

Discontinuation of anti-programmed cell death protein 1 immune checkpoint inhibition after complete remission in head and neck squamous cell carcinoma: A case report and literature review

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Abstract. Programmed cell death protein 1 (PD-1) inhibition plays a central role in the current treatment of recurrent or metastatic head and neck squamous cell carcinoma (R/M-HNSCC). Some patients achieve a durable response, and even complete remission (CR) is possible, though it occurs rarely. In cases of durable CR, there are no guidelines regarding a possible discontinuation of immunotherapy. Since clinical experience on this issue is limited, the present study reported on a case of a durable CR following discontinuation of PD-1 inhibition in R/M-HNSCC and additionally presented an overview on the current literature. The present study reported on a case of CR of recurrent oropharyngeal cancer after four cycles of PD-1 monotherapy with Nivolumab. The therapy was discontinued after overall 46 cycles. Even after 3 more years of follow-up, there was no sign of tumor recurrence. Overall, according to reports from the literature, CR seems to be an indicator for durable disease control after therapy discontinuation. Since data on therapy termination is rare, decisions about when to stop successful immunotherapy in R/M-HNSCC have to be made individually for each patient.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is currently the sixth most common tumor entity worldwide and represents a heterogeneous group of malignancies arising from the oral cavity, pharynx, and larynx (1). Tumors are related to habitual alcohol drinking and smoking (2). Furthermore, there is an increasing number of high-risk human papillomavirus-associated cancers especially within the oropharynx (3). Multidisciplinary treatment comprises surgery and adjuvant radiotherapy with or without conventional chemotherapy, or primary chemoradiation. In cases of treatment failure prognosis is dismal and therapeutic options are limited to salvage surgery, radiotherapy and medical therapy. There was hardly any improvement for survival in recurrent or metastatic HNSCC (R/M-HNSCC) during the last decades (4) until the rise of immune checkpoint inhibition (ICI) targeting programmed cell death protein 1 (PD-1). With the approval of the two PD-1 inhibitors nivolumab and pembrolizumab in R/M-HNSCC, patients were for the first time able to benefit from a better survival accompanied by a stable quality of life compared to standard of care (5,6). However, the objective response rate remains modest with only 13.3% for nivolumab (5) and 17% for pembrolizumab, depending on the tumor programmed death ligand 1 (PD-L1) status (6). Nonetheless, in case of a response to therapy it can potentially be durable and even complete remission (CR) is possible. In cases of a durable CR the question arises whether treatment can ever be stopped without the risk of recurrence. In particular, it remains unclear whether ICI in R/M-HNSCC patients who achieve a durable CR can be discontinued after a certain treatment duration. As clinical experience on this issue is limited, the current manuscript reports on a case of discontinued ICI after durable CR of R/M-HNSCC and gives an overview on the current literature.

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Abbreviations: CR, complete remission; CT, computed tomography; ICI, immune checkpoint inhibition; FDG-PET, 18-Fluoro-deoxyglucose positron emission tomography; HPV, human papillomavirus; irAE, immune related adverse events; PD-L1, programmed death ligand 1; PD-1, programmed cell death protein 1; R/M-HNSCC, recurrent or metastatic head and neck squamous cell carcinoma

Key words: head and neck squamous cell carcinoma, PD-L1, complete remission, immunotherapy

Case report

A 62-year-old male patient was referred to our Department of Head and Neck Surgery in November 2016 with a new

