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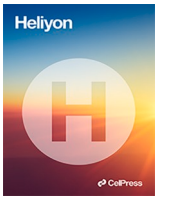

Efficiency of B-RAF-/MEK-inhibitors in B-RAF mutated Ameloblastoma: Case report and review of literature

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ABSTRACT

Background: Ameloblastoma is a benign but locally invasive and aggressive odontogenic tumor harboring activating *BRAF* V600E mutations in about two thirds of the cases.
Case presentation: Neoadjuvant therapy with Dabrafenib and Trametinib was given to a 42-year-old male patient with recurrent ameloblastoma of the right mandible with a BRAF V600E mutation for 18 months. The patient manifested an excellent response to the therapy with remarkable reduction in tumor size from 72.6 mm to 55.9 mm. Histopathologically, the tumor underwent significant degenerative changes with only a few sparse vital residuals revealing 0 % Ki67 proliferative index.
Conclusions: Neoadjuvant therapy with BRAF-inhibitors or BRAF-MEK-inhibitors is an effective means to reduce the size of mandibulary ameloblastomas. We propose the consideration of neoadjuvant therapy in future treatment modalities to minimize post-surgical morbidity and facial deformations.

1. Introduction

World Health Organization (WHO) and International Agency for Research on Cancer (IARC) classifications define ameloblastoma as a benign tumor consisting of mature fibrous stroma surrounded by odontogenic epithelium without odontogenic ectomesenchyme. Ameloblastoma is further subclassified into conventional, peripheral/extraosseous, unicystic and adenoid types [1]. Typically, ameloblastomas grow slowly but are locally invasive and hence these tumors eventually elicit significant morbidity when extended surgery is needed for radical resection. Ameloblastomas account for approximately 1 % of all oral tumors and for approximately 9–11 % of odontogenic tumors[1]. Ameloblastomas originate from either the residual epithelium of the tooth germ, the epithelium of odontogenic cysts or the enamel organ [2].

B-RAF V600E mutations were detected as oncogenic driver mutations across different tumor types with a total incidence of about 7 % in human cancers [3]. Due to their frequency, (neo)adjuvant therapy with BRAF inhibitors was applied to many tumors and proposed in a number of studies as a promising therapy also for ameloblastomas [4–6].

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Abbreviations

SMO	encoding Smoothened
TKI	Tyrosine-kinase inhibitor
MRI	Magnetic Resonance Imaging

In this study, we present the case of a male patient with recurrent ameloblastoma harboring a *B-RAF* V600E mutation who received neoadjuvant treatment with *B-RAF*-and *MEK*-inhibitors for approximately eighteen months. Excellent tumor response to this therapy showcased with remarkable reduction in tumor size. Few regressive tumor residues were detected and surgically resected within distinct fibrotic changes. Our case clearly demonstrates that neoadjuvant *B-RAF* inhibitor therapy may reduce the extent of surgery and thereby post-surgical morbidity.

1.1. Case presentation

A 36-year-old male patient presented at the University Hospital of Cologne in November 2013 with a painless, firm swelling at the angle of his right mandible, which he noticed approximately three months before his visit. Intraoral examination demonstrated a firm tumor within the posterior right mandible extending to the buccal and lingual margins. Radiological examination revealed a large, well-defined multilobulated radiolucent lesion extending to the ramus of the right mandible with substantial buccolingual expansion. There was remarkable root resorption of the neighboring teeth and cortex of the alveolar bone affecting the adjacent soft tissues. An incisional biopsy was carried out under local anesthesia, followed by histological examination of the lesion.

The specimen was composed of islands, cords and sheets of partly anastomosing neoplastic odontogenic epithelial cell nests. Cells at the periphery of the islands were columnar, hyperchromatic and lined up in a palisaded fashion with the nuclei being displaced from the basement membrane in a pattern of reverse polarity. The cytoplasm was vacuolated and in the center of the follicles, loosely arranged cells resembling stellate-reticulum were apparent upon microscopic examination. Cystic degeneration was also widely observed. These histologic criteria were compatible with the diagnosis of conventional ameloblastoma with mixed follicular and plexiform histological subtypes (Fig. 1 A, B).

Complete enucleation of the tumor sparing the mandibular bone margins was performed in December 2013. The tumor measured 2.5 cm and its surgical margins were histologically free of tumor cells.

