 tested patients had a CPS≥1 while non-ACC tumours showed 13/27 expressing levels of PD-L1 with a CPS≥1. There was no correlation between efficacy and PD-L1 expression as only two patients (one ACC and one non-ACC) with a CPS≥1 were not progressing at 6 months. Similarly, TILs scores were higher in the non-ACC samples with 16/27 TILs≥10%, while 3/20 ACC had TILs≥10%. TILs scores did not either correlate with efficacy.

Safety

A summary of AEs is presented in online supplemental table 4. Altogether, 97 patients (46/46 ACC; 51/52 non-ACC) experienced at least one AE during the NISCAHN study, among which 14/46 (30.4%) patients with ACC and 23/52 (44.2%) patients without ACC had a grade 3–4 clinical or biological AE. Moreover, 37/46 (80.4%) patients with ACC and 27/52 (51.9%) patients without ACC experienced at least one treatment-related AE. The most frequent treatment-related AEs are detailed in online supplemental table 5. Only eight grade 3–4 treatment-related AEs were reported in seven patients: lipase increase (n=2), amylase increase (n=2), blood bilirubin increase (n=1), hypothyroidism (n=1), hepatic failure (n=1) and asthenia (n=1). Three patients had a treatment-related serious adverse event (hypothyroidism, alanine aminotransferase increased associated with blood bilirubin increased that lead to treatment withdrawal, and asthenia), and treatment was withdrawn in five patients, all in the ACC cohort, due to toxicity (amylase and lipase evaluation, grade 2 asthenia and anxiety, Claude Bernard Homer syndrome, hepatic toxicity and grade 3 bilirubin increase).

Health-related quality of life

Compliance to QLQ-C30 and QLQ-H&N35 questionnaires was 86% (84/98 patients) at cycle 1, 86% (60/70 treated patients) at cycle 3, 77% (36/47) at cycle 5 and 54% (53/98 patients) at the end of treatment. In the ACC cohort, there was no great variation in term of HRQoL during the start of treatment and cycles 3 and 5 (online supplemental tables 6, 7, 9 and 10). Then, a slight decrease was registered at the end of the treatment when the majority of patient had stopped the treatment due to progression. This HRQoL seemed poorer at the end of treatment on the items of both QLQ-C30 (figure 2A) and QLQ-H&N35 (figure 2B) questionnaires. Similar data were observed in the non-ACC cohort (online supplemental tables 6, 8, 9 and 11).

DISCUSSION

The NISCAHN phase II study aimed to identify nivolumab activity on SGC cancers. Because of their natural history,

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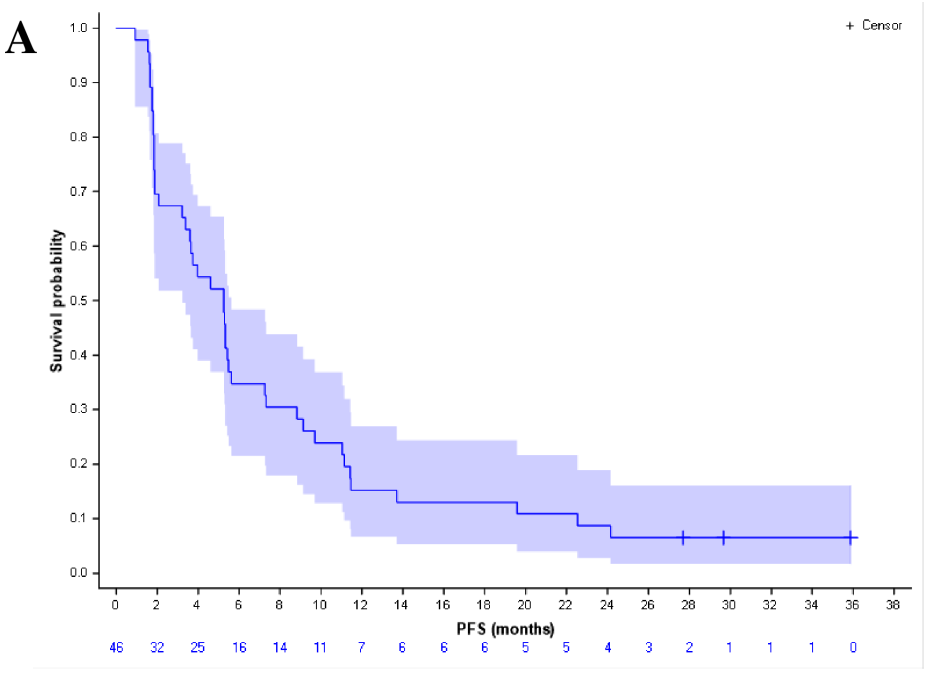
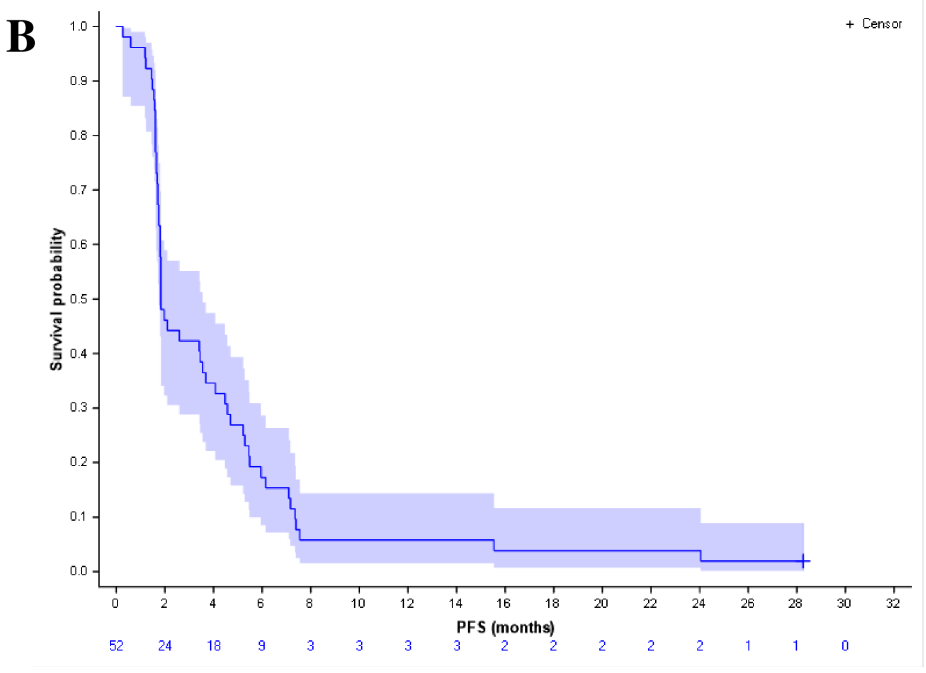


	Event/Total	Median (95% CI)[KM]	Survival Estimates (95% CI)[KM]
	43/46	5.3 (3.2-5.6)	6 months: 0.35 (0.22-0.48) 12 months: 0.15 (0.07-0.27)

[KM]Kaplan-Meier method;



	Event/Total	Median (95% CI)[KM]	Survival Estimates (95% CI)[KM]
	51/52	1.8 (1.7-3.5)	6 months: 0.17 (0.09-0.29)

[KM]Kaplan-Meier method;

Figure 1 Progression-free survival in the (A) adenoid cystic carcinoma (ACC) and (B) non-ACC cohorts. Consolidated Standards of Reporting Trials flow diagram.

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Table 3 Correlation between efficacy and PD-L1 expression or TIL scores

	ACC		Non-ACC	
	n=20	NPR_{6m}	n=27	NPR_{6m}
PD-L1 positive (CPS <1)	15	6	14	3
PD-L1 negative (CPS ≥1)	5	1	13	1
TILs low (<10%)	17	6	11	2
TILs high (≥10%)	3	1	16	2

ACC, adenoid cystic carcinoma; CPS, Combined Positive Score; NPR_{6m}, non-progression rate at 6 months; TILs, tumour-infiltrating lymphocytes.

SGC tumours were classified into two groups: ACC and non-ACC. Therefore, the two cohorts were analysed separately in the NISCAHN trial, and differential responses were observed. In the non-ACC cohort, the primary endpoint was not met with only seven non-progressive patients at 6 months and a lower bound of the one-sided 95% CI 6.8 to -, much lower than the 20% expected. In the ACC cohort, the primary endpoint was met but the response was not robust with only 15/45 non progressive patients showing an one-sided 95% of 21.8% which (>20% threshold) and a target efficacy of 40% included in the CI. If the null hypothesis could not be rejected, the 40% target was not reached. Moreover, median PFS and response rate were low in this cohort with 5.3 months and 8.7% (4/46), respectively. ACC is a heterogeneous group that comprises slow to relatively fast growing tumours. To minimise the heterogeneity of the disease, the NISCAHN cohort was limited to patients with confirmed disease progression within a 6-month period. However, despite this criterion, with no comparator arm, we cannot rule out that the 33.3% (one-sided 95% CI: 21.8 to -) of no progression at 6 months was not a reflect of the natural history of the indolent malignancy.

In the NISCAHN study, the relationship between the efficacy and the expression of biomarkers such as PD-L1 was also investigated. Indeed, high PD-L1 expression, which could result in sensitivity to anti-PD-1 blockage, was previously reported in high-grade SGC subtypes,[21] and the expression of PD-L1 and PD-L2 was correlated with nivolumab efficacy in other head and neck cancers like Head and Neck Squamous Cell Carcinomas.[28 29] Noteworthy, non-ACC tumours previously showed relatively higher PD-L1 protein expression than ACCs, which could result in a greater sensitivity to anti-PD-1 blockade.[21 22 30–34] Moreover, in the KEYNOTE-028 phase I study, pembrolizumab, another anti-PD-1 monoclonal antibody, demonstrated antitumor activity in patients with SGC, mostly non-ACC (92%).[35] In this basket trial, pembrolizumab was tested on 26 prescreened PD-L1 positive patients and demonstrated a NPR_{6m} of 23% (95% CI 9% to 44%).[35] In the NISCAHN non-ACC cohort, we observed a lower NPR_{6m} of 14% (one-sided 95% CI 7 to -), and PD-L1 expression observed in 13 out of the 27 tested patients was not correlated with efficacy since only 1/4 patient was both NPR_{6m} and CPS≥1. Another phase 2 prospective clinical study also evaluated the use of immunotherapy in combination with radiation therapy for the treatment of metastatic ACC.[36] The trial failed to demonstrate the efficacy of the combination over radiation alone but the authors hinted that patients with PD-L1 expression greater than 1% in tumour cells tended to achieve SD more frequently than patients with no PD-L1 expression. However, the difference was not significant due to the limited number of patients included in the trial. As expected, in the NISCAHN ACC cohort, PD-L1 expression was lower than in the non-ACC cohort. Indeed, a few ACC tumours expressed PD-L1 at a very low level (5/20 had a CPS≥1 among which none≥20), and only one out of the seven non-progressive patients at 6 months with available PD-L1 analyse had a CPS≥1. Despite the lack of PD-L1 expression, our data, based on a large cohort, suggest that patients with ACC still benefit from PD-1 inhibitor therapy.

The resistance to PD-1 blockage could be explained by the absence of mutations in SGC. Indeed, tumours with high mutational burden and increased neoantigens expression are generally more responsive to immunocheckpoint blockage therapy, and SGC often harbour no or few mutations.[37] Nevertheless, it was interesting to test the effect of an immune checkpoint inhibitor as cancers such as renal cell carcinoma (RCC),[38] which have lower mutational rates than other tumours, appear to be sensitive to nivolumab therapy, even though RCC being predominantly frameshift, low mutational burden could also result from high neoantigen levels. Moreover, the rate of progression (ROP), defined as the increase in the tumour burden per unit of time, and used to define slow and rapid tumour progression, has recently been correlated with survival prior to starting PD-1 inhibitors. In this study, PFS and OS were shorter in rapid ROP.[39] However, in the NISCAHN trial, the slow disease did not allow efficacy of anti-PD-1 checkpoint inhibitor. Taking together, these results highlight the importance of identifying factors able to predict standardised and reproductive responsiveness to anti-PD-1 treatment. The importance of a targeted therapy based on tumour molecular characteristics have already been demonstrated by the efficacy of anti-HER2 treatments for *HER-2*-amplified tumours[10 11] or specific NTKR inhibitors in case of NTRK-rearrangement.[12] Inclusion of patients with

