Docetaxel plus cisplatin in recurrent and/or metastatic non-squamous-cell head and neck cancer: a multicenter phase II trial

Imamura, Yoshinori ; Tanaka, Kaoru ; Kiyota, Naomi ; Hayashi, Hidetoshi ; Ota, Ichiro ; Arai, Akihito ; Iwae, Shigemichi ; Minami, Shujiro ;…

(Citation)
Medical Oncology,38(11):128

(Issue Date)
2021-11

(Resource Type)
journal article

(Version)
Accepted Manuscript

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Authors: Yoshinori Imamura,[1] Kaoru Tanaka,[2] Naomi Kiyota,*[1,3] Hidetoshi Hayashi,[2] Ichiro Ota,[4] Akihito Arai,[5] Shigemichi Iwae,[6] Shujiro Minami,[7] Katsunari Yane,[8] Tomoko Yamazaki,[9] Yoshiaki Nagatani,[1] Masanori Toyoda,[1] Takayuki Takahama,[10] Kazuko Sakai,[10] Kazuto Nishio,[10] Naoki Otsuki,[11] Ken-ichi Nibu,[11] and Hironobu Minami[1,3]

Affiliations: [1] Medical Oncology and Hematology, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan; [2]Department of Medical Oncology, Kindai University Faculty of Medicine, 377-2 Ohnohigashi, Osaka-Sayama, Osaka 589-8511, Japan; [3]Cancer Center, Kobe University Hospital, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan; [4]Department of Otolaryngology-Head and Neck Surgery, Nara Medical University, 840 Shijo-Cho, Kashihara, Nara 634-8521, Japan; [5]Department of Otolaryngology, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi-Hirokoji Kamigyo-ku, Kyoto 602-8566, Japan; [6]Department of Head and Neck Surgery, Hyogo Cancer Center, 13-70 Kitaoujicho, Akashi, Hyogo 673-8588, Japan; [7]Department of Otolaryngology, National Hospital Organization Tokyo Medical Center 2-5-1 Higashigaoka, Meguro-ku, Tokyo 152-8902, Japan; [8]Department of Otolaryngology, Nara Hospital, Faculty of Medicine, Kindai University, 1248-1 Otoda-cho, Ikoma, Nara 630-0293, Japan; [9]Division of Head and Neck Medical

Oncology, Miyagi Cancer Center 47-1 Nodayama, Medeshimashiode, Natori, Miyagi 981-1293, Japan; [10] Department of Genome Biology, Kindai University Faculty of Medicine 377-2 Ohnohigashi, Osaka-Sayama, Osaka 589-8511, Japan; and [11]Department of Otolaryngology-Head and Neck Surgery, Kobe University Hospital, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe, 650-0017, Japan.

***Address for correspondence:**

Naomi Kiyota, M.D., Ph.D.

Cancer Center, Kobe University Hospital

7-5-2 Kusunoki-cho, Chuo-ku, Kobe, Hyogo, 650-0017, Japan

Tel.: +81-78-382-5820; Fax: (+81)78-382-5821

Email: nkiyota@med.kobe-u.ac.jp

Author Contributions:

All authors contributed to the study conception and design. Patient recruitment were performed by Yoshinori Imamura, Kaoru Tanaka, Naomi Kiyota, Hidetoshi Hayashi, Ichiro Ota, Akihito Arai, Shigemichi Iwae, Shujiro Minami, Katsunari Yane, Yoshiaki Nagatani, Masanori Toyoda, Naoki Otsuki, Ken-ischi Nibu, and Hironobu Minami. Data collection and analysis were performed by Yoshinori Imamura, Takayuki Takahama, Kazuko Sakai, and Kazuto Nishio. The first draft of the manuscript was written by Yoshinori Imamura and Takayuki Takahama. All authors commented on

previous versions of the manuscript. Funding acquisition was conducted by Naomi Kiyota. All authors read and approved the final manuscript.

Acknowledgements

We thank Dr. Yutaka Fujiwara, Aichi Cancer Center Hospital, for his helpful advice on the conceptual stage of the protocol. This study was funded by a Grant-in-Aid for Scientific Research C (grant number: 26462605 and 17K11384) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

53 **Abstract**

54 ***Background.*** The clinical utility of systemic therapy and genomic profiling in non-
55 squamous-cell head and neck cancer (NSCHNC) has not been fully elucidated. This
56 phase II trial evaluated the efficacy and safety of docetaxel and cisplatin combination in
57 the first-line setting.

58 ***Patients and methods.*** Eligibility criteria were recurrent and/or metastatic NSCHNC;
59 progressive disease within the last 6 months; no prior systemic therapy; and ECOG
60 performance status of 0-1. Patients received docetaxel (75 mg/m^2 on day 1) and
61 cisplatin (75 mg/m^2 on day 1), repeated every 21 days for 6 cycles. The primary
62 endpoint was confirmed objective response rate (ORR). The secondary endpoints
63 included progression-free survival (PFS), overall survival (OS), and adverse events.
64 Next-generation sequencing (NGS) was performed using the Ion AmpliSeq Cancer
65 Hotspot Panel v2.

66 ***Results.*** Twenty-three patients were enrolled from November 2012 to October 2016, of
67 whom 8 were male. Median age was 57 years. Ninety-six percent of cases were
68 metastatic. Among 22 evaluable patients, confirmed ORR was 45% (95% confidential
69 interval, 24-68%). With a median follow-up period of 18.8 months, median PFS and OS
70 were 6.7 and 20.1 months, respectively. Grade 3/4 adverse events included febrile
71 neutropenia (39%) and anemia (22%). No treatment-related deaths were observed. NGS
72 analysis revealed potential treatment targets, including *ERBB2, KIT*, and *ALK*.

