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Targeted therapy for advanced salivary gland carcinoma based on molecular profiling: results from MyPathway, a phase IIa multiple basket study

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Abstract

Background: Systemic therapy options for salivary cancers are limited. MyPathway (NCT02091141), a phase IIa study, evaluates targeted therapies in non-indicated tumor types with actionable molecular alterations. Here, we present the efficacy and safety results for a subgroup of MyPathway patients with advanced salivary gland cancer (SGC) matched to targeted therapies based on tumor molecular characteristics.

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Patients and methods: MyPathway is an ongoing, multiple basket, open-label, non-randomized, multi-center study. Patients with advanced SGC received pertuzumab + trastuzumab (HER2 alteration), vismodegib (*PTCH-1/SMO* mutation), vemurafenib (*BRAF*V600 mutation), or atezolizumab [high tumor mutational burden (TMB)]. The primary endpoint is the objective response rate (ORR).

Results: As of January 15, 2018, 19 patients with SGC were enrolled and treated in MyPathway (15 with HER2 amplification and/or overexpression and one each with a *HER2* mutation without amplification or overexpression, *PTCH-1* mutation, *BRAF* mutation, and high TMB). In the 15 patients with HER2 amplification/overexpression (with or without mutations) who were treated with pertuzumab + trastuzumab, 9 had an objective response (1 complete response, 8 partial responses) for an ORR of 60% (9.2 months median response duration). The clinical benefit rate (defined by patients with objective responses or stable disease >4 months) was 67% (10/15), median progression-free survival (PFS) was 8.6 months, and median overall survival was 20.4 months. Stable disease was observed in the patient with a *HER2* mutation (pertuzumab + trastuzumab, $n = 1/1$, PFS 11.0 months), and partial responses in patients with the *PTCH-1* mutation (vismodegib, $n = 1/1$, PFS 14.3 months), *BRAF* mutation (vemurafenib, $n = 1/1$, PFS 18.5 months), and high TMB (atezolizumab, $n = 1/1$, PFS 5.5+ months). No unexpected toxicity occurred.

Conclusions: Overall, 12 of 19 patients (63%) with advanced SGC, treated with chemotherapy-free regimens matched to specific molecular alterations, experienced an objective response. Data from MyPathway suggest that matched targeted therapy for SGC has promising efficacy, supporting molecular profiling in treatment determination.

Keywords

advanced salivary gland carcinoma; targeted therapy; HER2-positive; pertuzumab; trastuzumab; molecular profiling

INTRODUCTION

The incidence of salivary gland cancer (SGC) has risen from 10.4 per 1 000 000 in 1973 to 16 per 1 000 000 in 2009.¹ Advanced salivary gland carcinomas are particularly unresponsive to traditional chemotherapies.² No standard of care for systemic therapy exists for metastatic disease,² and no treatments have been approved by the USA Food and Drug Administration (FDA) specifically for SGC. As such, patients with advanced SGC have a clear unmet need for effective systemic treatment options.

SGCs have high heterogeneity in their molecular and genomic characteristics and commonly harbor potentially actionable alterations.^{3–6} Human epidermal growth factor receptor 2 (HER2) alterations, for example, are particularly prevalent in aggressive or high-grade tumor subtypes, including salivary duct carcinoma (SDC) and other salivary carcinomas.^{6,7} Other potentially targetable alterations include *PIK3CA* and *BRAF* mutations, tumor mutational burden (TMB) >10 mutations/Mb, and *NTRK3* gene fusion, among others.⁶ Therapies targeting these molecular characteristics have demonstrated success in other cancer types, making SGC a prime candidate for existing targeted treatments.