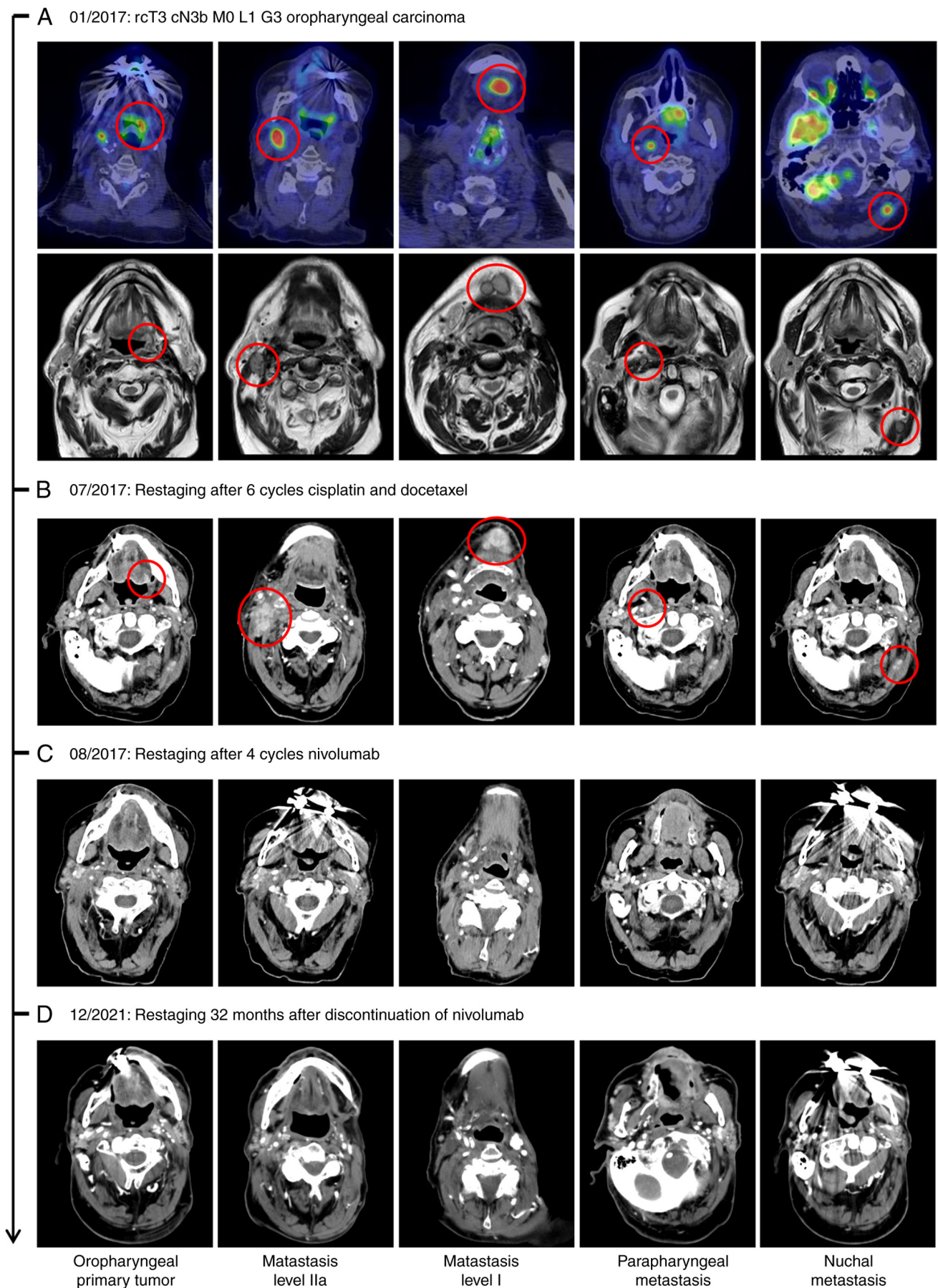


Figure 1. Radiological assessments. (A) FDG-PET-CT and MRI shows a primary tumor of the oropharynx with bilateral neck masses as indicated by red circles. (B) Progressive disease detected on CT scan of the neck following 6 cycles cisplatin and docetaxel as indicated by red circles. (C) Therapy was switched to nivolumab and CR was achieved after 4 cycles. (D) The patient received 42 overall cycles of nivolumab. Even after 32 months after discontinuation the patient remained under CR. CT, computed tomography; FDG-PET, 18-Fluoro-deoxyglucose positron emission tomography; CR, complete remission.

