A phase II study of poziotinib in patients with recurrent and/or metastatic head and neck squamous cell carcinoma

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Abstract
Background: In phase I studies, poziotinib has shown meaningful efficacy against various types of cancers. This phase 2 study aimed to investigate the efficacy and safety of poziotinib in recurrent and/or metastatic head and neck squamous cell carcinoma (R/M-HNSCC).

Methods: Overall, 49 patients were enrolled (median age, 62 years; age range, 21–78 years). Patients received a median of two prior treatments including chemotherapy and others and received 12 mg poziotinib orally once daily as part of a 28-day cycle. The primary endpoint was objective response rate (ORR), and the secondary endpoints were progression-free survival (PFS) and overall survival (OS). Targeted capture sequencing was performed using available tissues to identify translational biomarkers related to clinical response.

Results: ORR was 22.4%, median PFS was 4.0 months (95% confidence interval [CI], 1.8–6.2 months), and median OS was 7.6 months (95% CI, 4.4–10.8 months). The most common treatment-related adverse events were acneiform rash (85%) and mucositis (77%). A grade 3 or higher adverse event was acneiform rash (3%). Targeted capture sequencing was performed in 30 tissue samples. TP53 and PIK3CA were the most frequently mutated genes (43%), followed by CCND1 (33%) and EGFR (30%). Mutations in ERBB2, ERBB3, and ERBB4, which are HER family genes, were observed in 17%, 13%, and 10% samples, respectively. There was no difference in the frequency of somatic mutations in the HER family genes between the clinically benefitted and non-benefitted groups.

Conclusion: Compared to other pan-HER inhibitors, poziotinib showed clinically meaningful efficacy in heavily treated R/M-HNSCC.

Clinical trial registration number.: NCT02216916.

KEYWORDS
biomarker, head and neck cancer, poziotinib
1 INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide. Even in advanced disease, cure is possible through multi-modality therapy. However, recurrent and/or metastatic HNSCC (R/M-HNSCC) has poor prognosis, with a median survival of 6–10 months and 50–60% patients develop loco-regional or distant recurrence within 2 years.

Epithelial growth factor receptor (EGFR) is frequently overexpressed in HNSCC and is associated with poor prognosis. The relationship between the EGFR signaling pathway and tumor survival is well known, as demonstrated in several studies. EGFR targeted therapies, especially cetuximab, show clinical anticancer effects in HNSCC. In the EXTREME study, when 5FU and cetuximab were added to platinum chemotherapy as the primary drug, the median OS was 10.1 months compared with 7.4 months when only 5FU and platinum chemotherapy were used. However, cetuximab is the only approved targeted agent for HNSCC, with a response rate of 10–15% in patients with R/M-HNSCC.

Anti-programmed cell death 1 (PD-1) agents, including pembrolizumab and nivolumab, were recently approved for HNSCC that is refractory to platinum-based therapy. In the Keynote-048 trial, pembrolizumab and pembrolizumab +platinum drug +5-FU were used as a new first-line standard of treatment for R/M-HNSCC. However, the objective response was modest, and more effective treatment strategies are needed. In addition to immunotherapy, novel targeted therapies, such as tyrosine kinase inhibitor (TKI), should be developed.

Genomic characterization of HNSCC has recently been reported, and amplification of receptor tyrosine kinases, including EGFR and ERBB2, was commonly identified in HPV-negative HNSCC. The amplification of EGFR was reported in 15% cases and that of ERBB2 was reported in 5%, making these the most common gene amplifications. Therefore, EGFR and ERBB2 remain viable therapeutic targets for patients with HNSCC.

Poziotinib (HM781-36B) is an irreversible pan-HER TKI that targets EGFR, HER2, and HER4. It binds to the HER family of tyrosine kinase receptors and blocks downstream signaling pathway. Therefore, given the public genomic data that EGFR and ERBB2 play an important role in the carcinogenesis of HNSCC, we attempted to administer poziotinib to patients to examine its efficacy and tolerability. In phase I clinical trials, poziotinib showed notable clinical activity against various types of solid tumors.

In this study, we aimed to demonstrate the efficacy and safety of poziotinib in heavily treated R/M-HNSCC and identify translational biomarkers related to clinical response to poziotinib.

