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

(URL)
https://hdl.handle.net/20.500.14094/90008644

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

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.

Abstract

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

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

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

Conclusions. The docetaxel and cisplatin combination regimen can be considered a new 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

Introduction

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

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

discretion. Dose modifications (reduce first to 60 mg/m^2; may reduce further to 45 mg/m^2 for each drug) or delays were based on the worst grade of adverse events in accordance with the protocol. Adverse events were monitored at least bi-weekly throughout the study and evaluated using Common Terminology Criteria for Adverse Events version 4.0. Prophylactic antibiotics or hematopoietic colony-stimulating factors could be used at the investigator's discretion.

Efficacy assessment and statistical consideration

Response was assessed every 6-8 weeks by investigator assessment of computed tomography or magnetic resonance imaging based on RECIST version 1.1. The primary endpoint was confirmed ORR. In addition, disease control rate (DCR), progression-free survival (PFS) and OS were assessed as secondary endpoints. For the primary endpoint, the null hypothesis (ORR ≤10%) and alternative hypothesis (ORR ≥35%) were tested with a two-sided significance level of 5% and a power of 80%. Given an anticipated dropout rate of 10%, the target number of patients was calculated as 23.

All analyses were performed using SPSS for Windows, version 23.0 (IBM, Armonk, NY). Binominal confidence intervals (CIs) for ORR were estimated by the exact method. For time-to-event analyses, Kaplan-Meier estimates and 95% CIs were calculated. All statistical analyses were two-sided, and probability values of <0.05 were considered statistically significant.

Next generation sequencing (NGS) analysis

The methods for NGS have been described elsewhere [23]. Briefly, macro-dissected primary tumor DNA was subjected to NGS using the Ion AmpliSeq Cancer Hotspot Panel v2 (Thermo Fisher Scientific) and a focused panel for the detection of mutation and copy number gain (Table S1). The focused panel for the entire coding sequences of *ESR1*, *ESR2*, *AR*, *PGR*, *ERBB2*, *EGFR*, and *KIT* was designed with the use of Ion Ampliseq Designer ver. 5.2 (Thermo Fisher Scientific). Germline mutations were excluded using the Human Genetic Variation Database [24, 25]. For detection of copy number gain, the read counts of targeted regions were divided by normalized read counts from normal pooled samples. Adjusted read depth was log2-transformed, and the median log2 value per gene was used for copy number analysis. The log2 ratio cutoff value for copy number gain was set at 1.25 with reference to a previous study [26].

Results

Patient characteristics

Twenty-three patients were enrolled from November 2012 to October 2016. As summarized in Table 1, the most common primary site was salivary gland, and the most common histological diagnosis was adenoid cystic carcinoma. In previous treatment, the majority of patients had a history of local therapy, and no patient had received prior taxane or platinum agents.

By the censor date (October 31, 2016), 21 episodes of progression and 14 deaths had occurred. Median follow-up duration was 18.8 months (range 12.6-56.5 months). The

median number of delivered cycles was 5 (range, 1-6), and the average relative dose intensities of docetaxel and cisplatin were 91% (range, 66-100) and 91% (range, 66-100), respectively. Study treatment was discontinued due to completion of 6 cycles (n = 9), disease progression (n = 5), adverse events (n = 5), patient refusal related to adverse events (n=3), and patient refusal related to financial issue (n = 1).

Efficacy analysis

Treatment efficacy is summarized in Table 2. One patient refused to proceed with anticancer treatment prior to the first response evaluation. Among 22 evaluable patients, 2 showed a complete response and 8 achieved a partial response. Confirmed ORR was 45% (95% CI, 24-68), and the lower bound of the 95% CI of 24% exceeded the predefined null hypothesis of 10%. DCR was 95%. The best reduction from baseline was recorded in target lesions; 12 patients (55%) showed ≥30% tumor shrinkage relative to baseline (Figure 1). On subgroup analysis according to primary tumor site and histology (Table S2), confirmed ORR in patients with salivary gland cancer (n = 11) was 55%. Three of 10 patients (30%) with adenoid cystic carcinoma showed a partial response, while 2 of 2 patients with ocular sebaceous adenocarcinoma achieved a complete response.

In all patients, the median PFS and OS were 6.7 and 20.1 months, respectively (Figure 2). In 11 salivary gland cancer patients, the median PFS and OS were 6.6 and 18.8 months, respectively.