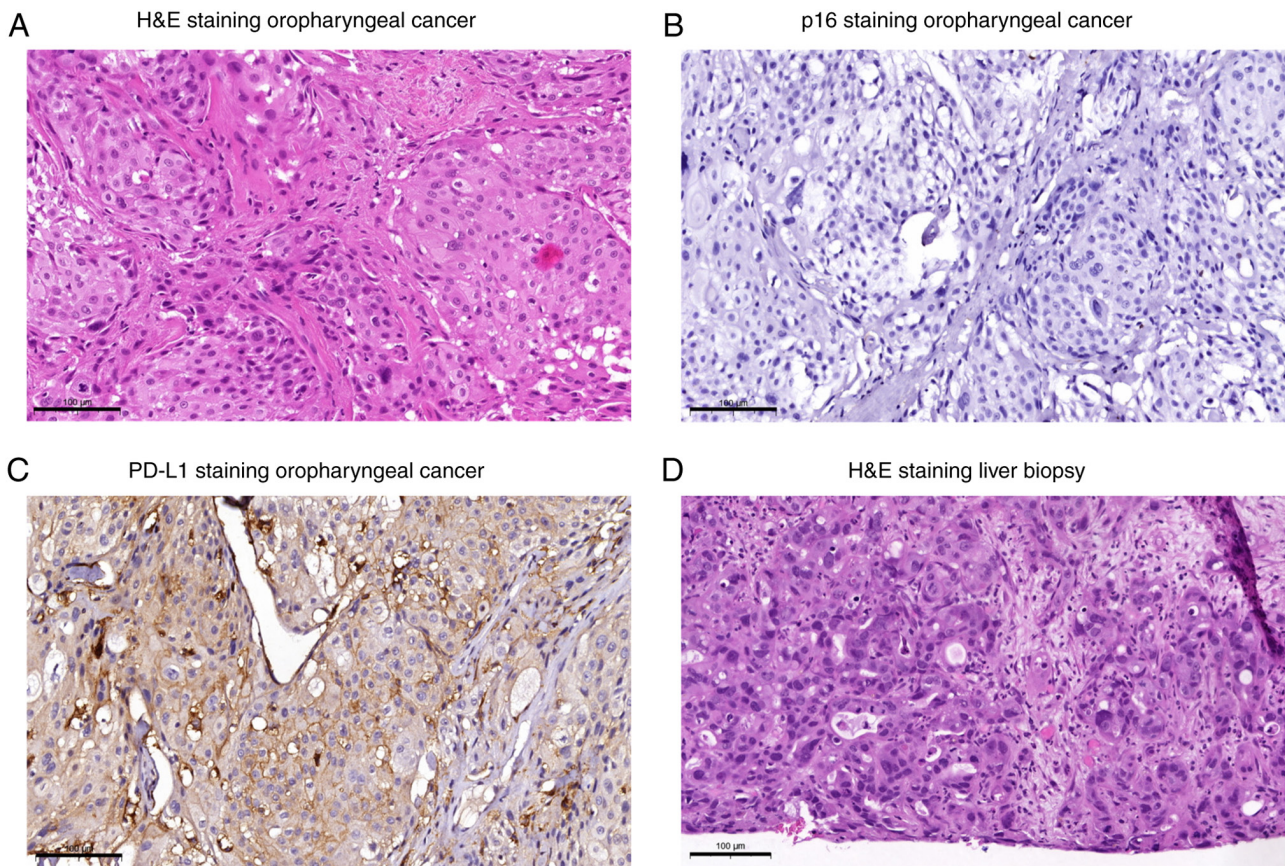


Figure 2. Histological tumor information. (A) H&E staining of the tumor biopsy taken from the base of the tongue confirms squamous cell carcinoma. (B) This biopsy stained negative for p16 and (C) positive for PD-L1. The combined positive score was 23. (D) Liver biopsy revealed pancreatic cancer metastasis. Scale bars, 100 μ m. H&E, hematoxylin and eosin; PD-L1, programmed death ligand 1.

lesion of his left oropharynx and bilateral masses of the neck. Histological confirmation of squamous cell carcinoma has already been performed by fine needle aspiration cytology at the referring hospital. He had a history of a pT2 pN1 M0 G2 hypopharyngeal cancer of the left side, which was successfully treated in curative intention by surgery and adjuvant radiotherapy at another hospital in 2006.

At the time of presentation at our institution, clinical examination revealed an ulcerating tumor of the left oropharynx. 18-Fluoro-deoxyglucose positron emission tomography (FDG-PET) computed tomography (CT) showed a hypermetabolic lesion of the left oropharynx as well as bilateral lesions of the neck in level Ib of the left side and IIa of the right side. Furthermore, there were parapharyngeal and nuchal lesions, which was also confirmed in MRI (Fig. 1A). Endoscopic examination was performed, which showed a tumor extending from the tonsil to the base of the tongue with infiltration of the midline. The biopsy confirmed the diagnosis of a rcT3 cN3b M0 L1 G3 p16 negative squamous cell carcinoma of the oropharynx (Fig. 2A, B). Due to the tumor extension, salvage surgery was not feasible. Also, re-irradiation was not possible. A palliative chemotherapy with cisplatin (75 mg/m²) and docetaxel (75 mg/m²) was started in February 2017. CT scan after 6 cycles showed progression of the cervical metastases (Fig. 1B). Therefore, an ICI with nivolumab (3 mg per kilogram of body weight) every two weeks was initiated in June