73 ***Conclusions.*** The docetaxel and cisplatin combination regimen can be considered a new
74 treatment option in recurrent and/or metastatic NSCHNC, although primary prophylaxis

for febrile neutropenia should be considered. Diverse genomic alterations may lead novel treatment options.

This trial was registered with the UMIN Clinical Trials Registry as UMIN000008333 on [September 1st, 2012]

Key words: docetaxel; cisplatin; non-squamous-cell head and neck cancer; phase II trial

83 **Introduction**

84 Worldwide, head and neck cancer accounts for more than 550,000 cases and 380,000
85 deaths annually [1], the great majority of which (more than 90%) are squamous cell
86 carcinoma (HNSCC). Regarding non-squamous-cell head and neck cancer (NSCHNC),
87 in contrast, this condition is rare and shows wide heterogeneity among subtypes. Partly
88 for these reasons, the role of systemic treatment for NSCHNC has not been fully
89 elucidated. Even for recurrent and/or metastatic salivary gland cancer, the most frequent
90 subset of NSCHNC, the current National Comprehensive Cancer Network guidelines
91 include no specific recommendations for chemotherapy regimens, albeit that
92 personalized therapies have received considerable attention, particularly for androgen
93 receptor-positive, *HER2*-amplified, or *NTRK* fusion-positive cases [2].

94 Platinum combination therapy is the standard therapy for recurrent and/or metastatic
95 HNSCC [3]. This therapy is also the preferred regimen for recurrent and/or metastatic
96 salivary gland cancer, based on the results of clinical trials with overall response rates
97 (ORR) of 27-47% and median overall survival (OS) of 10-21 months [4-9]. In several
98 studies, taxane plus platinum combination therapy had promising efficacy for recurrent
99 and/or metastatic HNSCC [10-15], and docetaxel 75 mg/m^2 plus cisplatin 75 mg/m^2
100 every 21 days has shown a favorable risk-benefit ratio in these patients [11-13]. For
101 recurrent and/or metastatic salivary gland cancer and NSCHNC, some retrospective
102 studies provided promising results using taxane plus platinum regimens [16, 17],
103 however, few prospective data have been reported. Regarding specific agents, cisplatin

104 appears preferable to carboplatin, given the lack of response observed in a phase II trial
105 which initiated therapy with carboplatin for advanced salivary gland cancer [18].
106 In addition to cytotoxic agents, targeted therapy is developing as an attractive
107 treatment strategy. With the development of next-generation sequencing (NGS)
108 technologies, DNA sequencing has been increasingly utilized in clinical
109 practice. Although several studies have reported genetic alterations in salivary gland
110 cancer, including *EGFR*, *KIT*, *BRAF*, *HRAS*, *PIK3CA*, *ERBB2* and *NTRK* [19-22], only
111 a few studies have focused on genetic events in other NSCHNC. NGS-based genomic
112 profiling has the potential to discover new targets of therapy for this rare entity.
113 Here, we evaluated the efficacy and safety of combination therapy with docetaxel
114 plus cisplatin (DC) in patients with recurrent and/or metastatic NSCHNC. In addition,
115 we conducted NGS-based genomic profiling as supplementary research to identify
116 potential targets of therapy.
117
118
119 **Methods**
120 *Patient population*
121 This open-label, non-randomized, multicenter phase II study was conducted at 8
122 centers in Japan. Inclusion criteria included age 20 years or older with cytologically or
123 histologically confirmed NSCHNC, excluding neuroendocrine tumors, lympho-
124 epithelial carcinoma, sarcoma, melanoma, and undifferentiated carcinoma. Other key
125 eligibility criteria included unresectable recurrent and/or metastatic disease and new or

126 progressive lesions on a radiologic imaging study and/or new/worsening disease-related
127 symptoms within 6 months of enrollment; no prior systemic palliative chemotherapy, no
128 previous taxane, and an interval of at least 24 weeks since last induction chemotherapy
129 or chemoradiotherapy with curative intent; Eastern Cooperative Oncology Group
130 performance status (ECOG-PS) of 0 to 1; life expectancy of 12 weeks or longer;
131 adequate organ function; and measurable lesion according to Response Evaluation
132 Criteria In Solid Tumors (RECIST) version 1.1. Key exclusion criteria included surgery
133 or radiotherapy within 4 weeks before study entry; pleural effusion, ascites and/or
134 pericardial effusion requiring drainage; active infection; active concomitant malignancy
135 except carcinoma in situ or intramucosal tumor within 5 years before study entry;
136 symptomatic central nervous system metastases; and lung fibrosis, acute lung damage
137 or intestinal lung disease.
138 The study protocol was approved by the institutional review board at each
139 participating center. The trial was conducted in accordance with the Declaration of
140 Helsinki, and all patients provided written informed consent before study entry. This
141 trial was registered with the UMIN Clinical Trials Registry as UMIN000008333.
142
143 *Study treatment and safety assessment*
144 The chemotherapy regimen consisted of docetaxel 75 mg/m^2 plus cisplatin 75 mg/m^2
145 on day 1. Treatment was repeated every 21 days and continued until disease
146 progression, the development of unacceptable toxicity, patient refusal, or cessation as
147 planned after 6 cycles. Treatment beyond 6 cycles was permitted at the physicians'