Recent reports have suggested potential for targeted treatment of SGC. A phase II trial of patients with HER2-positive SDC reported a response rate of 70.2% following treatment with trastuzumab + docetaxel, although 60% of patients experienced grade 4 decreased neutrophil count.⁸ Encouraging results have also been observed anecdotally with targeted regimens free of traditional chemotherapy, including almost complete disease resolution in a heavily pretreated patient with HER2-amplified and overexpressing SDC treated with trastuzumab + lapatinib + bevacizumab,⁹ and a patient with HER2-overexpressing metastatic SDC treated with second-line trastuzumab emtansine (T-DM1) who experienced a prolonged response with low toxicity.¹⁰ Vemurafenib, a BRAF inhibitor approved for the treatment of patients with melanomas or Erdheim–Chester disease harboring *BRAFV600* mutations, produced a complete response in a patient with *BRAFV600*-mutated SDC.¹¹ Finally, treatment of *TRK* fusion-positive salivary tumors with the tyrosine receptor kinase inhibitors entrectinib and larotrectinib have resulted in complete and partial responses.^{12,13}

MyPathway (NCT02091141), an ongoing, multiple basket, phase IIa study, evaluates the efficacy of established, chemotherapy-free targeted therapies for non-approved indications in patients with advanced solid tumors harboring potentially actionable genetic or molecular alterations.¹⁴ Eligible alterations include HER2 amplification, overexpression, and/or mutations (treated with pertuzumab + trastuzumab); Hedgehog pathway alterations (*PTCH-1* or *SMO* mutations, treated with vismodegib); *BRAFV600* mutations (treated with vemurafenib ± cobimetinib); high microsatellite instability, high TMB, or deficient mismatch repair (treated with atezolizumab); *ALK* genetic alterations (treated with alectinib); or *EGFR*-activating mutations (treated with erlotinib). This trial design allows MyPathway to address treatment efficacy in both common and rare tumor types, regardless of their site of origin. Here, we present the efficacy and safety results for the subgroup of MyPathway patients with advanced SGC treated on the basis of their molecular characteristics with pertuzumab + trastuzumab, vismodegib, vemurafenib, or atezolizumab.

METHODS

Study design and participants

MyPathway is a multiple basket, open-label, non-randomized, multi-center phase IIa trial of patients with treatment-refractory advanced solid tumors with potentially predictive molecular alterations (see supplementary Figure S1, available at *Annals of Oncology* online). Patients in this analysis were enrolled from 12 sites and had advanced SGC with HER2 amplification, overexpression, and/or mutations; a Hedgehog pathway alteration; a *BRAFV600* mutation; or high TMB (by FoundationOne). Molecular alterations were locally assessed by Clinical Laboratory Improvement Amendments certified laboratory tests, as determined by the treating physician before enrollment, and reviewed by a study medical monitor for eligibility. Patients were aged ≥ 18 years, had measurable or evaluable lesions, and had an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤ 2. Patients with active brain metastases, concurrent active anti-cancer therapy, pregnancy, or contraindications to study therapy were excluded.

The primary endpoint is objective response rate (ORR); secondary endpoints include clinical benefit rate [CBR; defined as the percentage of patients who achieved an objective

response or stable disease (SD) >4 months], duration of response, progression-free survival (PFS), overall survival (OS), and safety. Exploratory analyses include the molecular characterization of tumor biomarkers.

MyPathway is conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the institutional review board or ethics committee at each trial center. Patients provided written informed consent before screening.

Procedures and assessments

Patients were treated in accordance with the United States package inserts^{15–19} without systemic chemotherapy. Those with HER2 amplification, overexpression, and/or mutation received pertuzumab [840 mg intravenous infusion (i.v.) loading dose, followed by 420 mg i.v. every 3 weeks (q3w)] plus trastuzumab (8 mg/kg i.v. loading dose, followed by 6 mg/kg i.v. q3w). Patients with a Hedgehog pathway alteration (*PTCH-1* or *SMO* mutation) were administered vismodegib (150 mg orally once daily in 28-day cycles). Patients with *BRAF* V600 mutations received vemurafenib (960 mg orally twice daily in 28-day cycles). Finally, patients with high TMB received atezolizumab (1200 mg i.v. q3w). Tumor burden was investigator-evaluated. Treatments were administered until disease progression, unacceptable toxicity, or other discontinuation criteria were met. Details regarding tumor assessments and molecular profiling methodology are available in the supplementary Methods, available at *Annals of Oncology* online.