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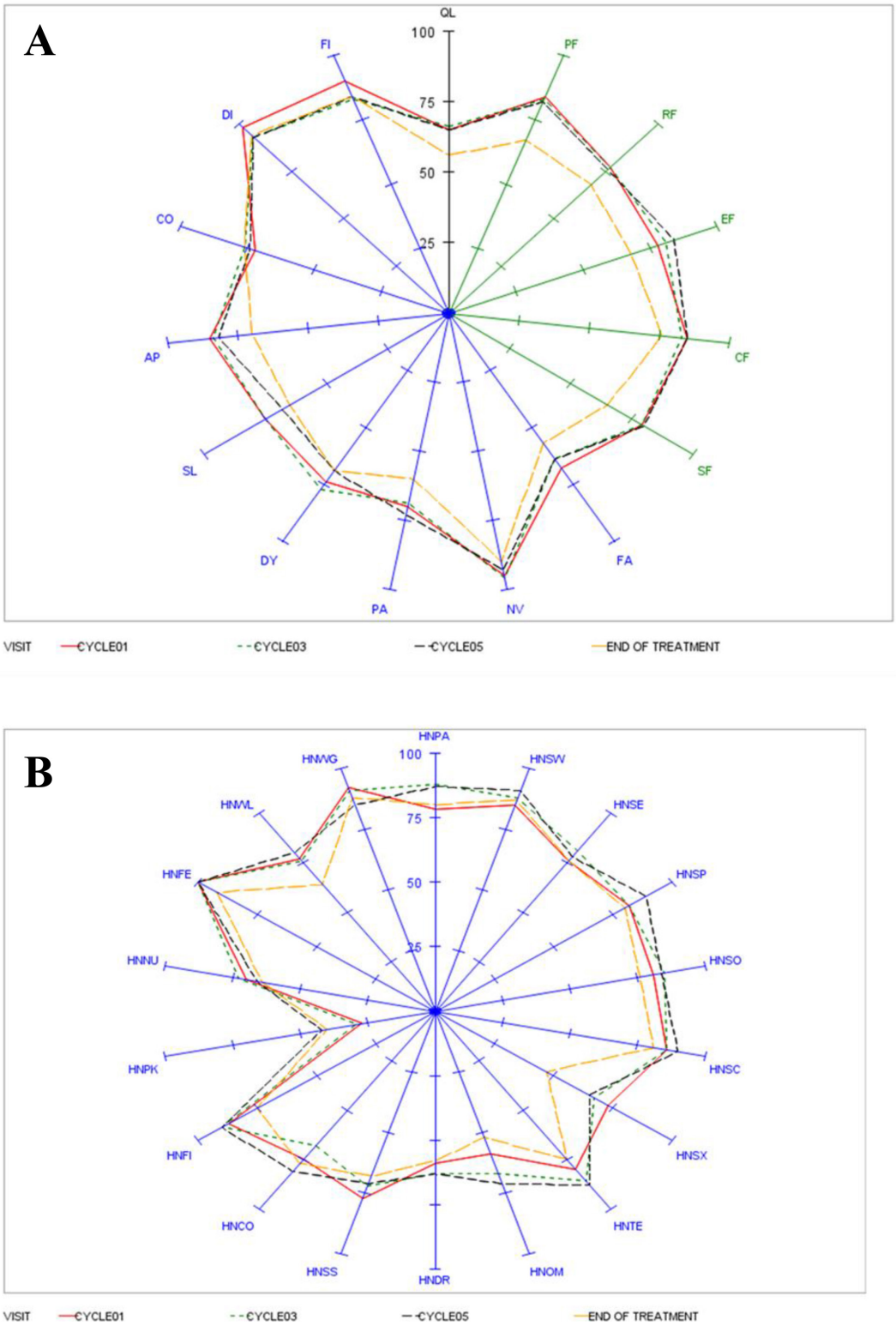

Figure 2 Evolution of the reported health-related quality of life scores at baseline, cycles 1, 3, 5 and end of treatment in patients with adenoid cystic carcinoma according to the European Organization for Research and Treatment of Cancer QLQ-C30 (A) and H&N35 (B) questionnaires. The symptom scales were reversed: the better the quality of life, the larger is the circle. The graphics represent the evolution of the cohort as a whole and not the evolution of each individual. AP, appetite loss; CF, cognitive functioning; CO, constipation; DI, ciarrhoea; DY, dyspnoea; EF, emotional functioning; FA, fatigue; FI, financial difficulties; HNCO, coughing; HNDR, dry mouth; HNFE, feeding tube; HNFI, felt ill; HNNU, nutritional supplements; HNOM, opening mouth; HNPA, pain; HNPK, pain killers; HNSC, trouble with social contact; HNSE, senses problems; HNSO, trouble with social eating; HNSP, speech problems; HNSS, sticky saliva; HNSW, swallowing; HNSX, less sexuality; HNTE, teeth; HNWG, weight gain; HNWL, weight loss; NV, nausea and vomiting; PA, pain; PF, physical functioning; QL, global health status; RF, role functioning; SF, social functioning; SL, insomnia.

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SGC in clinical trials proposing large molecular analysis such as the SPECTA programme of the EORTC could allow the identification of relevant genomic alterations that could be used as prognostic and predictive factors to validate appropriate treatments for these orphan group of diseases.

As only few patients benefit from immune checkpoints treatments, research currently focus on identifying the possible mechanisms leading to immunotherapy resistance and developing novel combination strategies to improve their effectiveness. In the NISCAHN study, the good tolerability of nivolumab was confirmed and was consistent with BMS-nivolumab investigator brochure and previously published data. No new signal of toxicity was reported and patients' HRQoL was not impaired or decreased during and after the treatment, outside of the degradation due to disease progression. Therefore, combination of nivolumab with other agents could be tested to improve its efficacy in ACC. For this test, two major classes of agents should be considered.

First, chemotherapy that can increase the release of tumour antigens by cell destruction and then increase inflammation. In lung cancers or in head and neck cancers, the combination of chemotherapy with immunotherapy increase its efficacy, mostly in tumour with lower response to anti-PD-1/PD-L1 monotherapy.[40] Moreover, reported early data showed that the combination of chemotherapy with nivolumab was feasible with promising early outcomes.[40 41]

Then, TKIs and mostly anti-VEGF(R) agents that can modulate immune microenvironment and potentiate anti-PD-1/PD-L1 treatments.[42] Of late, a phase II single-arm study previous studies have demonstrated a median PFS of 19.8 months, an ORR of 46.2% and a manageable toxicity in patients with recurrent or metastatic ACC treated with apatinib.[43]

This study presents with some limitations. For instance, no interim analysis was planned. The individual data were not revealed during the study and before the database lock in order to avoid bias of the results such as an overselection of the patients included. The availability of the FFPE blocks of the tumours samples was also an issue when PD-L1 expression and TILs score were analysed in only half of the samples. The data were missing completely at random due to end of stock, and storage difficulties that did not allow their staining and analyse.

To summarise, the NISCHAN study demonstrated limited clinical benefit of nivolumab monotherapy in patients with recurrent and/or metastatic SGC who have progressed during the 6-months period before entering the study. Currently, studies combining nivolumab with other agents to improve its efficacy are currently underway. Given the rarity of these tumours, this study showed the possibility to conduct an extensive trial on a rare group of tumours with the inclusion of 98 patients in 12 different centres in 1 year. This study also underlined the importance of molecular characterisation and profiling in the determination of treatment in SGC.

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Acknowledgements We thank the patients and their families, the REFCOR (French network of expertise on rare Head and neck cancers). We thank Dr Emilie Dassé who provided medical writing services on behalf of Unicancer.

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Funding The study sponsor (Unicancer) had a role in study design, data collection, data analysis, data interpretation, and writing of the report. BMS had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The supply of nivolumab was kindly provided by BMS.

Competing interests Nivolumab and financial support were provided by Bristol Myers Squib. JF participated in advisory boards of BMS, MSD, Merck Serono, Astra Zeneca, Rakuten, Roche, Innate Pharma. CE participated in advisory boards of MSD, BMS, Merck Serono, Innate Pharma. LD, DC, AFD, SZ, LB, SC-T, VC-M, AS-B, IJ, FG, AL-C and SC have no disclosure to declare. CB participated in advisory boards of MSD, Merck Serono, BMS, Astra Zeneca. LG participated in advisory boards of MSD, Merck Serono. FR participated in advisory boards of MSD, Merck Serono. JG participated in advisory boards of BMS, MSD, Merck Serono, Astra Zeneca, Innate Pharma. CLT participated in advisory boards of BMS, MSD, Merck Serono, Astra Zeneca, Rakuten, Seattle Genetics, Roche, GSK, Nanobiotix.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval The study protocol was first approved by the independent french ethical committee "Comité de Protection des Personnes (CPP) SUD-EST II" on the 03-Nov-2016. Patients had to confirm their consent in writing prior to starting the study and prior to any study-related procedures. The study was conducted in the rigorous standards set out in the International Conference on Harmonization Guideline for Good Clinical Practice and in accordance with the principles in the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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SUPPLEMENTARY DATA

Supplementary Table 1: Description of the metastatic sites at inclusion

	ACC cohort (N=46)	Non ACC cohort (n=52)
Metastatic sites at inclusion; n (%)		
Adrenal	2 (4.8)	2 (4.1)
Bones	11 (26.2)	15 (30.6)
Brain	1 (2.4)	5 (10.2)
Cutaneous	2 (4.8)	4 (8.2)
Liver	16 (38.1)	12 (24.5)
Lung	41 (97.6)	42 (85.7)
Lymph nodes	18 (42.9)	20 (40.8)
Mediastinal	7 (16.7)	15 (30.6)
Pleural	8 (19)	9 (18.4)
Renal	2 (4.8)	5 (10.2)
Other:	3 (4.8)	3 (6.1)
Ascites + node diaphragmatic carcinosis	1	0
Muscle	0	1
Nodes intra muscular	0	1
Pancreas	1	1
Parietal Muscle	1	0

Supplementary Table 2: Treatment compliance

	ACC (N = 46)		Non-ACC (N = 52)	
Status at data cut-off *(July 2020)*	7 still followed (2 have restarted)	39 stopped (26 (56.5%) dead)	3 still followed (2 have restarted)	49 stopped (32 (61.5%) dead)
Median Treatment Duration (range) Median Cycles Number (range)	5.6 months (0.5 – 11.5) 6 (1 – 12)		3.3 months (0.3 – 12.3) 4 (1 – 12)	
Reasons for End of Treatment End of first 12 cycles Progressive Disease Death (no toxic death) Other	10 (21.7%) 29 (63.0%) 0 0 (0%) 7 (15.3%) including: - 5 (10.9%) for AE - 1 (2.2%) for physician's decision - 1 (2.2%) for patient's decision		4 (7.7%) 41 (78.8%) 5 (9.6%) 2 (3.8%) including: - 2 (3.8%) patient withdrawal	

Supplementary Table 3a: List of prior anticancer treatments

Treatments	ACC cohort (N=46)	Non ACC cohort (n=52)
Neoadjuvant chemotherapy		
Cisplatin + docetaxel + 5-FU	0	1
Adjuvant chemotherapy [1]		
5-FU	0	1
Carboplatin + paclitaxel	0	2
Cetuximab	0	1
Cisplatin	0	1
Cisplatin + cetuximab	0	1
Radio-chemotherapy [2]		
5-FU	1	0
5-FU + cisplatin	0	1
Carboplatin	1	1
Cetuximab	0	3
Cisplatin	3	10
Targeted therapy [3]		
Axitinib	2	2
Bevacizumab	1	0
Cetuximab	1	1
Erlotinib	3	1
Everolimus	0	1
Everolimus + bevacizumab	0	1
Notch inhibitor	4	2
Pazopanib	4	4
Tomuzotuximab	0	1
Name not recorded [4]	1	0
Other treatments [5]		
Bicalutamide	0	1
Cryotherapy	1	0
Hepatic puncture biopsy	1	0
Hepatic radiofrequency	1	0
Hepatic radiofrequency ablation	0	1
Herceptin	0	1
Hormonotherapy	0	1
Proton therapy of skull	0	1
Pulmonary radiofrequency ablation	0	1
Radiofrequency ablation of left lung nodule	1	0
Sphenopalatine node neurolysis	0	1
Tamoxifen	1	0
Triptorelin	0	1

Treatments	ACC cohort (N=46)	Non ACC cohort (n=52)

1. One patient had concomitant cisplatin + cetuximab + 5-FU and one patient had cisplatin + cetuximab then carboplatin + paclitaxel
2. One ACC patient had Carboplatin + 5-FU and one non-ACC patient had cisplatin then cetuximab
3. In the ACC cohort, patient had Erlotinib followed by Pazopanib followed by Axitinib and one patient had Erlotinib followed Imatinib followed Notch inhibitor. In the non-ACC cohort, one patient had tomuzotuximab then cetuximab; one patient had erlotinib then notch inhibitor and one patient had pazopanib then everolimus then everolimus + bevacizumab then pazopanib (For this patient pazopanib was counted only once)
4. The name of target therapy and the number of administrated cycles were not recorded
5. One non-ACC patient had hepatic radiofrequency ablation then pulmonary radiofrequency ablation and one patient had triptorelin, Herceptin, and bicalutamide

Supplementary Table 3b: List of prior anticancer treatments in the metastatic setting

Treatments	ACC cohort (N=46) N (%)	Non ACC cohort (n=52) N (%)
5-FU	1 (2.2)	3 (5.8)
Capecitabine	2 (4.3)	6 (11.5)
Carboplatin	7 (15.2)	8 (15.4)
Carboplatin-paclitaxel	2 (4.3)	14 (26.9)
Carboplatin-paclitaxel-Herceptin	1 (2.2)	1 (1.9)
Carboplatin-vinorelbine	3 (6.5)	1 (1.9)
Cisplatin	6 (13)	4 (7.7)
Cisplatin-5-FU	0 (0.0)	2 (3.8)
Cisplatin-5-FU-methtrexate-bevacizumab	1 (2.2)	1 (1.9)
Cisplatin-cyclophosphamide-doxorubicin	0 (0.0)	1 (1.9)
Cisplatin-docetaxel	0 (0.0)	1 (1.9)
Cisplatin-doxorubicin-cyclophosphamide	0 (0.0)	1 (1.9)
Cisplatin-vinorelbine	2 (4.3)	0 (0.0)
Cyclophosphamide	1 (2.2)	2 (3.8)
Cyclophosphamide-doxorubicin	0 (0.0)	1 (1.9)
Cyclophosphamide-paclitaxel	0 (0.0)	1 (1.9)
Docetaxel	2 (4.3)	1 (1.9)
Doxorubicin	2 (4.3)	3 (5.8)
Doxorubicin-ifosfamide	0 (0.0)	1 (1.9)
Etoposide	1 (2.2)	0 (0.0)
Gemcitabine	1 (2.2)	5 (9.6)
Paclitaxel	5 (10.9)	11 (21.2)
Paclitaxel-carboplatin	0 (0.0)	1 (1.9)
Tamoxifen	4 (8.7)	2 (3.8)
Vinorelbine	11 (23.9)	8 (15.4)