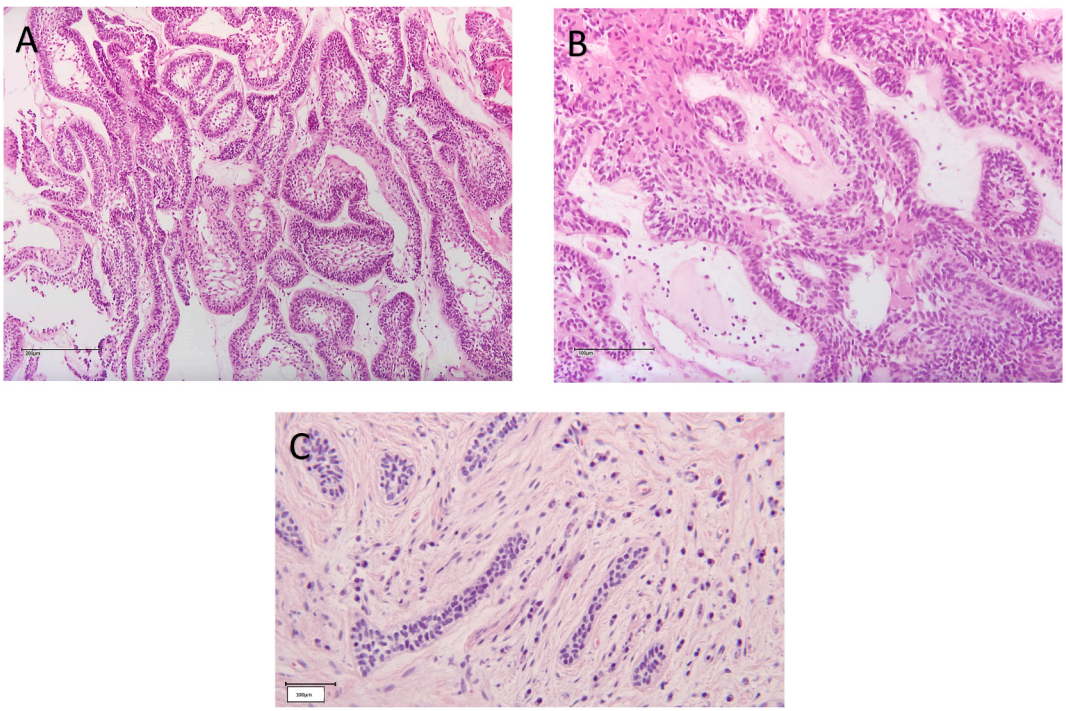

Fig. 1. (A): Conventional type ameloblastoma (mixed follicular and plexiform); islands of neoplastic odontogenic epithelial cells with stellate reticulum-like areas.Fig. 1 (B**):** Conventional type ameloblastoma (mixed follicular and plexiform); anastomosing sheets and cords with peripheral palisading and reverse polarity. Fig. 1 **(C):** Histology after 18 months of therapy with *B-RAF*-inhibitor; scarring fibrous changes with fewer residuals of ameloblastoma beside partly prominent macrophages with signs of ongoing absorptive reaction.

In May 2019, the patient showed up again at the Clinics of Maxillofacial Surgery suffering from tumor recurrence. Clinical and radiological examination confirmed the diagnosis of recurrent ameloblastoma. Radiologically, MRI showed the presence of a 6.2 × 7.2 × 6.6 cm sized multilobulated, radiolucent lesion at the posterior of the right mandible with prominent extensive bone resorption and tumor infiltration to the surrounding soft tissues. Clinically, the swelling of the masseter and other muscle was present. Local tumor infiltration caused significant space-occupying effects and padding of the right side of the oral cavity and the oropharynx reaching the hypopharynx with constriction of the oropharynx.

A new biopsy was planned and subsequent histological examination of the specimen verified recurrent conventional ameloblastoma with the same subtypes as in the previous specimens.

In the course of evaluation of possible therapeutic options, we examined a panel of 19 different genes by next generation sequencing. As expected, an activating p.V600E mutation in exon 15 of the *B-RAF* oncogene was detected (Table I).