Safety analysis

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

Subsequent treatment

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

Next generate sequencing (NGS)

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

Discussion

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

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

On the other hand, severe hematological adverse events were also seen. The incidence rate of febrile neutropenia of 39% was much greater than that in previous clinical trials, not only in those with CAP or PV [4, 7-9], but also in those with DC among Western patients with HNSCC [11-13] or Japanese patients with non-small cell lung cancer, endometrial carcinoma and ovarian cancer [39-41], in whom the incidence rates of febrile neutropenia were less than 20%. Although no mechanistic insights have been obtained, the different sensitivity to docetaxel toxicity of Japanese and Western populations is well known [42]. A Taiwanese phase II trial [15] with reduced-dose docetaxel (60 mg/m^2) combined with cisplatin (75 mg/m^2) in patients with HNSCC seemed less effective than other Western phase II trials [11-13] with DC (75 mg/m^2 each; same dose as in this study) (ORRs of 24% versus 33-53%). We therefore consider that reducing the dose of docetaxel is a suboptimum strategy in this setting. Our *post-hoc* analysis showed that prophylactic antibiotics are a good option in reducing the risk of febrile neutropenia (11% versus 57% with and without prophylactic antibiotics, respectively). Alternatively, because of the greater than 20% risk of febrile neutropenia, primary prophylaxis with hematopoietic colony-stimulating factors should be considered, in accordance with the current American Society of Clinical Oncology guideline [43].

Recently, personalized therapies for salivary gland tumors have been developed. Androgen receptor-positive or *HER2*-amplified salivary duct carcinoma, and *NTRK* fusion-positive mammary analogue secretory carcinoma of salivary glands are successfully treated entities [32-37]. In this context, NGS-based genomic profiling is

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

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

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

NSCHNC, although primary prophylaxis for febrile neutropenia should be considered. NGS revealed the diverse genomic alterations in recurrent and/or metastatic NSCHNC; 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:

The study protocol was approved by the institutional review board at each participating center. The trial was conducted in accordance with the Declaration of Helsinki. This trial was registered with the UMIN Clinical Trials Registry as UMIN000008333.

Consent to Participate: All patients provided written informed consent before study entry.

Consent to Publish: All authors consent to the publication of the manuscript in Medical Oncology.

References

1. Fitzmaurice C, Allen C, Barber RM et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2017;3:524-548. DOI: 10.1001/jamaoncol.2016.5688

2. Network NCC. NCCN Guidelines® for Head and Neck Cancers, version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed 26 March 2021.

3. Vermorken JB, Mesia R, Rivera F et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008;359:1116-1127. DOI: 10.1056/NEJMoa0802656

4. Licitra L, Cavina R, Grandi C et al. Cisplatin, doxorubicin and cyclophosphamide in advanced salivary gland carcinoma. A phase II trial of 22 patients. Ann Oncol. 1996;7:640-642. DOI: 10.1093/oxfordjournals.annonc.a010684

5. Venook AP, Tseng A, Jr., Meyers FJ et al. Cisplatin, doxorubicin, and 5-fluorouracil chemotherapy for salivary gland malignancies: a pilot study of the Northern California Oncology Group. J Clin Oncol. 1987;5:951-955. DOI: 10.1200/JCO.1987.5.6.951

6. Dimery IW, Legha SS, Hong WK et al. Fluorouracil, doxorubicin, cyclophosphamide, and cisplatin combination chemotherapy in advanced or

recurrent salivary gland carcinoma. J Clin Oncol. 1990;8:1056-1062. DOI: 10.1200/JCO.1990.8.6.1056

7. Airoldi M, Pedani F, Succo G et al. Phase II randomized trial comparing vinorelbine versus vinorelbine plus cisplatin in patients with recurrent salivary gland malignancies. Cancer. 2001;91:541-547. DOI: 10.1002/1097-0142(20010201)91:3<541::aid-cncr1032>3.0.co;2-y

8. Airoldi M, Garzaro M, Pedani F et al. Cisplatin+Vinorelbine Treatment of Recurrent or Metastatic Salivary Gland Malignancies (RMSGM): A Final Report on 60 Cases. Am J Clin Oncol. 2017;40:86-90. DOI: 10.1097/COC.0000000000000112