148 discretion. Dose modifications (reduce first to 60 mg/m^2; may reduce further to 45
149 mg/m^2 for each drug) or delays were based on the worst grade of adverse events in
150 accordance with the protocol. Adverse events were monitored at least bi-weekly
151 throughout the study and evaluated using Common Terminology Criteria for Adverse
152 Events version 4.0. Prophylactic antibiotics or hematopoietic colony-stimulating factors
153 could be used at the investigator's discretion.
154
155 *Efficacy assessment and statistical consideration*
156 Response was assessed every 6-8 weeks by investigator assessment of computed
157 tomography or magnetic resonance imaging based on RECIST version 1.1. The primary
158 endpoint was confirmed ORR. In addition, disease control rate (DCR), progression-free
159 survival (PFS) and OS were assessed as secondary endpoints. For the primary endpoint,
160 the null hypothesis (ORR ≤10%) and alternative hypothesis (ORR ≥35%) were tested
161 with a two-sided significance level of 5% and a power of 80%. Given an anticipated
162 dropout rate of 10%, the target number of patients was calculated as 23.
163 All analyses were performed using SPSS for Windows, version 23.0 (IBM, Armonk,
164 NY). Binominal confidence intervals (CIs) for ORR were estimated by the exact
165 method. For time-to-event analyses, Kaplan-Meier estimates and 95% CIs were
166 calculated. All statistical analyses were two-sided, and probability values of <0.05 were
167 considered statistically significant.
168
169 *Next generation sequencing (NGS) analysis*

170 The methods for NGS have been described elsewhere [23]. Briefly, macro-dissected
171 primary tumor DNA was subjected to NGS using the Ion AmpliSeq Cancer Hotspot
172 Panel v2 (Thermo Fisher Scientific) and a focused panel for the detection of mutation
173 and copy number gain (Table S1). The focused panel for the entire coding sequences of
174 *ESR1*, *ESR2*, *AR*, *PGR*, *ERBB2*, *EGFR*, and *KIT* was designed with the use of Ion
175 Ampliseq Designer ver. 5.2 (Thermo Fisher Scientific). Germline mutations were
176 excluded using the Human Genetic Variation Database [24, 25]. For detection of copy
177 number gain, the read counts of targeted regions were divided by normalized read
178 counts from normal pooled samples. Adjusted read depth was log2-transformed, and the
179 median log2 value per gene was used for copy number analysis. The log2 ratio cutoff
180 value for copy number gain was set at 1.25 with reference to a previous study [26].
181
182
183 **Results**
184 *Patient characteristics*
185 Twenty-three patients were enrolled from November 2012 to October 2016. As
186 summarized in Table 1, the most common primary site was salivary gland, and the most
187 common histological diagnosis was adenoid cystic carcinoma. In previous treatment,
188 the majority of patients had a history of local therapy, and no patient had received prior
189 taxane or platinum agents.
190 By the censor date (October 31, 2016), 21 episodes of progression and 14 deaths had
191 occurred. Median follow-up duration was 18.8 months (range 12.6-56.5 months). The

192 median number of delivered cycles was 5 (range, 1-6), and the average relative dose
193 intensities of docetaxel and cisplatin were 91% (range, 66-100) and 91% (range, 66-
194 100), respectively. Study treatment was discontinued due to completion of 6 cycles (n =
195 9), disease progression (n = 5), adverse events (n = 5), patient refusal related to adverse
196 events (n=3), and patient refusal related to financial issue (n = 1).
197
198 *Efficacy analysis*
199 Treatment efficacy is summarized in Table 2. One patient refused to proceed with
200 anticancer treatment prior to the first response evaluation. Among 22 evaluable patients,
201 2 showed a complete response and 8 achieved a partial response. Confirmed ORR was
202 45% (95% CI, 24-68), and the lower bound of the 95% CI of 24% exceeded the
203 predefined null hypothesis of 10%. DCR was 95%. The best reduction from baseline
204 was recorded in target lesions; 12 patients (55%) showed ≥30% tumor shrinkage
205 relative to baseline (Figure 1). On subgroup analysis according to primary tumor site
206 and histology (Table S2), confirmed ORR in patients with salivary gland cancer (n =
207 11) was 55%. Three of 10 patients (30%) with adenoid cystic carcinoma showed a
208 partial response, while 2 of 2 patients with ocular sebaceous adenocarcinoma achieved a
209 complete response.
210 In all patients, the median PFS and OS were 6.7 and 20.1 months, respectively
211 (Figure 2). In 11 salivary gland cancer patients, the median PFS and OS were 6.6 and
212 18.8 months, respectively.
213

214 *Safety analysis*

215 Adverse events occurring in 10% or more of patients are presented in Table 3. Nine
216 patients (39%) developed febrile neutropenia, and it was the major cause of
217 discontinuation of the study treatment (4 cases). Prophylactic fluoroquinolone was used
218 in 9 patients, in whom the rate of febrile neutropenia was significantly lower (1 of 9,
219 11%) than in those without this use (8 of 14, 57%) (Fisher's exact test, p=0.04). No
220 treatment-related deaths were observed.

221

222 *Subsequent treatment*

223 A total of 9 (39%) patients received subsequent treatment after the discontinuation of
224 study treatment. Of note, 5 (22%) of these patients received DC combination therapy
225 with or without a chemotherapy-free interval.

226

227 *Next generate sequencing (NGS)*

228 Thirteen of 23 specimens were available, of which 11 were evaluable for NGS. As
229 shown in Figure 3, genomic alterations were identified in 8 different genes among 7
230 patients. On average, there were 1.2 genomic alterations in each patient. The most
231 frequent genomic alterations were observed in *ERBB2*, followed by *TP53*. In addition,
232 several potential targets of therapy, including *KIT* and *ALK,* were identified in 1 patient
233 each.