1.2. Neoadjuvant therapy of relapsed ameloblastoma

As local resection of the relapsed tumor would have required extensive surgery with resection of the mandibular bone and surrounding soft tissues and peripheral nerves, we considered to first reduce the tumor size by neoadjuvant therapy. Thus, neoadjuvant therapy with combined *B-RAF-*/MEK-inhibitors was started from August 2019 with Dabrafenib 150 mg and Trametinib 2 mg daily for eighteen months.

To control the efficacy of therapy, a biopsy was performed after 6 months, which detected residues of ameloblastoma with significantly lower proliferation rate as compared to the primary biopsy with a Ki67-index close to 0 % (Fig. 2A as compared to Fig. 2B), indicating good response to therapy. Ki67 proliferation index in the primary biopsy of the relapsed tumor was approximately between 3 % and 8 % of the tumor cells (Fig. 2A and B). As the patient did not suffer from side-effects, neoadjuvant therapy was continued till March 2021.

Excellent response was documented after 14 months of therapy with Dabrafenib and Trametinib (Fig. 3, Table 2). MRI revealed remarkable reduction in tumor size from 72.6 mm in July 2019 to about 55.9 mm in November 2020. Sequential MRI (magnetic resonance) imaging starting from July 2019 (after relapse) until December 2022 (after completing neoadjuvant and surgical therapy of relapsed disease) is shown in Supplemental Fig. 1 and clearly demonstrates response to the combined *B-RAF/MEK*-inhibitor with subsequent complete surgical resection.

Response was confirmed through histologic examination of a tumor biopsy. It showed predominant soft tissue with scarring fibrous changes besides few residuals of ameloblastoma and partly prominent macrophages with signs of ongoing absorptive reaction (Fig. 1C and Supplementary Fig. 2). Finally, definitive surgical excision of the tumor was performed in March 2021 followed by autologous bone implantation from the iliac crest. Histological examination disclosed that the excised ameloblastoma, as a result of satellite extensions, was marginal to its surgical borders (R1-resection). However, the following clinical controls revealed no evidence of recurrence until today (Supplementary Figs. 1A–H).

Table 1
Molecular examination of the ameloblastoma using next generation sequencing of a panel of 19 different genes. Activating *B-RAF* V600E mutation was detected.

Gene	NM_number	Exon	Mutational Status	Allele Freq. (%)	Coverage	Interpretation
ALK	NM_004304	22–25	Wild-type			
BRAF	NM_004333	11, 15	EX15: c.1799T > A p.V600E	47.33	14153	Activating, (https://oncokb.org/)
CTNNB1	NM_001904	3	Wild-type			
EGFR	NM_005228	18–21	Wild-type			
ERBB2	NM_004448	8, 19, 20	Wild-type			
FGFR1	NM_023110	4 - 7, 10, 12 - 15	Wild-type			
FGFR2	NM_000141	6 - 15, 18	Wild-type			
FGFR2	NM_022970	8	Wild-type			
FGFR3	NM_000142	3, 7, 9, 10 (Codon 429–471), 12 (Codon 512–529), 16, 18 (Codon 769–807)	Wild-type			
FGFR4	NM_213647	3, 6,12, 13 (Codon 556–607), 15, 16	Wild-type			
IDH1	NM_005896	4	Wild-type			
IDH2	NM_002168	4	Wild-type			
KRAS	NM_033360	2–4	Wild-type			
MAP2K1	NM_002755	2, 3	Wild-type			
MET	NM_001127500	14, 16 - 19	Wild-type			
NRAS	NM_002524	2–4	Wild-type			
PIK3CA	NM_006218	10, 21	Wild-type			
PTEN	NM_000314	1–8	Wild-type			
ROS1	NM_002944	34–41	Wild-type			
TP53	NM_00546	4 (Codon 97–125), 5, 6, 7, 8	Wild-type			

