molecular tumor board

Lasting Complete Clinical Response of a Recurring Cutaneous Squamous Cell Carcinoma With *MEK* Mutation and *PIK3CA* Amplification Achieved by Dual Trametinib and Metformin Therapy

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CASE REPORT

This is the case of a 70-year-old, nonsmoker, nondrinker White man who developed a cutaneous squamous cell skin cancer in his right retroauricular region (Fig 1). Additionally, he suffered from myasthenia gravis (MG) since 2007, which, among other methods, has been treated with azathioprine (150 mg once daily) since 2011. The tumor was diagnosed in 2015 as cutaneous squamous cell carcinoma (cSCC) by biopsy. The tumor was surgically removed in December, with histology test confirming squamous cell carcinoma (SCC).

In January 2016, radiotherapy with a total dose of 30 Gy in 10 fractions was administered, yet a biopsy in March showed local recurrence. Restaging of the tumor in April confirmed two fluorodeoxyglucose-avid foci on positron emission tomography-computed tomography (CT) at the operation site (Figs 2A and 2B). Re-resection of the right retroauricular recurrent cSCC was performed in April. Postoperative radiotherapy of 50 Gy in 2 Gy fractions was administered in June (Fig 2C). Three months after radiotherapy (September 2016), local recurrence prompted cisplatin plus fluorouracil chemotherapy. Responses were assessed both after the third (November 2016) and sixth (January 2017) cycles of chemotherapy by magnetic resonance imaging revealing stable disease according to RECIST 1.1, but a definitive cure could not be achieved.

The investigators have obtained a written statement of informed consent to publish information and images from the patient. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the National Institute of Pharmacy and Nutrition (Approval ID: OGYÉI/50268/2017).

MOLECULAR TUMOR BOARD REVIEW

In November 2016, *PIK3CA* gene amplification was detected by fluorescence in situ hybridization (FISH; Table 1). *PIK3CA* amplification is responsible for hyperactivation of phosphatidylinositol 3-kinase (PI3K)–dependent pathways in many cancer types and shows significant association with phosphorylated AKT level.[1-3] Elevated AKT phosphorylation level has been observed in SCC samples compared with normal tissues suggesting that dysregulation of the PI3K pathway is common in this histology type.[4,5] Preclinical models have also demonstrated the effectiveness of PI3K pathway inhibition in cSCC.[6,7] The antidiabetic drug metformin, with mammalian target of rapamycin pathway inhibitor activities, was beneficial in human SCC xenografts and SCC cells by suppressing cell proliferation associated with the increased phosphorylation levels.[8,9] Metformin inhibits mammalian target of rapamycin signaling in head and neck SCC cell lines and inhibits head and neck SCC cell proliferation in vitro.[10] As metformin was more feasible for off-label use than specific PI3K inhibitors, the patient was put on metformin (3 × 500 mg daily) in May 2017 (Fig 2D) without adverse events (AEs). In January 2018, partial remission occurred. Nevertheless, gradual disease progression (DP) followed (Figs 2E and 2F), confirmed by CT scans throughout May, August, and October (RECIST 1.1; Fig 2G).

Meanwhile, next-generation sequencing (NGS) of a hotspot cancer panel designed for epithelial tumors involving 58 cancer-associated genes and FISH tests (*PIK3CA*, *EGFR*, and *FGFR1*) were performed, revealing *TP53* p.R248Q and p.R248W, *MEK1* p.E203K mutations and reconfirming *PIK3CA* amplification (Table 1).

