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Letter to the Editor

Deep and sustained radiological response after MEK-RAF inhibition in *HRAS* mutant apocrine carcinoma of the scalp

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Dear Editor,

Tumours of cutaneous sweat glands are rare and comprise a wide histological spectrum including eccrine, apocrine and other subtypes. Apocrine carcinoma is a highly aggressive adenocarcinoma thought to arise from normal or modified sweat glands, more frequently seen in middle-aged women. It generally occurs in areas rich in apocrine glands, such as the eyelid (in Moll's glands), ear and scalp, but especially the axilla. Wide surgical excision with complete removal of the tumour offers the best chance of cure. Radiotherapy can be used in case of local relapse or regional lymph node involvement.

There is very limited evidence on effective systemic treatment of metastatic apocrine carcinoma, ranging from single case reports to small case series. No standardised treatment guidelines for this rare tumour currently exist. These tumours are considered relatively chemotherapy-resistant, although some responses to single-agent or combined chemotherapy have been reported.

Harvey rat sarcoma viral oncogene homologue (*HRAS*) mutations can be found in head and neck (3.9%), bladder (5.1%), vulvar squamous cell (9.3%), and salivary duct (3.8%) cancers [1]. Interestingly, in a series of 27 naevus sebaceous samples which had been sequenced, 25 harboured *HRAS* G13R mutation and two exhibited a *KRAS* mutation [2]. In another study with 65 sebaceous naevi, 62 (95%) had mutations in *HRAS* and 3 (5%) had mutations in *KRAS*. Of note, the *HRAS* G13R mutation was present in 91% of lesions [3].

Le et al. performed a molecular and immunohistochemical analysis of 54 cutaneous appendageal carcinomas, including 10 apocrine carcinomas. Androgen receptor, oestrogen receptor, progesterone receptor, epidermal growth factor receptor and human epidermal growth factor receptor 2 (HER2) expression was seen in 36%, 27%, 16%, 85% and 12% of tumour samples, respectively [4]. There are reports of response with anti-HER2 therapy for cutaneous appendageal tumours with HER2 overexpression. Prevalence of *HRAS* mutation in apocrine carcinomas is not known.

The RAS-RAF-MEK-ERK pathway is commonly hyperactivated in various tumours, most frequently owing to activating mutations of the *KRAS*, *NRAS* and

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BRAF genes. Drugs targeting RAF and MEK have been approved for the treatment in *BRAF* mutant melanoma.

HRAS function can be inhibited by farnesyl transferase inhibitors (FTIs) as it is not alternatively prenylated like KRAS and NRAS [5]. There are multiple ongoing clinical trials evaluating FTIs in *HRAS* mutant cancers (NCT03719690, NCT02383927, NCT03496766). MEK and RAF proteins play their roles downstream of RAS, and it could be hypothesised that MEK and/or RAF inhibition could be effective in *HRAS*-driven cancers. Preclinical data showed that MEK inhibitors could induce apoptosis in *HRAS* mutant cell lines [1]. CH5126766/RO5126766 is a dual MEK-RAF inhibitor which causes MEK inhibition and in-complex inhibition of RAF and MEK [6]. We report, to our knowledge, the first patient with an *HRAS* mutant apocrine carcinoma of the scalp that has responded to a MEK inhibitor.

A 42-year-old female patient was diagnosed with metastatic apocrine carcinoma of the scalp (Fig. 1). She initially had noticed a lesion in the scalp two years before this diagnosis. The lesion developed a progressive growth over 6 months with concurrent appearance of cervical lymphadenopathy. She had a resection of her scalp lesion with a right neck dissection that showed 23/27 lymph nodes involved. Immunohistochemistry showed strong diffuse positivity for CK7 and patchy strong positivity for CK17. Staining for CK20, oestrogen receptor, CDX2, HER2 and TTF-1 were negative. These findings were consistent with apocrine neoplasm originating in the skin. After surgery, she received radiotherapy to the right side of the neck (50Gy in 20 fractions) and was found to have a lung metastasis. Given the lack of standard treatment for this neoplasm, she was referred to a phase I unit where she had tumour molecular characterisation. One hundred and thirteen genes were tested with a GeneRead™ custom DNA damage (Qiagen) panel described previously via next-generation sequencing [7]. Only mutations above 5% frequency were reported in this panel. A pathogenic (ClinVar) *HRAS* mutation c.37G>C (G13R) was detected, with a 46% allele frequency in sample. No other loss-of-function variants were found. The G13R mutation results in an amino acid substitution from a glycine to an arginine at position 13 in *HRAS*. Hibler *et al.* also reported one case of cutaneous adenocarcinoma of the scalp where genetic sequencing was performed; however, no somatic alterations were detected [8].

Screening investigations for the trial found a bone metastasis in the C7 vertebrae. This was not felt suitable for neurosurgical intervention. The patient was enrolled in a phase I clinical trial with a new dual inhibitor of the RAF-MEK proteins, CH5126766/RO5126766 (NCT02407509). The MEK-RAF inhibitor was planned to be given 4 mg twice weekly in 4-week cycles. A decrease in size of target lesions of 54% was seen after 2 cycles. Of note, none of the target lesions were previously irradiated. The patient has maintained partial response at the time of submission of this manuscript 15 months since entering the phase I clinical trial (Fig. 2).

