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REVIEW

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mTOR inhibitor use in head and neck squamous cell carcinoma: A meta-analysis on survival, tumor response, and toxicity

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Abstract

Background: Head and neck squamous cell carcinoma (HNSCC) has been rising in incidence primarily related to HPV-associated oropharyngeal cancers. Novel molecular therapeutics are evolving with the mTOR pathway as a new target. Previous studies have shown variable outcomes with relatively low toxicity. This study reports the tumor response, survivability, and toxicity of mTOR inhibitors (mTORi) in HNSCC. Despite expanding research on this pathway, there remains controversy around mTORi use for treatment of HNSCC.

Materials and methods: Studies were included if: (a) Used mTORi alone or in combination with other treatment modalities in HNSCC. (b) Site of cancer included were one of the following: nasopharyngeal, oral cavity, oropharynx, hypopharynx or larynx. (c) All stages of cancer and treatment stage (neoadjuvant, adjuvant, and palliative) were included. The rate of adverse events (AEs), tumor response, progression free survival, and overall survival were meta-analyzed.

Results: From 1299 publications only 11 studies met inclusion criteria with a combined 232 total patients treated. Two studies used mTORi neoadjuvantly, five adjuvantly, and four in palliative/unresectable/metastatic setting. Monotherapeutic mTORi resulted in stabilization of disease (52.5%), but partial response was the most common response when mTORi were combined with chemotherapy and/or radiation (CRT) (48.1%). Survival rate was the highest in the mTORi combined with CRT. Hyperglycemia of any grade was the most commonly reported toxicity while grade 3 or less AEs were the most common grade of toxicity.

Conclusion: The use of mTORi as monotherapy in HNSCC has thus far not yielded significant tumor response, however, in combination with other agents, an improved partial tumor response is evident that may or may not be associated with the addition

of mTORi. Although adverse events were common, grade 4/5 AEs were uncommon. Further prospective, randomized clinical trials are necessary to confirm the direct roles of these agents in HNSCC tumor response.

Level of evidence: 2a

KEYWORDS

head and neck cancer, head and neck squamous cell carcinoma, mTOR inhibitors, oral cancer, oropharyngeal cancer, outcomes

1 | INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) comprises of cancers in the nasal cavity, nasopharynx, oral cavity, oropharynx, hypopharynx, and larynx. Annually, approximately 600,000 new cases are reported worldwide, frequently found as locally advanced disease.[1,2] Epidemiologic study of cancers reports an increase in the incidence rate of oral cancer.[3] Moreover, oropharyngeal squamous cell carcinoma (OPSCC) is also on the rise with an association of the high risk strains of human papilloma virus (HPV) infection.[4] Due to the late diagnosis of these cancers, the morbidity is known to be tremendous with impact on cosmesis, eating, drinking, speech, swallowing, breathing, and physical and mental treatment related consequences.[5] Thus, treatments have evolved over the past few decades with surgery and radiation therapy as the mainstay of management to a multimodal approach including chemotherapy, targeted therapies, and immunotherapy.[6-8] One promising target is the mammalian target of rapamycin (mTOR), which is a seronine/threonine kinase involved in the activation of the oncogenic PI3K/AKT pathway. The hyperactivity and deregulation of the mTOR pathway has been found to be one of the most common molecular aberrations in HNSCC making it an optimal target for intervention.[9,10]

The origins of the mTOR protein can be derived from its name, "mammalian Target Of Rapamycin." Rapamycin is an antibiotic discovered almost half a century ago, but became popular in 1999, following FDA approval for kidney transplant recipients.[11] The neoplastic potential of the PI3K/AKT/mTOR signaling pathway came into question as a variety of growth factors including: insulin-like growth factor (IGF1), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF), facilitate the activation of their downstream targets through this pathway.[12] The pro-oncogenic nature of the PI3K/mTOR/AKT pathway became evident in various tumors, including HNSCC.[13,14] The use of rapamycin and rapalogs in cancer treatment began with a focus on identifying biomarkers to predict efficacy of treatment and prognosis of the patient.[15,16] Clinical trials with rapalogs have been investigated in the treatment of HNSCC.[11] There is evidence suggesting the prognostic association between alteration in this pathway for patients with HNSCC and the resultant poor survival rates.[16] However, no study to date has compared the use of the various agents and efficacy of mTOR inhibition in HNSCC with a focus on survival, the resultant response of the tumor and subsequent toxicity profile to the patient. Therefore, this meta-analysis will summarize the evidence regarding the use of mTOR inhibitors (mTORi) in HNSCC, and the ensuing survival rate, tumor response, and toxicity profile to the patient.

2 | METHODS

2.1 | Study design

2.1.1 | Inclusion criteria

This meta-analysis followed the Preferred Reporting Items for Systemics Reviews and Meta-Analysis (PRISMA) Checklist.[17] A meta-analysis was conducted on clinical trials using mTORi in HNSCC to quantify the rate of adverse events (AEs), tumor response, progression free survival (PFS), and overall survival (OS). Studies were included which met the following inclusion criteria: (a) Used mTORi alone or in combination with other treatment modalities in HNSCC. (b) Site of cancer must have included one of the following: nasopharyngeal, oral cavity, oropharynx, hypopharynx or larynx. (c) All stages of cancer and treatment stage (neoadjuvant, adjuvant, and palliative) were included.

2.1.2 | Exclusion criteria

Studies not in English were excluded, along with the following reasons: (a) upstream inhibition of the mTOR pathway without explicitly targeting the mTOR protein; (b) study included patients with cancer sites other than HNSCC and data was not extractable; (c) experimental analysis were conducted in vitro or in vivo models; (d) study did not report survival data, tumor response evaluation through the "Reporting the Response Evaluation Criteria in Solid Tumors" (RECIST) score or toxicity profile of the patient through the "Common Terminology Criteria for Adverse Events" (CTCAE); (e) published material were review articles, letters, personal opinions, book chapters, case reports or conference abstracts.

2.2 | Information sources and search terms

Search was conducted on May 6, 2019. The following data sources were investigated: PubMed, ScienceDirect, and Scopus. The search

terms included: mTOR inhibitor, mTOR/PI3K inhibitor, mTORC1 inhibitor, mTORC2 inhibitor, HNSCC subsites, and human. All references associated with this study were managed by Endnote reference manager (Thomas Reuters, Virginia).

2.3 | Study selection

After the search query, the articles were screened by two authors (J.P., S.N.); each independently reviewed the title and abstracts and removed articles that did not meet the inclusion criteria. Next, the authors read the sum of the remaining articles and excluded any articles based on the criteria previously outlined. Any discrepancy was resolved by the third author if needed.