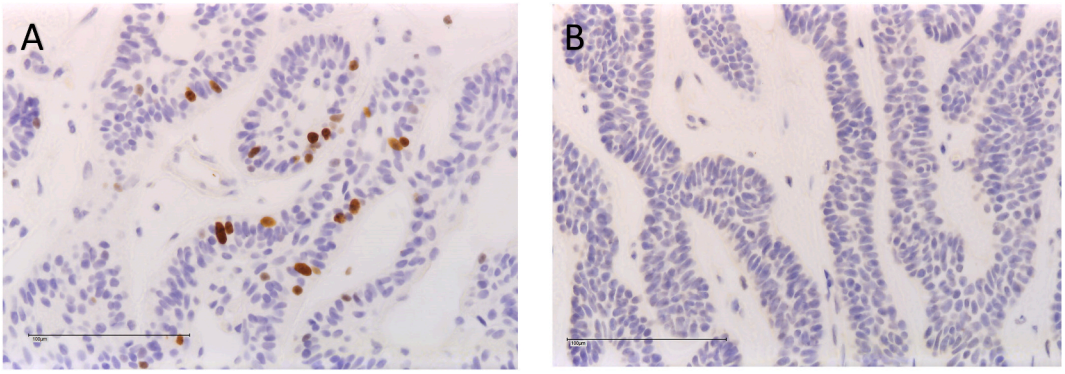

Fig. 2. (A): Comparison of Ki67-Index before and after the therapy: Ki67 positive tumor cells were approximately between 3 % and 8 % in May 2019 (before therapy). Fig. 2 **(B)**: Comparison of Ki67-Index before and after the therapy: Ki67 was close to 0 % (after 6 months of therapy with *B-RAF*-Inhibitor).

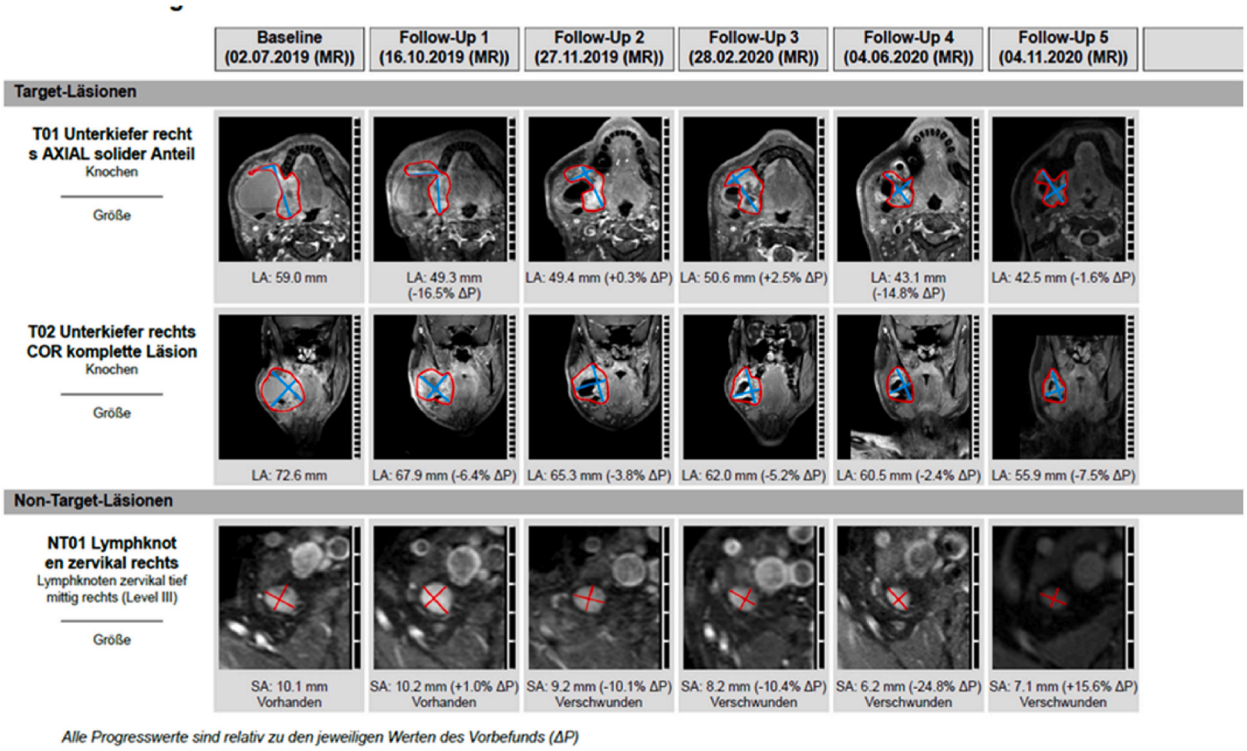

Fig. 3. Follow-up MRI of the mass before and during the therapy with *B-RAF*-inhibitor reaveled remarkable reduction in size (72.6 mm–55.9 mm).