As this is a rare tumour with no literature surrounding its genomic abnormalities or a recommended standard of care, we would like to make our readers aware of our findings of a genomic alteration with an *HRAS* mutation and a clinically meaningful response

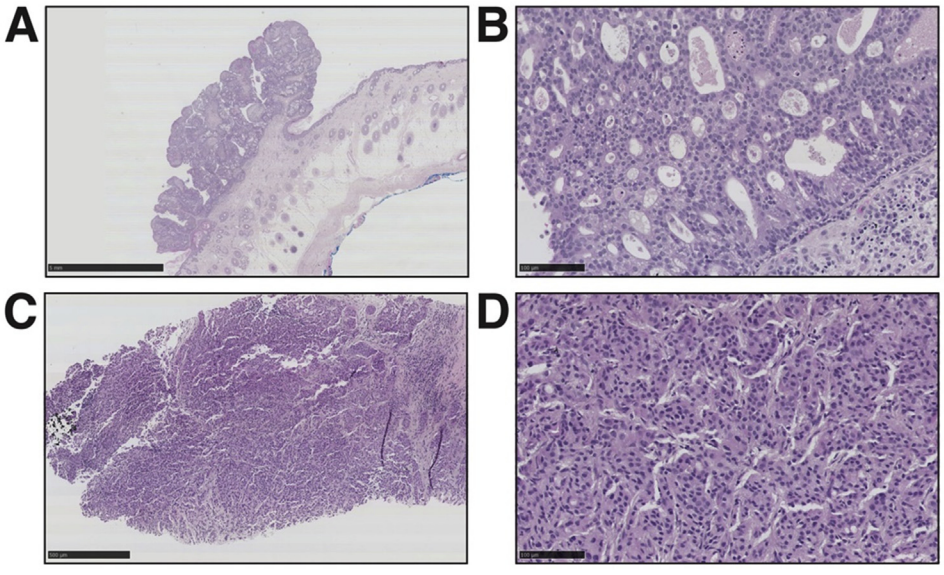

Fig. 1. Micrographs of primary and metastatic tumours showing histological features consistent with apocrine carcinoma (scale bars shown). (A) Scan magnification of a scalp excisional biopsy shows a polypoid structure constituted of an eosinophilic epithelial proliferation connected to the epidermis and lying over a broad dermal pedicle. (B) At 200x magnification, a gland forming tumour with cribriform architecture can be appreciated. Cytologically, there are indistinct cell borders, eosinophilic cytoplasm, and moderate nuclear atypia. (C) Incisional biopsy (5x magnification) of an enlarged cervical lymph node shows nested, trabecular, and gland forming tumour. (D) At 200x magnification, cells show eosinophilic cytoplasm, moderate nuclear pleomorphism and mitotic activity.

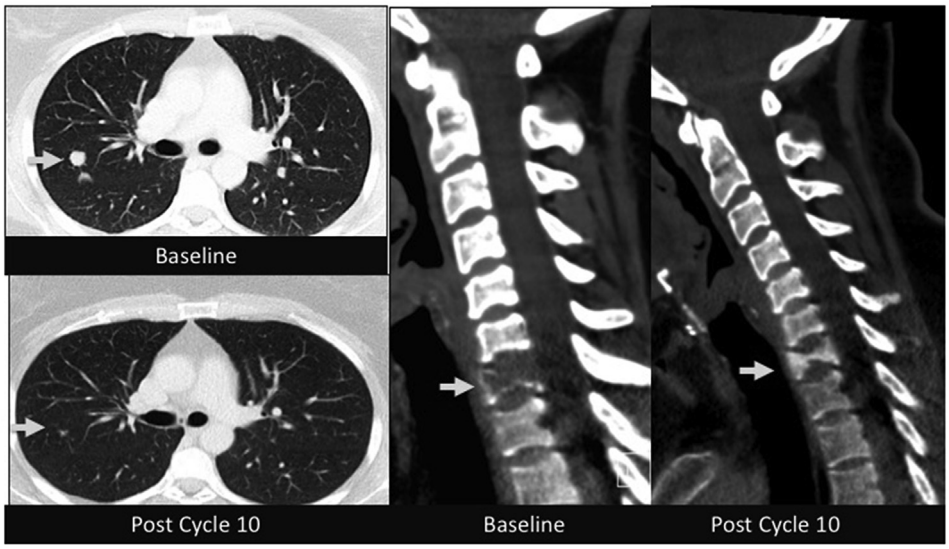

Fig. 2. Metastatic lung lesion with sustained radiological response on CT scan after 10 cycles of CH5126766/RO5126766. Secondary lesion on C7 vertebrae with sclerotic changes during the treatment with CH5126766/RO5126766.

when treated with the dual MEK-RAF inhibitor CH5126766/RO5126766. The frequency of *HRAS* mutations in apocrine carcinomas is still unknown and deserves investigation in large cohorts of these tumours. Equally, further prospective evaluation of *HRAS* mutant tumours with MEK-RAF inhibitors may be worthy of exploration.

Conflict of interest statement

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