Targeted therapies in ameloblastomas and amelobastic carcinoma—A systematic review

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ABSTRACT

Targeted therapy has the potential to be used in the neoadjuvant setting for odontogenic tumors, reducing the morbidities associated with major surgery. In this regard, the aim of this study was to summarize the current evidence on the different forms of targeted therapy, effectiveness, and drawbacks of this course of treatment. Four databases were searched electronically without regard to publication date or language. Grey literature searches and manual searches were also undertaken. Publications with sufficient clinical data on targeted therapy for odontogenic tumors were required to meet the criteria for eligibility. The analysis of the data was descriptive. A total of 15 papers comprising 17 cases (15 ameloblastomas and 2 ameloblastic carcinomas) were included. Numerous mutations were found, with BRAF V600E being most common. Dabrafenib was the most utilized drug in targeted therapy. Except for one case, the treatment reduced the size of the lesion (16/17 cases), showing promise. Most of the adverse events recorded were mild, such as skin issues, voice changes, abnormal hair texture, dry eyes, and systemic symptoms (e.g., fatigue, joint pain, and nausea). It is possible to reach the conclusion that targeted therapy for ameloblastoma and ameloblastic carcinoma may be a useful treatment strategy, based on the findings of the included studies.

Keywords: BRAF; ameloblastoma; genetic mutation; odontogenic tumor; targeted therapy.

1 INTRODUCTION

Odontogenic tumors (OTs) comprise a category of diverse lesions with various histological features and clinical presentations. The new 5th edition of the World Health Organization (WHO) divides OTs based on biologic behavior into benign epithelial, mixed epithelial and mesenchymal, mesenchymal OT, and malignant OTs (Soluk-Tekkesin & Wright, 2022; WHO Classification, 2022). Depending on the geographic region or the WHO classification used, lower or higher frequencies of OTs can be expected. In general, OTs represent 1–9% of diagnoses among oral and maxillofacial lesions (Al-Aroomy et al., 2022; Aregbesola et al., 2018; Buchner et al., 2006; da Silva et al., 2016; Kaur et al., 2022; Soluk-Tekkesin et al., 2020; Syed et al., 2019).

OTs can grow to significant sizes, often affecting vital nearby structures, and making their management challenging. The treatment of OTs is surgical in all cases, which may result in significant morbidity, affecting the quality of life of the patient (Mikami et al., 2022). In this sense, new modalities of therapy are necessary. One of the recent studies underlined that contemporary treatment regimens and follow-up methods focus on more than just ensuring survival; they also aim to enhance the quality of survival (van Kalsbeek et al., 2023). Targeted therapy has the potential to be a neoadjuvant therapy for odontogenic tumors. Preclinical studies have demonstrated promising results, suggesting a novel, potentially nonsurgical, adjuvant therapeutic approach for some OTs, mostly ameloblastomas (Kim et al., 2019; Li, Kim, et al., 2022; Pereira et al., 2020; Xiong et al., 2022). Some case reports utilizing targeted therapy on OTs have been published in the literature, showing a reduction of the morbidities associated with major surgery.

In this regard, the aim of this study was to summarize the current evidence on the different forms of targeted therapy, effectiveness, and drawbacks of this course of treatment.

2 MATERIALS AND METHODS

2.1 Eligibility criteria

The eligibility criteria were based on the PICOS acronym, as follows: P (population), individuals diagnosed with odontogenic tumor; I (intervention), targeted therapy; C (comparison), cases treated with other therapy or no compassion; O (outcome), response to the targeted therapy; S (study type), case reports, case series or observational studies.

In this sense, inclusion criteria were studies reporting cases of OTs treated with targeted therapy. Letters with enough data on clinical features were also included. No restriction on publication region, data, or language was applied.

Review articles, conference abstracts, and in vitro and animal studies were excluded.

2.2 Databases and search strategy

Electronic searches without restrictions on publication date or geographic region were undertaken in August 2023 in the following electronic databases: Embase (Elsevier), PubMed (National Library of Medicine), Web of Science (Clarivate Analytics), and Scopus (Elsevier). The grey literature was assessed by OpenGrey and Google Scholar, and the first 100 results of each database were analyzed. Additionally, manual search on the references of the included articles was performed.