234

235

236 **Discussion**

237 This phase II study showed that DC produces promising activity in first-line
238 treatment of recurrent and/or metastatic NSCHNC, with a confirmed ORR of 45%,
239 median PFS of 6.7 months, and median OS of 20.1 months. When subdivided by
240 histologic type, patients with the most common subtypes showed favorable efficacy
241 (Table S2, Figure 1). Regarding adverse events, the high rate of febrile neutropenia
242 (39%) warranted concern, although no treatment-related deaths were observed.

243 Due to the rarity and heterogeneity of NSCHNC, no randomized phase III trial has
244 yet been conducted, and studies on the clinical utility of systemic chemotherapy are
245 limited. To date, CAP (cyclophosphamide, doxorubicin, cisplatin) has been reported as
246 an active regimen in salivary gland cancer. Although the reported ORR for the CAP
247 regimen, based on multiple studies [4, 27-31] was 46% (43 of 92), these data should be
248 interpreted with caution due to publication bias; Licitra et al. [4], in the largest phase II
249 trial of 22 patients treated with CAP, reported that only 6 patients achieved PR with an
250 ORR of 27%. Other phase II trials showed that PV (cisplatin, vinorelbine) had
251 promising efficacy, with an ORR of 33-44% and median OS of 10-16.9 months [7-9].
252 The salivary gland cancer cohort in our study appeared to show greater efficacy, with a
253 confirmed ORR of 55% and median OS of 18.8 months, and high response rates were
254 observed in various histologic subtypes (Table S2, Figure 1), although observed median
255 PFS of 6.8 months that was slightly unsatisfactory and shorter than recent results of
256 personalized therapies (8.8+ months) [32-38].

257 On the other hand, severe hematological adverse events were also seen. The
258 incidence rate of febrile neutropenia of 39% was much greater than that in previous
259 clinical trials, not only in those with CAP or PV [4, 7-9], but also in those with DC
260 among Western patients with HNSCC [11-13] or Japanese patients with non-small cell
261 lung cancer, endometrial carcinoma and ovarian cancer [39-41], in whom the incidence
262 rates of febrile neutropenia were less than 20%. Although no mechanistic insights have
263 been obtained, the different sensitivity to docetaxel toxicity of Japanese and Western
264 populations is well known [42]. A Taiwanese phase II trial [15] with reduced-dose
265 docetaxel (60 mg/m^2) combined with cisplatin (75 mg/m^2) in patients with HNSCC
266 seemed less effective than other Western phase II trials [11-13] with DC (75 mg/m^2
267 each; same dose as in this study) (ORRs of 24% versus 33-53%). We therefore consider
268 that reducing the dose of docetaxel is a suboptimum strategy in this setting. Our *post-*
269 *hoc* analysis showed that prophylactic antibiotics are a good option in reducing the risk
270 of febrile neutropenia (11% versus 57% with and without prophylactic antibiotics,
271 respectively). Alternatively, because of the greater than 20% risk of febrile neutropenia,
272 primary prophylaxis with hematopoietic colony-stimulating factors should be
273 considered, in accordance with the current American Society of Clinical Oncology
274 guideline [43].
275 Recently, personalized therapies for salivary gland tumors have been developed.
276 Androgen receptor-positive or *HER2*-amplified salivary duct carcinoma, and *NTRK*
277 fusion-positive mammary analogue secretory carcinoma of salivary glands are
278 successfully treated entities [32-37]. In this context, NGS-based genomic profiling is

279 expected to guide targeted therapies for personalized treatment. Our accompanying
280 research using this technique detected a comparable number of genetic alterations to
281 Japanese lung cancer patients [23], and identified several potential targets of therapy,
282 including *ERBB2 (HER2), KIT*, and *ALK.* Although *HER2*-amplified salivary duct
283 carcinoma is one of the most successfully treated entities [33-35], the anti-tumor
284 activity of imatinib in adenoid cystic carcinoma, in which c-kit tyrosine kinase receptor
285 is expressed in up to 100% of cases, remains questionable [44, 45]. ALK-mutated
286 tumors, collectively called ALKoma, can be targeted with ALK inhibitors such as
287 crizotinib; nevertheless, no reports for ALK-mutated NSCHNC have yet appeared. At
288 present, further genomic profiling and clinical trials are required to evaluate the future
289 application of targeted treatments.

290 This study had several limitations. First, it was conducted under a non-randomized
291 design, and therefore requires external validation of the results. Second, sample size was
292 small, and patients with heterogeneous histologic subtypes and primary sites were
293 included owing to the rarity of recurrent and/or metastatic NSCHNC. Third, the NGS
294 panel we used in this study did not cover *NTRK* fusion. Finally, from the viewpoint of
295 risk-benefit balance, this DC regimen should be adopted carefully. Allowing for these
296 limitations, however, the strength of this study is that we included only progressive
297 cases within 6 months of enrollment to minimize the diversity.

298 In conclusion, this is the first prospective study to focus on recurrent and/or
299 metastatic NSCHNC. The study met its primary endpoint of confirmed ORR. This DC
300 regimen can be considered a new treatment option for recurrent and/or metastatic

301 NSCHNC, although primary prophylaxis for febrile neutropenia should be considered.

302 NGS revealed the diverse genomic alterations in recurrent and/or metastatic NSCHNC;

303 further investigation may reveal novel treatment options.

Declarations

Funding:

This study was funded by a Grant-in-Aid for Scientific Research C (grant number: 26462605 and 17K11384) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. The funding source had no role in the study.