Statistical analysis

The Cloppere–Pearson estimation method was used to calculate 95% confidence intervals (CIs) for ORR and CBR. Median PFS, OS, duration of response [in patients with complete response (CR) or partial response (PR)], and their 95% CIs were estimated using the Kaplan–Meier approach. Additional information on clinical outcome endpoints and planned sample size are provided in the supplementary Methods, available at *Annals of Oncology* online.

RESULTS

Patients

As of the data cutoff (15 January 2018), 19 patients with SGC were enrolled in MyPathway (supplementary Figure S2, available at *Annals of Oncology* online). Sixteen patients received pertuzumab + trastuzumab, of whom 15 had HER2 amplification and/or overexpression [with *HER2* mutations in two patients (G776V and L755F plus D769H)] and one had a *HER2* mutation (S310F) without amplification or overexpression (Table 1). The other three patients received vismodegib ($n = 1$, truncating *PTCH-1* Q400* mutation), vemurafenib ($n = 1$, *BRAF*V600E mutation), or atezolizumab ($n = 1$, high TMB of 31 mut/Mb). All treated patients were evaluable for efficacy.

All 19 patients had aggressive salivary gland carcinomas (salivary gland adenocarcinoma, $n = 11$; high-grade mucoepidermoid carcinoma, $n = 4$; and unspecified carcinoma, $n = 4$). The

median age was 61 (range, 37–82) years and patients received a median of one (range, 1–3) previous systemic treatment regimen. Most patients were male [$n = 16$ (84%)], white [$n = 14$ (74%)], and had an ECOG performance status score of 1 [$n = 17$ (89%)] (Table 1).

Clinical outcomes

The median follow-up duration was 10.6 (range, 3–26) months. Nine of 15 patients with HER2 amplification and/or overexpression had objective responses to treatment with pertuzumab + trastuzumab (one CR, eight PRs) for an ORR of 60% (95% CI 32% to 84%) (Table 2). One additional patient had SD for 11.7 months [CBR 67% ($n = 10$), 95% CI 38% to 88%]. Treatment duration ranged from 0.7 to 26.1 [ongoing (+)] months and estimated median response duration in patients with an objective response was 9.2 (range, 1.4+ to 19.7+) months, with five out of nine responses (including the CR) ongoing at the time of data cutoff. Time on treatment and best change in target lesion size by patient are shown in Figure 1A,B. By the data cutoff, nine patients with HER2 amplification and/or overexpression had progressed or died (Table 2). Median PFS was 8.6 [95% CI 2.3 to not estimable (NE)] months (Figure 2A) and median OS was 20.4 (95% CI 8.2 to NE) months (Figure 2B).

One patient with a *HER2* S310F mutation without amplification or overexpression had SD lasting 11.0 months as the best response following treatment with pertuzumab + trastuzumab (Table 2). The patients with a *PTCH-1* Q400* mutation (treated with vismodegib) and *BRAFV600E* mutation (treated with vemurafenib) experienced PRs lasting 10.7 and 15.1 months but had discontinued treatment due to clinical progression and progressive disease by the data cutoff, respectively. Finally, following SD of 5.4 months, a PR was reported in the atezolizumab-treated patient with high TMB (31 mut/Mb) at the last tumor assessment before the data cutoff; the patient remained on treatment.

Overall, 12 of 19 patients (63%) achieved an objective response when matched to therapy based on the genomic characteristics of their tumors. Including patients with SD >4 months, 14 of 19 patients (74%) experienced clinical benefit. Median PFS for all 19 patients was 11.7 months (95% CI 5.6% to 18.5%) and median OS was 20.4 months (95% CI 9.1 to NE). Case reports for one patient in each treatment arm are presented in the supplementary Results and Figures S3–S6, available at *Annals of Oncology* online.

Tumor molecular profiles

Genomic profiling data were available for 11 of 15 patients with HER2 amplification and/or overexpression, and all patients in the remaining cohorts (see supplementary Table S1, available at *Annals of Oncology* online). Mutational profiles are shown in Figure 3 and described in detail in the supplementary Results, available at *Annals of Oncology* online.