The entire search strategy is described in File 1: Data S1. Keywords included the following medical subject headings (Mesh) and free terms were used.

2.3 Study selection

Reference management was performed using the EndNote X7.4 software (Clarivate Analytics, Toronto, Canada). Duplicates were removed upon identification. After duplicate removal, the titles and abstracts of all studies were reviewed by one author. If the title and abstract met with the eligibility criteria, the study would be included. Doubts were resolved by a second author.

2.4 Data extraction

The following items were extracted from the articles: (1) name of author(s) year of publication and country, (2) odontogenic tumor, (3) sex and age, (4) anatomical location, (5) mutation, (6) type of therapy, (7) response to the therapy, (8) adverse effects, and (9) follow-up.

2.5 Data analysis

The data were analyzed descriptively.

2.6 Appraisal of the methodological quality of the included studies

The Joanna Briggs Institute (University of Adelaide) tools for case reports or case series were applied (Moola et al., 2017). For each parameter, the included article could be awarded a "yes," "no," "unclear," or "not applicable" comment.

2.7 Study protocol and registration

The Preferred Reporting Items for Systematic Reviews and Meta-analysis 2020 (PRISMA) checklist was used to conduct this systematic review as a reporting template (Page et al., 2021). The International Prospective Register of Systematic Reviews in Health and Social Care (PROSPERO, National Institute for Health Research, UK) received the study registration information.

3 RESULTS

3.1 Study selection

A total of 492 articles were found through the computerized search. The inclusion and exclusion criteria were used, and 31 articles were obtained for full-text analysis. For the reasons listed in File 2: Data S1, 16 of these studies were eliminated. No article was added despite a search of the gray literature and the reference lists of the included studies. Finally, 15 articles reporting 17 cases of OTs treated by targeted therapy were included in this systematic review. In two publications (Abramson et al., 2022; Kaye et al., 2014), an identical patient case was presented. We opted to retain both studies because they offer historical continuity and detailed information regarding the patient. The study selection procedure is depicted in a flowchart in File 3: Data S1.

3.2 Study characteristics

Table 1 describes the characteristics of the studies included in this systematic review. The articles were published between 2014 and 2022 in six countries, with nine of them being from the United States. Ameloblastomas (primary, recurrent, and metastasizing) were reported in 15 of the 17 papers, along with two cases of ameloblastic carcinoma.

Of the reported data about ameloblastoma cases, eight individuals were male, whereas five were female. The mean age was 38 years, ranging from 10 to 85 years. Mandible was affected in 10 cases, followed by two cases in maxilla. Also, two cases of metastatic ameloblastoma in lungs were identified. One case did not inform the anatomical location.

Regarding ameloblastic carcinoma, one case was identified in the mandible of a 14-year-old male individual. The other case was in a 59-year-old individual, without information of sex and anatomical location.

TABLE 1. Identified ameloblastoma/ameloblastic carcinoma treated with targeted therapy.

Author (s), year (country)	**Odontogenic tumor (tumor stage)**	**Sex, age**	**Anatomical location**	**Mutations**	**Therapy**	**Response**	**Adverse events**	**Follow-up**
Primary ameloblastoma								
Weaver et al. (2020) (United States)	Primary AME	Male, 62 years	Maxilla	*Positive: FGFR2 Y375C, SMO L412F, PALB2 H786Y* *Negative: BRAF, PTEN, PIK3CA, and TP53*	Lenvatinib	Partial response Decreased tumor size. Partial response at 6 months (40% shrinkage)	NI	The patient has been receiving this treatment for 13 months and has a continued partial response
Damodaran et al. (2022) (United States)	AME	NI	Mandible	*Positive: PIK3CA, BRAF V600E, MED12*	Copanlisib (60 mg intravenous) once weekly in 28-day cycles until progression or toxicity	Partial response	NI	In treatment
Daws et al. (2021) (United States)	Primary AME	Female, 13 years	Mandible	*Positive: BRAF V600E*	Trametinib	Failed response	Mild adverse drug reaction	Lack of significant disease response
Hirschhorn et al. (2021) (Israel)	Unicystic AME	Male, 15 years	Mandible	*Positive: BRAF V600E, CTNNB1* *Negative: KRAS,*	Dabrafenib (4.5 mg/kg/day) divided twice a day 150 + 75 mg, for 20 months	Partial response	Fever, abnormal hair texture, curly hair	No evidence of the disease in 38 months