2. Discussion

B-RAF mutations play a significant role as oncogenic drivers in developing different human cancers with total incidence of approximately 7 % among all cancer cases. Tumors harboring *B-RAF* mutations comprise a remarkably wide spectrum including hairy cell leukemia, melanoma, papillary thyroid carcinoma, and less frequently colorectal and non-small cell lung cancers [3]. Among *B-RAF* mutations, the p.V600E exchange is by far the most common mutation causing constitutive activation of its serine/threonine kinase. *B-RAF* encodes for a serine threonine protein kinase that is involved in the MEK/MAPK signaling pathway promoting cell survival and proliferation and hindering cell differentiation [7].

A recent study relating genetic alterations in ameloblastoma with clinical features provided better understanding of the genesis of these tumors and more comprehension of the relation between genetic alterations and the different subtypes of ameloblastoma as well as their relation to recurrence rate and clinical behavior [6]. These studies uncovered that *B-RAF* mutated ameloblastomas are almost exclusively located in the mandible, more common in younger patients and mainly associated with lower rate of recurrence, whereas

Table 2
Follow up MRI: Significant reduction in size of the tumor after therapy.

			Baseline (02.07.2019 (MR))	Follow-Up1 16.10.2019 (MR))	Follow-Up 2 27.11.2019 (MR))	Follow-Up 3 28.02.2020 (MR))	Follow-Up 4 04.06.2020 (MR))	Follow up 5 04.11.2020 (MR))
Target-Lesions	1	T01 Lower jaw right AXIAL solid part bone	LA: 59.0 mm	LA: 49.3 mm	LA: 49.4 mm	LA: 50.6 mm	LA: 43.1 mm	LA: 42.5 mm
	2	T02 Lower jaw right COR complete lesion Bone	LA: 72.6 mm	LA: 67.9 mm	LA: 66.3 mm	LA: 62.0 mm	LA: 60.5 mm	LA: 55.9 mm
Non-Target Lesions	1	NT01 Lymph nodes cervical right Lymph nodes cervical deep central right (level III)	SA: 10.1 mm Status: present	SA: 10.2 mm Status: present	SA: 9.2 mm Status: Disappeared	SA: 8.2 mm Status: Disappeared	SA: 6.2 mm Status: Disappeared	SA: 7.1 mm Status: Disappeared

Table 3
Comparison between the efficiency of therapies with BRAF-inhibitors in our patient and five other patients with ameloblastoma or metastatic ameloblastoma, who received therapies with BRAF-Inhibitors.

	Age	Sex	Clinical data	Size (pre therapy)	Therapy	Results	Side effects	Follow up
Patient 1 [4]	29	F	Last recurrence: Right cavernous sinus anterior to the cavus of Meckel First diagnosis: left mandible (at age of 7)	24 × 21 × 19 mm (sep. 2016)	Vemurafenib 960 mg twice daily for about 11 months	Reduction of the lesion size (18 × 13 × 14 mm)	Grade 1 anorexia, nausea and fatique	The patient remained asymtomatic (no recent data)
Patient 2 [5]	83	F	Right mandibular body First diagnosis: (at age of 16) (several surgeries and recurrences)	37.9 × 58.7 × 56.2 mm	Dabrafenib 75 mg twice daily Then was reduced to 50 % of the dosis Total 12 months	75 % reduction in tumor volume after 8 months	The dosis was reduced to 50 % to decrease comorbidities (not mentioned)	No data
Patient 3 [15]*	40	M	Last recurrence: left mandible of stage 4 metastatic Ameloblastoma (pulmonary metastasized) First diagnosis: left mandible (at age of 10) (several surgeries and recurrences)	Not mentioned	Dabrafenib 150 mg twice daily and Trametinib 2 mg once daily for 8 weeks	Reduction of the tumor masses after 8 weeks	No apparent toxicity	No data
Patient 4 [16]	85	M	Left angle of the mandible	45 mm	Dabrafenib 150 mg twice daily for 73 days	>90 % tumor volume reduction; Degeneration with squamous differentiation and sublumional cysts	Low energy Plaque-like skin lesions	No data
Patient 5 [17]*	33	F	Left mandible First diagnosis at age of 3 metastatic ameloblastoma with bilateral lung metastasis at age of 14 Several surgeries and recurrences	Lung metastasis: 56 mm and 64 mm	Vemurafenib 960 mg twice daily Dosis was reduced to 720 mg then to 480 mg twice daily	Lung metastasis were 30 % decreased in diameter	Arthralgia, nausea and rash	The response was persistent after 26 months of follow up
Patient 6 [14]*	26	F	Right Mandible First diagnosis at age of 13 Metastatic ameloblastoma with bilateral multiple lung metastaisis (One surgery and no recurrences)	Size is not available Numerous Nodules bilateral lungs	Dabrafenib (150 mg BID) Trametinib (2 mg QD) for 12 weeks	Complete remission	Not available	Complete response after 30 months of follow up
Patient presented in this report	43	M	Right mandible First diagnosis at age of 36	Max. 72.6 mm	Dabrafenib 150 mg and Trametinib 2 mg daily for 18 months	Max. 55.9 mm Ki67 about 0 %	No side effects	No recurrence till today