Safety

Of 16 patients treated with pertuzumab + trastuzumab, treatment-emergent adverse events (TEAEs) and TEAEs thought to be related to one or both study drugs were reported in 94% ($n = 15$) and 88% ($n = 14$) of patients, respectively. Serious TEAEs and grade 3–4 TEAEs were observed in 13% ($n = 2$) and 25% ($n = 4$) of patients, respectively, with no

serious or grade 3–4 TEAEs experienced by more than one patient. There were no deaths due to a TEAE. The most common drug-related TEAEs were diarrhea [50% (8/16)], pruritus [31% (5/16)], and chills [25% (4/16)] (see supplementary Table S2, available at *Annals of Oncology* online). One patient had grade 3 peripheral neuropathy considered related to the study drugs (supplementary Table S3, available at *Annals of Oncology* online). Of the three reported grade 4 TEAEs, none were considered related to the study drugs.

Each of the patients treated with vismodegib, vemurafenib, and atezolizumab experienced TEAEs, including at least one grade 3 TEAE. TEAEs thought to be related to the study drugs and serious TEAEs were reported in the vismodegib and vemurafenib-treated patients. Grade 3 drug-related TEAEs included diarrhea, decreased weight, and hypokalemia in the vismodegib-treated patient, and maculopapular rash in the vemurafenib-treated patient. No TEAEs higher than grade 3 were observed.

DISCUSSION

SGCs are refractory to many common chemotherapeutic treatments, but few studies have been conducted to identify effective systemic therapies due to the rarity of the disease. Data from MyPathway support the potential of chemotherapy-free targeted therapy for patients with advanced SGC. We observed promising efficacy in the subgroup of patients with HER2-amplified and/or overexpressing salivary gland carcinomas treated with pertuzumab + trastuzumab, the largest cohort assessed in this analysis [ORR, 60% (95% CI 32% to 84%); CBR, 67% (95% CI 38% to 88%); median PFS, 8.6 (95% CI 2.3 to NE) months; median OS, 20.4 (95% CI 8.2 to NE) months]. Responses were durable (median 9.2 months), and five of nine were ongoing at data cut off, including the CR. Furthermore, we observed promising results in individual patients with tumors harboring a *HER2* S310F mutation (pertuzumab + trastuzumab; SD, 11.0 months); a *PTCH-1* Q400* mutation (vismodegib; PR, 10.7 months); a *BRAF*V600E mutation (vemurafenib; PR, 15.1 months); and high TMB (atezolizumab; PR as of the data cutoff date, following a prolonged SD of 5.4 months).

Management of early SGC typically involves surgery or radiotherapy, with no standard of care for the systemic treatment of advanced cancer.² Previously investigated chemotherapeutic regimens were associated with low response rates and high toxicity.²⁰ Although the recent phase II study of trastuzumab + docetaxel in patients with HER2-positive SDC produced a high response rate, more than half of the patients experienced grade 4 decreased neutrophil count.⁸ In MyPathway, we observed a response rate of 60% with pertuzumab + trastuzumab in patients with HER2-amplified and/or overexpressing advanced SGCs. This chemotherapy-free regimen was well tolerated, with only one grade 3 TEAE considered to be related to the study drugs, and no grade 4 related TEAEs. The median 20.4-month OS in this cohort compares favorably with the 15-month OS previously observed after the development of distant metastases in patients with salivary gland carcinomas unselected for HER2 status.²¹ Finally, while the rarity of SGC limited the assessment of vismodegib, vemurafenib, and atezolizumab in only one patient each, the preliminary observations of extended PRs or SDs in each of these patients, all of whom had recurrent disease after previous treatment of salivary cancer, suggest that patients can be

successfully matched to a variety of targeted therapies based on the genomic characteristics of the tumors.