2 MATERIALS AND METHODS

2.1 Study design

This study was a single-center, phase II trial of poziotinib monotherapy in R/M-HNSCC patients who exhibited disease progression after platinum-based chemotherapy or were not eligible for platinum-based chemotherapy (ClinicalTrials.gov Identifier: NCT02216916). The objective response rate (ORR) was the primary endpoint, whereas progression-free survival (PFS), OS, and the safety profile of poziotinib therapy were the secondary endpoints.

This study was approved by the Institutional Review Board of Severance Hospital (4-2013-0794). The study conforms to the principles for research outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients before study enrolment.

2.2 Study population

The subjects were histologically confirmed R/M-HNSCC patients in Yonsei Cancer Center. Patients were eligible for enrolment if they were aged above 20 years, with an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 to 1, with at least one measurable disease based on Response Evaluation Criteria In Solid Tumors (RECIST, version 1.1), with documented progression after platinum-based systemic chemotherapy, and with a life expectancy of at least 3 months were included. Chemotherapy-naive patients who had inadequate renal function for platinum administration could be enrolled in the study. Patients with more than three lines of previous palliative chemotherapy for R/M-HNSCC and previous EGFR tyrosine kinase treatments were excluded, except for those who had received cetuximab. Patients with nasopharyngeal cancer or symptomatic brain metastases were also excluded.

2.3 Treatment plan

Patients were continuously treated with 12 mg oral poziotinib once daily until disease progression, death, or unacceptable adverse events (AEs). The duration of the treatment cycle was 28 days. Drug doses were held and/or reduced for intolerable grade 2 or 3/4 adverse events. Up to two dose reductions was allowed (8 mg followed by 6 mg). If treatment was not resumed within 3 weeks, patients discontinued the study.
2.4 | Assessment

Response evaluation was performed every 8 weeks after disease progression or when clinically indicated according to RECIST 1.1 guidelines. Safety assessments included physical examination, evaluation of AEs, and laboratory tests on day 1 of each cycle. All AEs were documented according to the Common Terminology Criteria for Adverse Events version 4.03. Patients with clinical benefits were defined as those with PFS ≥ 6 months using poziotinib.

2.5 | Somatic mutation and copy number alteration analysis

Formalin-fixed, paraffin-embedded tumor tissues, and blood samples were prepared using the Agilent SureSelect Target Enrichment Kit (Agilent Technologies, Inc.). Targeted deep sequencing data were generated using Illumina NovaSeq 6000 (Illumina) with a read length of 101 bp and a mean depth of target regions of 1,000X. Read alignment and somatic mutation calling were performed using the DNA Pipeline of the Illumina DRAGEN Bio-IT Platform v3.6 (Illumina). Tumor somatic mutation annotation was performed using Oncotator v1.9.9.0. Somatic copy number alterations (SCNA) were called using CNVkit v0.9.5. A combined somatic mutation and SCNA oncoplot was drawn using ComplexHeatmap v2.4.3. Copy number alterations were defined as copy number amplifications (copy number >5) and copy number deletions (copy number = 1 or 0).

2.6 | Statistical rationale for the study design

Statistical design was carried out according to Fleming’s one-stage design. The null hypothesis (P0) with a 5% significance level that the ORR is ≤ 5% versus the alternative hypothesis (P1) that the ORR is ≥ 15% was evaluated. Forty-four response-evaluable patients were required to provide an 80% power to reject P0 when the true ORR was 15%. With a 10% follow-up loss rate, a total of 49 patients were required.

PFS was defined as the time from the start date of poziotinib to progression or death from any cause, and OS was defined as the interval from the start date of poziotinib therapy to death from any cause. PFS and OS were evaluated using the Kaplan–Meier curve and were compared using log-rank test. All statistical analyses were performed using SPSS version 25.0.

### RESULTS

#### 3.1 | Patient characteristics

From July 2014 to March 2020, a total of 49 patients were enrolled. Patient demographics are listed in Table 1. The median age was 62 years (age range, 21–78 years). The number of male patients was 36 (73%). Patients who never
smoked accounted for 41% cases, and among smokers, those with a smoking history of more than 10 years accounted for 53%.

The most common sites of the primary lesion were the oral cavity (28.6%) and oropharynx (28.6%). Furthermore, 41% of patients had both loco-regional and distant disease in at least three organs. Three patients (6%) received poziotinib as the first-line treatment because of borderline impairment of renal function. About two-thirds (65%) of patients underwent all treatment modalities including surgery, chemotherapy, and radiotherapy before enrolment.