2.4 | Data collection process and data items

The following information was extracted from the selected studies: authors, publication date, country, tumor site, HPV status, number of patients, median age (years), median follow up (months), stage of cancer, treatment modality, stage of treatment, median overall survival (mOS), median progression free survival (mPFS), RECIST data, and AEs. Articles were critically appraised to assess level of evidence using the Oxford Center for Evidence-Based Medicine criteria.[18] In addition, potential publication bias was assessed with a funnel plot via the Sterne and Egger method.[19]

2.5 | Biostatistics

A meta-analysis of proportions was performed using MedCalc 18.10.2 (MedCalc Software bvba, Belgium). Primary outcomes, including rates of RECIST complete response (CR), partial responses (PR), stable disease (SD), progressive disease (PD), AEs grades, mOS, and mPFS were evaluated for each respective group (mTOR only, mTOR with combination chemotherapy and/or radiation and/or upstream inhibitor). Each technique was weighted according to the number of patients treated. The program MedCalc lists the proportions (expressed as a percentage),

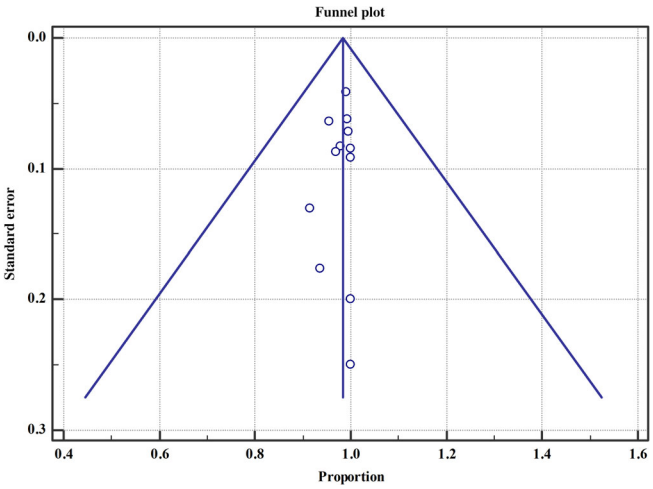

FIGURE 2 Funnel plot of included studies

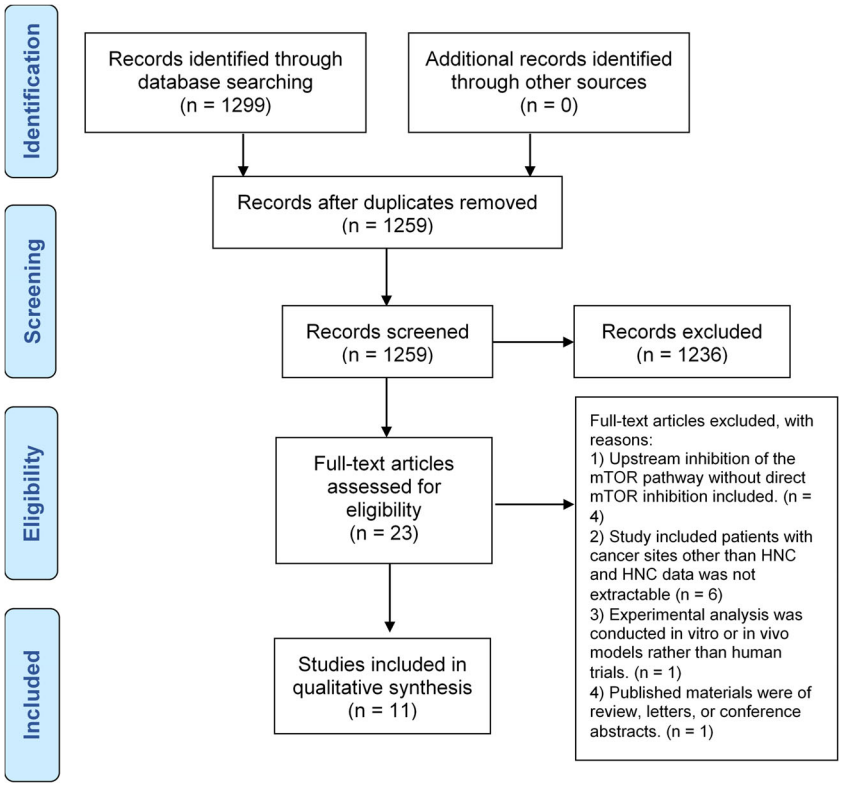

FIGURE 1 Flow diagram of literature search adapted from PRISMA flow diagram[17]

TABLE 1 Summary of descriptive characteristics of studies included

Author	Year	Country	Oxford LOE	Clinical trial phase	*N*	Tumor site (n)	HPV+ (n)	Median age (Y)	Median follow up (M)	Stage	Treatment modality
Ekshyyan et al	2010	USA	2b	0	16	OC (1) OP (15)	-	NR	NR	I-IV	Temsirolimus
Fury et al	2012	USA	2b	I	18	OC (2) HP (1) OP (8) PS (1) L (6)	-	56 (33-78)	NR	IV	Paclitaxel, Carboplatin, Temsirolimus
Bauman et al	2013	USA	2b	II	12	OC (4) UP (1) OP (6) PS (1)	6	61.5 (45-87)	16	IV	Erlotinib, Temsirolimus
Fury M, Lee N et al	2013	USA	2b	I	13	OC (4) SG (4) OP (2) NP (1) Sc (1) UP (1)	2	52 (37-65)	19.4	I-IVb	RT, Cisplatin, Everolimus
Fury et al	2013	USA	2b	I	18	OC (1) OP (14) NC (1) NP (1) HP (1)	7	56 (44-70)	17.8	III - IVb	Docetaxel, Cisplatin, Everolimus
Saba et al	2014	USA	2b	I	20	OC (6) HP (1) OP (6) NP (2) L (3) UP (1) Sk (1)	-	65 (44-75)	23	I-IV	Cetuximab, Carboplatin, Everolimus
Grunwald et al	2015	Germany	2b	II	40	OC (10) OP (15) L (5) HP (5) O (5)	4	61.5 (42-79)	12	NR	Temsirolimus
Massarelli et al	2015	USA	2b	II	36	OP (19) O (17)	9	NR	NR	IV	Erlotinib, Everolimus
Geiger et al	2016	USA	2b	II	9	OC (1) HP (2) OP (2) SG (2) L (2)	3	63 (30-85)	7	IV	Everolimus
Dunn et al	2017	USA	2b	II	36	OC (10) OP (11) HP (1) L (11) UP (2)	7	57 (30-85)	5.3	NR	Paclitaxal, Carboplatin, Temsirolimus
Day et al	2019	USA	2b	I/II	16	OC (8) OP (8)	8	60 (11.5)[a]	12	II-IVa	Rapamycin
Total/Average					232		46	59	14.1		

Abbreviations: HP, hypopharyngeal; L, laryngeal; LOE, level of evidence; NC, nasal cavity; NP, nasopharyngeal; NR, not reported; O, other; OC, oral cavity; OP, oropharynx; PS, paranasal sinus; RT, radiation therapy; Sc, scalp; SG, salivary gland; Sk, skin; U, unknown primary with neck nodes involvement; UP, unknown primary.

[a]Mean age was reported with SD.

with their 95% CIs, found in the individual studies included in the meta-analysis. The pooled proportion with 95% CI is given both for the fixed effects model and the random effects model. Each technique was weighted according to the number of patients treated. MedCalc used a Freeman-Tukey transformation to calculate the weighted summary proportion under the fixed and random effects model.[20,21] Both the fixed effects model and the random effects model were used in this study. If there is high heterogeneity (I^2 > 50%), then a random effects model is used; if low heterogeneity, then a fixed effects model is allowable. Using random effect modeling is more conservative, thus, it is preferable to assume random effects modeling unless I^2 is small. Potential publication bias was assessed with a funnel plot. Two diagonal lines represent (pseudo) 95% confidence intervals (effect size ± 1.96 SE) around the summary effect for each SE on the vertical axis. These show the expected distribution of studies in the absence of heterogeneity or selection bias. In the absence of heterogeneity, 95% of the studies should lie within the funnel defined by these diagonal lines. A *P* value of <.05 was considered to indicate a statistically significant difference for all statistical tests.