9. Hong MH, Kim CG, Koh YW et al. Efficacy and safety of vinorelbine plus cisplatin chemotherapy for patients with recurrent and/or metastatic salivary gland cancer of the head and neck. Head Neck. 2018;40:55-62. DOI: 10.1002/hed.24933

10. Gibson MK, Li Y, Murphy B et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. J Clin Oncol. 2005;23:3562-3567. DOI: 10.1200/JCO.2005.01.057

11. Specht L, Larsen SK, Hansen HS. Phase II study of docetaxel and cisplatin in patients with recurrent or disseminated squamous-cell carcinoma of the head and neck. Ann Oncol. 2000;11:845-849. DOI: 10.1023/a:1008355315205

12. Gedlicka C, Formanek M, Selzer E et al. Phase II study with docetaxel and cisplatin in the treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck. Oncology. 2002;63:145-150. DOI: 10.1023/a:1008355315205

13. Glisson BS, Murphy BA, Frenette G et al. Phase II Trial of docetaxel and cisplatin combination chemotherapy in patients with squamous cell carcinoma of the head and neck. J Clin Oncol. 2002;20:1593-1599. DOI: 10.1200/JCO.2002.20.6.1593

14. Caponigro F, Massa E, Manzione L et al. Docetaxel and cisplatin in locally advanced or metastatic squamous-cell carcinoma of the head and neck: a phase II study of the Southern Italy Cooperative Oncology Group (SICOG). Ann Oncol. 2001;12:199-202. DOI: 10.1023/a:1008322415335

15. Chang PM, Tzeng CH, Chen MH et al. Triweekly reduced-dose docetaxel combined with cisplatin in recurrent/metastatic head and neck squamous cell carcinoma: a multicenter phase II study. Cancer Chemother Pharmacol. 2011;68:1477-1484. DOI: 10.1007/s00280-011-1645-5

16. Nakano K, Sato Y, Sasaki T et al. Combination chemotherapy of carboplatin and paclitaxel for advanced/metastatic salivary gland carcinoma patients: differences in responses by different pathological diagnoses. Acta Otolaryngol. 2016;136:948-951. DOI: 10.3109/00016489.2016.1170876

17. Airoldi M, Fornari G, Pedani F et al. Paclitaxel and carboplatin for recurrent salivary gland malignancies. Anticancer Res. 2000;20:3781-3783.

18. Laurie SA, Siu LL, Winquist E et al. A phase 2 study of platinum and gemcitabine in patients with advanced salivary gland cancer: a trial of the NCIC Clinical Trials Group. Cancer. 2010;116:362-368. DOI: 10.1002/cncr.24745

19. Stenman G, Persson F, Andersson MK. Diagnostic and therapeutic implications of new molecular biomarkers in salivary gland cancers. Oral Oncol. 2014;50:683-690. DOI: 10.1016/j.oraloncology.2014.04.008

20. Cros J, Sbidian E, Hans S et al. Expression and mutational status of treatment-relevant targets and key oncogenes in 123 malignant salivary gland tumours. Ann Oncol. 2013;24:2624-2629. DOI: 10.1093/annonc/mdt338

21. Clauditz TS, Reiff M, Gravert L et al. Human epidermal growth factor receptor 2 (HER2) in salivary gland carcinomas. Pathology. 2011;43:459-464. DOI: 10.1097/PAT.0b013e3283484a60

22. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitory therapy. Nat Rev Clin Oncol. 2018;15:7370747. DOI: 10.1038/s41571-018-0113-0.

23. Takeda M, Sakai K, Terashima M et al. Clinical application of amplicon-based next-generation sequencing to therapeutic decision making in lung cancer. Ann Oncol. 2015;26:2477-2482. DOI: 10.1093/annonc/mdv475