*metastatic Ameloblastoma.

tumors harboring mutations in the signaling transducer *SMOOTHENED* (*SMO)* commonly arise in the maxilla of older patients and have a higher tendency to recur [6].

Ameloblastoma, being benign tumors still harbor the ability to grow locally aggressive, destructing the adjacent soft tissue and bone with high tendency of recurrence, especially when treated by enucleation. Therefore, a radical surgical resection with approximately one cm safety margin of each side is recommended but elicits significantly more post-resectional morbidity and the need for mandibular or maxillar reconstruction [8,9]. Also facial deformation and secondary degradation of mandibular or maxillar function pose severe morbidity in this relatively young patient population.

To reduce the area of surgical interventions, many studies proposed *B-RAF*-inhibitors as promising neoadjuvant therapy to minimize the tumor size first and then to allow more localized and limited surgical resection. Since the first introduction of the BRAF-inhibitor Vemurafinib for treatment of melanoma with BRAF V600E mutations, it became clear that this treatment was very limited with respect to duration and that combination with MEK-inhibitors increased both response rates and perlonged duration of response [10]. This lead to approval of combined BRAF/MEK inhibitor treatment for all tumors with *BRAFV600E* mutations (melanoma, colorectal carcinomas, lung cancer, hairy cell leukemia), and this combination elicits tolerable toxicity. Hence, we decided to use combined *BRAF/V600E* inhibitors as it became clear that our patient with a huge tumor recurrency needed long-term neoadjuvant therapy and thus emergence of resistance to a single TKI could pose a potential risk. This therapy approach offers excellent clinical results with markedly reduced post-surgical morbidity [4,5]. The validity of this concept and its clinical utility is clearly underscored and evident also from our case presented here. Review of the literature demonstrated five case reports with *BRAF* inhibitory therapy in ameloblastomas (Table 3). Fernandes et al. reported a case of a 29-year-old female patient with recurrent ameloblastoma despite of repetitive surgeries. The first diagnosis with ameloblastoma was confirmed in the ascending branch of the left mandible at the age of 7, which was followed by several tumor recurrences. The last one involved the right cavernous sinus anterior to the cavus of Meckel. She was treated with Vemurafenib for about eleven months with satisfying results in reducing the size of the lesion from 24 mm to 18 mm [4].

Similar case studies presented remarkable downsizing of the *BRAF*-mutated ameloblastoma or metastatic ameloblastoma after receiving therapies with different doses of *BRAF*-inhibitors or combined *BRAF-MEK*-inhibitors [11–13]. Even a case of metastasized ameloblastoma responding remarkably well to *BRAF/MEK* inhibitor therapy has been documented ion the literature and underscores the clinical utility of neoadjuvant therapy [14].

Most of the patients received Dabrafenib in dosis between 75 and 150 mg twice daily (Table 3). Only one patient with metastatic ameloblastoma obtained neoadjuvant therapy with both *BRAF*- and *MEK*-inhibitors, thus we here report the second ameloblastoma case with this therapy combination. Both patients had no significant side effects [15]. As this therapy seems to be well tolerated and less prone to emergence of resistance we recommend using the combined approach.