				MAP2K1, NRAS, TP53				
	Unicystic AME	Male, 13 years	Mandible	*Positive: BRAF V600E* *Negative: CTNNB1, KRAS, MAP2K1, NRAS, TP53*	Dabrafenib (4.5 mg/kg/day) 100 mg bid, for 16 months	Partial response	Fever, acneiform, rash	No evidence of the disease in 31 months
	Unicystic AME	Male, 10 years	Mandible	*Positive: BRAF V600E* *Negative: CTNNB1, KRAS, MAP2K1, NRAS, TP53*	Dabrafenib (4.5 mg/kg/day) 100 mg twice a day, for 15 months	Partial response	Erythema, nodosum, folliculitis	No evidence of the disease in 26 months
Recurrent ameloblastoma								
Kaye et al. (2014) (United States)[a]	Recurrent AME (lung metastasis)	Male, 40 years	Mandible and lung	*Positive: BRAF V600E* *Negative: KRAS, NRAS, EGFR, ERBB2, PIK3CA*	Dabrafenib (150 mg twice daily) + trametinib (2 mg once daily)	Partial response Decreased tumor size and metastasis	No	At 20 weeks, chest, and maxillofacial CT scans showed a persistent tumor response at all sites of prior disease
Tan et al. (2016) (United States)	Recurrent AME (locally advanced)	Male, 85 years	Mandible	*Positive: BRAF V600E*	Dabrafenib (150 mg orally every 12 h)	Partial response Decreased tumor size	Low energy, plaque-like skin lesions on his face, back, and scalp; the voice was becoming thickened	After a total of 16 weeks from the beginning of therapy, the tumor had a dramatic response with

								>90% tumor volume reduction
Faden and Algazi (2016) (United States)	Recurrent AME (locally advanced)	Female, 83 years	Mandible	*Positive: BRAF V600E*	Dabrafenib (75 mg twice daily and reduced by 50%)	Partial response Decreased tumor size. In 8 months, 75% shrinkage	NI	At 12 months, the tumor has continued to visibly reduce in size, demonstrating durable response to single-agent inhibition
Fernandes et al. (2018) (Brazil)	Recurrent AME (locally advanced)	Female, 29 years	Mandible	*Positive: BRAF V600E*	Vemurafenib (960 mg PO twice daily)	Partial response Decreased tumor size	Grade 1 anorexia, nausea, and fatigue, without any severe therapy-related adverse events	The patient currently remains asymptomatic with excellent tolerance to the medication
Metastatic ameloblastoma								
Broudic-Guibert et al. (2019) (France)	Metastatic AME	Female, 33 years	Lung	*Positive: BRAF V600E* *Negative: KRAS, EGFR, ALK, c-Kit*	Vemurafenib (960 mg twice daily for 12 months, changing to 720 mg twice daily and finally, to 480 mg twice daily)	Partial response Decreased size in 3.5 months (30% shrinkage)	First 12 months: grade 1–2 arthralgia, nausea, and rash	The response was persistent and was still present at the patient's last evaluation after 26 months of follow-up
Brunet et al. (2019) (France)	Metastatic AME	Female, 26 years	Lung	*Positive: BRAF V600E*	Dabrafenib (150 mg twice a day) + trametinib (2 mg once a day)	Complete response	NI	The patient is still doing well and in complete remission 30 weeks after treatment initiation
Cleary et al. (2021) (United States)	Metastatic AME[b]	NI	NI	*Positive: NRAS*	Binimetinib	Partial response Durable partial response	Grade 2 myalgia	The patient had a durable 26-month partial response