All 19 patients with SGC enrolled in the MyPathway study had high-grade carcinomas. While genomic and molecular alterations associated with adverse outcomes are common in such tumors,⁶ some of the reported alterations are potentially targetable with currently available agents, providing new opportunities for the treatment of these challenging salivary tumor subtypes. HER2 alterations, in particular, are common in aggressive tumor subtypes, such as SDCs.^{6,7} In the largest study of comprehensive molecular profiling in salivary gland cancers, HER2 alterations occurred in 32% of SDCs and 17% of other adenocarcinomas.⁶ The high incidence of HER2 alterations and the efficacy of HER2-targeted therapy suggest similarities between SDC and breast intraductal carcinomas. Salivary and mammary glands share similar histogenetic origins; in addition to frequent HER2 alterations, carcinomas arising from these tissues share similar histology, morphology, and gene expression profiles.^{22–25} These similarities, in addition to the high response rate we observed in patients with HER2 amplified and/or overexpressing salivary gland carcinomas, suggest that the success of HER2-targeted therapy in breast cancer may extend to patients with HER2-positive salivary gland carcinomas.

Limitations of this analysis include small patient cohorts and non-blinded investigator assessments. In addition, local molecular alteration testing was conducted at the investigator's discretion using site-determined methodology, with central genomic re-testing limited to two patients with available and sufficient archival samples for next-generation sequencing. Because of the limited sample size, the impact of co-mutations on efficacy could not be determined; this merits study in future investigations. Although data from MyPathway suggest that targeted therapy has potential in the treatment of SGC, the small number of patients with this rare cancer may necessitate additional study to assess efficacy. Preliminary data from other recent or ongoing basket trials have indicated positive results for the targeted treatment of SGC with trastuzumab emtansine (T-DM1), neratinib, vemurafenib, entrectinib, and larotrectinib^{11–13,26–28}; additional results from these and other studies are anticipated.

Results from MyPathway provide a proof-of-principle for matching patients to effective, chemotherapy-free treatment of tumors based on molecular characteristics rather than site of origin, a particularly valuable opportunity for cancer patients with limited treatment options or who are unable to tolerate traditional chemotherapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Del Signore AG, Megwalu UC. The rising incidence of major salivary gland cancer in the United States. *Ear Nose Throat J.* 2017;96:E13–E16.
2. Chintakuntlawar AV, Okuno SH, Price KA. Systemic therapy for recurrent or metastatic salivary gland malignancies. *Cancers Head Neck.* 2016;1:11. [PubMed: 31093341]
3. Kato S, Elkin SK, Schwaederle M, et al. Genomic landscape of salivary gland tumors. *Oncotarget.* 2015;6:25631–25645. [PubMed: 26247885]