2017. Immunohistochemical analysis of the tumor tissue was performed prior to therapy initiation. This showed a dense lymphocytic infiltrate and a PD-L1 tumor cell score (Cologne Score (7)) of 3. The combined positive score (CPS) was introduced into the clinical assessment of PD-L1 expression only at a later stage (6). Therefore, a retrospective evaluation was performed, which revealed a CPS of 23 (Fig. 2C). During CT re-staging after four doses of nivolumab, a complete response was noted. Therapy with nivolumab was continued following the international recommendations. Further follow-up examinations and restaging (CT scan of the neck, chest and abdomen every 3 months) confirmed an ongoing complete response. After a total of 46 cycles of nivolumab the patient asked for a break from therapy as he found the regular clinic visits too demanding. The Patient was informed about the risk of a possible relapse after a break in therapy. As to the patients wish, ICI was finally terminated in April 2019. No immune-related adverse events (irAE) occurred during and after therapy. Under continuous clinical and radiological control (CT scan of the neck, chest and abdomen every 3 months during the first year, followed by controls twice a year), there were no signs of tumor recurrence. Due to a post-therapeutic laryngeal chondritis the patient presented with acute decompensating dyspnea. Re-tracheostomy was necessary. Repeated endoscopies with biopsy did not show any signs of local recurrence. In December 2021, 32 months after nivolumab therapy was stopped, there was still no

Table I. Overview of published cases on discontinuation of anti-programmed death receptor 1 therapy after complete remission in recurrent or metastatic head and neck squamous cell carcinoma.

Authors	Cancer type	Patients with discontinued ICI	Patients with CR	Relapse after ICI discontinuation despite CR	(Refs.)
Sekido <i>et al</i>	R/M-HNSCC	1	1	0	(33)
Yasumatsu <i>et al</i>	R/M-HNSCC	14	5	0	(34)
Gauci <i>et al</i>	Miscellaneous ^a	39	17	2	(31)
Lopez-Flores <i>et al</i>	Miscellaneous ^a	14	14	0	(35)

^aIncludes one R/M-HNSCC case. ICI, immune checkpoint inhibition; CR, complete remission; R/M-HNSCC, recurrent or metastatic head and neck squamous cell carcinoma.

evidence of HNSCC tumor recurrence. However, two suspicious masses of the pancreas and multiple new lesions of the liver were found in re-staging. Sonographic puncture of the liver revealed hepatic metastases of a pancreatic cancer (Fig. 2D). The patient did not wish any further therapy in a palliative overall setting, was switched to best supportive care and deceased March 2022 due to his metastasized pancreatic cancer.

Discussion

Durable complete responses can occasionally be seen during ICI in R/M-HNSCC. However, they are not specific to ICI but can also be observed during targeted therapy (8), radiotherapy (9) and chemotherapy (10). Still, durable responses and especially a durable complete response is a rare event during palliative therapy in R/M-HNSCC.

Despite the breakthrough in the treatment of R/M-HNSCC by ICI, most patients do not benefit. Multiple clinical and molecular factors have been suggested to be associated with a favorable prognosis during ICI. Nevertheless, it remains unclear, which exact factors influence a response to therapy. A predictive role of PD-L1 expression is recognized. However, PD-L1 based assays inherent several crucial limitations, such as a lack of standardization (11) or intratumoral heterogeneity of PD-L1 (12). Human papillomavirus (HPV) positivity is another factor which is proposed to correlate with a favorable clinical outcome. The phase I/II CheckMate 358 trial evaluated neoadjuvant nivolumab in HNSCC patients with previously untreated, resectable HPV positive or negative tumors. Here, radiologic and pathologic response were seen more frequently in HPV positive tumors (13). In contrast, a meta-analysis of clinical trials using ICI in HNSCC including 732 patients with reported HPV status, failed to identify any statistically significant advantages in tumor response and overall survival for HPV positive patients (14). In another meta-analysis of five randomized controlled trials including 2015 patients with reported HPV status, anti-PD-1-based ICI seemed to be more efficient in HPV negative tumors while anti-PD-L1-based ICI seemed to be more efficient in HPV positive tumors (15). Interestingly, there is experimental and clinical data indicating a role of HPV E5 oncoprotein in mediating resistance to anti-PD-1/PD-L1 ICI by down-regulation of major histocompatibility complex expression