Supplementary Table 4: Summary of AEs observed during the NISCAHN study

	ACC cohort N=46	Non ACC cohort n=52
At least one AE	46 (100.%)	1 (1.9%)
At least one grade 3/4 AE	14 (30.4%)	23 (44.2%)
At least one AE leading to treatment withdrawal	8 (17.4%)	2 (3.8%)
At least one treatment-related AE	37 (80.4%)	27 (51.9%)
At least one treatment-related grade 3/4 AE	5 (10.9%)	2 (3.8%)
Serious adverse event (SAE)	10 (21.7%)	15 (28.8%)

Supplementary Table 5: Most frequently reported treatment-related AEs (any grade)

NCI CTCAE V4.03	ACC N=46	Non-ACC N=52
Asthenia	13 (28.3%)	9 (17.3%)
Hyperthyroidism	8 (17.4%)	0
Diarrhoea	7 (15.2%)	2 (3.8%)
Rash	6 (13%)	3 (5.8%)
Hypothyroidism	5 (10.9%)	2 (3.8%)
Pruritus	5 (10.9%)	7 (13.5%)

Supplementary Table 6: QLQC-30 scores at C1D1

	ACC cohort N=40	Non-ACC cohort N=44
Global health status QL		
N	40	40
Mean (Std)	65.6 (18.1)	65.6 (18.1)
Median (min; max)	66.7 (25; 100)	66.7 (25; 100)
QLC-C30 Pysical functioning PF		
N	40	40
Mean (Std)	84.5 (14.9)	84.5 (14.9)
Median (min; max)	89.2 (47; 100)	89.2 (47; 100)
QLC-C30 Role functioning RF		
N	40	40
Mean (Std)	77.9 (26.8)	77.9 (26.8)
Median (min; max)	83.3 (0; 100)	83.3 (0; 100)
QLC-C30 Emotional functionong EF		
N	40	40
Mean (Std)	79.0 (18.0)	79.0 (18.0)
Median (min; max)	83.3 (42; 100)	83.3 (42; 100)
QLC-C30 Cognitive functioning CF		
N	40	40
Mean (Std)	85.4 (21.4)	85.4 (21.4)
Median (min; max)	100.0 (33; 100)	100.0 (33; 100)
QLC-C30 Social functioning SF		
N	40	40
Mean (Std)	79.6 (26.8)	79.6 (26.8)
Median (min; max)	91.7 (0; 100)	91.7 (0; 100)
QLC-C30 Fatigue FA		
N	40	40
Mean (Std)	31.4 (26.3)	31.4 (26.3)
Median (min; max)	27.8 (0; 89)	27.8 (0; 89)
QLC-C30 Nausea Vomiting NV		
N	40	40
Mean (Std)	4.2 (9.1)	4.2 (9.1)
Median (min; max)	0.0 (0; 33)	0.0 (0; 33)
QLC-C30 Pain PA		
N	40	40
Mean (Std)	29.6 (32.1)	29.6 (32.1)
Median (min; max)	16.7 (0; 100)	16.7 (0; 100)
QLC-C30 Dyspnoea DY		
N	40	40
Mean (Std)	25.8 (27.7)	25.8 (27.7)
Median (min; max)	33.3 (0; 100)	33.3 (0; 100)
QLC-C30 Insomnia SL		
N	40	40
Mean (Std)	24.2 (23.9)	24.2 (23.9)
Median (min; max)	33.3 (0; 100)	33.3 (0; 100)
QLC-C30 Appetite loss AP		
N	40	40
Mean (Std)	14.2 (28.1)	14.2 (28.1)
Median (min; max)	0.0 (0; 100)	0.0 (0; 100)
QLC-C30 Constipation CO		
N	40	40
Mean (Std)	27.5 (29.1)	27.5 (29.1)
Median (min; max)	33.3 (0; 100)	33.3 (0; 100)
QLC-C30 Diarrhoea DI		
N	40	40
Mean (Std)	1.7 (7.4)	1.7 (7.4)
Median (min; max)	0.0 (0; 33)	0.0 (0; 33)
QLC-C30 Financial difficulties FI		
N	40	40
Mean (Std)	10.0 (22.9)	10.0 (22.9)
Median (min; max)	0.0 (0; 100)	0.0 (0; 100)

Supplementary Table 7: Evolution of the QLQC-30 scores in the ACC cohort

	Visit					
	CYCLE03 N=35	CYCLE05 N=21	CYCLE07 N=16	CYCLE09 N=13	CYCLE11 N=12	END OF TREATMENT N=25
Absolute variation of Global health status QL						
N	32	21	16	13	12	24
Mean (Std)	-1.6 (14.0)	-7.1 (18.3)	-4.2 (12.9)	-12.2 (24.4)	-8.3 (19.8)	-9.4 (26.5)
Median (min; max)	0.0 (-33; 33)	0.0 (-33; 42)	0.0 (-33; 17)	-8.3 (-67; 17)	0.0 (-42; 17)	-8.3 (-75; 50)
Functional scales						
Physical functionning PF						
N	35	21	15	13	12	25
Mean (Std)	-2.0 (9.4)	-3.7 (14.4)	-1.2 (8.8)	-5.0 (15.4)	-3.7 (19.8)	-16.6 (27.9)
Median (min; max)	0.0 (-20; 27)	0.0 (-40; 20)	0.0 (-13; 20)	0.0 (-40; 13)	-2.5 (-53; 20)	-6.7 (-80; 27)
Role functionning RF						
N	35	21	16	13	12	25
Mean (Std)	-4.8 (24.4)	-5.6 (30.4)	-6.3 (14.8)	-5.1 (37.5)	-1.4 (32.9)	-10.7 (41.4)
Median (min; max)	0.0 (-67; 33)	0.0 (-100; 33)	0.0 (-50; 0)	0.0 (-100; 33)	0.0 (-83; 33)	0.0 (-100; 100)
Emotional functioning EF						
N	34	21	16	13	12	25
Mean (Std)	-0.7 (12.5)	0.8 (13.2)	1.6 (9.7)	-2.6 (19.1)	-4.9 (20.2)	-9.9 (27.6)
Median (min; max)	0.0 (-25; 33)	0.0 (-25; 33)	0.0 (-17; 25)	0.0 (-42; 33)	-4.2 (-33; 42)	-8.3 (-75; 42)
Cognitive functioning CF						
N	34	21	16	13	12	25
Mean (Std)	-4.9 (20.3)	-4.0 (15.7)	-4.2 (9.6)	-6.4 (16.0)	-5.6 (8.2)	-6.7 (25.0)
Median (min; max)	0.0 (-67; 33)	0.0 (-33; 33)	0.0 (-33; 0)	0.0 (-50; 17)	0.0 (-17; 0)	0.0 (-83; 50)
Social functioning SF						
N	34	21	16	13	12	25
Mean (Std)	-2.0 (21.6)	-6.3 (20.7)	1.0 (11.3)	-2.6 (30.3)	-1.4 (29.7)	-16.0 (29.5)
Median (min; max)	0.0 (-67; 50)	0.0 (-67; 17)	0.0 (-17; 33)	0.0 (-67; 50)	0.0 (-83; 33)	-16.7 (-100; 33)
Symptom scales / items						
Fatigue FA						
N	35	21	16	13	12	25
Mean (Std)	5.4 (21.3)	10.6 (25.2)	11.1 (23.0)	16.2 (27.1)	13.9 (25.6)	12.9 (29.5)
Median (min; max)	0.0 (-56; 44)	11.1 (-44; 56)	5.6 (-44; 44)	22.2 (-44; 56)	11.1 (-33; 78)	11.1 (-44; 100)
Nausea and vomiting NV						
N	35	21	16	13	12	25
Mean (Std)	-0.5 (7.5)	2.4 (10.9)	1.0 (7.4)	1.3 (10.7)	0.0 (10.1)	6.0 (17.3)
Median (min; max)	0.0 (-17; 17)	0.0 (-17; 33)	0.0 (-17; 17)	0.0 (-17; 17)	0.0 (-17; 17)	0.0 (-17; 50)
Pain PA						
N	35	21	16	13	12	25
Mean (Std)	2.9 (24.1)	2.4 (31.7)	5.2 (19.9)	15.4 (25.0)	8.3 (25.1)	15.3 (36.6)
Median (min; max)	0.0 (-50; 50)	0.0 (-50; 67)	0.0 (-50; 33)	16.7 (-50; 50)	16.7 (-50; 50)	16.7 (-100; 100)
Dyspnoea DY						
N	35	21	16	13	12	25
Mean (Std)	-3.8 (30.0)	7.9 (36.4)	0.0 (34.4)	-7.7 (45.4)	-8.3 (40.5)	9.3 (29.7)
Median (min; max)	0.0 (-67; 67)	0.0 (-67; 100)	0.0 (-100; 67)	0.0 (-100; 67)	0.0 (-67; 100)	0.0 (-67; 67)
Insomnia SL						
N	34	21	16	13	12	25
Mean (Std)	2.9 (25.1)	7.9 (29.6)	2.1 (14.8)	12.8 (32.0)	13.9 (26.4)	12.0 (35.8)
Median (min; max)	0.0 (-33; 100)	0.0 (-67; 67)	0.0 (-33; 33)	0.0 (-33; 67)	0.0 (-33; 67)	0.0 (-67; 100)
Appetite loss AP						
N	35	21	16	13	12	25
Mean (Std)	1.0 (26.2)	-1.6 (24.7)	2.1 (19.1)	2.6 (21.4)	5.6 (23.9)	20.0 (36.0)
Median (min; max)	0.0 (-100; 33)	0.0 (-67; 33)	0.0 (-33; 33)	0.0 (-33; 33)	0.0 (-33; 33)	0.0 (-33; 100)
Constipation CO						
N	34	21	16	13	12	25
Mean (Std)	-2.9 (20.7)	3.2 (31.5)	-2.1 (19.1)	0.0 (27.2)	0.0 (24.6)	0.0 (27.2)
Median (min; max)	0.0 (-33; 33)	0.0 (-33; 100)	0.0 (-33; 33)	0.0 (-33; 67)	0.0 (-33; 67)	0.0 (-33; 67)
Diarrhoea DI						
N	34	21	16	13	12	25