Abramson et al. (2022)[a] (United States)	Recurrent AME with lung and neck nodal metastasis	Male, 47 years	Mandible, neck nodal and lung	*Positive: BRAF V600E*	Restarted standard dose of dabrafenib (150 mg twice a day) and trametinib (2 mg once daily)	Partial response Resolution of jaw and face pain within 2 weeks and decreased tumor size	Without toxicity nor evidence for drug-resistant tumor progression	The patient has more than 8 years since initially presenting with metastatic AME to mediastinal nodes and bilateral lungs without progression of drug-resistant clonal expansion
Lawson-Michod et al. (2022) (United States)	Recurrent AME	Male, 40 years	Pterygopalatine fossa, skull base, and maxilla	*Positive: FGFR2 and SMO*	Erdafitinib (8 mg daily)	Partial response Decreased tumor size	Hyperphosphatemia and dry eyes, which resolved with routine use of calcium carbonate and ocular lubricants	The disease remained in radiologic partial response without treatment for 14 months, when the patient developed multicentric progression associated with recurrent pain, trismus, and proptosis. Erdafitinib was restarted at 8 mg daily; the clinical response was again observed after 4 weeks with improvement in pain, and repeat CT demonstrated near-complete response at 12 weeks
Ameloblastic carcinoma								
Li, Kim, et al. (2022); Li, Li, et al. (2022) (China)	Ameloblastic carcinoma	Male, 14 years	Mandible and lung	*Positive: GTF2IRD1-ALK, ALK, ARID1B, SMRACB1, RUNX1*	Alectinib (450 mg twice a day)	Complete response	No	The patient continues to receive alectinib without any side effects and the mandibular lesion did not recur after 18 months

Mathew et al. (2022) (India)	Ameloblastic carcinoma	NI, 59 years	NI	*Positive: PIK3CA, HRAS, FGFR2*	Trametinib and lenvatinib	Response for 8 months	NI	Patient was in therapy at the time of the last follow-up

Abbreviations: AME, ameloblastoma; CT, computed tomography; NI, no information.

[a] It is the same case. The patient self-discontinued dabrafenib/trametinib in June 2018 and did not return for examination or surveillance imaging until January 2021 when he presented to the clinic with painful enlargement of his left jaw tumor.

[b] The authors used the term “Malignant AME.”

The therapy response was assessed, where instances reporting a “decrease in tumor size” were classified as a partial response. Thirteen cases demonstrated a partial response, two cases exhibited a complete response, and one case showed therapy failure. Additionally, one case is currently under treatment, and there is insufficient information available to determine the response as partial or complete. Figure 1 schematizes the different target therapies used to date in OTs. Specific drugs and their action in each signaling pathway can be observed.