3 | RESULTS

3.1 | Study selection

Initially, 1299 citations were identified with 1259 remaining after duplicates were removed. Comprehensive evaluation of the titles and abstracts removed 1236 citations, leaving 23 remaining articles. A full-text review excluded 12 articles. The remaining 11 were selected for analysis.[22-32] The PRISMA diagram is shown in Figure 1. According to funnel plot (Figure 2) and the Egger's test, there was no indication of publication bias among the set of studies included in this meta-analysis.

3.2 | Study characteristics

Of the included studies, all were prospective in nature, but none were randomized or controlled; there is one phase zero study, four phase I, five phase II, and one phase I/II study. A total of 232 patients were assessed with the largest study comprising 40 patients and the smallest,

TABLE 2 Summary of study methods

Author	Prior tx (n)	Tx stage	P/R/M	Treatment Modality	Route	Dosage (mg)	Interval	MTD (mg)
Ekshyyan et al	None (12)	Neoadjuvant (NPT)	P	Temsirolimus	IV	25	3 times a week	-
Fury et al (2012)	CT (14) RT (12)	Adjuvant	R/M	Paclitaxel Carboplatin Temsirolimus	IV IV IV	80 1.5[b] 15, 20, 25	Weekly Weekly Weekly	 25
Bauman et al	CT (5) TKI (2) None (5)	Palliative (TF)	R/M	Erlotinib Temsirolimus	PO IV	150 15	Daily Weekly	-
Fury M, Lee N et al (2013)	Surgery (10) CT (2)	Adjuvant	P/R	RT Cisplatin Everolimus	- IV PO	- 30 2.5,5, 7,10[a]	- Weekly Daily	 5
Fury et al (2013)	None (18)	Adjuvant	P	Docetaxel Cisplatin Everolimus Pegfilgrastim	IV IV PO SQ	75 75 5, 7.5, 10[a] 6	Every 21 days Every 21 days Weekly Day 2/21 cycle	 7.5
Saba et al	CT (14) Surgery (10) RT (17) None (2)	Adjuvant	R/M	Cetuximab Carboplatin Everolimus	IV IV PO	400 LD, 250 2[b] 2.5, 4, 7.5, 10[a]	Weekly Weekly Daily	 2.5[c]
Grunwald et al	CT (40)	Palliative (TF)	R/M	Temsirolimus	IV	25	Weekly	-
Massarelli et al	CT (36)	Palliative (TF)	R/M	Erlotinib Everolimus	PO PO	150 5	Daily Daily	- -
Geiger et al	CT (9)	Palliative (TF)	R/M	Everolimus	PO	10	Daily	-
Dunn et al	None (24) CT (12)	Adjuvant	R/M	Paclitaxal Carboplatin Temsirolimus	IV IV IV	80 1.5[b] 25	Day 1,8, 21 Day 1,8,21 Day 1,8,21	-
Day et al	None (16)	Neoadjuvant (NPT)	P	Rapamycin	PO	15 LD, 5	Daily	-

Abbreviations: CT, chemotherapy; IV, intravenous; LD, loading dose on day 1; MTD, maximum tolerated dose of mTOR inhibitor; NPT, no prior treatment; P/R/M, primary/recurrent/metastatic; RT, radiation therapy; SQ, subcutaneous; TF, treatment failure; Tx, treatment; TKI, tyrosine kinase inhibitor PO, oral; "-"not applicable or available data.

[a]Dosing groups.

[b]Dosing based on area under the curve in mg/ml/min.

[c]MTD 2.5 mg every other day.

7 patients. The mean of the median age of patients is 59 years (30-87). All but one was conducted in the United States, the remainder was based in Germany.[26] The most common cancer subsites were oropharyngeal (45.7%), oral cavity (20.3%), and laryngeal (11.6%). Of patients tested for HPV status (47.0%), a total of 46 (42.2%) were deemed HPV+. Two studies used mTORi neoadjuvantly in primary HNSCC prior to standard of care;[30,32] five used mTORi in the adjuvant setting with chemotherapy and/or radiation therapy (CRT). Of these five, three treated patients for recurrent and/or metastatic HNSCC (RMHNSCC),[25,29,31] one for primary HNSCC,[24] and one for both primary and recurrent HNSCC.[23] Lastly, four used mTORi in a palliative setting for RMHNSCC.[22,26-28] Two of the four studies used a upstream inhibitor of the mTOR pathway in combination with a direct mTORi.[22,27] Notably, there was heterogeneity in the previous treatments received by the patients with RMHNSCC. All of these patients failed platinum based chemotherapy prior to receiving mTORi. Summary of the demographics and methods is reported in Tables 1 and 2. In addition, the mOS, mPFS, RECIST scores, and CTCAE grades, are summarized in Table 3.

3.3 | Synthesis of results

3.3.1 | mTORi as monotherapy

The phase zero study neoadjuvantly treated primary oral cavity or oropharynx cancer with temsirolimus.[32] They recruited 16 patients to their

TABLE 3 Summary of RECIST, CTCAE, mPFS, and mOS

Author	RECIST	All adverse events (CTCAE)	mOS mPFS (months) (95% CI)	Author	RECIST	All adverse events (CTCAE)	mOS mPFS (months) (95% CI)
Bauman et al	CR-0 PR-1 SD-0 PD-4	G1-23 G2-17 G3-13 G4-4 G5-1 ≤G3-51	mOS: 4 (NR) mPS: NR	Massarelli et al	CR-0 PR-1 SD-11 PD-24	G1-110 G2-59 G3-24 G4-1 G5-NR ≤G3-193	mOS: 10.25 (NR) mPFS: 2.98 (NR)
Fury M, Lee N et al	NR	G1-NR G2-NR G3-NR G4-0 G5-NR ≥G3-44[a]	mOS: 92% @ 2 years (54-99) mPFS: 85% @ 2 years (51-96)	Geiger et al	CR-0 PR-0 SD-2 PD-5	G1-67 G2-55 G3-16 G4-NR G5-NR ≤G3-138	mOS: 18 (NR) mPFS: 6 (NR)
Fury et al (2013)	NR	G1-NR G2-NR G3-30 G4-11 G5-NR ≤G3-235	mOS: 91% @ 2 years (50.8-98.7) mPFS: 87.5% @ 2 years (56.8-96.7)	Dunn et al	CR-0 PR-15 SD-19 PD-0	G1-NR G2-NR G3-92 G4-4 G5-1[b] ≤G3-575	mOS: 12.8 (9.8-15.8) mPFS: 5.9 (4.8-7.1)
Fury et al (2012)	CR-0 PR-4 SD-2 PD-NR	G1-NR G2-NR G3-26 G4-3 G5-NR ≤G3-141	mOS: 15.7 (6.6-18.5) mPFS: NR	Ekshyyan et al	NR	G1-12 G2-3 G3-0 G4-0 G5-0 ≤G3-15	NR
Saba et al	CR-0 PR-9 SD-0 PD-3	G1-NR G2-NR G3-NR G4-NR G5-NR ≥G3-40[a]	mOS: NR mPFS: 8.15 (NR)	Day et al	CR-1 PR-3 SD-12 PD-0	G1-17 G2-6 G3-1 G4-0 G5-NR ≤G3-24	NR
Grunwald et al	CR-0 PR-0 SD-19 PD-10	G1-NR G2-NR G3-15 G4-4 G5-NR ≤G3-125	mOS: 5.06 (2.53-8.53) mPFS: 1.86 (1.2-3.77)				

Abbreviations: CI, confidence interval; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; G, grade (1–5); mOS, median overall survival; mPFS, median progression free survival; NR, not reported; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

[a]Author reports ≥grade 3 compared to ≤grade 3.