	Visit					
	CYCLE03 N=35	CYCLE05 N=21	CYCLE07 N=16	CYCLE09 N=13	CYCLE11 N=12	END OF TREATMENT N=25
Mean (Std)	4.9 (18.6)	4.8 (19.1)	6.3 (18.1)	2.6 (9.2)	0.0 (14.2)	4.0 (14.7)
Median (min; max)	0.0 (-33; 67)	0.0 (-33; 67)	0.0 (-33; 33)	0.0 (0; 33)	0.0 (-33; 33)	0.0 (-33; 33)
Financial difficulties FI						
N	34	21	16	13	12	25
Mean (Std)	4.9 (21.9)	1.6 (16.6)	2.1 (22.7)	5.1 (18.5)	5.6 (19.2)	10.7 (26.7)
Median (min; max)	0.0 (-67; 67)	0.0 (-33; 33)	0.0 (-67; 33)	0.0 (-33; 33)	0.0 (-33; 33)	0.0 (-33; 100)
Absolute variation of (Qualitatif)						
Global health status QL						
Missing data	3	0	0	0	0	1
WORSENED	8 (25.0%)	8 (38.1%)	5 (31.3%)	6 (46.2%)	5 (41.7%)	11 (45.8%)
STABLE	19 (59.4%)	11 (52.4%)	10 (62.5%)	4 (30.8%)	5 (41.7%)	8 (33.3%)
IMPROVED	5 (15.6%)	2 (9.5%)	1 (6.3%)	3 (23.1%)	2 (16.7%)	5 (20.8%)
Functional scales						
Physical functionning PF						
Missing data	0	0	1	0	0	0
WORSENED	8 (22.9%)	4 (19.0%)	2 (13.3%)	3 (23.1%)	4 (33.3%)	10 (40.0%)
STABLE	25 (71.4%)	15 (71.4%)	11 (73.3%)	9 (69.2%)	5 (41.7%)	13 (52.0%)
IMPROVED	2 (5.7%)	2 (9.5%)	2 (13.3%)	1 (7.7%)	3 (25.0%)	2 (8.0%)
Role functionning RF						
WORSENED	9 (25.7%)	8 (38.1%)	3 (18.8%)	3 (23.1%)	3 (25.0%)	10 (40.0%)
STABLE	19 (54.3%)	8 (38.1%)	13 (81.3%)	6 (46.2%)	5 (41.7%)	10 (40.0%)
IMPROVED	7 (20.0%)	5 (23.8%)	0 (0.0%)	4 (30.8%)	4 (33.3%)	5 (20.0%)
Emotional functioning EF						
Missing data	1	0	0	0	0	0
WORSENED	5 (14.7%)	3 (14.3%)	2 (12.5%)	3 (23.1%)	4 (33.3%)	10 (40.0%)
STABLE	24 (70.6%)	15 (71.4%)	13 (81.3%)	7 (53.8%)	7 (58.3%)	11 (44.0%)
IMPROVED	5 (14.7%)	3 (14.3%)	1 (6.3%)	3 (23.1%)	1 (8.3%)	4 (16.0%)
Cognitive functioning CF						
Missing data	1	0	0	0	0	0
WORSENED	8 (23.5%)	7 (33.3%)	3 (18.8%)	4 (30.8%)	4 (33.3%)	9 (36.0%)
STABLE	22 (64.7%)	11 (52.4%)	13 (81.3%)	8 (61.5%)	8 (66.7%)	13 (52.0%)
IMPROVED	4 (11.8%)	3 (14.3%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	3 (12.0%)
Social functioning SF						
Missing data	1	0	0	0	0	0
WORSENED	7 (20.6%)	6 (28.6%)	2 (12.5%)	3 (23.1%)	2 (16.7%)	13 (52.0%)
STABLE	21 (61.8%)	11 (52.4%)	12 (75.0%)	7 (53.8%)	7 (58.3%)	9 (36.0%)
IMPROVED	6 (17.6%)	4 (19.0%)	2 (12.5%)	3 (23.1%)	3 (25.0%)	3 (12.0%)
Symptom scales / items						
Fatigue FA						
IMPROVED	9 (25.7%)	3 (14.3%)	2 (12.5%)	2 (15.4%)	1 (8.3%)	6 (24.0%)
STABLE	10 (28.6%)	5 (23.8%)	6 (37.5%)	2 (15.4%)	3 (25.0%)	5 (20.0%)
WORSENED	16 (45.7%)	13 (61.9%)	8 (50.0%)	9 (69.2%)	8 (66.7%)	14 (56.0%)
Nausea and vomiting NV						
IMPROVED	4 (11.4%)	2 (9.5%)	1 (6.3%)	2 (15.4%)	2 (16.7%)	3 (12.0%)
STABLE	28 (80.0%)	15 (71.4%)	13 (81.3%)	8 (61.5%)	8 (66.7%)	16 (64.0%)
WORSENED	3 (8.6%)	4 (19.0%)	2 (12.5%)	3 (23.1%)	2 (16.7%)	6 (24.0%)
Pain PA						
IMPROVED	8 (22.9%)	5 (23.8%)	2 (12.5%)	1 (7.7%)	2 (16.7%)	2 (8.0%)
STABLE	15 (42.9%)	7 (33.3%)	7 (43.8%)	3 (23.1%)	3 (25.0%)	10 (40.0%)
WORSENED	12 (34.3%)	9 (42.9%)	7 (43.8%)	9 (69.2%)	7 (58.3%)	13 (52.0%)
Dyspnoea DY						
IMPROVED	8 (22.9%)	4 (19.0%)	2 (12.5%)	6 (46.2%)	5 (41.7%)	3 (12.0%)
STABLE	22 (62.9%)	10 (47.6%)	11 (68.8%)	4 (30.8%)	6 (50.0%)	13 (52.0%)
WORSENED	5 (14.3%)	7 (33.3%)	3 (18.8%)	3 (23.1%)	1 (8.3%)	9 (36.0%)
Insomnia SL						
Missing data	1	0	0	0	0	0
IMPROVED	5 (14.7%)	3 (14.3%)	1 (6.3%)	2 (15.4%)	1 (8.3%)	3 (12.0%)
STABLE	23 (67.6%)	10 (47.6%)	13 (81.3%)	6 (46.2%)	6 (50.0%)	14 (56.0%)
WORSENED	6 (17.6%)	8 (38.1%)	2 (12.5%)	5 (38.5%)	5 (41.7%)	8 (32.0%)
Appetite loss AP						
IMPROVED	5 (14.3%)	4 (19.0%)	2 (12.5%)	2 (15.4%)	2 (16.7%)	2 (8.0%)
STABLE	22 (62.9%)	13 (61.9%)	11 (68.8%)	8 (61.5%)	6 (50.0%)	13 (52.0%)
WORSENED	8 (22.9%)	4 (19.0%)	3 (18.8%)	3 (23.1%)	4 (33.3%)	10 (40.0%)
Constipation CO						
Missing data	1	0	0	0	0	0

	Visit											
	CYCLE03 N=35		CYCLE05 N=21		CYCLE07 N=16		CYCLE09 N=13		CYCLE11 N=12		END OF TREATMENT N=25	
IMPROVED	8	(23.5%)	5	(23.8%)	3	(18.8%)	3	(23.1%)	2	(16.7%)	7	(28.0%)
STABLE	21	(61.8%)	11	(52.4%)	11	(68.8%)	8	(61.5%)	9	(75.0%)	12	(48.0%)
WORSENED	5	(14.7%)	5	(23.8%)	2	(12.5%)	2	(15.4%)	1	(8.3%)	6	(24.0%)
Diarrhoea DI												
Missing data	1		0		0		0		0		0	
IMPROVED	1	(2.9%)	1	(4.8%)	1	(6.3%)	0	(0.0%)	1	(8.3%)	1	(4.0%)
STABLE	29	(85.3%)	17	(81.0%)	11	(68.8%)	12	(92.3%)	10	(83.3%)	20	(80.0%)
WORSENED	4	(11.8%)	3	(14.3%)	4	(25.0%)	1	(7.7%)	1	(8.3%)	4	(16.0%)
Financial difficulties FI												
Missing data	1		0		0		0		0		0	
IMPROVED	2	(5.9%)	2	(9.5%)	1	(6.3%)	1	(7.7%)	1	(8.3%)	1	(4.0%)
STABLE	25	(73.5%)	16	(76.2%)	12	(75.0%)	9	(69.2%)	8	(66.7%)	18	(72.0%)
WORSENED	7	(20.6%)	3	(14.3%)	3	(18.8%)	3	(23.1%)	3	(25.0%)	6	(24.0%)

Supplementary Table 8: Evolution of the QLQC-30 scores in the non-ACC cohort

	Visit			
	CYCLE03 N=25	CYCLE05 N=15	CYCLE07 N=10	END OF TREATMENT N=28
Absolute variation of				
Global health status QL				
N	21	14	9	28
Mean (Std)	-2.4 (30.9)	3.0 (18.9)	0.9 (24.5)	-7.4 (19.7)
Median (min; max)	0.0 (-75; 50)	4.2 (-33; 33)	0.0 (-42; 33)	0.0 (-50; 33)
Functional scales				
Physical functionning PF				
N	24	15	10	28
Mean (Std)	-5.7 (17.2)	-1.6 (18.8)	1.0 (22.6)	-16.9 (28.7)
Median (min; max)	0.0 (-50; 13)	0.0 (-40; 27)	6.7 (-60; 20)	-6.7 (-93; 20)
Role functionning RF				
N	23	15	10	28
Mean (Std)	-2.2 (41.5)	10.0 (34.4)	6.7 (37.8)	-11.3 (36.0)
Median (min; max)	0.0 (-83; 67)	16.7 (-67; 67)	8.3 (-83; 50)	0.0 (-83; 33)
Emotional functioning EF				
N	23	15	10	28
Mean (Std)	-3.1 (25.6)	2.6 (26.7)	6.4 (11.2)	-12.3 (29.4)
Median (min; max)	0.0 (-83; 25)	8.3 (-42; 67)	4.2 (-8; 22)	0.0 (-67; 33)
Cognitive functioning CF				
N	23	15	10	28
Mean (Std)	-2.9 (18.6)	-2.2 (28.1)	-3.3 (18.9)	-3.6 (18.3)
Median (min; max)	0.0 (-50; 33)	0.0 (-50; 50)	0.0 (-33; 17)	0.0 (-33; 33)
Social functioning SF				
N	23	15	10	28
Mean (Std)	3.6 (32.9)	-6.7 (26.6)	1.7 (16.6)	-6.0 (31.5)
Median (min; max)	0.0 (-67; 100)	0.0 (-50; 33)	0.0 (-33; 33)	0.0 (-67; 67)
Symptom scales / items				
Fatigue FA				
N	23	15	10	28
Mean (Std)	7.5 (32.2)	8.9 (37.1)	1.1 (35.3)	18.3 (31.9)
Median (min; max)	0.0 (-44; 78)	11.1 (-56; 67)	5.6 (-56; 56)	22.2 (-56; 89)
Nausea and vomiting NV				
N	24	15	10	28
Mean (Std)	2.8 (11.7)	-1.1 (4.3)	1.7 (5.3)	5.4 (21.3)
Median (min; max)	0.0 (-17; 50)	0.0 (-17; 0)	0.0 (0; 17)	0.0 (-50; 67)
Pain PA				
N	24	15	10	28
Mean (Std)	-2.8 (37.0)	-1.1 (43.4)	-10.0 (25.1)	10.1 (37.5)
Median (min; max)	0.0 (-67; 100)	0.0 (-83; 100)	0.0 (-50; 17)	0.0 (-67; 83)
Dyspnoea DY				
N	24	15	10	28
Mean (Std)	2.8 (23.9)	2.2 (23.5)	-6.7 (26.3)	7.1 (35.6)
Median (min; max)	0.0 (-33; 67)	0.0 (-33; 33)	0.0 (-67; 33)	0.0 (-67; 100)
Insomnia SL				
N	22	15	10	28
Mean (Std)	3.0 (27.0)	11.1 (32.5)	13.3 (28.1)	4.8 (29.7)
Median (min; max)	0.0 (-33; 67)	33.3 (-33; 67)	33.3 (-33; 33)	0.0 (-33; 100)
Appetite loss AP				
N	23	15	9	25
Mean (Std)	2.9 (22.3)	2.2 (29.5)	-3.7 (26.1)	21.3 (33.2)
Median (min; max)	0.0 (-33; 67)	0.0 (-33; 67)	0.0 (-33; 33)	0.0 (-33; 100)
Constipation CO				
N	23	15	10	28
Mean (Std)	8.7 (25.1)	6.7 (36.1)	-3.3 (29.2)	9.5 (33.8)
Median (min; max)	0.0 (-33; 67)	0.0 (-67; 67)	0.0 (-67; 33)	0.0 (-33; 100)
Diarrhoea DI				
N	23	15	10	28
Mean (Std)	-4.3 (15.3)	-2.2 (15.3)	3.3 (10.5)	-1.2 (32.1)
Median (min; max)	0.0 (-33; 33)	0.0 (-33; 33)	0.0 (0; 33)	0.0 (-67; 100)
Financial difficulties FI				
N	23	15	10	28
Mean (Std)	7.2 (20.0)	8.9 (26.6)	0.0 (0.0)	-1.2 (16.9)
Median (min; max)	0.0 (-33; 67)	0.0 (0; 100)	0.0 (0; 0)	0.0 (-33; 67)
Absolute variation of (Qualitatif)				