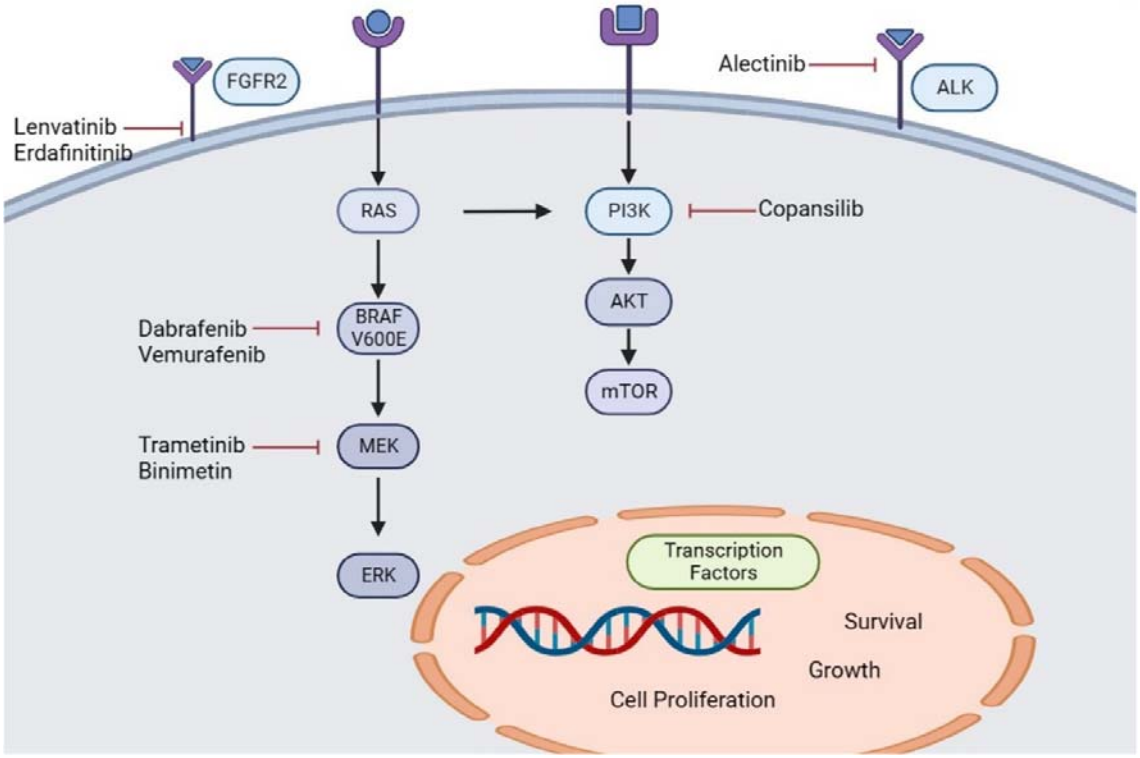

FIGURE 1. The different target therapies used to date in odontogenic tumors (OTs).

3.3 Mutation and targeted therapy in ameloblastoma cases

3.3.1 BRAF V600E *inhibitor*

Eleven cases reported a *BRAF V600E* mutation (Abramson et al., 2022; Broudic-Guibert et al., 2019; Brunet et al., 2019; Daws et al., 2021; Faden & Algazi, 2016; Fernandes et al., 2018; Hirschhorn et al., 2021; Kaye et al., 2014; Tan et al., 2016). From these cases, dabrafenib was the most commonly used drug (five cases), followed by the combination of dabrafenib and tramatinib (three cases), vemurafenib (two cases), and trametinib (one case). In relation to the treatment response, nine cases had partial response, one case presented complete remission, and one case had a failed response.

3.3.2 FGFR2 *inhibitor*

Two cases of ameloblastoma with the *FGFR2* mutation were identified. One of them was treated with lenvatinib (Weaver et al., 2020) and showed a partial response. The other case

was treated with erdafitinib (Lawson-Michod et al., 2022) and the patient obtained a sustained response.

3.3.3 PIK3 *inhibitor*

One case of ameloblastoma with a *PIK3CA mutation was identified* (Damodaran et al., 2022). Notably, mutations involving *BRAF V600E* and *MED12* were also observed in this case. The patient was treated with copanlisib and achieved a partial response.

3.3.4 NRAS *inhibitor*

NRAS mutation was observed in one patient (Cleary et al., 2021). Treatment with binimetinib was performed and a durable partial response was obtained.

3.4 Mutation and targeted therapy in ameloblastic carcinoma cases

One patient was identified with *GTF2IRD1-ALK* mutation, and received alectinib, showing a complete resolution of the mandibular lesion (Li, Kim, et al., 2022; Li, Li, et al., 2022). The other patient had three mutations detected—*PIK3CA*, *HRAS*, and *FGFR2* (Mathew et al., 2022). In this case, treatment with trametinib and lenvatinib was performed, and the patient presented response in 8 months of therapy.

3.5 Adverse events

Eleven cases reported adverse events. In three cases, there were no observed adverse effects of therapy. The other cases listed mild events in skin (i.e., plaque-like skin lesions, rash cutaneous, acneiform, erythema nodosum, and folliculitis), voice thickened, abnormal hair texture, and dry eyes. Some systemic events included anorexia, fatigue, arthralgia, nausea, fever, and hyperphosphatemia.