[b]Author reports one sudden death categorized as grade 5 but not proven to be related to mTOR inhibition.

study, of which 12 (75%) had AEs. These patients most commonly had a grade 1 or 2 rash. Additionally, 8 patients had a reduction in tumor size, however, it was not classified by the RECIST criteria. The phase II study from Germany recruited 40 RMHNSCC patients for palliative therapy with temsirolimus.[26] No objective response was achieved, however 19 (47.5%) patients maintained SD. Thirteen (32.5%) achieved some form of tumor shrinkage but did not meet criteria for PR. In addition, 10 (25%) patients had PD. Ten (25%) had an early death, and 1 patient (2.5%) was nonassessable. The mPFS was 1.86 months (95% CI 1.20-3.77) with a mOS of 5.06 months (95%CI 2.53-8.53). The most common toxicities were fatigue, anemia, nausea, and pneumonia. In another phase II trial, 9 patients with RMHNSCC were treated with monotherapy of everolimus.[28] Seven (78%) were evaluable for a response but no objective response was observed. Only two had SD and the remaining 5 had PD. The mPFS was 1.5 months and the mOS was 4.5 months. Only grade 3 or less AEs were observed. The combined phase I/II study utilized rapamycin monotherapy in treatment naive HNSCC.[30] Sixteen patients were recruited to the study, of which one (6%), had a CR, three (19%) had PD, and 12 (75%) had SD. The most common AEs were thrombocytopenia and neutropenia with majority being grade 1 or 2 with one exception of grade 3 hypokalemia.

Analysis of mTORi monotherapy resulted in grade 3 or less AEs in 98.8% (95% CI 96.8-99.7) of the patients. Grade 4 and 5 symptoms were minimally noted with a rate of 5.38% and 1.1% (95% CI 1.1-11.5, 0.0-4.5) respectively. The rate of SD was 52.5% (95% CI 39.8-64.9), PR rate was 5.5% (95% CI 0.1-22.9), and PD was 25.2% (95% CI 1.6-63.7). Of note, CR was observed in only 1 patient throughout the study, therefore it was excluded from analysis. The weighted mPFS and mOS rate of 1.8 months and 5 months, respectively.

3.3.2 | mTORi with combination CRT

Five studies used mTORi with CRT, of which four were phase I and one phase II. In 2012, a phase I study of temsirolimus in combination with paclitaxel, and carboplatin was undertaken with 18 RMHNSCC patients.[31] There were 4 (22%) PR and two (11%) SD. The mOS was 15.7 months (95% CI 6.6-18.5). The most common AEs included pancytopenia, hyperglycemia and fatigue with majority being grade 1 through 3. Additionally, this drug combination produced a maximum tolerated dose (MTD) of 25 mg of temsirolimus. In 2013, two phase I studies were performed. One investigated everolimus and cisplatin in

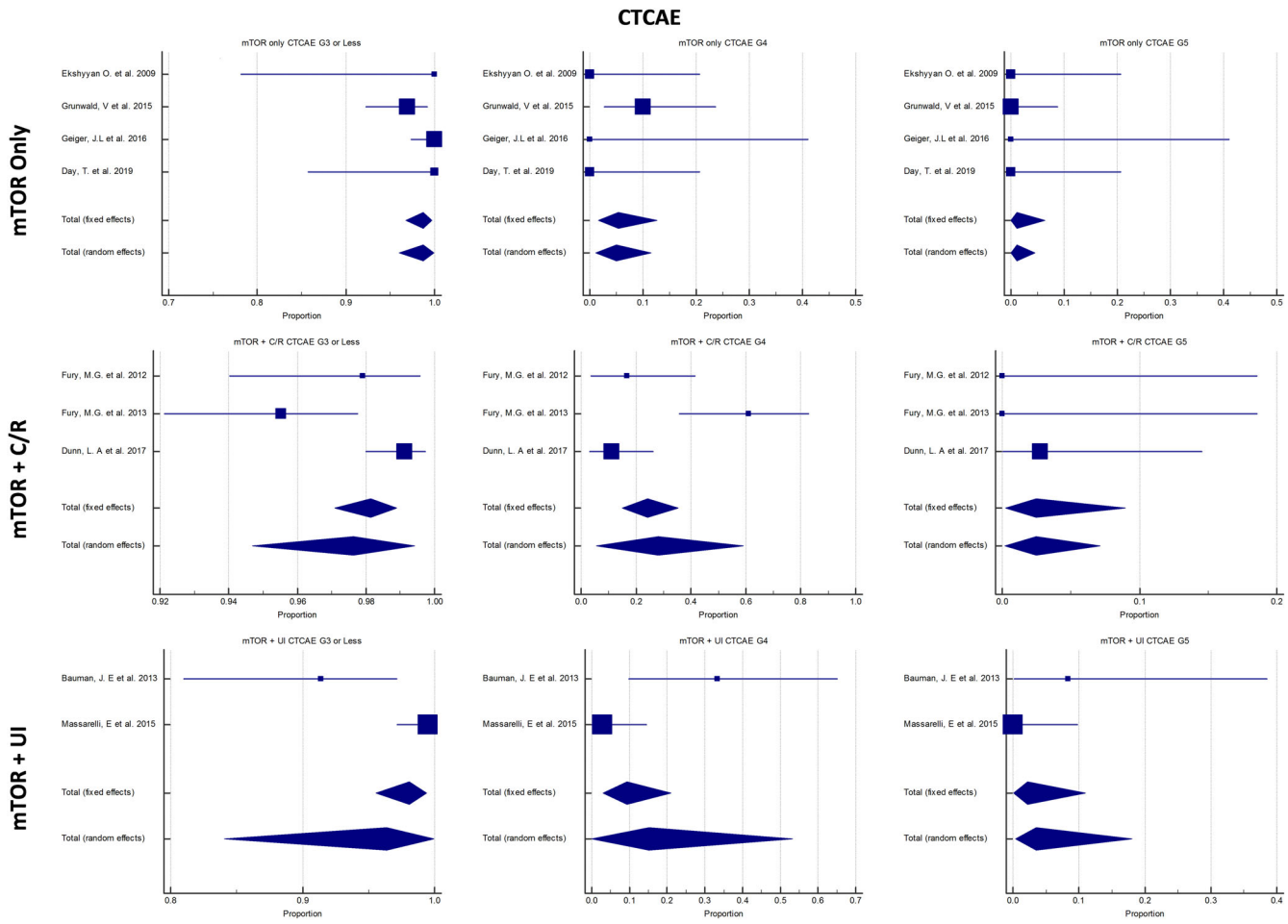

FIGURE 3 Individual treatment group analysis of CTCAE. C/R, chemotherapy/radiation group; UI, upstream inhibitor (EGFR)