	Visit							
	CYCLE03 N=25		CYCLE05 N=15		CYCLE07 N=10		END OF TREATMENT N=28	
Global Health status								
Global health status QL								
WORSENED	6	(28.6%)	3	(21.4%)	3	(33.3%)	12	(42.9%)
STABLE	8	(38.1%)	7	(50.0%)	3	(33.3%)	12	(42.9%)
IMPROVED	7	(33.3%)	4	(28.6%)	3	(33.3%)	4	(14.3%)
Functional scales								
Physical functionning PF								
WORSENED	7	(29.2%)	4	(26.7%)	1	(10.0%)	12	(42.9%)
STABLE	13	(54.2%)	6	(40.0%)	6	(60.0%)	12	(42.9%)
IMPROVED	4	(16.7%)	5	(33.3%)	3	(30.0%)	4	(14.3%)
Role functionning RF								
WORSENED	7	(30.4%)	4	(26.7%)	2	(20.0%)	10	(35.7%)
STABLE	7	(30.4%)	3	(20.0%)	3	(30.0%)	10	(35.7%)
IMPROVED	9	(39.1%)	8	(53.3%)	5	(50.0%)	8	(28.6%)
Emotional functioning EF								
WORSENED	4	(17.4%)	4	(26.7%)	0	(0.0%)	10	(35.7%)
STABLE	12	(52.2%)	6	(40.0%)	6	(60.0%)	14	(50.0%)
IMPROVED	7	(30.4%)	5	(33.3%)	4	(40.0%)	4	(14.3%)
Cognitive functioning CF								
WORSENED	6	(26.1%)	5	(33.3%)	3	(30.0%)	10	(35.7%)
STABLE	12	(52.2%)	5	(33.3%)	4	(40.0%)	12	(42.9%)
IMPROVED	5	(21.7%)	5	(33.3%)	3	(30.0%)	6	(21.4%)
Social functioning SF								
WORSENED	5	(21.7%)	5	(33.3%)	1	(10.0%)	11	(39.3%)
STABLE	10	(43.5%)	7	(46.7%)	7	(70.0%)	10	(35.7%)
IMPROVED	8	(34.8%)	3	(20.0%)	2	(20.0%)	7	(25.0%)
Symptom scales / items								
Fatigue FA								
IMPROVED	8	(34.8%)	5	(33.3%)	4	(40.0%)	6	(21.4%)
STABLE	5	(21.7%)	2	(13.3%)	1	(10.0%)	3	(10.7%)
WORSENED	10	(43.5%)	8	(53.3%)	5	(50.0%)	19	(67.9%)
Nausea and vomiting NV								
IMPROVED	1	(4.2%)	1	(6.7%)	0	(0.0%)	4	(14.3%)
STABLE	20	(83.3%)	14	(93.3%)	9	(90.0%)	15	(53.6%)
WORSENED	3	(12.5%)	0	(0.0%)	1	(10.0%)	9	(32.1%)
Pain PA								
IMPROVED	10	(41.7%)	7	(46.7%)	3	(30.0%)	7	(25.0%)
STABLE	7	(29.2%)	4	(26.7%)	5	(50.0%)	9	(32.1%)
WORSENED	7	(29.2%)	4	(26.7%)	2	(20.0%)	12	(42.9%)
Dyspnoea DY								
IMPROVED	4	(16.7%)	3	(20.0%)	2	(20.0%)	5	(17.9%)
STABLE	15	(62.5%)	8	(53.3%)	7	(70.0%)	16	(57.1%)
WORSENED	5	(20.8%)	4	(26.7%)	1	(10.0%)	7	(25.0%)
Insomnia SL								
IMPROVED	5	(22.7%)	4	(26.7%)	2	(20.0%)	6	(21.4%)
STABLE	11	(50.0%)	3	(20.0%)	2	(20.0%)	14	(50.0%)
WORSENED	6	(27.3%)	8	(53.3%)	6	(60.0%)	8	(28.6%)
Appetite loss AP								
IMPROVED	3	(13.0%)	4	(26.7%)	3	(33.3%)	2	(8.0%)
STABLE	16	(69.6%)	7	(46.7%)	4	(44.4%)	11	(44.0%)
WORSENED	4	(17.4%)	4	(26.7%)	2	(22.2%)	12	(48.0%)
Constipation CO								
IMPROVED	1	(4.3%)	2	(13.3%)	2	(20.0%)	6	(21.4%)
STABLE	18	(78.3%)	10	(66.7%)	6	(60.0%)	12	(42.9%)
WORSENED	4	(17.4%)	3	(20.0%)	2	(20.0%)	10	(35.7%)
Diarrhoea DI								
IMPROVED	4	(17.4%)	2	(13.3%)	0	(0.0%)	5	(17.9%)
STABLE	18	(78.3%)	12	(80.0%)	9	(90.0%)	20	(71.4%)
WORSENED	1	(4.3%)	1	(6.7%)	1	(10.0%)	3	(10.7%)
Financial difficulties FI								
IMPROVED	1	(4.3%)	0	(0.0%)	0	(0.0%)	3	(10.7%)
STABLE	17	(73.9%)	13	(86.7%)	10	(100.0%)	24	(85.7%)
WORSENED	5	(21.7%)	2	(13.3%)	0	(0.0%)	1	(3.6%)

Supplementary Table 9: QLQC-H&N35 scores at C1D1

	ACC cohort N=40	Non-ACC cohort N=43
QLC-HN35 Pain HNPA		
N	40	43
Mean (Std)	21.5 (26.5)	18.9 (21.2)
Median (min; max)	8.3 (0; 92)	8.3 (0; 92)
QLC-HN35 Swallowing HNSW		
N	40	43
Mean (Std)	15.0 (23.8)	15.8 (21.4)
Median (min; max)	8.3 (0; 100)	8.3 (0; 75)
QLC-HN35 Senses problems HNSE		
N	40	43
Mean (Std)	23.8 (32.0)	15.9 (19.9)
Median (min; max)	8.3 (0; 100)	0.0 (0; 67)
QLC-HN35 Speech problems HNSP		
N	40	43
Mean (Std)	17.8 (21.2)	17.4 (18.5)
Median (min; max)	11.1 (0; 100)	11.1 (0; 67)
QLC-HN35 Trouble with social eating HNSO		
N	40	42
Mean (Std)	18.1 (26.9)	20.0 (24.1)
Median (min; max)	0.0 (0; 100)	9.7 (0; 83)
QLC-HN35 Trouble with social contact HNSC		
N	40	43
Mean (Std)	13.1 (18.5)	16.1 (19.0)
Median (min; max)	6.7 (0; 80)	6.7 (0; 80)
QLC-HN35 Less sexuality HNSX		
N	36	32
Mean (Std)	26.9 (31.7)	40.6 (42.1)
Median (min; max)	16.7 (0; 100)	33.3 (0; 100)
QLC-HN35 Teeth HNTE		
N	40	43
Mean (Std)	20.0 (36.0)	20.2 (33.4)
Median (min; max)	0.0 (0; 100)	0.0 (0; 100)
QLC-HN35 Opening mouth HNOM		
N	40	43
Mean (Std)	40.8 (40.3)	48.1 (39.4)
Median (min; max)	33.3 (0; 100)	33.3 (0; 100)
QLC-HN35 Dry mouth HNDR		
N	40	43
Mean (Std)	40.8 (38.8)	52.7 (33.5)
Median (min; max)	33.3 (0; 100)	66.7 (0; 100)
QLC-HN35 Sticky saliva HNSS		
N	38	43
Mean (Std)	22.8 (30.1)	39.5 (35.1)
Median (min; max)	0.0 (0; 100)	33.3 (0; 100)
QLC-HN35 Coughing HNCO		
N	40	42
Mean (Std)	24.2 (29.2)	27.0 (29.7)
Median (min; max)	16.7 (0; 100)	33.3 (0; 100)
QLC-HN35 Felt ill HNFI		
N	40	43
Mean (Std)	12.5 (22.2)	17.1 (23.4)
Median (min; max)	0.0 (0; 67)	0.0 (0; 100)
QLC-HN35 Pain killers HNPK		
N	40	43
Mean (Std)	72.5 (45.2)	72.1 (45.4)
Median (min; max)	100.0 (0; 100)	100.0 (0; 100)
QLC-HN35 Nutritional supplements HNNU		
N	40	43
Mean (Std)	30.0 (46.4)	18.6 (39.4)
Median (min; max)	0.0 (0; 100)	0.0 (0; 100)
QLC-HN35 Feeding tube HNFE		
N	40	43
Mean (Std)	0.0 (0.0)	4.7 (21.3)
Median (min; max)	0.0 (0; 0)	0.0 (0; 100)
QLC-HN35 Weight loss HNWL		
N	40	43

	ACC cohort N=40	Non-ACC cohort N=43
Mean (Std)	22.5 (42.3)	37.2 (48.9)
Median (min; max)	0.0 (0; 100)	0.0 (0; 100)
QLC-HN35 Weight gain HNWG		
N	40	42
Mean (Std)	7.5 (26.7)	23.8 (43.1)
Median (min; max)	0.0 (0; 100)	0.0 (0; 100)

Supplementary Table 10: Evolution of QLQC-H&N35 scores in the ACC cohort

	Visit					
	CYCLE03 N=34	CYCLE05 N=21	CYCLE07 N=16	CYCLE09 N=13	CYCLE11 N=12	END OF TREATMENT N=25
Absolute variation of						
Pain						
N	30	20	16	13	12	23
Mean (Std)	-5.6 (21.0)	-2.5 (19.3)	2.4 (13.2)	0.2 (13.1)	3.5 (22.6)	-3.3 (19.3)
Median (min; max)	0.0 (-75; 50)	0.0 (-50; 58)	0.0 (-33; 25)	0.0 (-33; 25)	0.0 (-33; 50)	0.0 (-50; 42)
Swallowing						
N	32	20	16	13	12	24
Mean (Std)	1.8 (9.7)	0.4 (7.3)	1.0 (12.7)	3.2 (14.2)	0.7 (9.3)	-1.5 (16.8)
Median (min; max)	0.0 (-17; 25)	0.0 (-17; 25)	0.0 (-17; 42)	0.0 (-17; 33)	0.0 (-11; 25)	0.0 (-50; 33)
Senses problems						
N	32	20	16	13	12	24
Mean (Std)	-0.5 (17.7)	3.3 (23.9)	-3.1 (10.9)	0.0 (25.5)	4.2 (12.6)	2.8 (21.8)
Median (min; max)	0.0 (-50; 50)	0.0 (-33; 67)	0.0 (-33; 17)	0.0 (-50; 67)	0.0 (-17; 33)	0.0 (-67; 50)
Speech problems						
N	34	21	16	12	12	25
Mean (Std)	-2.3 (16.8)	-5.3 (16.0)	-4.2 (11.4)	-6.5 (12.0)	-3.7 (11.9)	3.6 (20.7)
Median (min; max)	0.0 (-33; 44)	0.0 (-33; 44)	0.0 (-22; 11)	-5.6 (-22; 11)	0.0 (-22; 11)	0.0 (-33; 56)
Trouble with social eating						
N	34	21	16	12	12	25
Mean (Std)	-1.6 (20.6)	3.2 (25.7)	-0.5 (7.1)	-1.4 (7.8)	2.1 (19.8)	10.3 (26.1)
Median (min; max)	0.0 (-67; 58)	0.0 (-33; 83)	0.0 (-17; 17)	0.0 (-17; 17)	0.0 (-25; 58)	0.0 (-25; 100)
Trouble social contact						
N	34	21	16	12	12	25
Mean (Std)	0.4 (9.4)	0.3 (11.8)	1.7 (10.5)	2.8 (15.9)	9.4 (21.2)	6.2 (16.1)
Median (min; max)	0.0 (-20; 27)	0.0 (-27; 40)	0.0 (-13; 33)	0.0 (-13; 47)	3.3 (-13; 60)	0.0 (-13; 67)
Less sexuality						
N	29	18	12	10	10	20
Mean (Std)	5.7 (29.3)	7.4 (22.3)	9.7 (19.4)	11.7 (35.2)	21.7 (29.4)	26.7 (38.0)
Median (min; max)	0.0 (-67; 100)	0.0 (-33; 67)	8.3 (-33; 33)	0.0 (-33; 100)	16.7 (0; 100)	0.0 (0; 100)
Teeht						
N	32	20	16	13	12	23
Mean (Std)	-1.0 (24.7)	1.7 (13.1)	6.3 (13.4)	12.8 (25.6)	2.8 (33.2)	2.9 (33.2)
Median (min; max)	0.0 (-67; 67)	0.0 (-33; 33)	0.0 (0; 33)	0.0 (0; 67)	0.0 (-67; 67)	0.0 (-67; 100)
Opening mouth						
N	32	20	16	13	12	24
Mean (Std)	-1.0 (21.6)	3.3 (18.4)	2.1 (8.3)	10.3 (21.0)	11.1 (16.4)	11.1 (27.2)
Median (min; max)	0.0 (-67; 67)	0.0 (-33; 33)	0.0 (0; 33)	0.0 (0; 67)	0.0 (0; 33)	0.0 (-33; 67)
Dry mouth						
N	32	20	16	12	12	24
Mean (Std)	-2.1 (22.3)	3.3 (28.4)	0.0 (24.3)	-5.6 (27.8)	-5.6 (19.2)	1.4 (31.8)
Median (min; max)	0.0 (-33; 33)	0.0 (-67; 33)	0.0 (-33; 33)	0.0 (-67; 33)	0.0 (-33; 33)	0.0 (-67; 67)
Sticky saliva						
N	30	19	16	11	12	22
Mean (Std)	6.7 (32.0)	10.5 (29.5)	4.2 (31.9)	15.2 (40.5)	11.1 (29.6)	3.0 (41.0)
Median (min; max)	0.0 (-33; 100)	0.0 (-67; 67)	0.0 (-67; 67)	0.0 (-33; 100)	16.7 (-67; 33)	0.0 (-100; 100)
Coughing						
N	31	20	16	13	12	24
Mean (Std)	6.5 (27.8)	-1.7 (22.9)	-4.2 (24.0)	2.6 (31.8)	2.8 (17.2)	4.2 (31.6)
Median (min; max)	0.0 (-67; 100)	0.0 (-33; 67)	0.0 (-67; 33)	0.0 (-33; 100)	0.0 (-33; 33)	0.0 (-67; 100)
Felt ill						
N	31	20	16	13	12	24
Mean (Std)	1.1 (23.5)	1.7 (25.3)	8.3 (28.5)	12.8 (34.8)	11.1 (35.8)	12.5 (35.2)
Median (min; max)	0.0 (-67; 67)	0.0 (-67; 33)	0.0 (-67; 67)	0.0 (-67; 67)	0.0 (-67; 67)	0.0 (-67; 100)
Pain killer						
N	34	21	16	11	12	25
Mean (Std)	2.9 (38.8)	-9.5 (43.6)	0.0 (36.5)	0.0 (0.0)	-8.3 (51.5)	-4.0 (45.5)
Median (min; max)	0.0 (-100; 100)	0.0 (-100; 100)	0.0 (-100; 100)	0.0 (0; 0)	0.0 (-100; 100)	0.0 (-100; 100)
Nutritional supplements						
N	34	21	16	12	12	25
Mean (Std)	0.0 (24.6)	4.8 (21.8)	6.3 (25.0)	-8.3 (28.9)	-8.3 (28.9)	8.0 (40.0)
Median (min; max)	0.0 (-100; 100)	0.0 (0; 100)	0.0 (0; 100)	0.0 (-100; 0)	0.0 (-100; 0)	0.0 (-100; 100)
Feeding tube						