Although the detected *TP53* p.R248W (rs121912651) and *TP53* p.R248Q (rs11540652) are well-known pathogenic variants,[11-15] currently, there are no specific therapies that efficiently target p53 alterations. In contrast, *MEK1* p.E203K was a promising target. E203 is located between the conserved kinase subdomains VIb and VII of MEK1; it is a highly conserved residue

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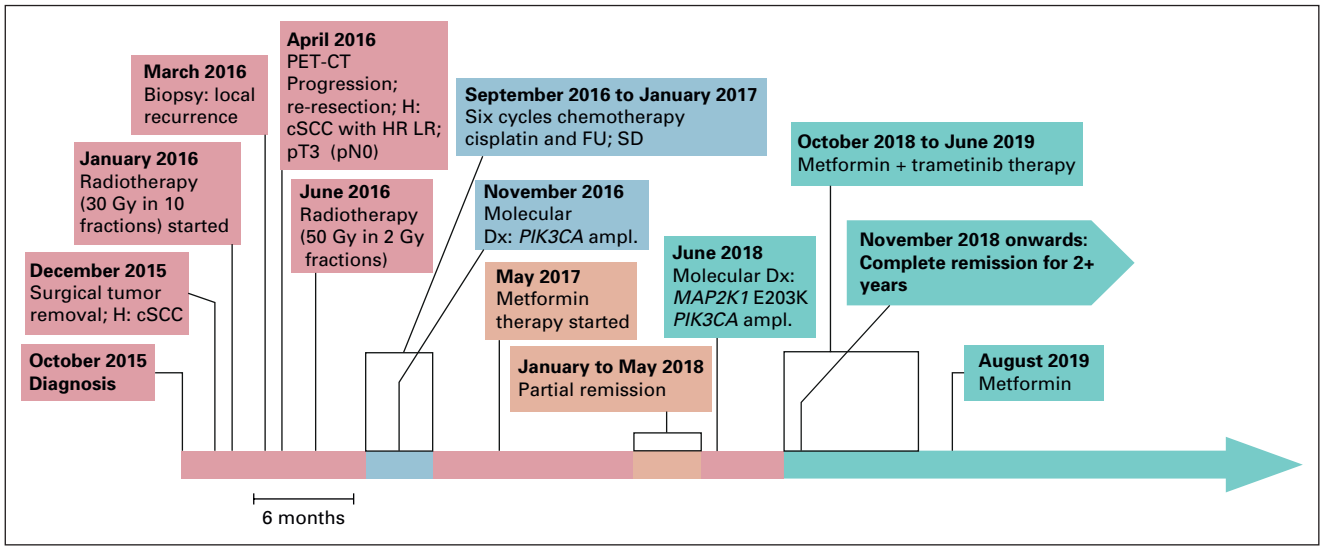

FIG 1. Time course of the case presented. The patient was diagnosed with cSCC, which recurred aggressively despite repeated surgery and irradiations. Cisplatin and FU chemotherapy provided transient disease control (SD for 3 months); however, gradual DP ensued. Meanwhile, *PIK3CA* amplification was revealed by fluorescence in situ hybridization assay, and metformin monotherapy was initiated leading to a transient partial remission. During the eventual DP, a more detailed molecular diagnostic test was performed, revealing an activating MEK1 mutation (*MAP2K1* p.E203K) and confirming *PIK3CA* amplification. On the basis of the recommendation of the molecular tumor board, metformin plus trametinib combinational therapy was initiated resulting in a rapid and dramatic tumor response. The tumor clinically disappeared only 1 month into the therapy, and complete remission has been consequently confirmed since then by checkups and imaging diagnoses. After 8 months, the combination therapy was suspended because of complications related to the long-standing myasthenia gravis of the patient and sepsis caused by nosocomial infection. Metformin monotherapy was resumed 2 months later and is ongoing to date. Trametinib treatment was withdrawn for an indefinite period and has not been restarted since because of the continuous complete tumor response. ampl., amplification; cSCC, cutaneous squamous cell carcinoma; Dx, diagnosis; FU, fluorouracil; H, histology; HR LR, high risk of local recurrance; PET-CT, positron emission tomography computed tomography; SD, stable disease.

across eukaryotes,[16] strongly underscoring its functional importance. *MEK1* p.E203K is described as an activating mutation: It leads to increased MEK1 autophosphorylation and constitutive ERK phosphorylation and it is transforming in cell culture.[17-20] E203 is juxtaposed to helix A in the 3D structure of the MEK kinase domain, and E203K has been characterized as having basal activity that can be further enhanced by RAF.[18,20] E203K and functionally similar mutations can sometimes be detected together with *RAS*, *RAF*, or *NF1* mutations and have been described as a secondary resistance mutation to RAF inhibitors.[21,22] Accordingly, allosteric MEK inhibitors may be effective against such mutations in wild-type RAF background.