combination with intensity modulated radiation therapy in both primary and recurrent disease.[23] Complete RECIST data was not reported explicitly in this study. The MTD of everolimus was reported to be 5 mg daily. The two-year PFS rate was 85% and the two-year OS rate was 92%. The most common grade 3 or greater AEs were lymphopenia, mucositis, oral pain, dysphagia, hyperglycemia, and leukopenia. The second study investigated everolimus in combination with pegfilgrastim and docetaxel plus cisplatin in patients with primary HNSCC.[24] Eighteen patients were recruited for the study. Tumor response was reported with percentage of shrinkage, but not reported through the RECIST criteria. The most common AEs were anemia, thrombocytopenia, hyperglycemia, and fatigue with two incidences of grade 3 or worse events. The rates of mOS and mPFS at 2 years were 91% and 87.5%, respectively. In 2014, a phase I study of cetuximab, carboplatin and everolimus was conducted in RMHNSCC.[25] Twenty patients were enrolled but only 13 were included in the final analysis. Nine of the 13 had a PR and three had PD. The mPFS was 8.15 months. The most common grade 3 or greater AEs reported were neutropenia, hyperglycemia, anaphylaxis, hypokalemia, and leukopenia. The MTD was found to be 2.5 mg of everolimus every other day in combination with the other drugs. The phase II study combined temsirolimus with carboplatin and paclitaxel in 36 patients with RMHNSCC.[29] Fifteen patients had a PR and 19 had SD. The mPFS was 5.9 months (95% CI 4.8-7.1) and the mOS was 12.8 months (95% CI 9.8-15.8). The toxicity profile was grade 3 or less, with the exception of one patient who experienced grade 4 toxicity.

Combining mTORi with CRT showed a different toxicity profile than that of mTORi alone. The rate of grade 4 AEs was 28% (95% CI 5.6 to 59.1). However, the rates of grade 3 or less and grade 5 AEs were similar at 97.6% (95% CI 94.7-99.4) and 2.5% (95% CI 0.3-9.0) respectively. The PR and PD rates were 48.1% (95% CI 34.0-62.4) and 7.7% (95% CI 1.7-40.8%). The rate of SD was 21.2% (95% CI 3.5-83.1). The weighted mPFS and mOS of patients on combination CRT was 6.5 months and 13.8 months respectively.

3.3.3 | mTORi with EGFRi

Upstream inhibition of the EGFR has also been investigated as a combination treatment with mTORi. Two phase II studies with erlotinib

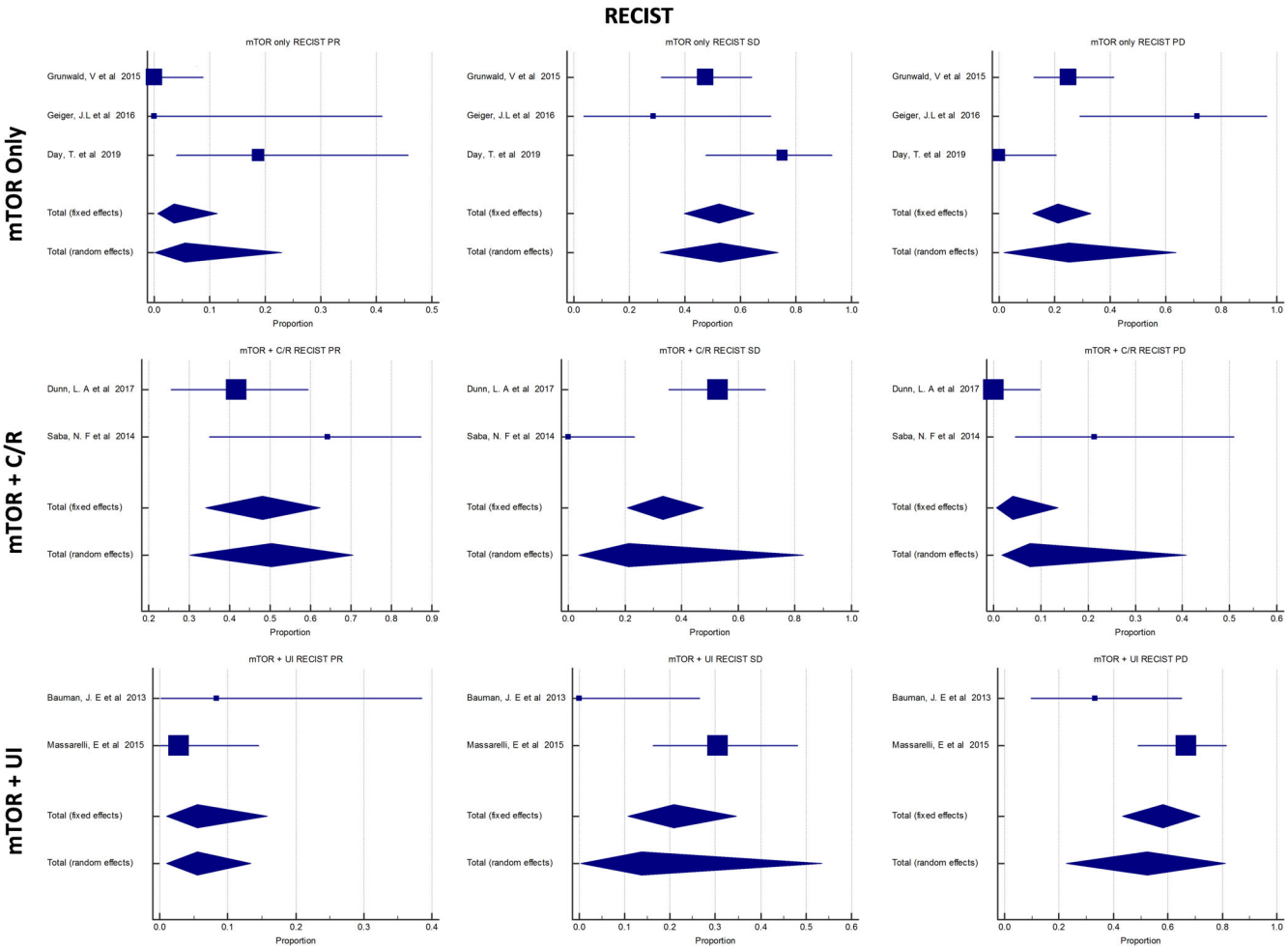

FIGURE 4 RECIST outcome of mTOR monotherapy or combination therapy. C/R, chemotherapy/radiation group; PD, progressive disease; PR, partial response; SD, stable disease; UI, upstream inhibitor (EGFR)