	Visit											
	CYCLE03 N=34		CYCLE05 N=21		CYCLE07 N=16		CYCLE09 N=13		CYCLE11 N=12		END OF TREATMENT N=25	
N	33		20		16		12		12		25	
Mean (Std)	0.0 (0.0)		0.0 (0.0)		0.0 (0.0)		0.0 (0.0)		0.0 (0.0)		8.0 (27.7)	
Median (min; max)	0.0 (0; 0)		0.0 (0; 0)		0.0 (0; 0)		0.0 (0; 0)		0.0 (0; 0)		0.0 (0; 100)	
Weight loss												
N	34		21		16		12		12		25	
Mean (Std)	-5.9 (54.7)		-4.8 (66.9)		-6.3 (44.3)		0.0 (60.3)		0.0 (42.6)		20.0 (64.5)	
Median (min; max)	0.0 (-100; 100)		0.0 (-100; 100)		0.0 (-100; 100)		0.0 (-100; 100)		0.0 (-100; 100)		0.0 (-100; 100)	
Weight gain												
N	34		21		16		12		12		25	
Mean (Std)	2.9 (38.8)		4.8 (38.4)		18.8 (40.3)		16.7 (38.9)		8.3 (28.9)		8.0 (40.0)	
Median (min; max)	0.0 (-100; 100)		0.0 (-100; 100)		0.0 (0; 100)		0.0 (0; 100)		0.0 (0; 100)		0.0 (-100; 100)	
Absolute variation of (Qualitatif)												
Pain												
Missing data	4		1		0		0		0		2	
WORSENED	8	(26.7%)	4	(20.0%)	1	(6.3%)	1	(7.7%)	3	(25.0%)	6	(26.1%)
STABLE	20	(66.7%)	15	(75.0%)	12	(75.0%)	11	(84.6%)	6	(50.0%)	15	(65.2%)
IMPROVED	2	(6.7%)	1	(5.0%)	3	(18.8%)	1	(7.7%)	3	(25.0%)	2	(8.7%)
Swallowing												
Missing data	2		1		0		0		0		1	
WORSENED	2	(6.3%)	1	(5.0%)	1	(6.3%)	1	(7.7%)	1	(8.3%)	3	(12.5%)
STABLE	26	(81.3%)	18	(90.0%)	13	(81.3%)	8	(61.5%)	10	(83.3%)	19	(79.2%)
IMPROVED	4	(12.5%)	1	(5.0%)	2	(12.5%)	4	(30.8%)	1	(8.3%)	2	(8.3%)
Senses problems												
Missing data	2		1		0		0		0		1	
WORSENED	7	(21.9%)	4	(20.0%)	3	(18.8%)	3	(23.1%)	1	(8.3%)	3	(12.5%)
STABLE	19	(59.4%)	12	(60.0%)	12	(75.0%)	8	(61.5%)	8	(66.7%)	16	(66.7%)
IMPROVED	6	(18.8%)	4	(20.0%)	1	(6.3%)	2	(15.4%)	3	(25.0%)	5	(20.8%)
Speech problems												
Missing data	0		0		0		1		0		0	
WORSENED	11	(32.4%)	9	(42.9%)	6	(37.5%)	6	(50.0%)	5	(41.7%)	7	(28.0%)
STABLE	14	(41.2%)	10	(47.6%)	7	(43.8%)	4	(33.3%)	4	(33.3%)	9	(36.0%)
IMPROVED	9	(26.5%)	2	(9.5%)	3	(18.8%)	2	(16.7%)	3	(25.0%)	9	(36.0%)
Trouble with social eating												
Missing data	0		0		0		1		0		0	
WORSENED	7	(20.6%)	4	(19.0%)	1	(6.3%)	1	(8.3%)	2	(16.7%)	1	(4.0%)
STABLE	24	(70.6%)	15	(71.4%)	14	(87.5%)	10	(83.3%)	9	(75.0%)	18	(72.0%)
IMPROVED	3	(8.8%)	2	(9.5%)	1	(6.3%)	1	(8.3%)	1	(8.3%)	6	(24.0%)
Trouble social contact												
Missing data	0		0		0		1		0		0	
WORSENED	4	(11.8%)	2	(9.5%)	1	(6.3%)	1	(8.3%)	1	(8.3%)	1	(4.0%)
STABLE	26	(76.5%)	18	(85.7%)	13	(81.3%)	9	(75.0%)	8	(66.7%)	16	(64.0%)
IMPROVED	4	(11.8%)	1	(4.8%)	2	(12.5%)	2	(16.7%)	3	(25.0%)	8	(32.0%)
Less sexuality												
Missing data	5		3		4		3		2		5	
WORSENED	5	(17.2%)	3	(16.7%)	1	(8.3%)	1	(10.0%)	0	(0.0%)	0	(0.0%)
STABLE	15	(51.7%)	8	(44.4%)	5	(41.7%)	6	(60.0%)	3	(30.0%)	12	(60.0%)
IMPROVED	9	(31.0%)	7	(38.9%)	6	(50.0%)	3	(30.0%)	7	(70.0%)	8	(40.0%)
Teeht												
Missing data	2		1		0		0		0		2	
WORSENED	6	(18.8%)	1	(5.0%)	0	(0.0%)	0	(0.0%)	2	(16.7%)	4	(17.4%)
STABLE	21	(65.6%)	17	(85.0%)	13	(81.3%)	10	(76.9%)	7	(58.3%)	15	(65.2%)
IMPROVED	5	(15.6%)	2	(10.0%)	3	(18.8%)	3	(23.1%)	3	(25.0%)	4	(17.4%)
Opening mouth												
Missing data	2		1		0		0		0		1	
WORSENED	4	(12.5%)	2	(10.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(8.3%)
STABLE	25	(78.1%)	14	(70.0%)	15	(93.8%)	10	(76.9%)	8	(66.7%)	15	(62.5%)
IMPROVED	3	(9.4%)	4	(20.0%)	1	(6.3%)	3	(23.1%)	4	(33.3%)	7	(29.2%)
Dry mouth												
Missing data	2		1		0		1		0		1	
WORSENED	8	(25.0%)	4	(20.0%)	4	(25.0%)	3	(25.0%)	3	(25.0%)	7	(29.2%)
STABLE	18	(56.3%)	9	(45.0%)	8	(50.0%)	7	(58.3%)	8	(66.7%)	9	(37.5%)
IMPROVED	6	(18.8%)	7	(35.0%)	4	(25.0%)	2	(16.7%)	1	(8.3%)	8	(33.3%)
Sticky saliva												
Missing data	4		2		0		2		0		3	

	Visit											
	CYCLE03 N=34		CYCLE05 N=21		CYCLE07 N=16		CYCLE09 N=13		CYCLE11 N=12		END OF TREATMENT N=25	
WORSENED	5	(16.7%)	1	(5.3%)	2	(12.5%)	2	(18.2%)	1	(8.3%)	5	(22.7%)
STABLE	18	(60.0%)	12	(63.2%)	11	(68.8%)	5	(45.5%)	5	(41.7%)	12	(54.5%)
IMPROVED	7	(23.3%)	6	(31.6%)	3	(18.8%)	4	(36.4%)	6	(50.0%)	5	(22.7%)
Coughing												
Missing data	3		1		0		0		0		1	
WORSENED	3	(9.7%)	4	(20.0%)	3	(18.8%)	2	(15.4%)	1	(8.3%)	4	(16.7%)
STABLE	20	(64.5%)	14	(70.0%)	11	(68.8%)	10	(76.9%)	9	(75.0%)	14	(58.3%)
IMPROVED	8	(25.8%)	2	(10.0%)	2	(12.5%)	1	(7.7%)	2	(16.7%)	6	(25.0%)
Felt ill												
Missing data	3		1		0		0		0		1	
WORSENED	4	(12.9%)	3	(15.0%)	1	(6.3%)	1	(7.7%)	1	(8.3%)	3	(12.5%)
STABLE	22	(71.0%)	12	(60.0%)	10	(62.5%)	7	(53.8%)	7	(58.3%)	12	(50.0%)
IMPROVED	5	(16.1%)	5	(25.0%)	5	(31.3%)	5	(38.5%)	4	(33.3%)	9	(37.5%)
Pain killer												
Missing data	0		0		0		2		0		0	
WORSENED	2	(5.9%)	3	(14.3%)	1	(6.3%)	0	(0.0%)	2	(16.7%)	3	(12.0%)
STABLE	29	(85.3%)	17	(81.0%)	14	(87.5%)	11	(100.0%)	9	(75.0%)	20	(80.0%)
IMPROVED	3	(8.8%)	1	(4.8%)	1	(6.3%)	0	(0.0%)	1	(8.3%)	2	(8.0%)
Nutritional supplements												
Missing data	0		0		0		1		0		0	
WORSENED	1	(2.9%)	0	(0.0%)	0	(0.0%)	1	(8.3%)	1	(8.3%)	1	(4.0%)
STABLE	32	(94.1%)	20	(95.2%)	15	(93.8%)	11	(91.7%)	11	(91.7%)	21	(84.0%)
IMPROVED	1	(2.9%)	1	(4.8%)	1	(6.3%)	0	(0.0%)	0	(0.0%)	3	(12.0%)
Feeding tube												
Missing data	1		1		0		1		0		0	
STABLE	33	(100.0%)	20	(100.0%)	16	(100.0%)	12	(100.0%)	12	(100.0%)	23	(92.0%)
IMPROVED	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(8.0%)
Weight loss												
Missing data	0		0		0		1		0		0	
WORSENED	6	(17.6%)	5	(23.8%)	2	(12.5%)	2	(16.7%)	1	(8.3%)	3	(12.0%)
STABLE	24	(70.6%)	12	(57.1%)	13	(81.3%)	8	(66.7%)	10	(83.3%)	14	(56.0%)
IMPROVED	4	(11.8%)	4	(19.0%)	1	(6.3%)	2	(16.7%)	1	(8.3%)	8	(32.0%)
Weight gain												
Missing data	0		0		0		1		0		0	
WORSENED	2	(5.9%)	1	(4.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(4.0%)
STABLE	29	(85.3%)	18	(85.7%)	13	(81.3%)	10	(83.3%)	11	(91.7%)	21	(84.0%)
IMPROVED	3	(8.8%)	2	(9.5%)	3	(18.8%)	2	(16.7%)	1	(8.3%)	3	(12.0%)

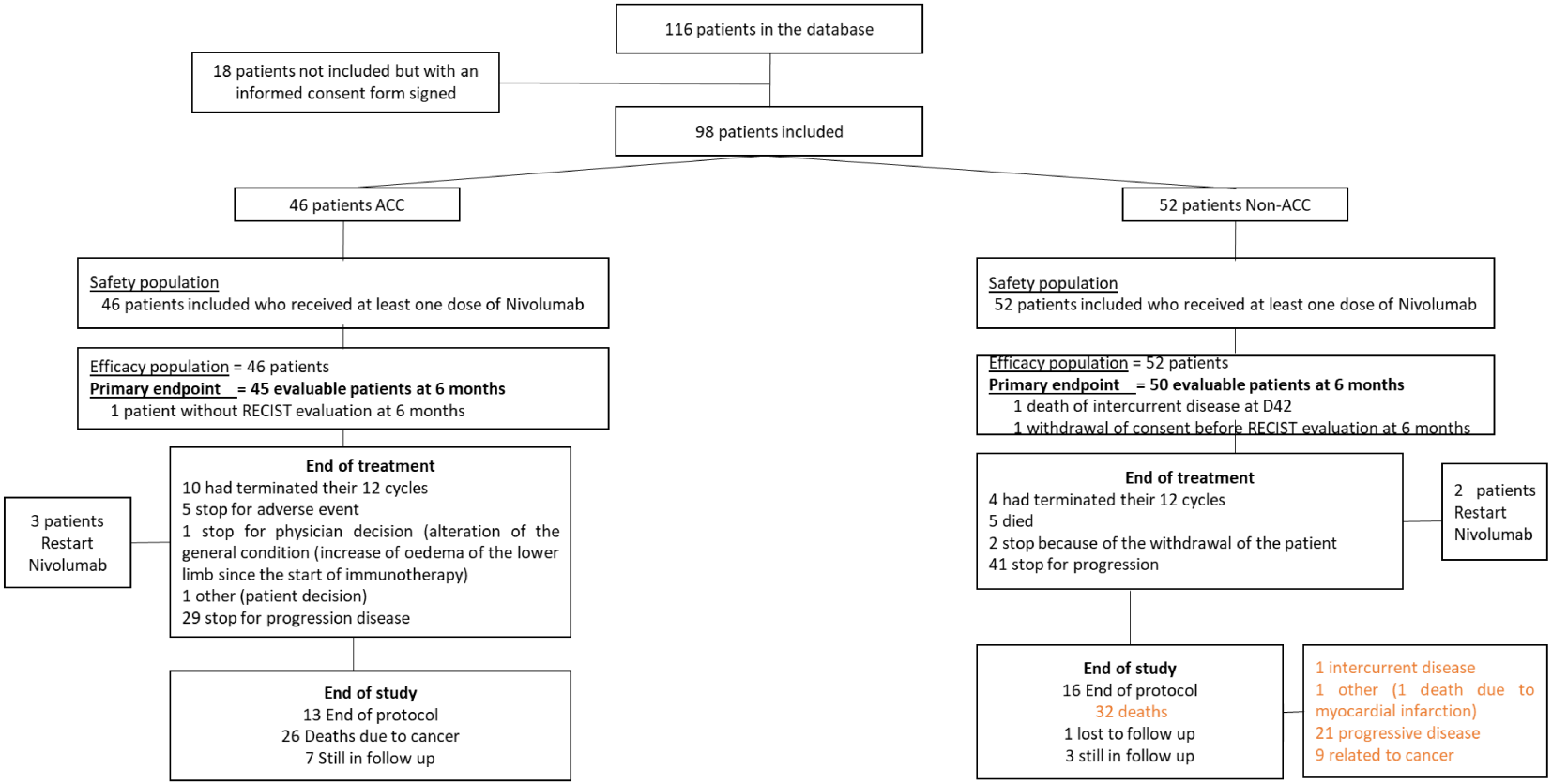
Supplementary Table 11: Evolution of QLQC-H&N35 scores in the non-ACC cohort