The identified alterations were analyzed by our digital drug assignment system (RealTime Oncology Treatment Calculator 1.57).[23] This computational system calculates a digital drug assignment score, the aggregated evidence level for each alteration and the associated targeted drugs, on the basis of a network of evidence-based associations between all genetic alterations harbored by the tumor and potentially druggable targets and targeted therapies. On the basis of the scientific evidence in relation to the molecular profile, the system ranked the MEK inhibitor trametinib as of the highest relevance. Thus, the previously started metformin therapy was complemented with trametinib between October 2018 and June 2019 when it had to be suspended because of complications related to MG and sepsis.

Remarkably, in November 2018, one month into the combined targeted treatment, the tumor almost completely disappeared clinically (Figs 2H and 2I). Treatment-related AEs were grade 2 skin rash and dermatitis, which were successfully controlled with anti-inflammatory drugs. In February 2019, complete radiologic remission was confirmed by CT (Fig 2J). Clinical complete response in March 2019 is shown in Figure 2K. This status has been stable since then (Fig 3), despite of a serious AE: sepsis started in June 2019, caused by nosocomial infection during hospitalization for progressing symptoms of MG. Consequently, anticancer drugs were withdrawn from June. Metformin treatment was resumed in July 2019, whereas trametinib has not been readministered because of the continued complete remission status at regular checkups (Figs 3A-3E).

DISCUSSION

cSCC is one of the most common malignancies worldwide, with a trend of increasing incidence, particularly in the aging population.[24] Currently, there is very limited published experience with precision oncology approaches in cSCC. The main underlying mechanism is the accumulation of cancer driver mutations due to UV-induced DNA