24. Kyoto University Human Genetic Variation Database. https://www.hgvd.genome.med.kyoto-u.ac.jp. Accessed March 2021.

422 25. Narahara M, Higasa K, Nakamura S et al. Large-scale East-Asian eQTL
423 mapping reveals novel candidate genes for LD mapping and the genomic
424 landscape of transcriptional effects of sequence variants. PLoS One.
425 2014;9:e100924. DOI: 10.1371/journal.pone.0100924. eCollection 2014.
426 26. Gevensleben H, Garcia-Murillas I, Graeser MK et al. Noninvasive detection of
427 HER2 amplification with plasma DNA digital PCR. Clin Cancer Res.
428 2013;19:3276-3284. DOI: 10.1158/1078-0432.CCR-12-3768
429 27. Alberts DS, Manning MR, Coulthard SW et al. Adriamycin/cis-
430 platinum/cyclophosphamide combination chemotherapy for advanced
431 carcinoma of the parotid gland. Cancer. 1981;47:645-648. DOI: 10.1002/1097-
432 0142(19810215)47:4<645::aid-cncr2820470404>3.0.co;2-a
433 28. Kaplan MJ, Johns ME, Cantrell RW. Chemotherapy for salivary gland cancer.
434 Otolaryngol Head Neck Surg; 1986;95:165-170. DOI:
435 10.1177/019459988609500206.
436 29. Belani CP, Eisenberger MA, Gray WC. Preliminary experience with
437 chemotherapy in advanced salivary gland neoplasms. Med Pediatr Oncol.
438 1988;16:197-202. DOI: 10.1002/mpo.2950160309
439 30. Dreyfuss AI, Clark JR, Fallon BG et al. Cyclophosphamide, doxorubicin, and
440 cisplatin combination chemotherapy for advanced carcinomas of salivary gland
441 origin. Cancer. 1987;60:2869-2872. DOI: 10.1002/1097-
442 0142(19871215)60:12<2869::aid-cncr2820601203>3.0.co;2-y

31. Creagan ET, Woods JE, Schaid DJ et al. Cisplatin-based chemotherapy for neoplasms arising from salivary glands and contiguous structures in the head and neck. Cancer 1988;62:2313-2319. DOI: 10.1002/1097-0142(19881201)62:11<2313::aid-cncr2820621110>3.0.co;2-4

32. Fushimi C, Tada Y, Takahashi H et al. A prospective phase II study of combined androgen blockade in patients with androgen receptor-positive metastatic or locally advanced unresectable salivary gland carcinoma. Ann Oncol. 2018;29:979-984. DOI: 10.1093/annonc/mdx771

33. Jhaveri KL, Wang XV, Makker V et al. Ado-trastuzumab emtansine (T-DM1) in patients with HER2-amplified tumors excluding breast and gastric/gastroesophageal junction (GEJ) adenocarcinomas: results from the NCI-MATCH trial (EAY131) subprotocol Q. Ann Oncol. 2019;30:1821-1830. DOI: 10.1093/annonc/mdz291

34. Kurzrock R, Bowles DW, Kang H et al. Targeted therapy for advanced salivary gland carcinoma based on molecular profiling: results from MyPathway, a phase IIa multiple basket study. Ann Oncol. 2020;31:412-421. DOI: 10.1016/j.annonc.2019.11.018

35. Takahashi H, Tada Y, Saotome T et al. Phase II Trial of Trastuzumab and Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2-Positive Salivary Duct Carcinoma. J Clin Oncol. 2019;37:125-134. DOI: 10.1200/JCO.18.00545

464 36. Drilon A, Laetsch TW, Kummar S et al. Efficacy of larotrectinib in TRK
465 fusion-positive cancers in adults and children. N Engl J Med. 2018;378:731-
466 739. DOI: 10.1056/NEJMoa1714448
467 37. Doebele RC, Drilon A, Paz-Ares L et al. Entrectinib in patients with advanced
468 or metastatic NTRK fusion-positive solid tumours: integrated analysis of three
469 phase 1-2 trials. Lancet Oncol. 2020;21:271-282. DOI: 10.1016/S1470-
470 2045(19)30691-6
471 38. Tchekmedyian V, Sherman EJ, Dunn L et al. Phase II study of lenvatinib in
472 patients with progressive, recurrent or metastatic adenoid cystic carcinoma. J
473 Clin Oncol. 2019;37:1529-1537. DOI 10.1200/JCO.18.01859.
474 39. Kubota K, Sakai H, Katakami N et al. A randomized phase III trial of oral S-1
475 plus cisplatin versus docetaxel plus cisplatin in Japanese patients with
476 advanced non-small-cell lung cancer: TCOG0701 CATS trial. Ann Oncol.
477 2015;26:1401-1408. DOI: 10.1093/annonc/mdv190
478 40. Nomura H, Aoki D, Takahashi F et al. Randomized phase II study comparing
479 docetaxel plus cisplatin, docetaxel plus carboplatin, and paclitaxel plus
480 carboplatin in patients with advanced or recurrent endometrial carcinoma: a
481 Japanese Gynecologic Oncology Group study (JGOG2041). Ann
482 Oncol.2011;22:636-642. DOI: 10.1093/annonc/mdq401
483 41. Aoki D, Watanabe Y, Jobo T et al. Favourable prognosis with modified dosing
484 of docetaxel and cisplatin in Japanese patients with ovarian cancer. Anticancer
485 Res. 2009;29:561-566.