Conflict of Interest:

Naomi Kiyota has received honoraria for Bristol-Myers Squibb, and grant support from Bristol-Myers Squibb outside the submitted work. Hidetoshi Hayashi has received honoraria for Astra-Zeneca, Bristol-Myers Squibb, and Ono Pharma, and grant support from Boehringer Ingelheim and Ono Pharma outside the submitted work. Tomoko Yamazaki has received grant support from Astra-Zeneca, MSD, and Ono Pharma outside the submitted work. Ken-ichi Nibu has received honoraria for Ono Pharma outside the submitted work. Hironobu Minami has received grant support from Bristol-Myers Squib and Pfizer outside the submitted work. The other authors declare that they have no conflict of interest for this study.

Availability of Data and Material: Not applicable.

Code Availability: Not applicable.

Ethics Approval:

326 The study protocol was approved by the institutional review board at each participating
327 center. The trial was conducted in accordance with the Declaration of Helsinki. This
328 trial was registered with the UMIN Clinical Trials Registry as UMIN000008333.
329
330 **Consent to Participate:** All patients provided written informed consent before study
331 entry.
332
333 **Consent to Publish:** All authors consent to the publication of the manuscript in
334 Medical Oncology.
335

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499 Tables

500 Table 1. Patient characteristics

Characteristic	N	(%)
Age, years – median (range)	57	(32-76)
Sex		
Male	8	(35)
Female	15	(65)
ECOG Performance status		
0	11	(48)
1	12	(52)
Primary tumor site		
Salivary gland	12	(52)
Nasal cavity/paranasal sinus	3	(13)
Ocular	3	(13)
Others	5	(22)
Histology		
Adenoid cystic carcinoma	10	(43)
Adenocarcinoma, NOS	5	(22)
Salivary duct carcinoma	3	(13)
Sebaceous adenocarcinoma	2	(9)
Others	3	(13)

Disease status		
Primary untreated metastatic	9	(39)
Recurrent, locoregional	1	(4)
Recurrent, metastatic ± locoregional	13	(57)
Organ involved		
Lung	17	(74)
Liver	5	(22)
Bone	4	(17)
Cervical lymph node	4	(17)
Others	3	(13)
Previous treatment	21	(91)
Surgery	20	(87)
Irradiation	14	(61)
Definitive concurrent cetuximab with radiotherapy	1	(4)
Definitive concurrent S-1 with radiotherapy	1	(4)
Androgen blockade therapy with palliative intent	1	(4)

501

502 Table 2. Treatment efficacy.

Efficacy	N	(%)	95% CI
Evaluable patients	22	(95.7)	-
CR	2	(9.1)	0.1-29.2
PR	8	(36.4)	17.2-59.3
SD	11	(50.0)	28.2-71.8
PD	1	(4.5)	0.0-22.8
Confirmed objective response (CR + PR)	10	(45.5)	24.4-68.8
Disease control rate (CR + PR + SD)	21	(95.5)	77.2-99.9
Median PFS, months	6.7		4.8-8.5
Median OS, months	20.1		14.3-25.9
Median time to response, months	1.4		0.6-7.3
Median duration of response, months	4.0		1.9-12.8

503 CR, complete response; PR, partial response; SD, stable disease; PD, progressive

504 disease; PFS, progression-free survival; OS, overall survival; CI, confidence interval

505 Table 3. Grade (Gr) 1 or worse adverse events in 10% or more of patients.

Adverse events	All Gr	(%)	Gr2	(%)	Gr3	(%)	Gr4	(%)
Hematological								
Anemia	23	(100)	9	(39)	5	(22)	0	
Neutropenia	22	(96)	0		9	(39)	12	(52)
Platelet count decreased	15	(65)	0		0		1	(4)
Febrile neutropenia	9	(39)	0		8	(35)	1	(4)
Non-hematological								
Fatigue	21	(91)	4	(18)	3	(13)	0	
Appetite loss	21	(91)	8	(35)	3	(13)	1	(4)
Nausea	20	(87)	6	(26)	2	(9)	0	
Hair loss	19	(83)	15	(65)	0		0	
Constipation	14	(61)	5	(22)	0		1	(4)
Diarrhea	12	(52)	2	(9)	2	(9)	0	
Peripheral neuropathy	11	(48)	5	(22)	1	(4)	0	
Vomiting	8	(35)	3	(13)	0		0	
Edema	7	(30)	4	(18)	0		0	
Mucositis, oral	7	(30)	1	(4)	0		0	
Hypoalbuminemia	23	(100)	9	(39)	1	(4)	0	
Hyponatremia	21	(91)	0		5	(22)	0	

Aspartate aminotransferase increased	16 (70)	1 (4)	1 (4)	0
Hypocalcemia	14 (61)	2 (9)	1 (4)	0
Hypomagnesemia	10 (48)	0	0	0
Alanine aminotransferase increased	10 (44)	1 (4)	2 (9)	0
Creatinine increased	8 (35)	2 (9)	0	0
Alkaline phosphatase increased	7 (30)	2 (9)	1 (4)	0
Hyperkalemia	4 (17)	0	0	0
Blood bilirubin increased	3 (13)	0	0	0

506

507 **Figure legends:**

508 **Fig.1** Best % change in target legions from baseline (n=22)

509

510 **Fig.2** Kaplan–Meier curves. (A) Progression-free survival. (B) Overall survival (n=23)

511

512 **Fig.3** Tile plot. Next-generation sequencing was performed with using multiplex PCR

513 for enrichment of cancer related gene loci covering hotspots of 50 cancer genes (Ion