in HNSCC tumors (16). Furthermore, HPV is a potential target for therapeutic vaccination in HPV positive HNSCC. Combining ICI with HPV vaccination might be a promising therapeutic option to improve clinical outcome (17). Immunohistochemical positivity of p16 is a surrogate marker for HPV association in oropharyngeal cancer, which is negative in our case. However, discrepancy between p16 and HPV DNA or RNA status exists in some patients with oropharyngeal cancer (18). In our case, further molecular tests like RNA *in situ* hybridization were not performed in addition to p16 status to detect HPV infection. Therefore, a limitation of the case we present is that there is no information about the HPV status of the tumor. Alternative biomarkers that may correlate with a response to ICI including tumor immune cell infiltrate, blood-based markers, tumor metabolic profile and mutational burden are under investigation (19).

In the case of a response to ICI, the identification of predictive factors for prolonged disease control could be of great utility to identify long-term responder and to guide their follow-up. Furthermore, in the case of a patients wish to discontinue treatment such factors could contribute to estimate the risk of relapse upon therapy discontinuation. In various tumor entities including R/M-HNSCC irAE were shown to be associated with an improved PFS, as well as ORR and OS (20,21). Furthermore, in other tumor entities such as non-small cell lung cancer (NSCLC) (22) and malignant melanoma (23) PFS and OS seems to be improved in case of a CR before ICI discontinuation.

In cases of persistent stable disease under ICI a metabolic response evaluation by FDG-PET-CT might help to improve response evaluation by determine whether vital tumor tissue is still present or whether there is a complete metabolic response (CMR), defined as complete resolution of FDG uptake within the target lesion (24). There is data suggesting that a CMR may be associated with a favorable outcome upon ICI discontinuation in NSCLC and malignant melanoma (22,25). However, there is a lack of data for HNSCC. Nevertheless, it might be worth to consider an additional FDG-PET-CT scan before ICI discontinuation to identify patients with a CMR. Whether these patients have a lower risk for tumor progression upon ICI discontinuation needs to be evaluated in future studies. In our case, PET-CT was performed only prior to ICI initiation, but was not repeated at a later stage.

A durable response after ICI discontinuation has also been reported for various tumor entities (22,26-29). For R/M-HNSCC the broadly accepted concept is an ICI treatment until disease progression or unacceptable toxicity such as irAE. Interruption of therapy due to a durable complete response challenges this concept. For patients, a long-lasting ICI therapy is associated with regular visits to the oncology outpatient clinic, the need of transportation and often significant financial expenses. Likewise, an enduring therapy has a significant financial impact on the health care system (30). Thus, in the rare cases of a durable CR, the question as to the definitive duration of therapy or a possible break in therapy arises. However, the effect of a discontinued ICI after CR on disease control and prognosis in R/M-HNSCC is unclear.

While CR is defined as disappearance of all detectable evidence of cancer, the literature lacks a clear definition of a durable response. Various definitions exist, defining long responders as patients with a treatment response that has lasted at least one or two years (31). Another definition for a durable response to treatment is a progression-free survival that exceeds three times the median progression-free survival of the whole population (32). Several cases of therapy discontinuation after durable CR can be found in the literature (Table I). In that context, the most common reasons for therapy interruption are irAEs. Sekido *et al* presented a case of oral squamous cell carcinoma with lung metastasis, who was treated with nivolumab. After 33 cycles, ICI had to be stopped due to interstitial lung disease as a pulmonary irAE that was treated with prednisone. During follow-up no tumor recurrence was detected for six more months (33). Yasumasu *et al* presented a case series of 14 R/M-HNSCC patients with interrupted nivolumab therapy due to irAEs. Five patients had a CR before discontinuation of the therapy. Interestingly, these patients showed no signs of tumor recurrence during a follow-up of up to 20 months after therapy discontinuation. In contrast, progression occurred in three patients with previous partial response and in one patient with previous stable disease. The authors suggest, that CR before therapy discontinuation is a positive prognostic factor for a durable disease control upon discontinuation due to irAE in R/M-HNSCC (34). Gauci *et al* also consider CR before therapy discontinuation to be a positive factor for a durable response upon ICI discontinuation in different kinds of cancer. In 39 analyzed patients who responded to ICI, therapy was interrupted due to a prolonged response, adverse events or per protocol. Interestingly, relapse was seen in 87% of patients with stable disease or partial remission. Whereas, 88% of patients with a prior CR showed an ongoing response (31). Similar observations could be made in another case series of 14 patients with discontinued ICI after CR in metastatic solid tumors, including one HNSCC patient. In none of the cases a relapse was detected during a median follow-up of over 20 months from the end of treatment. The authors suggested, that ICI discontinuation in patients who achieved CR appears feasible (35).