3.2 | Efficacy and treatment delivery

The response of 49 patients was evaluated (Table 2). Five patients were not evaluated because of early withdrawal. In addition, 22.4% patients (11/49) showed partial response (PR), 53.1% (26/49) showed stable disease (SD), and 14.3% (7/49) had progressive disease (PD) as the best response (Figure 1). The median duration of treatment was 23.1 weeks (95% CI, 13.5–32.7 weeks). The reasons for treatment discontinuation were disease progression (n = 34, 69%), patient withdrawal (n = 7, 14%), unacceptable toxicity (n = 3, 6%), and death (n = 5, 10%).

With a median follow-up of 7.6 months (95% CI, 8.1–14.3 months), the median PFS was 4.0 months (95% CI, 1.8–6.2 months) and the median OS was 7.6 months (95% CI, 4.4–10.8 months) (Figure 2). Median duration of response was 8.3 months (95% CI 8.1–12.2 months). Among previous chemotherapy regimens, platinum-based chemotherapy accounted for 72% cases. Patients had also received atezolizumab, durvalumab, M7824, nivolumab, and tremelimumab. Two patients had received PI3K inhibitors (buparlisib and alpelisib) in other clinical trials.

| Characteristic          | Patients, n (%) |
|-------------------------|-----------------|
| Best response           |                 |
| Complete response       | 0 (0.0)         |
| Partial response        | 11 (22.4)       |
| Stable disease          | 26 (53.1)       |
| Progressive disease     | 7 (14.3)        |
| Not evaluated*          | 5 (10.2)        |
| Best overall response rate | 22.4% (13.0–35.9) |

Abbreviation: CI, confidence interval.

*Response was not evaluable in five patients because of withdrawal from the study.

Previous chemotherapy regimens administered are described in Supplementary Table 1.

3.3 | Safety

As for treatment-related AEs, 48 patients were assessed (Table 3). AEs were mainly grade 1–2 and easily manageable. The most common AEs were acniform rash (85%) and mucositis (77%). Grade 3 AEs occurred in five patients. Grade 3 acniform rash occurred in two patients, grade 3 fatigue in one patient, grade 3 mucositis in one patient, and grade 3 lung infection in one patient.

In total, 22 (45.8%) and 16 (33.3%) patients underwent dose reduction to 8 and 6 mg due to AEs, respectively. Common AEs responsible for dose reduction were acniform rash and mucositis. Four (8.3%) patients discontinued poziotinib therapy due to toxicity, two patients due to skin rash, and others due to lung infection.

3.4 | Detection of somatic aberrations

Biomarker analyses were available for 30 patients (Figure 3A). Baseline biopsy was not mandatory in this trial, and 14 patients had no archival tissues for biomarker analysis. Target capture sequencing identified a total of 820 point mutations, 6 insertions, and 17 deletions, but in this report, we presented the alterations of the 18 genes previously implicated in the TCGA HNSCC database.15 The median sequencing depth in the target regions was greater than 1,000X. The frequency of somatic mutations is illustrated in Figure 3. TP53 (R282W, R273C, R248G, G245V, W10L, H193R, R175H, E11Q) and PIK3CA (N345L, R832L) were the most frequently altered genes (43%) followed by CCND1 (E70*) (33%) and EGFR (P518L, R574L, P753Q, R836S, G901W) (30%). Alterations in ERBB2 (R978S), ERBB3 (G623E, R1173W), and ERBB4 (L713W, R393L, W10L), which are HER family genes, were observed in 17%, 13%, and 10% patients, respectively (Figure 3B). Detailed mutation profiles are summarized in Table S3.

Most DNA copy number amplifications and deletions were also observed in genes involved in cell cycle (CDKN2A and CCND1), receptor tyrosine kinase (FGFR1, EGFR, and ERBB2), and genes related to proliferation (PIK3CA). Copy number amplifications were observed in PIK3CA, EGFR, ERBB2, MYC, DDR2, and FGFR1, whereas copy number deletions were observed in TP53, FGFR3, CDKN2A, HRAS, FGFR2, PTEN, and PIK3R1 (Figure 3A,B).