4. Wang K, McDermott JD, Schrock AB, et al. Comprehensive genomic profiling of salivary mucoepidermoid carcinomas reveals frequent BAP1, PIK3CA, and other actionable genomic alterations. *Ann Oncol.* 2017;28:748–753. [PubMed: 28327999]
5. Wang K, Russell JS, McDermott JD, et al. Profiling of 149 salivary duct carcinomas, carcinoma ex pleomorphic adenomas, and adenocarcinomas, not otherwise specified reveals actionable genomic alterations. *Clin Cancer Res.* 2016;22:6061–6068. [PubMed: 27334835]
6. Ross JS, Gay LM, Wang K, et al. Comprehensive genomic profiles of metastatic and relapsed salivary gland carcinomas are associated with tumor type and reveal new routes to targeted therapies. *Ann Oncol.* 2017;28:2539–2546. [PubMed: 28961851]
7. Glisson B, Colevas AD, Haddad R, et al. HER2 expression in salivary gland carcinomas: dependence on histological subtype. *Clin Cancer Res.* 2004;10:944–946. [PubMed: 14871971]
8. Takahashi H, Tada Y, Saotome T, et al. Phase II trial of trastuzumab and docetaxel in patients with human epidermal growth factor receptor 2-positive salivary duct carcinoma. *J Clin Oncol.* 2019;37:125–134. [PubMed: 30452336]
9. Falchook GS, Lippman SM, Bastida CC, et al. Human epidermal receptor 2-amplified salivary duct carcinoma: regression with dual human epidermal receptor 2 inhibition and anti-vascular endothelial growth factor combination treatment. *Head Neck.* 2014;36:E25–E27. [PubMed: 23852769]
10. Corrêa TS, Matos GDR, Segura M, et al. Second-line treatment of HER2-positive salivary gland tumor: ado-trastuzumab emtansine (T-DM1) after progression on trastuzumab. *Case Rep Oncol.* 2018;11:252–257. [PubMed: 29867432]
11. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N Engl J Med.* 2015;373:726–736. [PubMed: 26287849]
12. Drilon A, Li G, Dogan S, et al. What hides behind the MASC: clinical response and acquired resistance to entrectinib after ETV6-NTRK3 identification in a mammary analogue secretory carcinoma (MASC). *Ann Oncol.* 2016;27:920–926. [PubMed: 26884591]
13. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med.* 2018;378:731–739. [PubMed: 29466156]
14. Hainsworth JD, Meric-Bernstam F, Swanton C, et al. Targeted therapy for advanced solid tumors on the basis of molecular profiles: results from MyPathway, an open-label, phase IIa multiple basket study. *J Clin Oncol.* 2018;36:536–542. [PubMed: 29320312]
15. Erivedge (vismodegib). [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2017.
16. Herceptin (trastuzumab). [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2018.
17. Perjeta (pertuzumab). [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2018.
18. Tecentriq (atezolizumab). [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2018.
19. Zelboraf (vemurafenib). [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2017.
20. Wang X, Luo Y, Li M, et al. Management of salivary gland carcinomas – a review. *Oncotarget.* 2017;8:3946–3956. [PubMed: 27992367]
21. Nam SJ, Roh JL, Cho KJ, et al. Risk factors and survival associated with distant metastasis in patients with carcinoma of the salivary gland. *Ann Surg Oncol.* 2016;23:4376–4383. [PubMed: 27338749]
22. Luk PP, Weston JD, Yu B, et al. Salivary duct carcinoma: clinicopathologic features, morphologic spectrum, and somatic mutations. *Head Neck.* 2016;38(suppl 1):E1838–E1847. [PubMed: 26699379]
23. Dalin MG, Desrichard A, Katabi N, et al. Comprehensive molecular characterization of salivary duct carcinoma reveals actionable targets and similarity to apocrine breast cancer. *Clin Cancer Res.* 2016;22:4623–4633. [PubMed: 27103403]
24. D'heygere E, Meulemans J, Vander Poorten V. Salivary duct carcinoma. *Curr Opin Otolaryngol Head Neck Surg.* 2018;26:142–151. [PubMed: 29373327]

25. Boecker W, Stenman G, Loening T, et al. K5/K14-positive cells contribute to salivary gland-like breast tumors with myoepithelial differentiation. *Mod Pathol.* 2013;26:1086–1100. [PubMed: 23558567]
26. Jhaveri KL, Makker V, Wang XV, et al. Ado-trastuzumab emtansine (T-DM1) in patients (pts) with HER2 amplified (amp) tumors excluding breast and gastric/gastro-esophageal junction (GEJ) adenocarcinomas: results from the National Cancer Institute (NCI) Molecular Analysis for Therapy Choice (MATCH) trial. *J Clin Oncol.* 2018;36(suppl):abstr 100.
27. Hyman DM, Piha-Paul SA, Won H, et al. HER kinase inhibition in patients with HER2- and HER3-mutant cancers. *Nature.* 2018;554:189–194. [PubMed: 29420467]
28. Li BT, Makker V, Buonocore DJ, et al. A multi-histology basket trial of ado-trastuzumab emtansine in patients with HER2 amplified cancers. *J Clin Oncol.* 2018;36(suppl):abstr 2502.