	Visit			
	CYCLE03 N=25	CYCLE05 N=14	CYCLE07 N=10	END OF TREATMENT N=28
Absolute variation of				
Pain				
N	20	14	8	26
Mean (Std)	-1.7 (18.1)	10.1 (19.1)	-1.0 (12.1)	5.3 (26.5)
Median (min; max)	0.0 (-33; 42)	4.2 (-17; 58)	-4.2 (-17; 17)	8.3 (-50; 58)
Swallowing				
N	21	14	9	26
Mean (Std)	-4.4 (17.4)	0.6 (9.5)	-0.9 (12.8)	7.6 (20.5)
Median (min; max)	0.0 (-33; 42)	0.0 (-25; 17)	0.0 (-25; 25)	8.3 (-42; 56)
Senses problems				
N	22	14	9	26
Mean (Std)	3.0 (29.8)	11.9 (36.1)	0.0 (28.9)	7.1 (25.5)
Median (min; max)	0.0 (-50; 67)	0.0 (-33; 100)	0.0 (-33; 67)	0.0 (-33; 67)
Speech problems				
N	22	14	10	26
Mean (Std)	5.3 (16.8)	7.1 (17.8)	-4.4 (7.8)	7.3 (22.4)
Median (min; max)	0.0 (-33; 44)	0.0 (-11; 44)	0.0 (-22; 0)	0.0 (-33; 67)
Trouble with social eating				
N	22	14	10	27
Mean (Std)	3.0 (19.7)	6.7 (21.9)	0.8 (15.9)	13.7 (29.1)
Median (min; max)	0.0 (-33; 58)	0.0 (-17; 67)	0.0 (-17; 42)	8.3 (-33; 83)
Trouble social contact				
N	23	14	10	27
Mean (Std)	3.8 (20.4)	1.9 (20.8)	0.0 (7.7)	7.3 (22.6)
Median (min; max)	0.0 (-33; 60)	0.0 (-27; 67)	0.0 (-13; 13)	0.0 (-33; 73)
Less sexuality				
N	18	10	8	13
Mean (Std)	-1.9 (16.1)	1.7 (12.3)	8.3 (37.8)	0.0 (23.6)
Median (min; max)	0.0 (-33; 50)	0.0 (-17; 33)	0.0 (-17; 100)	0.0 (-33; 50)
Teeht				
N	20	13	8	25
Mean (Std)	-8.3 (28.4)	-10.3 (28.5)	-8.3 (23.6)	-10.7 (23.0)
Median (min; max)	0.0 (-100; 33)	0.0 (-100; 0)	0.0 (-67; 0)	0.0 (-67; 33)
Opening mouth				
N	22	14	9	26
Mean (Std)	-9.1 (25.6)	-14.3 (17.1)	-11.1 (16.7)	-7.7 (28.8)
Median (min; max)	0.0 (-33; 67)	0.0 (-33; 0)	0.0 (-33; 0)	0.0 (-67; 67)
Dry mouth				
N	22	14	9	25
Mean (Std)	-6.1 (26.5)	-4.8 (22.1)	-3.7 (35.1)	-2.7 (23.4)
Median (min; max)	0.0 (-67; 33)	0.0 (-33; 33)	0.0 (-67; 33)	0.0 (-33; 67)
Sticky saliva				
N	22	14	8	23
Mean (Std)	-1.5 (26.2)	4.8 (12.1)	0.0 (17.8)	-4.3 (30.7)
Median (min; max)	0.0 (-33; 67)	0.0 (0; 33)	0.0 (-33; 33)	0.0 (-100; 67)
Coughing				
N	22	14	9	25
Mean (Std)	3.0 (35.5)	0.0 (37.0)	0.0 (23.6)	1.3 (34.0)
Median (min; max)	0.0 (-67; 100)	0.0 (-67; 67)	0.0 (-33; 33)	0.0 (-67; 100)
Felt ill				
N	22	14	9	26
Mean (Std)	3.0 (22.8)	-4.8 (25.7)	-3.7 (20.0)	6.4 (32.7)
Median (min; max)	0.0 (-33; 67)	0.0 (-33; 33)	0.0 (-33; 33)	0.0 (-67; 67)
Pain killer				
N	23	14	10	27
Mean (Std)	0.0 (60.3)	-7.1 (61.6)	-30.0 (48.3)	0.0 (62.0)
Median (min; max)	0.0 (-100; 100)	0.0 (-100; 100)	0.0 (-100; 0)	0.0 (-100; 100)
Nutritional supplements				
N	23	13	10	27
Mean (Std)	17.4 (57.6)	0.0 (0.0)	10.0 (56.8)	18.5 (48.3)
Median (min; max)	0.0 (-100; 100)	0.0 (0; 0)	0.0 (-100; 100)	0.0 (-100; 100)
Feeding tube				
N	23	14	10	27
Mean (Std)	0.0 (30.2)	0.0 (0.0)	0.0 (0.0)	-3.7 (19.2)
Median (min; max)	0.0 (-100; 100)	0.0 (0; 0)	0.0 (0; 0)	0.0 (-100; 0)

	Visit							
	CYCLE03 N=25		CYCLE05 N=14		CYCLE07 N=10		END OF TREATMENT N=28	
Weight loss								
N	22		14		10		27	
Mean (Std)	-4.5 (57.5)		0.0 (55.5)		0.0 (47.1)		0.0 (62.0)	
Median (min; max)	0.0 (-100; 100)		0.0 (-100; 100)		0.0 (-100; 100)		0.0 (-100; 100)	
Weight gain								
N	21		14		10		26	
Mean (Std)	-19.0 (51.2)		14.3 (66.3)		-20.0 (42.2)		0.0 (40.0)	
Median (min; max)	0.0 (-100; 100)		0.0 (-100; 100)		0.0 (-100; 0)		0.0 (-100; 100)	
Absolute variation of (Qualitatif)								
Pain								
Missing data	5		0		2		2	
WORSENED	5	(25.0%)	1	(7.1%)	1	(12.5%)	7	(26.9%)
STABLE	11	(55.0%)	8	(57.1%)	5	(62.5%)	9	(34.6%)
IMPROVED	4	(20.0%)	5	(35.7%)	2	(25.0%)	10	(38.5%)
Swallowing								
Missing data	4		0		1		2	
WORSENED	5	(23.8%)	1	(7.1%)	1	(11.1%)	4	(15.4%)
STABLE	14	(66.7%)	12	(85.7%)	7	(77.8%)	12	(46.2%)
IMPROVED	2	(9.5%)	1	(7.1%)	1	(11.1%)	10	(38.5%)
Senses problems								
Missing data	3		0		1		2	
WORSENED	7	(31.8%)	3	(21.4%)	2	(22.2%)	6	(23.1%)
STABLE	9	(40.9%)	6	(42.9%)	6	(66.7%)	9	(34.6%)
IMPROVED	6	(27.3%)	5	(35.7%)	1	(11.1%)	11	(42.3%)
Speech problems								
Missing data	3		0		0		2	
WORSENED	3	(13.6%)	2	(14.3%)	3	(30.0%)	6	(23.1%)
STABLE	11	(50.0%)	8	(57.1%)	7	(70.0%)	11	(42.3%)
IMPROVED	8	(36.4%)	4	(28.6%)	0	(0.0%)	9	(34.6%)
Trouble with social eating								
Missing data	3		0		0		1	
WORSENED	3	(13.6%)	1	(7.1%)	1	(10.0%)	4	(14.8%)
STABLE	14	(63.6%)	10	(71.4%)	8	(80.0%)	12	(44.4%)
IMPROVED	5	(22.7%)	3	(21.4%)	1	(10.0%)	11	(40.7%)
Trouble social contact								
Missing data	2		0		0		1	
WORSENED	3	(13.0%)	2	(14.3%)	1	(10.0%)	4	(14.8%)
STABLE	15	(65.2%)	10	(71.4%)	8	(80.0%)	16	(59.3%)
IMPROVED	5	(21.7%)	2	(14.3%)	1	(10.0%)	7	(25.9%)
Less sexuality								
Missing data	7		4		2		15	
WORSENED	4	(22.2%)	1	(10.0%)	2	(25.0%)	4	(30.8%)
STABLE	13	(72.2%)	8	(80.0%)	5	(62.5%)	6	(46.2%)
IMPROVED	1	(5.6%)	1	(10.0%)	1	(12.5%)	3	(23.1%)
Teeht								
Missing data	5		1		2		3	
WORSENED	3	(15.0%)	2	(15.4%)	1	(12.5%)	7	(28.0%)
STABLE	16	(80.0%)	11	(84.6%)	7	(87.5%)	17	(68.0%)
IMPROVED	1	(5.0%)	0	(0.0%)	0	(0.0%)	1	(4.0%)
Opening mouth								
Missing data	3		0		1		2	
WORSENED	9	(40.9%)	6	(42.9%)	3	(33.3%)	10	(38.5%)
STABLE	11	(50.0%)	8	(57.1%)	6	(66.7%)	12	(46.2%)
IMPROVED	2	(9.1%)	0	(0.0%)	0	(0.0%)	4	(15.4%)
Dry mouth								
Missing data	3		0		1		3	
WORSENED	7	(31.8%)	4	(28.6%)	3	(33.3%)	6	(24.0%)
STABLE	11	(50.0%)	8	(57.1%)	3	(33.3%)	16	(64.0%)
IMPROVED	4	(18.2%)	2	(14.3%)	3	(33.3%)	3	(12.0%)
Sticky saliva								
Missing data	3		0		2		5	
WORSENED	6	(27.3%)	0	(0.0%)	1	(12.5%)	5	(21.7%)
STABLE	12	(54.5%)	12	(85.7%)	6	(75.0%)	15	(65.2%)
IMPROVED	4	(18.2%)	2	(14.3%)	1	(12.5%)	3	(13.0%)
Coughing								
Missing data	3		0		1		3	
WORSENED	5	(22.7%)	4	(28.6%)	2	(22.2%)	6	(24.0%)
STABLE	12	(54.5%)	7	(50.0%)	5	(55.6%)	14	(56.0%)

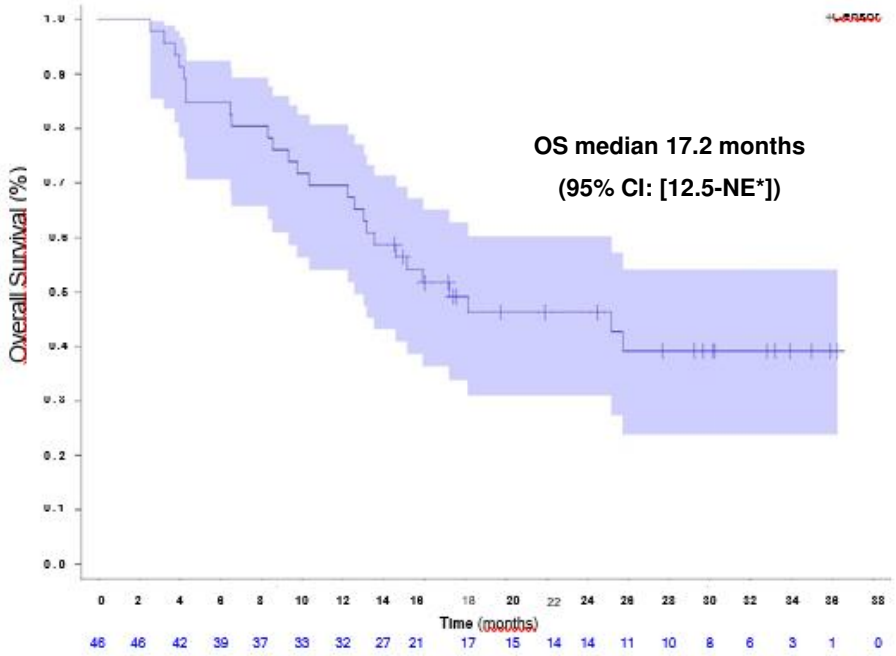
	Visit							
	CYCLE03 N=25		CYCLE05 N=14		CYCLE07 N=10		END OF TREATMENT N=28	
IMPROVED	5	(22.7%)	3	(21.4%)	2	(22.2%)	5	(20.0%)
Felt ill								
Missing data	3		0		1		2	
WORSENED	3	(13.6%)	5	(35.7%)	2	(22.2%)	5	(19.2%)
STABLE	15	(68.2%)	6	(42.9%)	6	(66.7%)	13	(50.0%)
IMPROVED	4	(18.2%)	3	(21.4%)	1	(11.1%)	8	(30.8%)
Pain killer								
Missing data	2		0		0		1	
WORSENED	4	(17.4%)	3	(21.4%)	3	(30.0%)	5	(18.5%)
STABLE	15	(65.2%)	9	(64.3%)	7	(70.0%)	17	(63.0%)
IMPROVED	4	(17.4%)	2	(14.3%)	0	(0.0%)	5	(18.5%)
Nutritional supplements								
Missing data	2		1		0		1	
WORSENED	2	(8.7%)	0	(0.0%)	1	(10.0%)	1	(3.7%)
STABLE	15	(65.2%)	13	(100.0%)	7	(70.0%)	20	(74.1%)
IMPROVED	6	(26.1%)	0	(0.0%)	2	(20.0%)	6	(22.2%)
Feeding tube								
Missing data	2		0		0		1	
WORSENED	1	(4.3%)	0	(0.0%)	0	(0.0%)	1	(3.7%)
STABLE	21	(91.3%)	14	(100.0%)	10	(100.0%)	26	(96.3%)
IMPROVED	1	(4.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Weight loss								
Missing data	3		0		0		1	
WORSENED	4	(18.2%)	2	(14.3%)	1	(10.0%)	5	(18.5%)
STABLE	15	(68.2%)	10	(71.4%)	8	(80.0%)	17	(63.0%)
IMPROVED	3	(13.6%)	2	(14.3%)	1	(10.0%)	5	(18.5%)
Weight gain								
Missing data	4		0		0		2	
WORSENED	5	(23.8%)	2	(14.3%)	2	(20.0%)	2	(7.7%)
STABLE	15	(71.4%)	8	(57.1%)	8	(80.0%)	22	(84.6%)
IMPROVED	1	(4.8%)	4	(28.6%)	0	(0.0%)	2	(7.7%)