TABLE 4 Comparison of rates

	CTCAE G3 or less	CTCAE G4	CTCAE G5	RECIST PR	RECIST SD	RECIST PD
mTOR only	Total effect = 98.8% 95% CI = 96.8 to 99.7 *P* = .1311	Total effect = 5.38% 95% CI = 1.1 to 11.5 *P* = .3171	Total effect = 1.1% 95% CI = 0.0 to 4.5 *P* = .9523	Total effect = 5.5% 95% CI = 0.1 to 22.9 *P* = .0250	Total effect = 52.5% 95% CI = 39.8 to 64.9 *P* = .0726	Total effect = 25.2% 95% CI = 1.6 to 63.7 *P* = .0002
mTOR + C/R	Total effect = 97.6% 95% CI = 94.7 to 99.4 *P* = .0060	Total effect = 28.0% 95% CI = 5.6 to 59.1 *P* = .0006	Total effect = 2.5% 95% CI = 0.3 to 9.0 *P* = .7668	Total effect = 48.1% 95% CI = 34.0 to 62.4 *P* = .1567	Total effect = 21.2% 95% CI = 3.5 to 83.1 *P* < .0001	Total effect = 7.7% 95% CI = 1.7 to 40.8 *P* = .0060
mTOR + UI	Total effect = 96.4% 95% CI = 84.1 to 99.9 *P* = .0026	Total effect = 15.1% 95% CI = 0.0 to 53.3 *P* = .0078	Total effect = 2.2% 95% CI = 0.1 to 11.0 *P* = .1075	Total effect = 5.5% 95% CI = 1.0 to 15.9 *P* = .3779	Total effect = 13.7% 95% CI = 0.4 to 53.5 *P* = .0052	Total effect = 52.4% 95% CI = 22.6 to 81.2 *P* = .0457
mTOR vs mTOR C/R	% Difference = 1.2% 95% CI = −0.9 to 2.6 *P* = .2033	% Difference = 22.6% 95% CI = 10.9 to 34.3 *P* = .0002	% Difference = 1.4% 95% CI = −4.3 to 8.1 *P* = .5157	% Difference = 42.6% 95% CI = 26.8 to 56.5 *P* < .0001	% Difference = 31.3% 95% CI = 13.4 to 46.2 *P* = .0007	% Difference = 17.5% 95% CI = 3.4 to 30.3 *P* = .0154
mTOR vs mTOR UI	% Difference = 2.4% 95% CI = −0.2 to 5.6 *P* = .00592	% Difference = 9.72% 95% CI = −0.8 to 22.8 *P* = .0652	% Difference = 1.1% 95% CI = −4.6 to 10.0 *P* = .6241	% Difference = 0% 95% CI = −9 to 10 *P* = 1	% Difference = 38.9% 95% CI = 21.5 to 52.6 *P* < .0001	% Difference = 27.2% 95% CI = 9.0 to 43.4 *P* = .0034
mTOR C/R vs mTOR UI	% Difference = 1.2% 95% CI = −0.9 to 4.4 *P* = .2906	% Difference = 12.9% 95% CI = −2.7 to 26.4 *P* = .1005	% Difference = 0.3% 95% CI = −8.8 to 7.2 *P* = .9162	% Difference = 42.6% 95% CI = 25.8 to 56.6 *P* < .0001	% Difference = 7.5% 95% CI = −7.9 to 22.4 *P* = .3314	% Difference = 44.7% 95% CI = 27.2 to 58.9 *P* < .0001
mTOR use overall	Total effect = 97.9% 95% CI = 96.2 to 99.1 *P* = .0013	Total effect = 1.95% 95% CI = 0.81 to 3.58 *P* = .0017	Total effect = 0.24% 95% CI = 0.06-0.6 *P* = .86	Total effect = 16.2% 95% CI = 3.1 to 36.7 *P* < .0001	Total effect = 31.0% 95% CI = 13.2 to 52.3 *P* < .0001	Total effect = 26% 95% CI = 6.6 to 52.4 *P* < .0001

Abbreviations: CI, confidence interval; CTCAE, common terminology criteria for adverse events; C/R, chemotherapy/radiation; G, grade; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease; UI, upstream inhibitor.

and temsirolimus were conducted in a palliative setting.[22,27] Bauman et al recruited 12 patients of which 6 had to withdraw due to toxicity or death. Since the observed toxicity rate was greater than 30%, the study was terminated. The mPFS was 1.9 months. Six patients experienced head and neck edema, possibly a side effect of temsirolimus. The second combination study recruited 36 patients.[27] One patient (3%) had a PR, 11 (31%) had SD, with an overall mPFS at 2.98 months and mOS at 10.25 months. Only one AE was grade 4, the remainder were grade 3 or less.

The rate of grade 4 AEs was 15.1% (95% CI 0.0-53.3). Otherwise, the rates of grade 3 or less AEs occurred at 96.4% (95% CI 84.1-99.9) and grade 5 occurred at 2.2% (95% CI 0.1-11.0). The PR rate in this group is 5.5% (95% CI 1.0-15.9), SD rate was 13.7% (95% CI 0.4-53.5) and rate of PD was 52.4% (95% CI 22.6-81.2). The weighed mPFS and mOS was 3.2 and 8.7 months, respectively. Forest plots of the AEs and RECIST criterion are shown in Figures 3 and 4. Additionally, Table 4 summarizes the rates of AEs based on grades and RECIST outcomes of each treatment modality, and compares the differences.

4 | DISCUSSION

To our knowledge, this is the first meta-analysis to conduct a head to head analysis of mTORi in HNSCC as either monotherapy or as combination therapy. Our study excluded CR rate from analysis because only one study reported a single result for this category. Interestingly, this study used neoadjuvant rapamycin as monotherapy in primary HNSCC.[30] However, it is difficult to extrapolate this finding and was considered as an outlier. In the setting of monotherapeutic neoadjuvant therapy, the majority of patients (52.5%) achieved SD while fewer (5.5%) reached PR and 25.2% were found to have PD. This may be hypothesized as the likely outcome due to the inhibition of the downstream metabolic targets that the mTOR protein facilitates.[7,12] Thus, future studies should consider combination therapy to reach levels of response that may improve survival and quality of life. In terms of palliative therapy, the patients maintaining SD may benefit if the response is durable with no other options, thus, warranting the need for further investigation. With respect to mOS and mPFS, only two studies reported these outcomes in this group. This does reduce the weight of the reported outcome, however both of the studies had similar mOS and mPFS.[26,28] In regards of safety, the rate of severe grade 4 and 5 AEs were minimal while grade 3 or less AEs occurred at the greatest rate. Clinicians report that these symptoms were manageable, however, monotherapeutic mTORi are not without risk.

Utilizing the cytostatic potential of mTORi with the cytotoxic power of CRT, the rate of PR was the highest (48.1%) and the PD rate (7.7%) was the lowest in the CRT combination group. It is important to note that only two studies reported RECIST outcomes. These two studies adjuvantly treated only RMHNSCC with different combination chemotherapies. They both had greater than 50% of their patients having PR with one study having zero PD.[29] An additional consideration may be that the 7 HPV positive patients in Saba et al study may incur an additional response benefit from CRT.[25,33] The mOS was reported by only two studies as was the mPFS. The greatest duration of mOS was reported by Fury et al and Saba et al had to best mPFS.[25,31] Two of the studies reported only grade 3 or greater AEs making it impossible to stratify grade 4 or 5 events. These studies were excluded from AEs analysis. Regardless, grade 4 were found to be highest in this group. This is likely due to each of the three studies reporting grade 4 events when compared to the other treatment groups. Additionally, only one grade 5 AE occurred out of the three studies analyzed. Differences in grade 4 AEs were statistically significant ($P < .05$), while grade 5 events were not. The most common AEs were hyperglycemia of any grade followed by rash and anemia. Meta-analysis of mTORi in other cancers have reported similar findings.[34-36] Thus, it is of no surprise that CRT had greater rates of severe AEs, as these treatment modalities are known to be toxic. Of note, consideration must be given to the fact that these findings are not from phase III studies or with randomized-control groups, warranting caution when interpreting these findings.