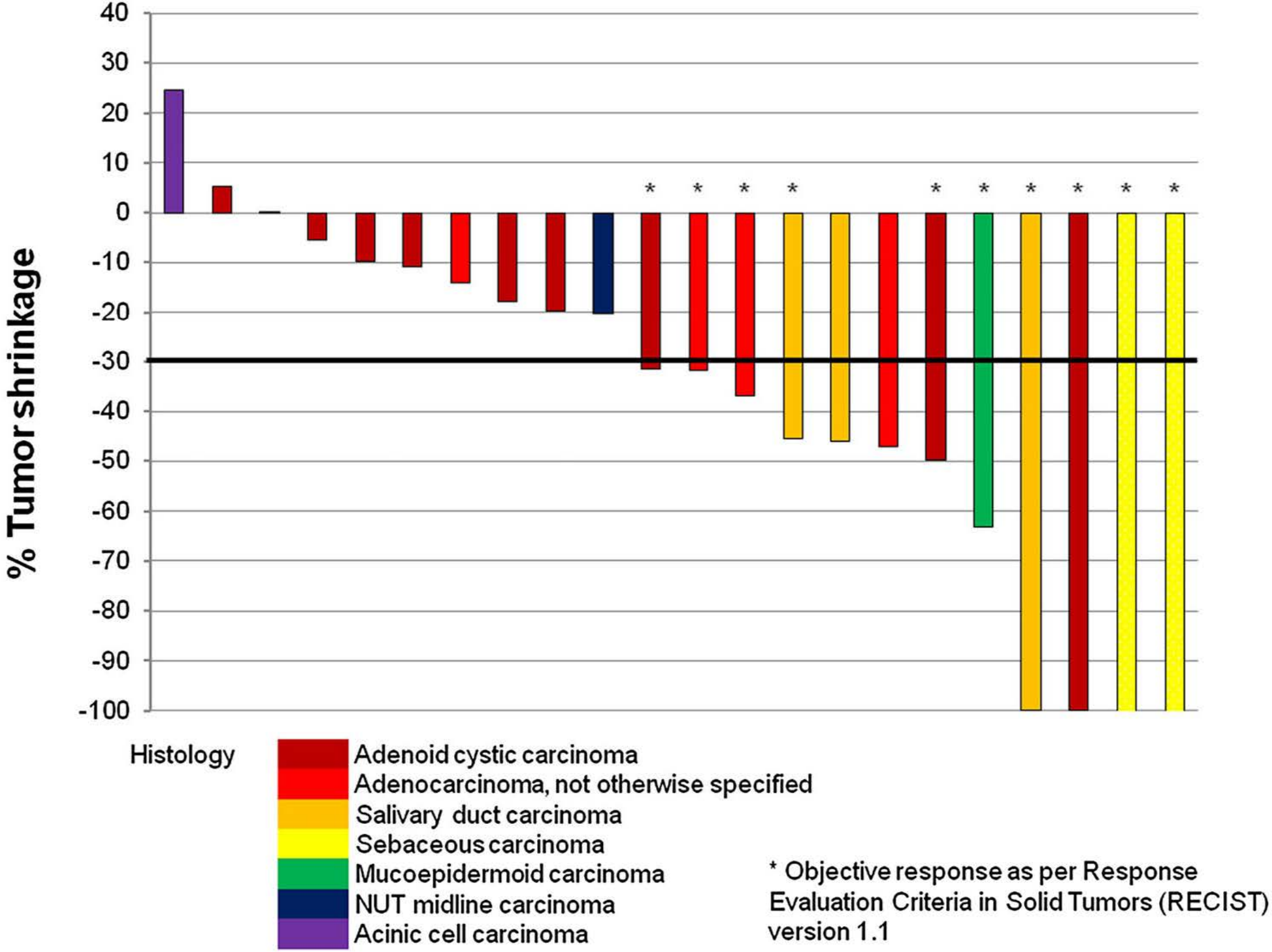
514 AmpliSeq Cancer Hotspot Panel v2) and additional 4 hormonal genes (*ESR1*, *ESR2*,