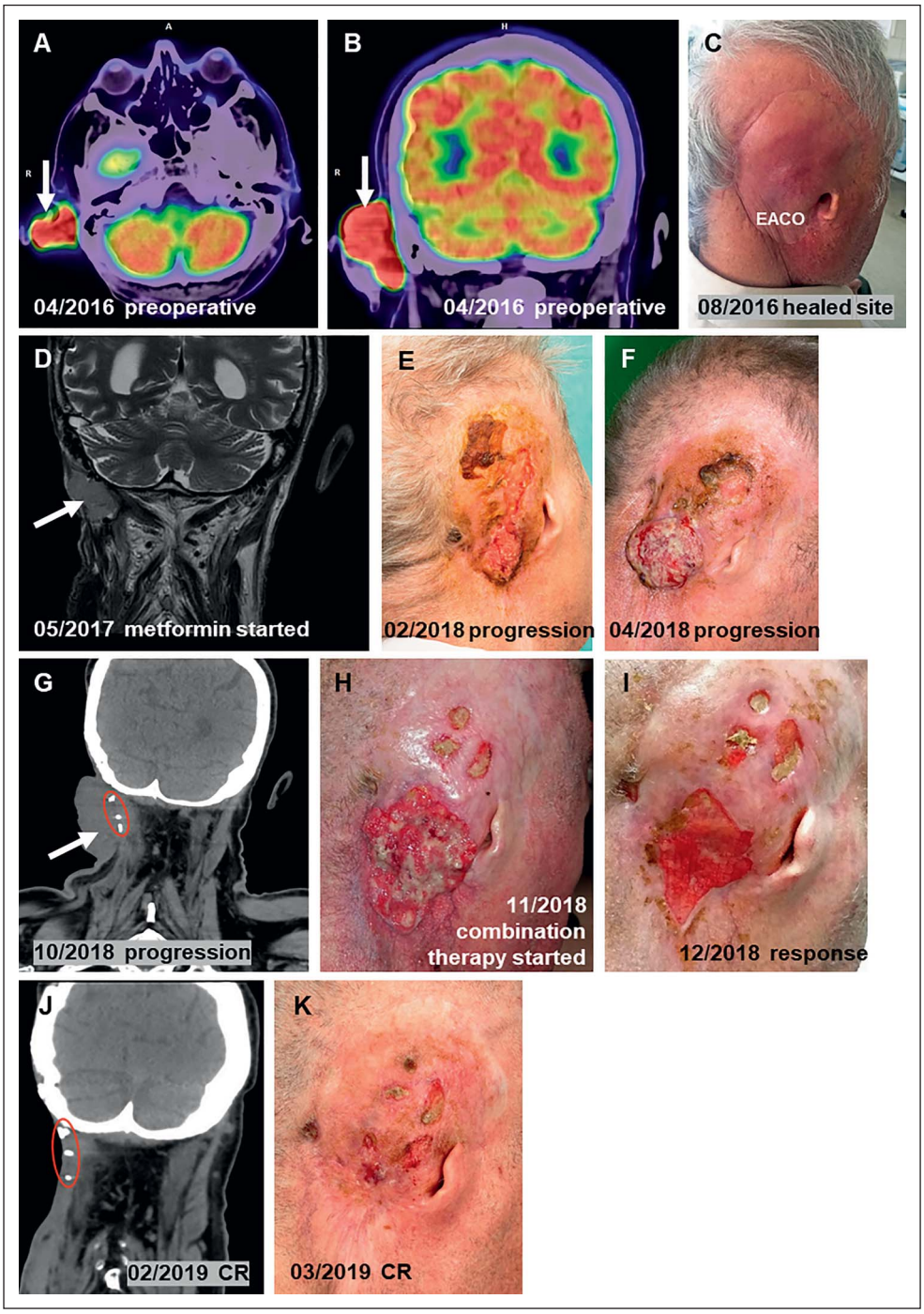

FIG 2. Course of the tumor to complete remission. (A and B) Representative PET-CT slices showing preoperative metabolic activity and size (26 × 26 × 52 mm) of the tumor (arrows) in the right postauricular region infiltrating the back of the auricle as well. Neither local bone involvement nor intracranial progression or tumor dissemination was detected by the PET-CT. (C) Re-resection of the right retroauricular recurrent skin cancer, subtotal ablation of the right auricle, and selective dissection of level II-III-V/A and occipital lymph node regions of the right side of the neck were performed in April 2016. The defect was reconstructed by a right radial forearm free flap. Histology confirmed poorly differentiated squamous cell carcinoma, longest diameter: 72 mm, maximum thickness: 25 mm, and the deepest invasion level was in the subcutis. Cartilage or bone invasion was not detected. Perineural invasion was present, but vascular invasion was not seen. None of the 37 resected neck lymph nodes were metastatic (pN0). Postoperative radiotherapy of 50 Gy in 2 Gy fractions was administered in June. The photograph shows the healed site of the repeatedly resected tumors and irradiations. In the next month (September 2016), local recurrence was proven by fine-needle aspiration biopsy. Administration of six planned chemotherapy cycles was started in September 2016: 100 mg/m^2 cisplatin (day 1) and 1,000 mg/m^2 FU (days 1-5), repeated every three weeks with a cumulative dose of cisplatin: 936 mg and FU: 56, 500 mg, achieving stable disease. (D) Representative MRI slice of the residual cancer (arrow) at the beginning of metformin monotherapy that resulted in a transient partial response from May 2017 until January 2018 on the basis of MRI scans. (E and F) Photographs of starting and advancing progression at nine and 11 months into metformin therapy. (G) Baseline CT staging of the tumor (arrow) before combined trametinib and metformin therapy; surgical clips (encircled) mark the course of the forearm flap's vascular pedicle. (H-K) Stages of remission under metformin and trametinib combination therapy that resulted in CR. (H) Photograph of the tumor regressed but still present at about one month after the beginning of combination therapy. (I) Tumor response after two months of treatment: de-epithelized, clinically tumor-free area. (J) Radiologic and (K) clinical CR. (J) Note the position of the metal clips right under the skin surface (encircled), in stark contrast to (G) the previous status, where they are located deep beneath the tumor. (K) Fragmentary necrotic spots on the skin of the flap. CR, complete response; CT, computed tomography; EAOC, external auditory canal orifice; FU, fluorouracil; MRI, magnetic resonance imaging; PET, positron emission tomography.