Additional clinical information on tissues used for target capture sequencing is provided in Table S2.
Association of somatic alterations with clinical outcomes

Kaplan–Meier curves of median PFS (4.0 months) and OS (7.6 months) are shown in Figure 1. There was no difference in the frequency of somatic mutations in EGFR, ERBB2, ERBB3, and ERBB4 between the clinically benefitted and non-benefitted groups. The median PFS (5.8 vs. 2.8 months; log-rank test, \( p = 0.180 \); Figure 4A) and median OS (12.0 vs. 5.9 months; log-rank test, \( p = 0.093 \); Figure 4B) were not different according to the presence of HER family gene mutations. Regarding other genetic alterations in the PIK3CA/Akt pathway, cell cycle machinery, and FGFR pathway, there was no statistical difference in survival according to the presence of alterations.

4 | DISCUSSION

We investigated the efficacy and safety of poziotinib in heavily treated R/M-HNSCC and identified translational biomarkers related to clinical response to poziotinib. Characterization of somatic mutation, DNA copy number, and gene expression was performed.

Patients with HNSCC exhibiting disease progression after platinum-based chemotherapy have poor prognosis and limited treatment options. Based on the results of the EXTREME study that showed overall survival benefits with no decrease in the quality of life, the research interest on EGFR inhibitors has increased.7 However, despite numerous research efforts targeting EGFR, drugs developed to date have shown limited activity in patients with HNSCC. Suppression of EGFR with tyrosine kinase inhibitors including gefitinib, erlotinib, and lapatinib showed a limited response.18-21 As a single agent, cetuximab in R/M-HNSCC showed limited activity (ORR13%, time to progression of 70 days; ref.12).7 The drug with higher ORR was followed by cetuximab and 500 mg of gefitinib. However, 500mg of gefitinib in R/M-HNSCC also reached only 10.6% ORR, 3.4 months PFS, and 8.1 months OS.22 In Phase 2 study with lapatinib, a competitive reversible inhibitor of EGFR and ERBB2, no
complete or partial responses were observed, and stable disease was the best response.\textsuperscript{23}

Poziotinib is considered a new treatment option as a promising TKI in carcinomas with \textit{EGFR} mutations.\textsuperscript{24} Compared with previous studies on EGFR TKIs, our study showed comparable data with the ORR of 22.4\%, median PFS of 4.0 months, and OS of 7.6 months. Among patients with R/M-HNSCC who exhibited disease progression after platinum-based chemotherapy or who were not eligible for platinum-based chemotherapy, treatment with poziotinib showed longer survival than that with the standard therapy.

Poziotinib showed similar toxicity to other pan-HER inhibitors, but it might be related to early dose reduction due to AEs. The most common AEs were acneiform rash and mucositis, and most patients showed manageable toxicity of grades 1–2. These AEs could be managed through supportive care and oral medications.

Our study did not show an association between any \textit{EGFR} mutation and the response to poziotinib. This may be because of the small sample size of our study. Although there was no statistical difference between patients with or without \textit{EGFR} mutation, median OS increased in patients with \textit{EGFR} mutation.

Recently, numerous studies on immunotherapy in patients with R/M-HNSCC showed noticeable responses.\textsuperscript{8,25} The recurrence and metastasis of HNSCC are facilitated by immune evasion,\textsuperscript{26} which is mediated in part by the expression of programmed death-ligand (PD-L1 and PD-L2), which binds to the T-cell suppressive immune checkpoint receptor PD-1.\textsuperscript{22,27}

In a preclinical study, activation of the EGFR pathway induced PD-L1 expression and enhanced susceptibility of the lung tumors to PD-1 blocker, suggesting that a combination of PD-1 blocker with EGFR TKIs may be a promising treatment to extend the duration of response and delay resistance.\textsuperscript{28,29} Thus, the combination of EGFR TKI with immunotherapy may show better responses in HNSCC. In addition, in case of elderly patients or patients who are ineligible for cytotoxic chemotherapy, the combination of immunotherapy and poziotinib is expected to be effective without severe toxicity. However, these attempts (NCT03695510) should be further validated in prospective trials.