Whether or not immunotherapy discontinuation should be considered after CR is currently discussed for various tumor entities such as melanoma (29), renal cell carcinoma (36) or

NSCLC (22). However, the issue remains unsolved. In line, there is no broad consent on the duration of ICI therapy in R/M-HNSCC patients with durable CR. As in our case, the decision process on whether to pause immunotherapy is primarily based on the patient's wish. Should the patient seek an interruption of therapy, several factors should be considered when counseling the patient. A CR appears to be a favorable factor for a durable response. In the case of persistent stable disease, a complementary FDG-PET-CT scan may be considered. In this way, a complete metabolic response may be detected. However, there is a lack of data regarding the prognostic value of a CMR in ICI of R/M-HNSCC. Other factors that should be considered when counselling the patient regarding a break in therapy include the duration of response, the presence of irAE, the patient's age and comorbidities.

In summary, R/M-HNSCC can experience durable responses and in rare cases even a durable CR during ICI. Reports in the literature suggest that CR might be a positive prognostic factor for a durable response upon ICI discontinuation. However, there is still a lack of data to make a clear recommendation. Therefore, decisions about when to stop a successful immunotherapy have to be discussed for every patient individually.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MSt, TM, TG, RH, MSc, SH and AS conceptualized the study. MSt, TM and AS contributed to data collection and interpretation. MSt and TG participated in data visualization. RH, MS, SH and AS contributed to supervision. MSt, MS, SH and AS drafted the manuscript. MSt, TM, TG, RH, MSc, SH and AS participated in revising the manuscript. MSt, TM and AS confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study protocol was reviewed and approved by the Ethics Committee of the Medical Faculty of the Julius-Maximilians-University Würzburg (approval no. 2023062901). Patient informed consent was waived due to the study's retrospective nature by the ethic committee of the medical faculty of the Julius-Maximilians-University Würzburg, taking into account the national legal bases. Data