Upstream inhibition of EGFR when combined with mTORi had the worst results of the three treatment groups. A meta-analysis investigating the use of EGFRi in HNSCC based on p16 status found that there was limited benefits from EGFRi in p16 negative patients and no benefits to p16 positive patients. Additionally, when EGFRi were combined with chemoradiotherapy, they had no survival benefits regardless of p16 status.[37] In our meta-analysis only two studies combined mTORi with EGFRi. These two had only 31.2% (n = 15) patients that were p16 positive. This treatment group had the worst outcomes, specifically PD (52.4%) and SD (21.2%) as well as the duration of mPFS and mOS. Both studies reported greater than 50% of their patients having PD, while one study had no patients with SD.[22] Bauman et al study had be terminated early due to the toxicity of the treatment.[22] They reported four grade 4 AEs and one grade 5 AEs. Of note, the reason this treatment group had a lower rate of grade 5 AEs is because it had less weight when compared to mTORi with CRT. Therefore, it is difficult to assess if EGFRi are more or less likely to produce grade 5 AEs when compared to CRT. Overall, one reason why patients on EGFRi combination therapy had the worst outcomes is likely due to these patients being treated for palliative care. Therefore, it is not possible to infer these results to different patient populations. In addition, we are unable to discern if AEs were related to specifically mTORi or EGFRi, making it difficult to draw a conclusion on the safety profile of mTORi from these studies.

Molecular targeted therapeutics have allowed for some cancers such as breast cancer and CLL to be treated as chronic diseases.[38,39] As many studies have shown minimal residual disease/positive surgical margins results in a higher rate of recurrence, mTORi could play a role as adjuvant therapy in a minimal residual disease model.[40-42] Currently, a number of ongoing investigations with mTORi are underway in HNSCC (Table 5). Specifically, monotherapy of mTORi is being explored in a randomized phase II trial with everolimus v/s placebo as adjuvant therapy for high risk HNSCC patients.[43] However, to date no phase III studies have been published with mTORi in HNSCC. Future prospective, randomized trials will be important to provide relevant data regarding the role of mTORi as monotherapy and/or in

TABLE 5 Summary of clinical trials and conference abstracts of direct mTOR inhibition in HNC

Identification	Status	Drugs	Phase	Conditions
NCT01057277	Terminated	Everolimus + Cisplatin + RT	I	IHNSCC
NCT01111058	Unknown	Everolimus or Placebo	II	LAHNSCC
NCT01326468	Withdrawn	Temsirolimus + Cetuximab + Cisplatin + RT	NA	LAHNC
NCT01058408	Terminated	Everolimus + Cisplatin + IMRT	I	LAHNSCC
NCT00858663	Completed	Everolimus + Cisplatin + IMRT	I	HNC
NCT01333085	Completed	Everolimus + Carboplatin + paclitaxel	I/II	IHNSCC
NCT03578432	Recruiting	Everolimus + previous RT	I	HNC
NCT01283334	Completed	Everolimus + Carboplatin + Cetuximab	I/II	RMHNSCC
NCT01172769	Completed	Temsirolimus	II	RHNSCC
NCT00942734	Completed	Everolimus + Erlotinib	II	RHNSCC
NCT01009346	Terminated	Everolimus + Cetuximab + Cisplatin + Carboplatin	I/II	RMHNSCC
NCT00935961	Completed	Everolimus + Docetaxel + Cisplatin	I	LAHNSCC
NCT01313390	Terminated	Everolimus + Docetaxel	I/II	LAMHNSCC
NCT01133678	Active / NR	Everolimus or Placebo	II	LAHNSCC
NCT01016769	Completed	Temsirolimus + Paclitaxel + Carboplatin	I/II	RMHNSCC
NCT01256385	Completed	Temsirolimus + Cetuximab	II	RMHNC
NCT01332279	Withdrawn	Everolimus + Erlotinib + RT	I	RHNC
NCT01051791	Terminated	Everolimus	II	LAHNSCC
NCT01195922	Completed	Rapamycin	I/II	LAHNSCC
NCT00195299	Completed	Temsirolimus	NA	AHNSCC
NCT01009203	Terminated	Temsirolimus + Erlotinib	II	TRHNSCC
NCT01015664	Terminated	Temsirolimus + Cisplatin + Cetuximab	I/II	RMHNSCC

Abbreviations: INHNSCC, inoperable HNSCC; LAHNSCC, locally advanced HNSCC; LAHNC, locally advanced HNC; LAMHNSCC, locally advanced or metastatic HNSCC; NR, not recruiting; RMHNSCC, recurrent or metastatic HNSCC; RHNSCC, recurrent HNSCC; RMHNC, recurrent or metastatic HNC; TRHNSCC, therapy resistant HNSCC.

combination with other therapies to assess the true significance of mTORi therapy in HNSCC.

A number of limitations need to be considered for our meta-analysis. First, there are limited number of studies in each treatment group, with analysis of summary data. This impedes our ability to confirm reported data and limits our analysis. Additionally, there is known heterogeneity amongst the studies due to differences in the primary cancer, stage of the cancer and spread, treatment stage, previous treatment failures and responses, patient characteristics, sample size, and the treatment modality used in combination with mTOR inhibition. Additionally, there is variability amongst the studies in terms of the phase of the clinical trial and no study was designed with a control group. This weakens the clinical findings from our study. Physiologically, the pharmacodynamics of each mTOR drug must also be considered as a limitation. Moreover, not all outcomes are extractable or reported for each analyzed element. RECIST criteria typically examines one targetory lesion in metastatic disease. Patients may have improvement in one specific location while the other locations are deteriorating their overall well-being. In addition, mechanism by which mTORi treatment inhibits tumor growth/proliferation alone or in combination with CRT in HNSCC patients remain unclear. It is possible that in addition to attenuation of PI3K/AKT signaling, alterations of autophagy-mediated cell death might also be involved in response to mTORi.[9,44] Overall, our work is retrospective with confounders, therefore, a large randomized-control study would be ideal to eliminate the risk of bias and ascertain the true impact of mTORi in HNSCC.