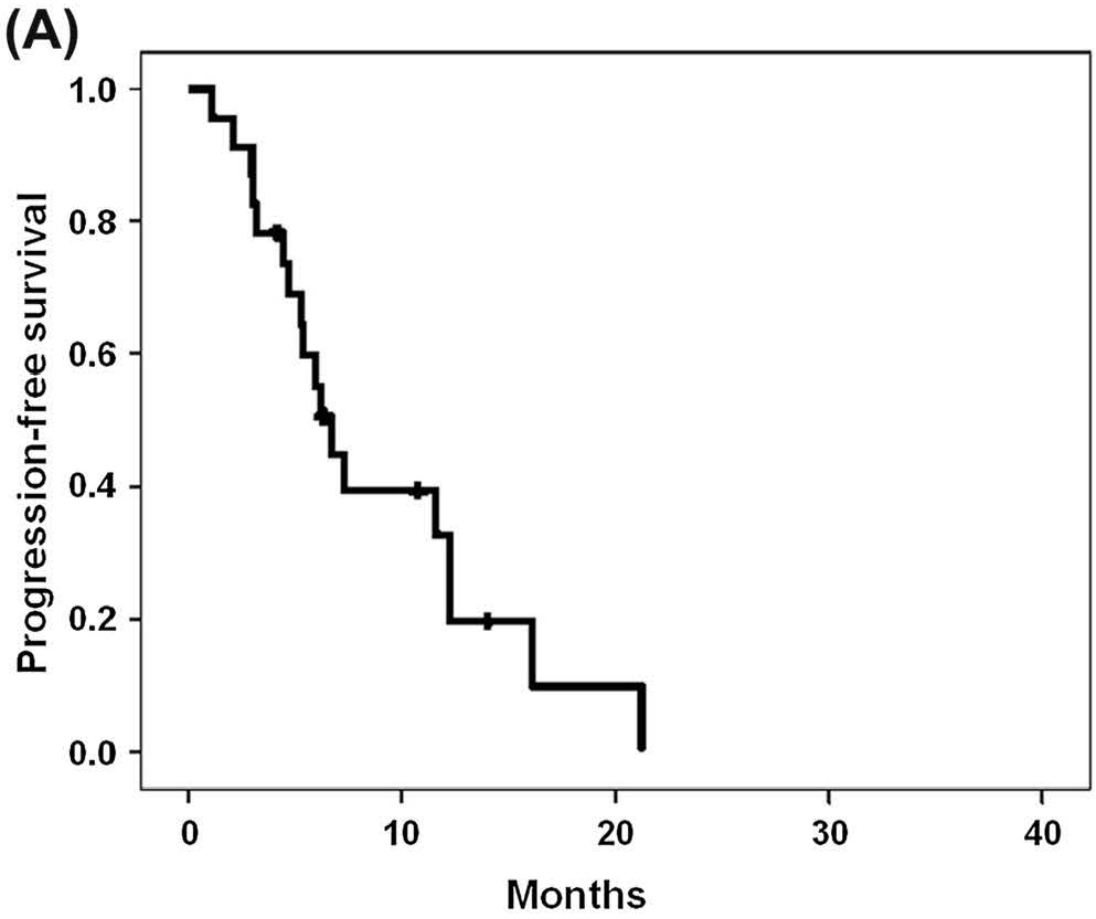
515 *PGR*, and *AR*). ANOS, adenocarcinoma, not otherwise specified; SDC, salivary duct

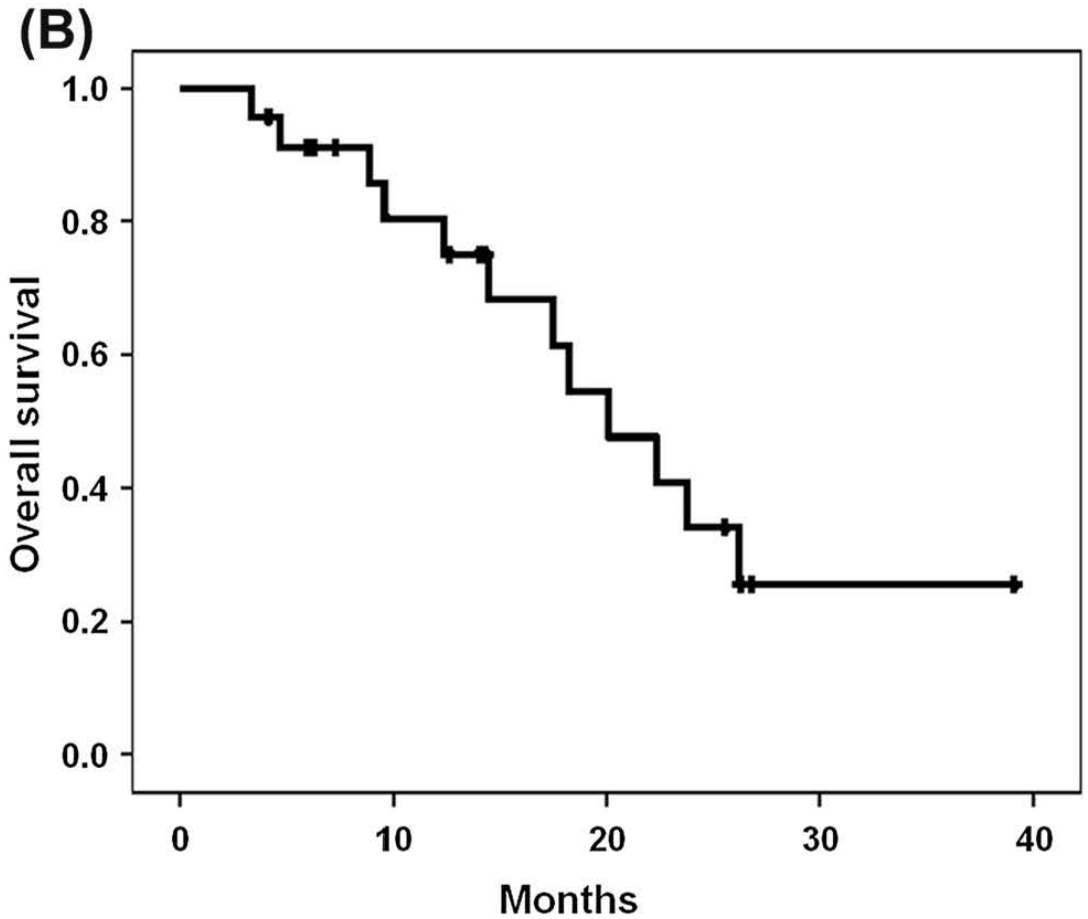
516 carcinoma; SA sebaceous adenocarcinoma; MEC, mucoepidermoid carcinoma; AdCC,

517 adenoid cystic carcinoma; NUT, NUT midline carcinoma; CR, complete response; PR,

518 partial response; SD, stable disease.