collection and publication were carried out in compliance with the guidelines for ensuring good scientific practice. Only data generated in compliance with relevant legal requirements and professional ethics were evaluated. The applicable data protection regulations and the institute's internal guidelines for handling patient data were observed.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Johnson DE, Burtneß B, Leemans CR, Lui VWY, Bauman JE and Grandis JR: Head and neck squamous cell carcinoma. *Nat Rev Dis Primers* 6: 92, 2020.
- Decker J and Goldstein JC: Risk factors in head and neck cancer. *N Engl J Med* 306: 1151-1155, 1982.
- zur Hausen H: Papillomaviruses in the causation of human cancers-a brief historical account. *Virology* 384: 260-265, 2009.
- Forastiere A, Koch W, Trotti A and Sidransky D: Head and neck cancer. *N Engl J Med* 345: 1890-1900, 2001.
- Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, Harrington K, Kasper S, Vokes EE, Even C, *et al*: Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med* 375: 1856-1867, 2016.
- Burtneß B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G Jr, Psyrri A, Basté N, Neupane P, Bratland Å, *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. *Lancet* 394: 1915-1928, 2019.
- Scheel AH, Dietel M, Heukamp LC, Jöhrens K, Kirchner T, Reu S, Rüschoff J, Schildhaus HU, Schirmacher P, Tiemann M, *et al*: Predictive PD-L1 immunohistochemistry for non-small cell lung cancer: Current state of the art and experiences of the first German harmonization study. *Pathologe* 37: 557-567, 2016 (In German).
- Thinn MM, Hsueh CT and Hsueh CT: Sustained complete response to erlotinib in squamous cell carcinoma of the head and neck: A case report. *World J Clin Cases* 7: 616-622, 2019.
- Roh KW, Jang JS, Kim MS, Sun DI, Kim BS, Jung SL, Kang JH, Yoo EJ, Yoon SC, Jang HS, *et al*: Fractionated stereotactic radiotherapy as reirradiation for locally recurrent head and neck cancer. *Int J Radiat Oncol Biol Phys* 74: 1348-1355, 2009.
- Albers AE, Grabow R, Qian X, Jumah MD, Hofmann VM, Krannich A and Pecher G: Efficacy and toxicity of docetaxel combination chemotherapy for advanced squamous cell cancer of the head and neck. *Mol Clin Oncol* 7: 151-157, 2017.
- de Ruiter EJ, Mulder FJ, Koomen BM, Speel EJ, van den Hout MFCM, de Roest RH, Bloemen E, Devriese LA and Willems SM: Comparison of three PD-L1 immunohistochemical assays in head and neck squamous cell carcinoma (HNSCC). *Mod Pathol* 34: 1125-1132, 2021.
- Rasmussen JH, Lelkaitis G, Hakansson K, Vogelius IR, Johannesen HH, Fischer BM, Bentzen SM, Specht L, Kristensen CA, von Buchwald C, *et al*: Intratumor heterogeneity of PD-L1 expression in head and neck squamous cell carcinoma. *Br J Cancer* 120: 1003-1006, 2019.
- Ferris RL, Spanos WC, Leidner R, Gonçalves A, Martens UM, Kyi C, Sharfman W, Chung CH, Devriese LA, Gauthier H, *et al*: Neoadjuvant nivolumab for patients with resectable HPV-positive and HPV-negative squamous cell carcinomas of the head and neck in the CheckMate 358 trial. *J Immunother Cancer* 9: e002568, 2021.
- Patel JJ, Levy DA, Nguyen SA, Knochelmann HM and Day TA: Impact of PD-L1 expression and human papillomavirus status in anti-PD1/PDL1 immunotherapy for head and neck squamous cell carcinoma-Systematic review and meta-analysis. *Head Neck* 42: 774-786, 2020.
- Botticelli A, Cirillo A, Strigari L, Valentini F, Cerbelli B, Scagnoli S, Cerbelli E, Zizzari IG, Rocca CD, D'Amati G, *et al*: Anti-PD-1 and Anti-PD-L1 in head and neck cancer: A network meta-analysis. *Front Immunol* 12: 705096, 2021.
- Miyauchi S, Sanders PD, Guram K, Kim SS, Paolini F, Venuti A, Cohen EEW, Gutkind JS, Califano JA and Sharabi AB: HPV16 E5 mediates resistance to PD-L1 blockade and can be targeted with rimantadine in head and neck cancer. *Cancer Res* 80: 732-746, 2020.
- Massarelli E, William W, Johnson F, Kies M, Ferrarotto R, Guo M, Feng L, Lee JJ, Tran H, Kim YU, *et al*: Combining immune checkpoint blockade and tumor-specific vaccine for patients with incurable human papillomavirus 16-related cancer: A phase 2 clinical trial. *JAMA Oncol* 5: 67-73, 2019.
- Mehanna H, Taberna M, von Buchwald C, Tous S, Brooks J, Mena M, Morey F, Grønhoj C, Rasmussen JH, Garset-Zamani M, *et al*: Prognostic implications of p16 and HPV discordance in oropharyngeal cancer (HNCIG-EPIC-OPC): A multicentre, multinational, individual patient data analysis. *Lancet Oncol* 24: 239-251, 2023.
- Park JC, Krishnakumar HN and Saladi SV: Current and future biomarkers for immune checkpoint inhibitors in head and neck squamous cell carcinoma. *Curr Oncol* 29: 4185-4198, 2022.
- Matsuki T, Okamoto I, Fushimi C, Takahashi H, Okada T, Kondo T, Sato H, Ito T, Tokashiki K, Tsukahara K, *et al*: Real-World, long-term outcomes of nivolumab therapy for recurrent or metastatic squamous cell carcinoma of the head and neck and impact of the magnitude of best overall response: A retrospective multicenter study of 88 patients. *Cancers (Basel)* 12: 3427, 2020.
- Foster CC, Couey MA, Kochanny SE, Khattry A, Acharya RK, Tan YC, Brisson RJ, Leidner RS and Seiwert TY: Immune-related adverse events are associated with improved response, progression-free survival, and overall survival for patients with head and neck cancer receiving immune checkpoint inhibitors. *Cancer* 127: 4565-4573, 2021.
- Bilger G, Girard N, Doubre H, Levra MG, Giroux-Leprieur E, Giraud F, Decroisette C, Carton M and Massiani MA: Discontinuation of immune checkpoint inhibitor (ICI) above 18 months of treatment in real-life patients with advanced non-small cell lung cancer (NSCLC): INTEPI, a multicentric retrospective study. *Cancer Immunol Immunother* 71: 1719-1731, 2022.
- Perez L, Samlowski W and Lopez-Flores R: Outcome of elective checkpoint inhibitor discontinuation in patients with metastatic melanoma who achieved a complete Remission: Real-World data. *Biomedicine* 10: 1144, 2022.
- Wahl RL, Jacene H, Kasamon Y and Lodge MA: From RECIST to PERCIST: Evolving considerations for PET response criteria in solid tumors. *J Nucl Med* 50 (Suppl 1): 122S-150S, 2009.
- Tan AC, Emmett L, Lo S, Liu V, Kapoor R, Carlino MS, Guminski AD, Long GV and Menzies AM: FDG-PET response and outcome from anti-PD-1 therapy in metastatic melanoma. *Ann Oncol* 29: 2115-2120, 2018.
- Sato K, Akamatsu H, Murakami E, Sasaki S, Kanai K, Hayata A, Tokudome N, Akamatsu K, Koh Y, Ueda H, *et al*: Correlation between immune-related adverse events and efficacy in non-small cell lung cancer treated with nivolumab. *Lung Cancer* 115: 71-74, 2018.
- Martini DJ, Hamieh L, McKay RR, Harshman LC, Brandao R, Norton CK, Steinharter JA, Krajewski KM, Gao X, Schutz FA, *et al*: Durable clinical benefit in metastatic renal cell carcinoma patients who discontinue PD-1/PD-L1 therapy for immune-related adverse events. *Cancer Immunol Res* 6: 402-408, 2018.
- Yatsuda Y, Hirose S, Ito Y, Onoda T, Sugiyama Y, Nagafuchi M, Suzuki H, Niisato Y, Tange Y, Ikeda T, *et al*: A durable response after the discontinuation of nivolumab in an advanced gastric cancer patient. *Intern Med* 60: 1011-1017, 2021.
- Davies MA: Is it safe to stop Anti-PD-1 immunotherapy in patients with metastatic melanoma who achieve a complete response? *J Clin Oncol* 38: 1645-1647, 2020.
- Andrews A: Treating with checkpoint inhibitors-figure \$1 million per patient. *Am Health Drug Benefits* 8(Spec Issue): 9, 2015.