5 | CONCLUSION

The use of mTORi has emerged as a novel treatment option in clinical trials for HNSCC. To date, no prospective, randomized Phase III trials have been published limiting this study's ability to confirm the direct role of these agents in HNSCC tumor response or survival. Using mTORi as monotherapy does not appear to provide significant response rates, however, in combination with chemotherapy and/or radiation therapy, there appears to be improved partial response rates that may or may not be related to the addition of mTORi. The rate of stable disease may deserve further study if this were to result in durable response rates in the future as monotherapy or in combination with other agents. Although adverse events including hyperglycemia were common, grade 4 and 5 toxicity was uncommon.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. 2015;65:5-29.
2. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136:E359-E386.
3. Cronin KA, Lake AJ, Scott S, et al. Annual report to the nation on the status of cancer, part I: national cancer statistics. *Cancer*. 2018;124:2785-2800.
4. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol*. 2011;29:4294-4301.
5. Ringash J, Bernstein LJ, Devins G, et al. Head and neck cancer survivorship: learning the needs, meeting the needs. *Semin Radiat Oncol*. 2018;28:64-74.
6. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2006;354:567-578.
7. Tan FH, Bai Y, Saintigny P, Darido C. mTOR signalling in head and neck cancer: heads up. *Cell*. 2019;8:1-13.
8. Lyford-Pike S, Peng S, Young GD, et al. Evidence for a role of the PD-1:PD-L1 pathway in immune resistance of HPV-associated head and neck squamous cell carcinoma. *Cancer Res*. 2013;73:1733-1741.
9. Tian T, Li X, Zhang J. mTOR signaling in cancer and mTOR inhibitors in solid tumor targeting therapy. *Int J Mol Sci*. 2019;20:1-6, 13.
10. Iglesias-Bartolome R, Martin D, Gutkind JS. Exploiting the head and neck cancer oncogenome: widespread PI3K-mTOR pathway alterations and novel molecular targets. *Cancer Discov*. 2013;3:722-725.
11. Nguyen SA, Walker D, Gillespie MB, Gutkind JS, Day TA. mTOR inhibitors and its role in the treatment of head and neck squamous cell carcinoma. *Curr Treat Options Oncol*. 2012;13:71-81.
12. Vander Haar E, Lee SI, Bandhakavi S, Griffin TJ, Kim DH. Insulin signalling to mTOR mediated by the Akt/PKB substrate PRAS40. *Nat Cell Biol*. 2007;9:316-323.
13. Ocana A, Vera-Badillo F, Al-Mubarak M, et al. Activation of the PI3K/mTOR/AKT pathway and survival in solid tumors: systematic review and meta-analysis. *PloS One*. 2014;9:e95219.
14. Amornphimoltham P, Patel V, Sodhi A, et al. Mammalian target of rapamycin, a molecular target in squamous cell carcinomas of the head and neck. *Cancer Res*. 2005;65:9953-9961.
15. Meng LH, Zheng XF. Toward rapamycin analog (rapalog)-based precision cancer therapy. *Acta Pharmacol Sin*. 2015;36:1163-1169.
16. Marques AE, Elias ST, Porporatti AL, et al. mTOR pathway protein immunoexpression as a prognostic factor for survival in head and neck cancer patients: a systematic review and meta-analysis. *J Oral Pathol Med*. 2016;45:319-328.
17. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010;8:336-341.
18. Jeremy Howick ICJLL, Glasziou P, Greenhalgh T, Heneghan C, Liberati A, Moschetti I, Phillips B, Thornton H, Goddard O, Hodgkinson M. OCEBM Levels of Evidence Working Group.
19. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol*. 2001;54:1046-1055.
20. Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Ann Math Stat*. 1950;21:607-611.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.
22. Bauman JE, Arias-Pulido H, Lee SJ, et al. A phase II study of temsirolimus and erlotinib in patients with recurrent and/or metastatic, platinum-refractory head and neck squamous cell carcinoma. *Oral Oncol*. 2013;49:461-467.
23. Fury MG, Lee NY, Sherman E, et al. A phase 1 study of Everolimus + weekly cisplatin + intensity modulated radiation therapy in head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2013;87:479-486.
24. Fury MG, Sherman E, Ho AL, et al. A phase 1 study of everolimus plus docetaxel plus cisplatin as induction chemotherapy for patients with locally and/or regionally advanced head and neck cancer. *Cancer*. 2013;119:1823-1831.
25. Saba NF, Hurwitz SJ, Magliocca K, et al. Phase 1 and pharmacokinetic study of everolimus in combination with cetuximab and carboplatin for recurrent/metastatic squamous cell carcinoma of the head and neck. *Cancer*. 2014;120:3940-3951.
26. Grunwald V, Keilholz U, Boehm A, et al. TEMHEAD: a single-arm multicentre phase II study of temsirolimus in platin- and cetuximab refractory recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) of the German SCCHN group (AIO). *Ann Oncol*. 2015;26:561-567.
27. Massarelli E, Lin H, Ginsberg LE, et al. Phase II trial of everolimus and erlotinib in patients with platinum-resistant recurrent and/or metastatic head and neck squamous cell carcinoma. *Ann Oncol*. 2015;26:1476-1480.
28. Geiger JL, Bauman JE, Gibson MK, et al. Phase II trial of everolimus in patients with previously treated recurrent or metastatic head and neck squamous cell carcinoma. *Head Neck*. 2016;38:1759-1764.
29. Dunn LA, Fury MG, Xiao H, et al. A phase II study of temsirolimus added to low-dose weekly carboplatin and paclitaxel for patients with recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). *Ann Oncol*. 2017;28:2533-2538.
30. Day TA, Shirai K, O'Brien PE, et al. Inhibition of mTOR signaling and clinical activity of rapamycin in head and neck cancer in a window of opportunity trial. *Clin Cancer Res*. 2019;25:1156-1164.
31. Fury MG, Sherman E, Ho A, et al. A phase I study of temsirolimus plus carboplatin plus paclitaxel for patients with recurrent or metastatic (R/M) head and neck squamous cell cancer (HNSCC). *Cancer Chemother Pharmacol*. 2012;70:121-128.
32. Ekshyyan O, Mills GM, Lian T, et al. Pharmacodynamic evaluation of temsirolimus in patients with newly diagnosed advanced-stage head and neck squamous cell carcinoma. *Head Neck*. 2010;32:1619-1628.
33. Prevc A, Niksic Zakelj M, Kranjc S, et al. Electrochemotherapy with cisplatin or bleomycin in head and neck squamous cell carcinoma: improved effectiveness of cisplatin in HPV-positive tumors. *Bioelectrochemistry*. 2018;123:248-254.
34. Rotundo MS, Galeano T, Tassone P, Tagliaferri P. mTOR inhibitors, a new era for metastatic luminal HER2-negative breast cancer? A systematic review and a meta-analysis of randomized trials. *Oncotarget*. 2016;7:27055-27066.
35. Xu J, Tian D. Hematologic toxicities associated with mTOR inhibitors temsirolimus and everolimus in cancer patients: a systematic review and meta-analysis. *Curr Med Res Opin*. 2014;30:67-74.
36. Yamanaka K, Petrulionis M, Lin S, et al. Therapeutic potential and adverse events of everolimus for treatment of hepatocellular carcinoma—systematic review and meta-analysis. *Cancer Med*. 2013;2:862-871.
37. Su Y, Cui J, Xu D, et al. p16(INK4a) status and survival benefit of EGFR inhibitors in head and neck squamous cell cancer: a systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2018;124:11-20.
38. Nagini S. Breast cancer: current molecular therapeutic targets and new players. *Anticancer Agents Med Chem*. 2017;17:152-163.

39. Burger JA, O'Brien S. Evolution of CLL treatment—from chemo-immunotherapy to targeted and individualized therapy. *Nat Rev Clin Oncol*. 2018;15:510-527.
40. Poeta ML, Manola J, Goldenberg D, et al. The Ligamp TP53 assay for detection of minimal residual disease in head and neck squamous cell carcinoma surgical margins. *Clin Cancer Res*. 2009;15:7658-7665.
41. Nathan CO, Amirghahari N, Rong X, et al. Mammalian target of rapamycin inhibitors as possible adjuvant therapy for microscopic residual disease in head and neck squamous cell cancer. *Cancer Res*. 2007;67:2160-2168.
42. Nathan CO, Amirghahari N, Abreo F, et al. Overexpressed eIF4E is functionally active in surgical margins of head and neck cancer patients via activation of the Akt/mammalian target of rapamycin pathway. *Clin Cancer Res*. 2004;10:5820-5827.
43. Randomized Phase II Trial of Everolimus Versus Placebo as Adjuvant Therapy in Patients With Locally Advanced Squamous Cell Cancer of the Head and Neck (SCCHN) (Clinical Trial). Available at: https://clinicaltrials.gov/ct2/show/NCT01111058. Accessed November 1, 2019.
44. Sentelle RD, Senkal CE, Jiang W, et al. Ceramide targets autophagosomes to mitochondria and induces lethal mitophagy. *Nat Chem Biol*. 2012;8:831-838.

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