damage in the skin. cSCC primarily affects White elderly individuals and usually arises from extensively sun-exposed areas of the body.[25]

Somatic mutations are the consequences of various mutational processes, which generate unique mutational signatures.[26,27] Signature 7, mainly found in malignant

TABLE 1. Mutations Detected in Tumor DNA Isolated From Surgical Specimen (tumor cell ratio: 85%)

Gene	Mutation	Genotype	Allele Frequency (%)	Mutational Signature 7 Type	Untranscribed Strand
TP53	p.R248Q	c.743_744GG>AA	22	Yes	Yes
TP53	p.R248W	c.741_742CC>TT	24	Yes	No
MEK1 (MAP2K1)	p.E203K	c.607G>A	22	Yes	Yes
PIK3CA	Amplification	3.2 copies/cell[a]			
SMARCB1	p.R37H	c.110G>A	22	Yes	Yes
DDR2	p.E799D	c.2397G>C	51	No	
FGFR3	Silent	c.1953G>A	100	Yes	Yes
PDGFRA	Silent	c.1701A>G	100	No	
APC	Silent	c.4479G>A	47	Yes	Yes
EGFR	Silent	c.2361G>A	100	Yes	Yes
SMO	Silent	c.1239C>T	19	Yes	No
HRAS	Silent	c.81T>C	54	Yes	No
TP53	Silent	c.741C>T	22	Yes	Yes
MAP2K1	Silent	c.711G>A	53	Yes	Yes
JAK1	Silent	c.2199A>G	52	Yes	Yes

[a]*PIK3CA* fluorescence in situ hybridization assay was performed by using ZytoVision ZytoLight SPEC PIK3CA/CEN3 dual color probe in 50 cells in two cancer areas. Average chromosome 3 number: 1.2 (hypoploidity), average *PIK3CA* copy/CEN3: 2.7.

melanoma and squamous carcinoma of the head and neck, shows a higher prevalence of C>T and T>A mutation types, induced by UV exposure through the formation of pyrimidine dimers.[28] These are typically repaired by transcription-coupled nucleotide excision repair leading to a higher prevalence of mutations on the untranscribed strand. The substitution profile of the tumor aligns well with that of the UV-induced mutational signature 7.[26,27] Fourteen mutations were identified in the tumor sample (five missense and nine silent nucleotide substitutions; Table 1). Of the 14 mutations, 12 (86%) fall into the substitution types characteristic to mutational signature 7, and 9 of these 12 (75%) occur on the untranscribed strand (Table 1), strongly supporting the notion that the tumor was under a UV-induced mutational burden.