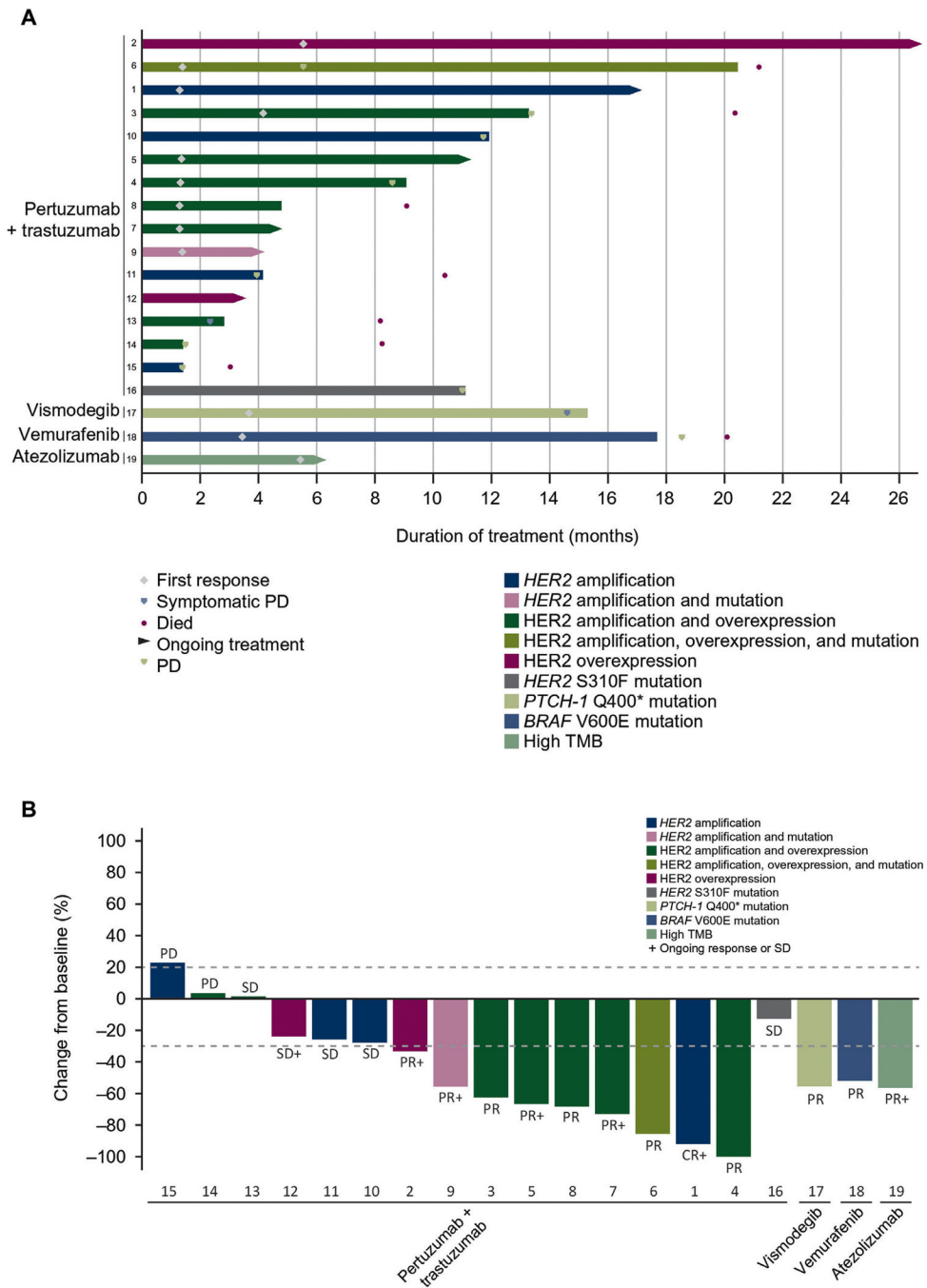


Figure 1. Time on treatment and (B) best change in target lesion size by patient (A) ($n = 19$).^a CR, complete response; HER2, human epidermal growth factor receptor 2; Hh, Hedgehog; PD, progressive disease; PR, partial response; PTCH-1, patched homolog-1; SD, stable disease; TMB, tumor mutational burden.
^a Lanes represent individual patients.