3.6 Quality assessment

Overall, the articles provided sufficient and clear data. File 4: Data S1 describes the quality assessment analysis.

4 DISCUSSION

The present systematic review summarized the evidence regarding the treatment of OTs with targeted therapy. In general, the key benefit of targeted therapy is the potential to reduce surgical resection morbidity, recurrence rates, and the likelihood of metastasis development (Wilkes, 2018). In our findings, complete remission was only observed in one case (Li, Kim, et al., 2022; Li, Li, et al., 2022). Nevertheless, in some clinical situations involving OTs, a partial response could be helpful. These might include tumors with an advanced local stage where a neoadjuvant reduction could reduce the extent of surgery, and local recurrence situations when there are few surgical choices. Except in one included case (Daws et al., 2021), the targeted therapy promoted a persistent reduction of tumor size during the follow-up. In this sense, it appears that targeted therapy might delay recurrence rather than guarantee elimination. Nonetheless, longer-term studies are crucial to substantiate this observation.

The literature has established the importance of identifying the genetic profile of OTs, not only for elucidating the etiology of a particular lesion but also for investigating the actions of specific drugs in relation to its pathways (Diniz et al., 2015; Gomes et al., 2023). Diverse types of mutations were observed in the present systematic review. Since ameloblastoma was diagnosed in 15 cases, it was reasonable to assume that the *BRAF V600E* mutation would be the most common. A recent systematic review showed that this mutation is found in about 70% of cases of ameloblastoma (Mamat Yusof et al., 2022). Moreover, employing more specialized techniques, such as Sequeom MassARRAY System, holds promise in refining the identification of the BRAF mutation. In a recent study by Togni et al. (2022), this method exhibited remarkable diagnostic accuracy, boasting 100% sensitivity and 98.1% specificity. These findings underscore the potential involvement of the MAP-kinase pathway in ameloblastic tumorigenesis. Consequently, the authors advocate for the integration of molecular evaluation of mutational status in odontogenic lesions as part of routine histopathological diagnostic protocols. Considering this, research into targeted therapies that operate in this way became necessary.

Of the medications included in this systematic review, dabrafenib was most frequently used, either alone or in combination with trametinib. The dabrafenib is a reversible inhibitor of *RAF* kinases (Kainthla et al., 2014). Despite being a drug that has been approved for use in treating several tumors, including melanoma and breast cancer, its use for ameloblastoma is still not suggested, leading to the lack of reports in the literature (Ebeling et al., 2023). According to our results, dabrafenib demonstrated positive outcomes. Also, when combined with trametinib, there was complete response in one of the cases. In fact, studies have shown that using dabrafenib in combination with trametinib, a MEK inhibitor, increased overall effectiveness (Degirmenci et al., 2021; Grob et al., 2015). In the Food and Drugs Administration (FDA) guide (June 2022), for dabrafenib and trametinib one patient with mandibular ameloblastoma was included (https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/202806s022lbl.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/204114s024lbl.pdf). When used alone, trametinib demonstrated a failed response in a case included in our review.

Regarding the efficacy of targeted therapy, another point to consider is the heterogeneity concerning ages in the present systematic review. Five cases included in our study reported pediatric individuals (i.e., up to 20 years old): four with primary ameloblastoma and one with ameloblastic carcinoma. The only case where therapy failed was in a 13-year-old girl diagnosed with primary ameloblastoma in the mandible. The literature appoints some differences between pediatrics and adults regarding targeted therapies. These variances often stem from several factors such as drug response, side effects, and tumor biology (Laetsch et al., 2021; Smith & Reaman, 2015). When using targeted therapies in pediatric cases, it is vital to adjust dosages for children's varying sizes and metabolisms. Monitoring and managing side effects specific to growth and development is crucial. Understanding differences in tumor biology, conducting pediatric-focused trials, and assessing long-term effects are essential. A multidisciplinary approach ensures tailored treatments, considering individual needs and ethical and legal standards in pediatric care. These differences highlight the need for specialized considerations when employing targeted therapy in pediatric patients.