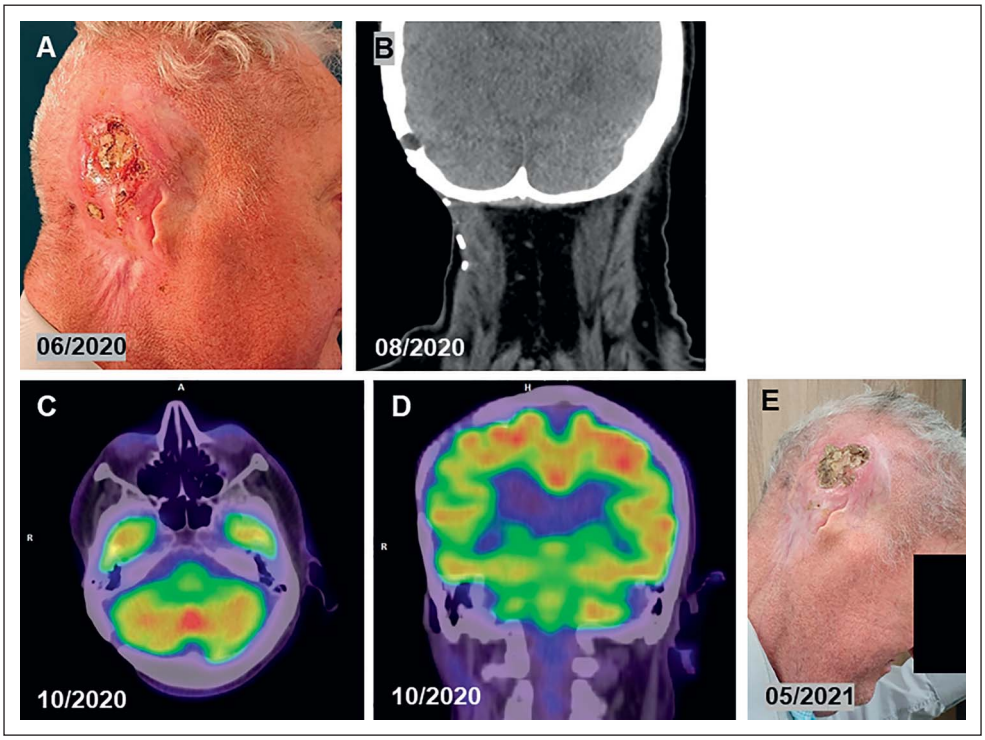

FIG 3. Follow-up of continued complete remission status. (A) Continuous CR at the end of the combined metformin and trametinib treatment. (B) Representative CT slice reconfirming CR with metformin monotherapy after withdrawal of trametinib during treatment of a serious nosocomial infection. (C and D) Representative PET-CT slices showing no abnormal metabolic activity indicating functional CR 24 mo after the beginning of combination therapy. (E) Thirty-one months after starting trametinib and metformin, the tumor status remains CR; dry bone surface is seen in tumor-free, scarred tissue. CT, computed tomography; CR, complete response; PET, positron emission tomography.

It has been proposed that in an early stage of tumor evolution toward cSCC, UV damage generates specific mutations (C-to-T and CC-to-TT due to the formation of thymidine dimers) in *TP53*. UV-damaged keratinocytes with a single *TP53* mutation undergo apoptosis, whereas keratinocytes with a secondary *TP53* mutation fail to undergo apoptosis resulting in clonal expansion, leading to the development of actinic keratosis. Ultimately, the proliferation of abnormal cells leads to the formation of in situ and invasive squamous cell carcinoma.[29] Footprints of UV-induced DNA damage were clearly detectable in the tumor DNA; moreover, in line with the above scenario, two CC-to-TT–type *TP53* mutations were detected. Allele frequency implies that both mutations are heterozygous; however, both variants are known to confer oncogenic gain of function to p53, and they are also dominant negative variants, which can block wild-type p53 expressed from the other allele. It is thus highly likely that the cSCC in this case was initiated in the conventional fashion by acquiring the two *TP53* mutations disabling apoptosis. Thus, these results appear to be well generalizable to this tumor type.