3. Conclusion

Understanding the molecular pathology of ameloblastoma provides us with more comprehension of their genesis and behavior; thus allowing us to develop targeted therapies to efficiently treat these locally aggressive and destructing tumors.

Neoadjuvant therapy with *BRAF-/MEK*-inhibitors hurls us forward in treating *BRAF*-mutated ameloblastoma and in reducing significantly postsurgical morbidity. The overall life quality and confidence level of the patients is immensely improved compared to tumors typically being treated by radical resection with wide safety margins resulting in massive facial deformation and dysfunction for the patient.

These findings, together with the outcomes of previous clinical trials and genetic studies of ameloblastoma, suggest that neoadjuvant treatment and tumor reduction by tyrosine kinase inhibitors should be considered in every case of ameloblastoma that can be surgically resected only with significant morbidity.

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Patient consent

Patient consented to histological and molecular investigation and to the case study (BioMaSOTA protocol 13-091 approved by Ethics Committee).

Data availability statement

The original sequencing data have been compiled to storage space of the University (Hospital) of Cologne and are available upon request (reinhard.buetter@uk-koeln.de) and identification of scientists.

CRediT authorship contribution statement

Reinhard Büttner: Formal analysis, Project administration, Supervision, Writing – review & editing. **Sibel Elif Gültekin:** Formal analysis, Project administration, Supervision, Writing – review & editing. **Carina Heydt:** Formal analysis. **Lucia Nogova:**

Investigation. **Sonja Meemboor:** Formal analysis, Writing – review & editing. **Matthias Kreppel:** Investigation. **Reem Aziz-Heiloun:** Investigation, Writing – original draft.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Reinhard Buettner reports a relationship with AbbVie that includes: board membership and speaking and lecture fees. Reinhard Buettner reports a relationship with Amgen that includes: speaking and lecture fees. Reinhard Buettner reports a relationship with AstraZeneca that includes: board membership and speaking and lecture fees. Reinhard Buettner reports a relationship with Bayer AG that includes: board membership and speaking and lecture fees. Reinhard Buettner reports a relationship with Bristol-Myers Squibb that includes: board membership and speaking and lecture fees. Reinhard Buettner reports a relationship with Boehringer Ingelheim that includes: board membership and speaking and lecture fees. Reinhard Buettner reports a relationship with Illumina that includes: board membership and speaking and lecture fees. Reinhard Buettner reports a relationship with Janssen that includes: board membership and speaking and lecture fees. Reinhard Buettner reports a relationship with Lilly that includes: board membership and speaking and lecture fees. Reinhard Buettner reports a relationship with Merck-Serono that includes: board membership and speaking and lecture fees. Reinhard Buettner reports a relationship with MSD that includes: board membership and speaking and lecture fees. Reinhard Buettner reports a relationship with Novartis that includes: board membership and speaking and lecture fees. Reinhard Buettner reports a relationship with Qiagen that includes: board membership and speaking and lecture fees. Reinhard Buettner reports a relationship with Pfizer und Roche that includes: speaking and lecture fees. Reinhard Buettner reports a relationship with Timer Therapeutics GmbH&Co KG that includes: board membership. Reinhard Buettner reports a relationship with Gnothis Inc. Stockholm that includes: board membership. Reinhard Büttner has received honoraria for lectures and advisory boards of following companies: AbbVie, Amgen, AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, Illumina, Janssen, Lilly, Merck-Serono, MSD, Novartis, Qiagen, Pfizer und Roche. Reinhard Büttner is founder and co-director of Timer Therapeutics GmbH&Co KG/Germany and Gnothis Inc./Stockholm. Sibel Elif Gültekin has no conflicts of interest. Carina Heydt has no conflicts of interest. Lucia Nogova has received honoraria for consulting/advisory roles as well as travel and accommodations expenses from following companies: Pfizer, Celgene, Novartis, Roche, Boehringer Ingelheim, Bristol-Myers Squibb, Takeda, Bayer, Janssen and Astra Zeneca. Sonja Meemboor has no conflicts of interest. Matthias Kreppel has no conflicts of interest. Reem Aziz-Heiloun has no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23206.

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