The limitation of this study is that it is a single-center, single-arm study with a relatively small number of patients available for response assessment. The response was not evaluated in five patients because of early withdrawal. One patient withdrew consent without taking poziotinib. Two patients withdrew consents before the first response evaluation due to decreased general condition. Another patient discontinued at the discretion of

| Toxicity                  | All grades patients, n(%) | Grade 1, 2 patients, n(%) | Grade 3,4 patients, n(%) |
|--------------------------|----------------------------|----------------------------|--------------------------|
| Rash acneiform           | 41 (85\%)                  | 39 (82\%)                  | 2 (3\%)                  |
| Paronychia               | 14 (29\%)                  | 14 (29\%)                  | 0                        |
| Pruritus                 | 12 (25\%)                  | 12 (25\%)                  | 0                        |
| Palmar-plantar Erythrodysesthesia | 4 (8\%)                   | 4 (8\%)                   | 0                        |
| Fatigue                  | 12 (25\%)                  | 11 (23\%)                  | 1 (2\%)                  |
| General weakness         | 2 (3\%)                    | 2 (3\%)                    | 0                        |
| Dry skin                 | 3 (6\%)                    | 3 (6\%)                    | 0                        |
| Conjunctivitis           | 2 (3\%)                    | 2 (3\%)                    | 0                        |
| Fever                    | 1 (2\%)                    | 1 (2\%)                    | 0                        |
| Lung infection           | 1 (2\%)                    | 0                          | 1 (2\%)                  |
| Nausea                   | 4 (8\%)                    | 4 (8\%)                    | 0                        |
| Vomiting                 | 1 (2\%)                    | 1 (2\%)                    | 0                        |
| Weight loss              | 3 (6\%)                    | 3 (6\%)                    | 0                        |
| Paresthesia              | 1 (2\%)                    | 1 (2\%)                    | 0                        |
| Insomnia                 | 1 (2\%)                    | 1 (2\%)                    | 0                        |
| Mucositis                | 37 (77\%)                  | 36 (75\%)                  | 1 (2\%)                  |
| Diarrhea                 | 27 (56\%)                  | 27 (56\%)                  | 0                        |
| Gastrointestinal pain    | 1 (2\%)                    | 1 (2\%)                    | 0                        |
| Creatinine increased     | 2 (3\%)                    | 2 (3\%)                    | 0                        |
| Hyperkalemia             | 1 (2\%)                    | 1 (2\%)                    | 0                        |

\*One patient was not evaluable because of early withdrawal from the study.
the investigator due to lung infection of grade 3 or higher and general weakness. The last patient died of sudden cardiac death, which was not considered to be related to the drug. Additionally, frequent low-grade and serious grade 3 or greater skin rash and mucositis need careful monitoring and frequent intervention. However, we believe that pre-emptive dose reduction and active prevention and education of adverse events could raise the adherence and efficacy of this drug.

In conclusion, compared with other previous EGFR TKIs, poziotinib showed clinically meaningful efficacy with manageable toxicity in patients with platinum-refractory R/M-HNSCC. Owing to the small number of tissues available for targeted capture sequencing, we could
not identify useful biomarkers involved in the response to poziotinib. The identification of molecular markers that could predict clinical response to targeted therapy will aid in the development of personalized targeted treatment, which should be the focus of future studies.

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CONFICT OF INTEREST
The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS
Ji Hyun Lee: contribution to the data acquisition, responsibility for writing the paper, and statistical analysis. Seong Gu Heo: software, statistical analysis, Beung-chul Ahn: participation in patient management and data collection. Min hee Hong: participation in patient management and data collection, Byoung Chul Cho: conceptualization, participation in patient management and data collection, responsibility for writing the paper. Hye Ryun Kim: conceptualization, study design, participation in patient management and data collection, responsibility for writing the paper. All authors reviewed the paper and approved the final version.