31. Gauci ML, Lanoy E, Champiat S, Caramella C, Ammari S, Aspeslagh S, Varga A, Baldini C, Bahleda R, Gazzah A, *et al*: Long-Term survival in patients responding to Anti-PD-1/PD-L1 therapy and disease outcome upon treatment discontinuation. Clin Cancer Res 25: 946-956, 2019.
32. Pons-Tostivint E, Latouche A, Vaflard P, Ricci F, Loirat D, Hescot S, Sablin MP, Rouzier R, Kamal M, Morel C, *et al*: Comparative analysis of durable responses on immune checkpoint inhibitors versus other systemic therapies: A pooled analysis of phase III trials. JCO Precis Oncol 3: 1-10, 2019.
33. Sekido K, Imaue S, Tomihara K, Tachinami H, Yamagishi K, Okazawa S, Ikeda A, Fujiwara K and Noguchi M: Durable complete response to immunotherapy with anti-PD-1 antibody nivolumab in a patient with oral squamous cell carcinoma presenting with lung metastasis: A case report. Clin Case Rep 9: e04545, 2021.
34. Yasumatsu R, Matsuo M, Wakasaki T, Masuda M, Takeuchi T, Manako T, Jiromaru R, Uchi R, Hashimoto K and Nakagawa T: Clinical outcome in recurrent and/or metastatic head and neck cancer patients after discontinuation of nivolumab monotherapy due to immune-related adverse events. Acta Otolaryngol 140: 1043-1048, 2020.
35. Lopez-Flores R, Samlowski W and Perez L: Elective checkpoint inhibitor discontinuation in metastatic solid tumor patients: A case series. Ann Case Rep 7: 894, 2022.
36. Zambrana F, Carril-Ajuria L, Gomez de Liano A, Martinez Chanza N, Manneh R, Castellano D and de Velasco G: Complete response and renal cell carcinoma in the immunotherapy era: The paradox of good news. Cancer Treat Rev 99: 102239, 2021.



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