% Tumor shrinkage
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
Histology
Adenoid cystic carcinoma
Adenocarcinoma, not otherwise specified
Salivary duct carcinoma
Sebaceous carcinoma
Mucoepidermoid carcinoma
NUT midline carcinoma
Acinic cell carcinoma
* Objective response as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1


(A)
Progression-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
Months


(B)
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
Months

Histology	ANOS	ANOS	SDC	SDC	SA	SA	MEC	AdCC	AdCC	AdCC	NUT
Primary site	Salivary	Salivary	Salivary	Salivary	Ocular	Ocular	Oral cavity	Salivary	Oro-pharynx	Nasal	Salivary
Response	PR	PR	PR	PR	CR	CR	PR	PR	SD	SD	SD
ERBB2	1.70	1.88	3.64		2385G>A						
TP53	400T>A		472C>T			517G>T					
KIT				502G>A							
ALK					1.67						
KRAS						2.20					
GNAS						1.77					
ESR2			1407-417A>C								
ESR1							707G>A				
AR											
PGR											

Gene amplification (copy number)
Substitution (coding region change in longest transcription)

Title: Docetaxel plus cisplatin in progressive recurrent and/or metastatic non-squamous-cell head and neck cancer: a multicenter phase II trial

Medical Oncology

Authors: Yoshinori Imamura,[1] Kaoru Tanaka,[2] Naomi Kiyota,*[1,3] Hidetoshi Hayashi,[2] Ichiro Ota,[4] Akihito Arai,[5] Shigemichi Iwae,[6] Shujiro Minami,[7] Katsunari Yane,[8] Tomoko Yamazaki,[9] Yoshiaki Nagatani,[1] Masanori Toyoda,[1] Takayuki Takahama,[10] Kazuko Sakai,[10] Kazuto Nishio,[10] Naoki Otsuki,[11] Ken-ichi Nibu,[11] and Hironobu Minami[1,3]

Affiliations: [1] Medical Oncology and Hematology, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan; [2]Department of Medical Oncology, Kindai University Faculty of Medicine, 377-2 Ohnohigashi, Osaka-Sayama, Osaka 589-8511, Japan; [3]Cancer Center, Kobe University Hospital, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan; [4]Department of Otolaryngology-Head and Neck Surgery, Nara Medical University, 840 Shijo-Cho, Kashihara, Nara 634-8521, Japan; [5]Department of Otolaryngology, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi-Hirokoji Kamigyo-ku, Kyoto 602-8566, Japan; [6]Department of Head and Neck Surgery, Hyogo Cancer Center, 13-70 Kitaoujicho, Akashi, Hyogo 673-8588, Japan; [7]Department of Otolaryngology,

National Hospital Organization Tokyo Medical Center 2-5-1 Higashigaoka, Meguro-ku, Tokyo 152-8902, Japan; [8]Department of Otolaryngology, Nara Hospital, Faculty of Medicine, Kindai University, 1248-1 Otoda-cho, Ikoma, Nara 630-0293, Japan; [9]Division of Head and Neck Medical Oncology, Miyagi Cancer Center 47-1 Nodayama, Medeshimashiode, Natori, Miyagi 981-1293, Japan; [10] Department of Genome Biology, Kindai University Faculty of Medicine 377-2 Ohnohigashi, Osaka-Sayama, Osaka 589-8511, Japan; and [11]Department of Otolaryngology-Head and Neck Surgery, Kobe University Hospital, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe, 650-0017, Japan.

***Address for correspondence:**

Naomi Kiyota, M.D., Ph.D.

Cancer Center, Kobe University Hospital

7-5-2 Kusunoki-cho, Chuo-ku, Kobe, Hyogo, 650-0017, Japan

Tel.: +81-78-382-5820; Fax: (+81)78-382-5821

Email: nkiyota@med.kobe-u.ac.jp

Table S1. Target genes.

Ion AmpliSeq Cancer Hotspot Panel v2				
ABL1	*AKT1*	*ALK*	*APC*	*ATM*
BRAF	*CDH1*	*CDKN2A*	*CSF1R*	*CTNNB1*
EGFR	*ERBB2*	*ERBB4*	*EZH2*	*FBXW7*
FGFR1	*FGFR2*	*FGFR3*	*FLT3*	*GNA11*
GNAS	*GNAQ*	*HNF1A*	*HRAS*	*IDH1*
IDH2	*JAK2*	*JAK3*	*KDR*	*KIT*
KRAS	*MET*	*MLH1*	*MPL*	*NOTCH1*
NPM1	*NRAS*	*PDGFRA*	*PIK3CA*	*PTEN*
PTPN11	*RB1*	*RET*	*SMAD4*	*SMARCB1*
SMO	*SRC*	*STK11*	*TP53*	*VHL*
An original focused panel				
ESR1	*ESR2*	*AR*	*PGR*	*ERBB2*
EGFR	*KIT*			

Table S2. Overall response according to primary tumor site and histology.

Overall response	Number of responses/total number of patients							
	AdCC	ANOS	SDC	SA	MEC	NUT	AcCC	Total
Salivary gland	2/4	2/3	2/3	-	-	0/1	-	6/11
Nasal cavity/paranasal sinus	1/3	-	-	-	-	-	-	1/3
Ocular	0/1	-	-	2/2*	-	-	-	2/3
Oral cavity/lip	-	-	-	-	1/1	-	0/1	1/2
Oropharynx	0/1	0/1	-	-	-	-	-	0/2
Ear	0/1	-	-	-	-	-	-	0/1
Total	3/10	2/4	2/3	2/2	1/1	0/1	0/1	10/22

AdCC, adenoid cystic carcinoma; ANOS, adenocarcinoma, not otherwise specified; SDC, salivary duct carcinoma; SA sebaceous adenocarcinoma; MEC, mucoepidermoid carcinoma; NUT, NUT midline carcinoma; AcCC, acinic cell carcinoma.

*Complete response