ETHICAL APPROVAL STATEMENT
This study was approved by the Institutional Review Board of Severance Hospital (4–2013–0794). The study conforms to the principles for research outlined in the Declaration of Helsinki.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES
1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7-34.
2. Chow LQM, Haddad R, Gupta S, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 expansion cohort. J Clin Oncol. 2016;34:3838.
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.
4. Kim HS, Kwon HJ, Jung I, et al. Phase II clinical and exploratory biomarker study of dacomitinib in patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. Clin Cancer Res. 2015;21:544-552.
5. Kalyankrishna S, Grandis JR. Epidermal growth factor receptor biology in head and neck cancer. J Clin Oncol. 2006;24:2666-2672.
6. Licitra L, Mesia R, Rivera F, et al. Evaluation of EGFR gene copy number as a predictive biomarker for the efficacy of cetuximab in combination with chemotherapy in the first-line treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck: EXTREME study. Ann Oncol. 2011;22:1078-1087.
7. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol. 2007;25:2171-2177.
8. Ferris RL, Blumenschein G, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 2016;375:1856-1867.
9. Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase Ib trial. Lancet Oncol. 2016;17:956-965.
10. Lim SM, Cho SH, Hwang IG, et al. Investigating the feasibility of targeted next-generation sequencing to guide the treatment
of head and neck squamous cell carcinoma. *Cancer Res Treat.* 2019;51:300-312.

11. Burtness B, Harrington KJ, Greil R, et al. KEYNOTE-048: phase III study of first-line pembrolizumab (P) for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). *Ann Oncol.* 2018;29:vii729.

12. Cancer Genome Atlas N. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature.* 2015;517:576-582.

13. Kim TM, Lee K-W, Oh D-Y, et al. Phase I studies of poziotinib, an irreversible Pan-HER tyrosine kinase inhibitor in patients with advanced solid tumors. *Cancer Res Treat.* 2018;50:835-842.

14. Park YH, Lee K-H, Sohn JH, et al. A phase II trial of the pan-HER inhibitor poziotinib, in patients with HER2-positive metastatic breast cancer who had received at least two prior HER2-directed regimens: results of the NOV120101-203 trial. *Int J Cancer.* 2018;143:3240-3247.

15. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228-247.

16. National Cancer Institute. Common Terminology Criteria for Adverse Events v 4.0. [Accessed May 13, 2013]. Available at http://evs.nci.nih.gov/ftp1/CTCAe/CTCAE_4.03_2010–06-14_QuickReference_8.5x11.pdf.

17. Hong J, Wu J, Huang OU, et al. Early response and pathological complete remission in Breast Cancer with different molecular subtypes: a retrospective single center analysis. *J Cancer.* 2020;11:6916-6924.

18. Kirby AM, A’Hern RP, D’Ambrosio C, et al. Gefitinib (ZD1839, Iressa) as palliative treatment in recurrent or metastatic head and neck cancer. *Br J Cancer.* 2006;94:631-636.

19. Soulieres D, Senzer NN, Vokes EE, Hidalgo M, Agarwala SS, Siu LL. Multicenter phase II study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of the head and neck. *J Clin Oncol.* 2004;22:77-85.

20. Abidoye OO, Cohen EE, Wong SJ, et al. A phase II study of poziotinib (GW572016) in recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN). *J Clin Oncol.* 2006;24:5568.

21. Lee YS, Johnson DE, Grandis JR. An update: emerging drugs to treat squamous cell carcinomas of the head and neck. *Expert Opin Emerg Drugs.* 2018;23:283-299.

22. Badoual C, Hans S, Merillon N, et al. PD-1-expressing tumor-infiltrating T cells are a favorable prognostic biomarker in HPV-associated head and neck cancer. *Cancer Res.* 2013;73:128-138.

23. de Souza JA, Davis DW, Zhang Y, et al. A phase II study of lapatinib in recurrent/metastatic squamous cell carcinoma of the head and neck. *Clin Cancer Res.* 2012;18:2336.

24. Le X, Goldman JW, Clarke JM, et al. Poziotinib shows activity and durability of responses in subgroups of previously treated EGFR exon 20 NSCLC patients. *J Clin Oncol.* 2020;38:9514.

25. Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *The Lancet.* 2019;394:1915-1928.

26. Ferris RL. Immunology and immunotherapy of head and neck cancer. *J Clin Oncol.* 2015;33:3293-3304.

27. Li J, Jie H-B, Lei YU, et al. PD-1/SHP-2 inhibits Tc1/Th1 phenotypic responses and the activation of T cells in the tumor microenvironment. *Cancer Res.* 2015;75:508-518.

28. Akbay EA, Koyama S, Carretero J, et al. Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors. *Cancer Discov.* 2013;3:1355.

29. Ahn M-J, Sun J-M, Lee S-H, Ahn JS, Park K. EGFR TKI combination with immunotherapy in non-small cell lung cancer. *Expert Opinion Drug Safety.* 2017;16:465-469.

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