42. Kenmotsu H, Tanigawara Y. Pharmacokinetics, dynamics and toxicity of docetaxel: Why the Japanese dose differs from the Western dose. Cancer Sci. 2015;106:497-504. DOI: 10.1111/cas.12647

43. Smith TJ, Bohlke K, Lyman GH et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015;33:3199-3212.

44. Hotte SJ, Winquist EW, Lamont E et al. Imatinib mesylate in patients with adenoid cystic cancers of the salivary glands expressing c-kit: a Princess Margaret Hospital phase II consortium study. J Clin Oncol. 2005;23:585-590. DOI: 10.1200/JCO.2005.06.125

~~45.~~ Pfeffer MR, Talmi Y, Catane R et al. A phase II study of Imatinib for advanced adenoid cystic carcinoma of head and neck salivary glands. Oral Oncol. 2007;43:33-36. DOI: 10.1016/j.oraloncology.2005.12.026

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

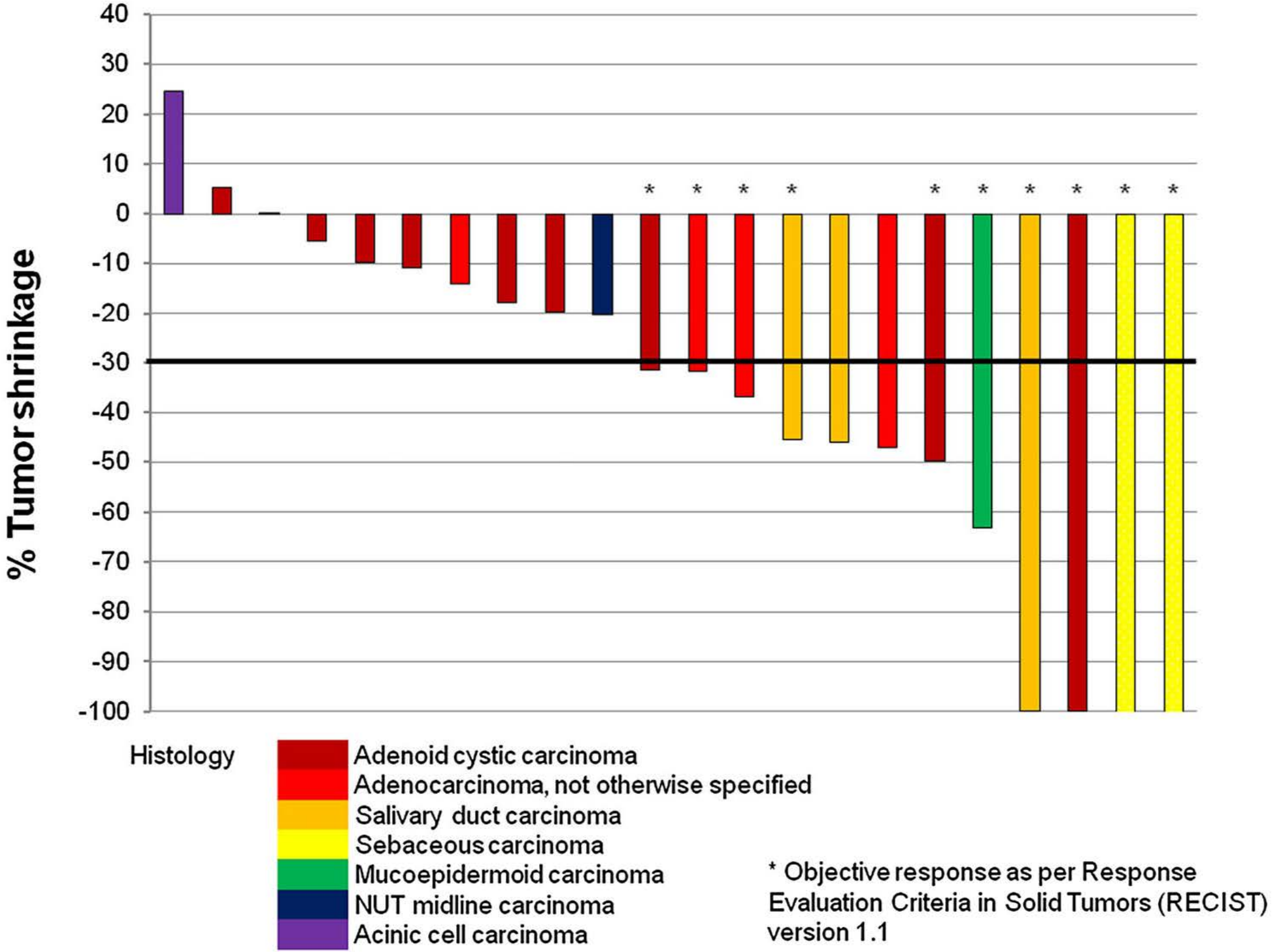
506

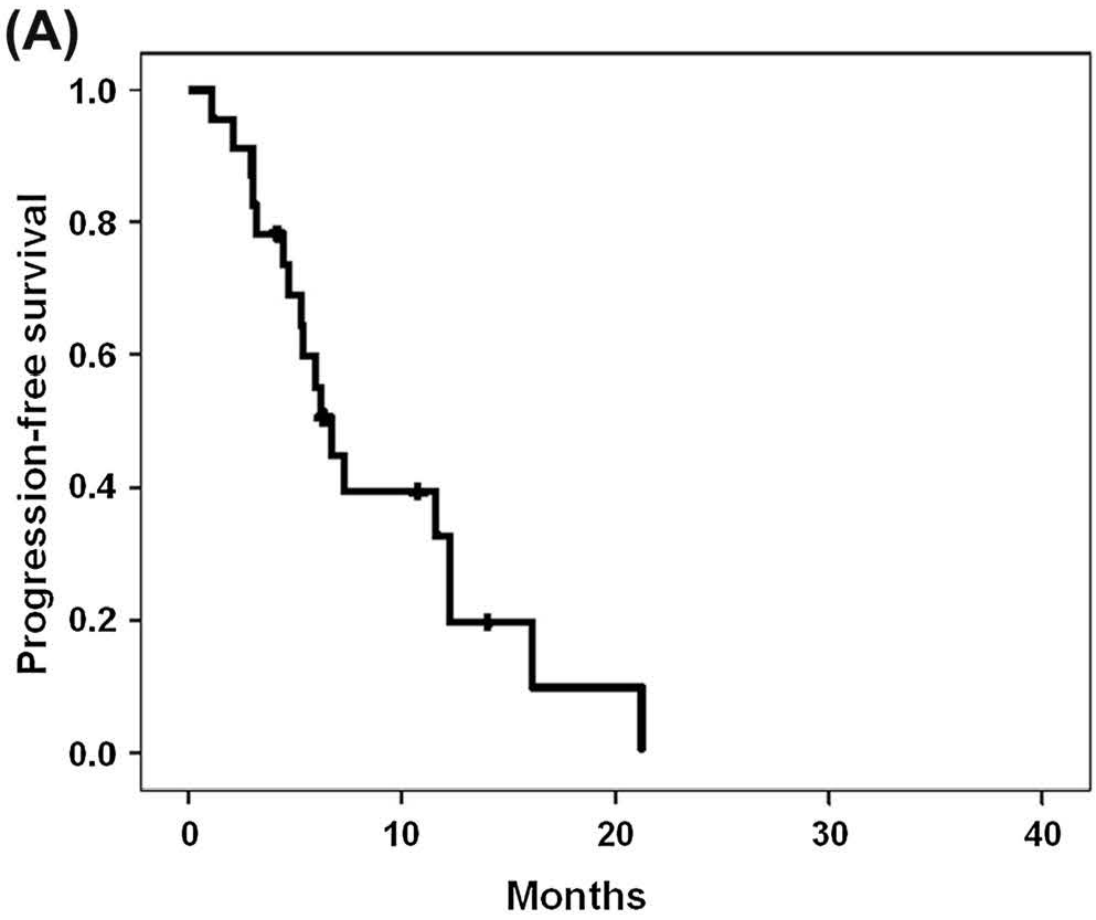
Figure legends:

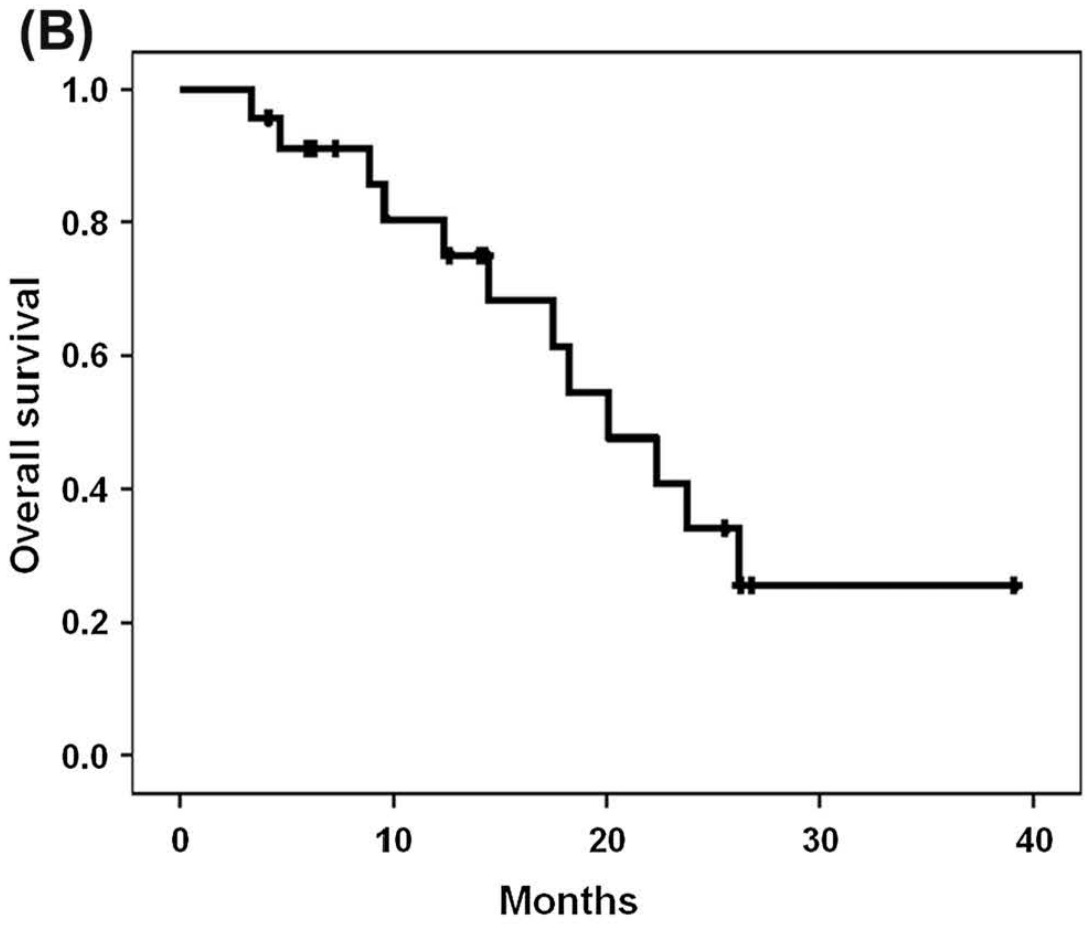
Fig.1 Best % change in target legions from baseline (n=22)

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

Fig.3 Tile plot. Next-generation sequencing was performed with using multiplex PCR for enrichment of cancer related gene loci covering hotspots of 50 cancer genes (Ion AmpliSeq Cancer Hotspot Panel v2) and additional 4 hormonal genes (*ESR1*, *ESR2*, *PGR*, and *AR*). ANOS, adenocarcinoma, not otherwise specified; SDC, salivary duct carcinoma; SA sebaceous adenocarcinoma; MEC, mucoepidermoid carcinoma; AdCC, adenoid cystic carcinoma; NUT, NUT midline carcinoma; CR, complete response; PR, partial response; SD, stable disease.


40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
% Tumor shrinkage
* * * * * * * * * *
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)
1.0
0.8
0.6
0.4
0.2
0.0
Progression-free survival
0
10
20
30
40
Months


(B)
1.0
0.8
0.6
0.4
0.2
0.0
Overall survival
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