A few limitations in the current systematic review should be acknowledged. Firstly, the studies were based on reported cases, which frequently lack comprehensive information. Additionally, a persistent lack of supervision is an issue. The follow-up of the studies in question ranged from three to 38 months. We emphasize the need for clinical trials with a larger sample size and effective follow-up period to accurately demonstrate the effectiveness of target therapy. Moreover, it is pertinent to emphasize the reported of limited occurrence of adverse events, underpinning the safety profile of the administered medications. Nonetheless, not all patients adhered to the prescribed therapeutic regimen. In several instances, discontinuation resulted from patient, rather than physician, decisions prompted by diverse reasons. Prolonged drug therapy may encompass a dimension of reduced quality of life that may not be fully accounted for in our evaluation of adverse events. In summary, while our findings offer valuable insights into the potential utility of targeted therapy in OTs, caution must be exercised in generalizing our results, mainly regarding: (1) the small sample size; (2) the descriptive nature of our data analysis necessitates cautious interpretation of the treatment outcomes. Although most cases showed reduced lesion size after targeted therapy, the lack of comparative control groups and standardized outcome measures prevents definitive conclusions about treatment efficacy; (3) the predominance of mild adverse events in our study population warrants consideration of potential biases in adverse event reporting and the need for comprehensive monitoring of treatment-related toxicities in future studies; (4) the heterogeneity in mutational profiles and treatment regimens observed in our sample underscores the complexity of OTs and the need for personalized therapeutic approaches.

5 CONCLUSION

Our results showed that using targeted therapy results in a reduction in tumor growth, and mild adverse events were observed. This partial response could be beneficial in specific clinical scenarios of ameloblastoma, involving advanced local stage tumors where a neoadjuvant reduction could impact the extent of surgery and cases of local recurrence when surgical options are limited, and some pediatric cases that may lead to certain serious developmental deformities. In this context, we should emphasize that, whenever feasible, the primary treatment for ameloblastoma should be surgery. Despite the absence of long-term studies on OTs, it is feasible to draw the conclusion that, in some clinical situations, such as when surgical options are initially restricted by the size of the tumors, targeted therapy for ameloblastoma and ameloblastic carcinoma may be promising to reduce the extent of surgery.

AUTHOR CONTRIBUTIONS

Ronell Bologna-Molina: Conceptualization; methodology; investigation; validation; formal analysis; supervision; project administration; funding acquisition; writing – original draft; writing – review and editing; resources; software. **Lauren Frenzel Schuch:** Methodology; validation; investigation; writing – original draft; data curation; formal analysis; supervision. **Magliocca Kelly:** Conceptualization; validation; data curation; supervision; writing – original draft; writing – review and editing; methodology. **Willie van Heerden:** Writing – review and editing; conceptualization; methodology; writing – original draft. **Liam Robinson:** Conceptualization; writing – original draft; writing – review and editing; methodology. **Elizabeth Ann Bilodeau:** Conceptualization; methodology; writing – review and editing;

writing – original draft. **Haizal Mohd Hussaini:** Conceptualization; methodology; writing – original draft; writing – review and editing. **Merva Soluk-Tekkesin:** Conceptualization; methodology; writing – original draft; writing – review and editing. **Akinyele Olumuyiwa Adisa:** Conceptualization; methodology; writing – original draft; writing – review and editing. **Wanninayake Mudiyanselage Tilakaratne:** Conceptualization; methodology; writing – original draft; writing – review and editing. **Jiang Li:** Conceptualization; methodology; writing – original draft; writing – review and editing. **Gomez Ricardo Santiago:** Conceptualization; methodology; writing – original draft; writing – review and editing; supervision; validation. **Keith David Hunter:** Conceptualization; methodology; supervision; validation; writing – original draft; writing – review and editing.

DATA AVAILABILITY STATEMENT

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

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