Other risk factors include immunosuppression, human papillomavirus, chronic scarring conditions, familial cancer syndromes, and environmental exposures (eg, arsenic).[30] Interestingly, the prolonged azathioprine treatment meant an additional potential mutagenic burden. This immunosuppressant has been described as a photosensitizer associated with squamous cell skin cancer development in immunosuppressed organ transplant patients.[31] Nevertheless, azathioprine treatment-induced mutations have a distinct substitution type, which is not present within the detected mutations, suggesting that azathioprine exposure was not a major contributor to tumor development.

MEK1 is part of the RAS-RAF-MEK-ERK signaling pathway, which plays a central role in the regulation of growth factor responses, for example, S phase entry. This pathway has been associated with skin cancer mainly through the prevalence of *BRAF* mutations in melanoma,[32] yet its role in cSCC is not straightforward. MAPK pathway alterations were not considered as main driver alterations in this tumor type,[24] but a gene set enrichment analysis highlighted a key role for the MAPK pathway in cSCC,[33] and it was proposed that inhibition of this pathway provides a potential approach to treat cSCC.[34] Accordingly, MEK inhibition prevents cell cycling and induces senescence in human models of cSCC and reduces tumor growth in a mouse model.[35] These findings are also in agreement with EGFR activity in this tumor type.[30] Unlike RAF-independently active *MEK1* mutations, which are resistant to allosteric MEK inhibitors,[18] *MEK1* p.E203K has been classified as a gain-of-function mutation type that can be further activated by RAF. Tumor regression in response to trametinib implies that *MEK1* p.E203K is a key driver, possibly hyperactive in cSCC because of the intrinsic RTK-MAPK pathway activity. The presented case thus demonstrates well the clinical utility of MAPK pathway inhibition in cSCC.

cSCCs usually bear a heavy mutational burden,[36] including cytogenetic alterations, of which one of the most affected is chromosome 3.[37] Although the performed assays were not designed to reveal the full complexity of chromosomal rearrangements, the number of alterations detected by a 58-gene NGS panel and a three-gene FISH is in line with high genetic complexity. On chromosome 3, both hypodiploidy and *PIK3CA* gene amplification were detected by FISH (Table 1). Loss of parts of or the entire chromosome 3 has been described in various tumors, particularly in epithelial tumors.[38-40] Increased mutational burden strongly correlates with responsiveness to immune checkpoint inhibitor therapies, and cemiplimab and pembrolizumab have been registered in SCC.[41,42] Thus, the therapeutic decision between targeted and immunotherapy must be carefully considered in light of the tumor molecular profile and the clinical situation. In the present case, the presence of strong targetable drivers and permanent immunosuppression necessitated by MG unequivocally prompted for targeted therapy.

It is important to note that although an initial single-marker test successfully identified *PIK3CA* amplification as a driver, its targeting by metformin achieved limited response only. Cancer genomes typically contain 4-5 driver mutations;[43] the average number of driver mutations in head and neck, when considering 369 known cancer genes, is approximately 2.[44] Accordingly, current understanding clearly articulates that iterative single-marker testing is not feasible and is expensive and wasteful of tissue.[45] Indeed, NGS identified another strong and targetable driver, *MEK1* p.E203K, strongly supporting the notion of complex molecular profiling in routine oncology practice.

Taken together, the case described here underscores the role of UV-induced DNA damage in skin malignancies, and to our knowledge, this is the first case demonstrating the clinical benefit of targeting MAPK and PI3K pathways in advanced recurrent cSCC on the basis of molecular profiling. Patients with cSCC of the head and neck who experience disease recurrence after definitive treatment with surgery and postoperative radiotherapy have poor survival, irrespective of their immune status.[46,47] However, appropriately selected molecularly targeted treatment combination overcame treatment resistance to conventional therapies in this fast-growing tumor and led to complete response with long-term clinical remission. Clinical trial data are usually not informative with regard to rare mutations, and although *MEK1* mutations are not prevalent in cSCC because of the high incidence of this malignancy, it still translates to a large number of patients who can potentially benefit from tumor sequencing and appropriate treatment decisions in precision oncology.

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