Supplementary Figure 1: CONSORT flow diagram



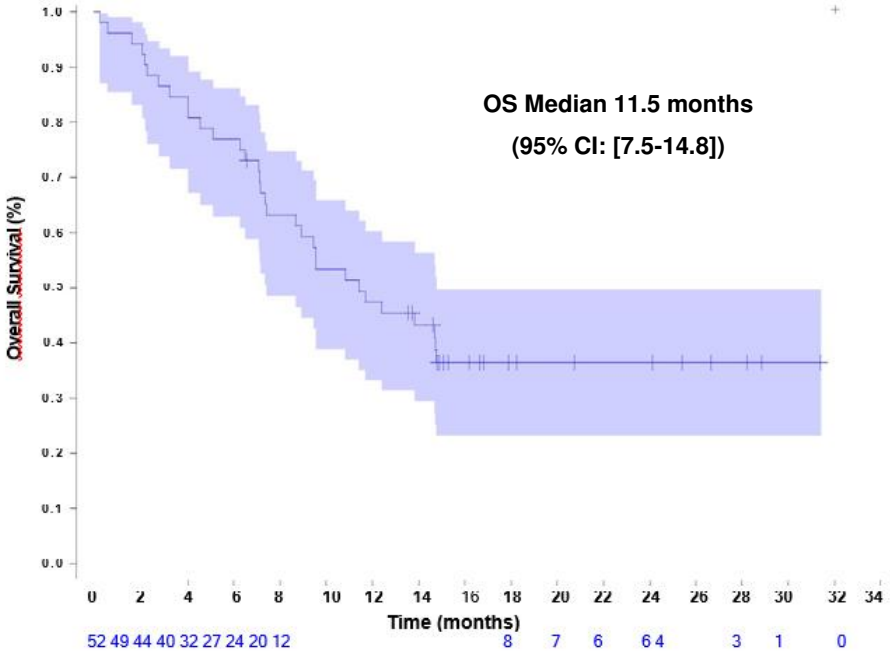
Supplementary Figure 2: Overall survival (OS) in the ACC (A) and non-ACC cohorts (B).

A

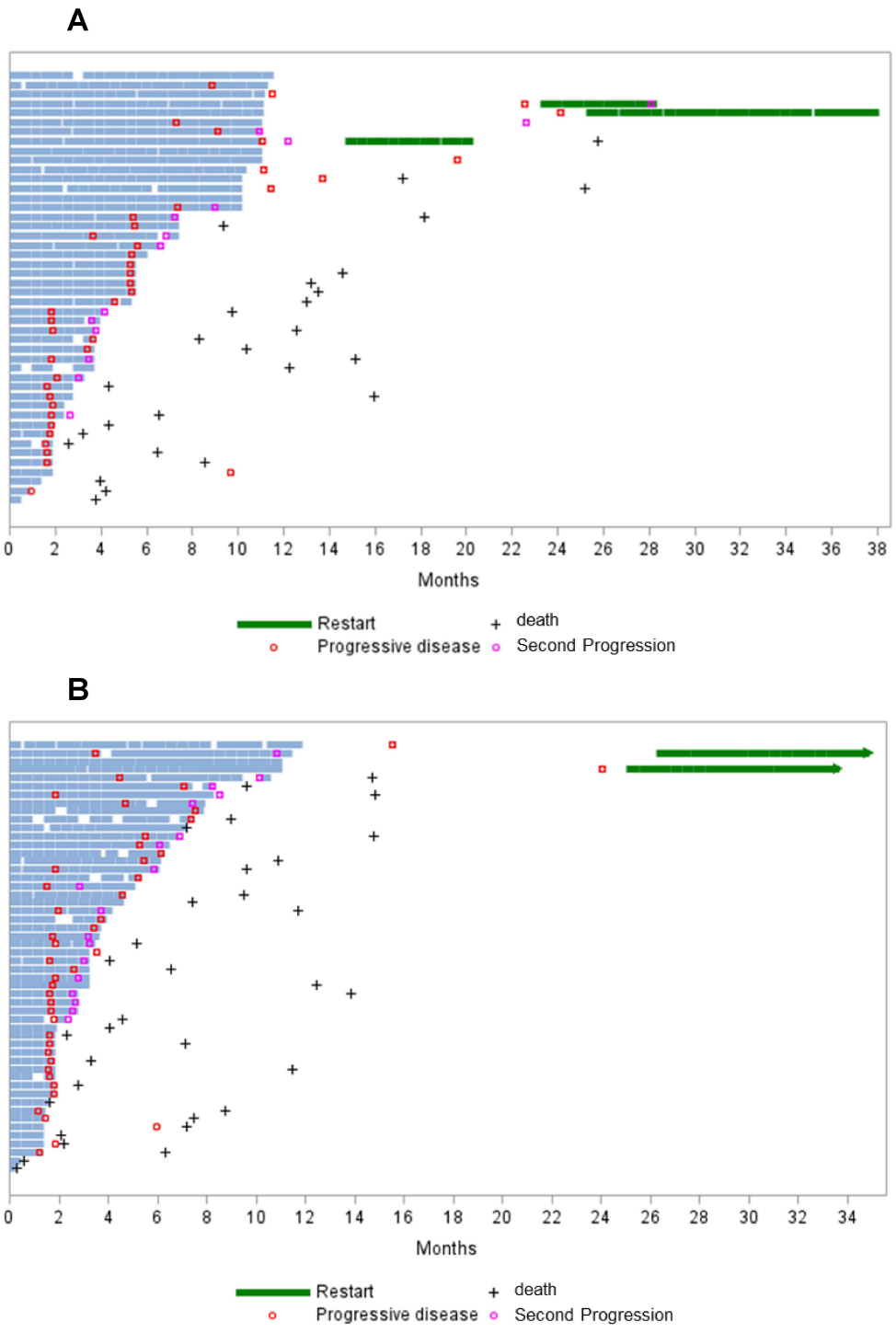


*NE: not evaluable

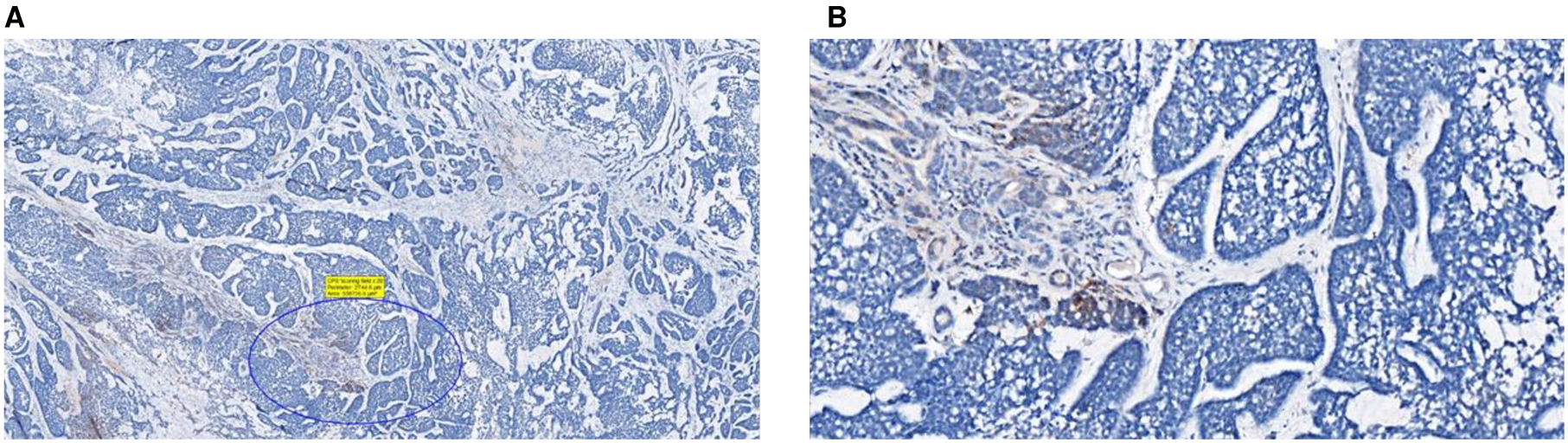
B

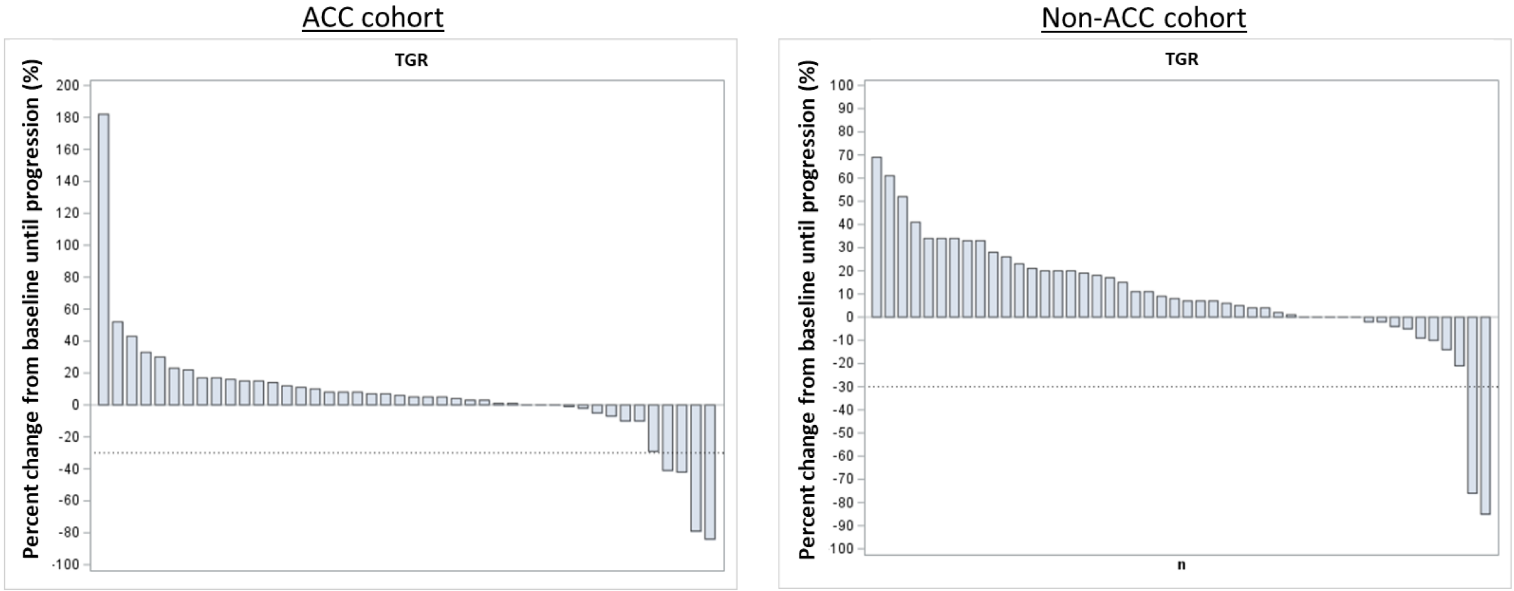


Supplementary Figure 3: Swimmer plots



Supplementary Figure 4: Representative images of PD-L1 expression



Example of immunohistochemical staining for PD-L1 using a 22C3 clone 22C3) on a Ventana ULTRA for combined proportion score (CPS) testing. Two experienced pathologists independently evaluated the cases. (A) The picture was taken at x5 magnification. (B) The region circle in blue was enlarged at x20 magnification.

Supplementary Figure 5