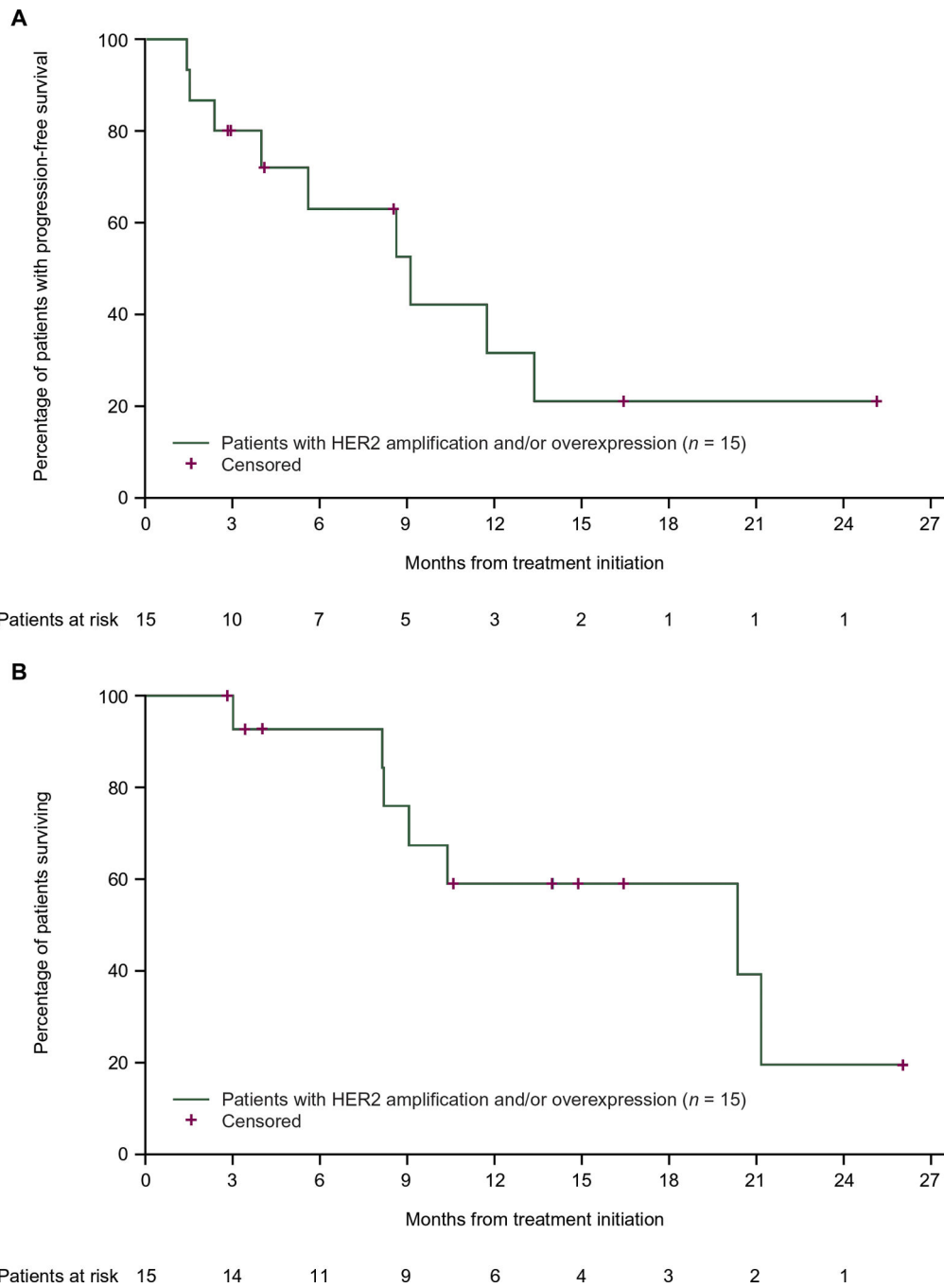


Figure 2. Progression-free survival and (B) overall survival in patients with HER2 amplification and/or overexpression ($n = 15$).

(A) HER2, human epidermal growth factor receptor 2.

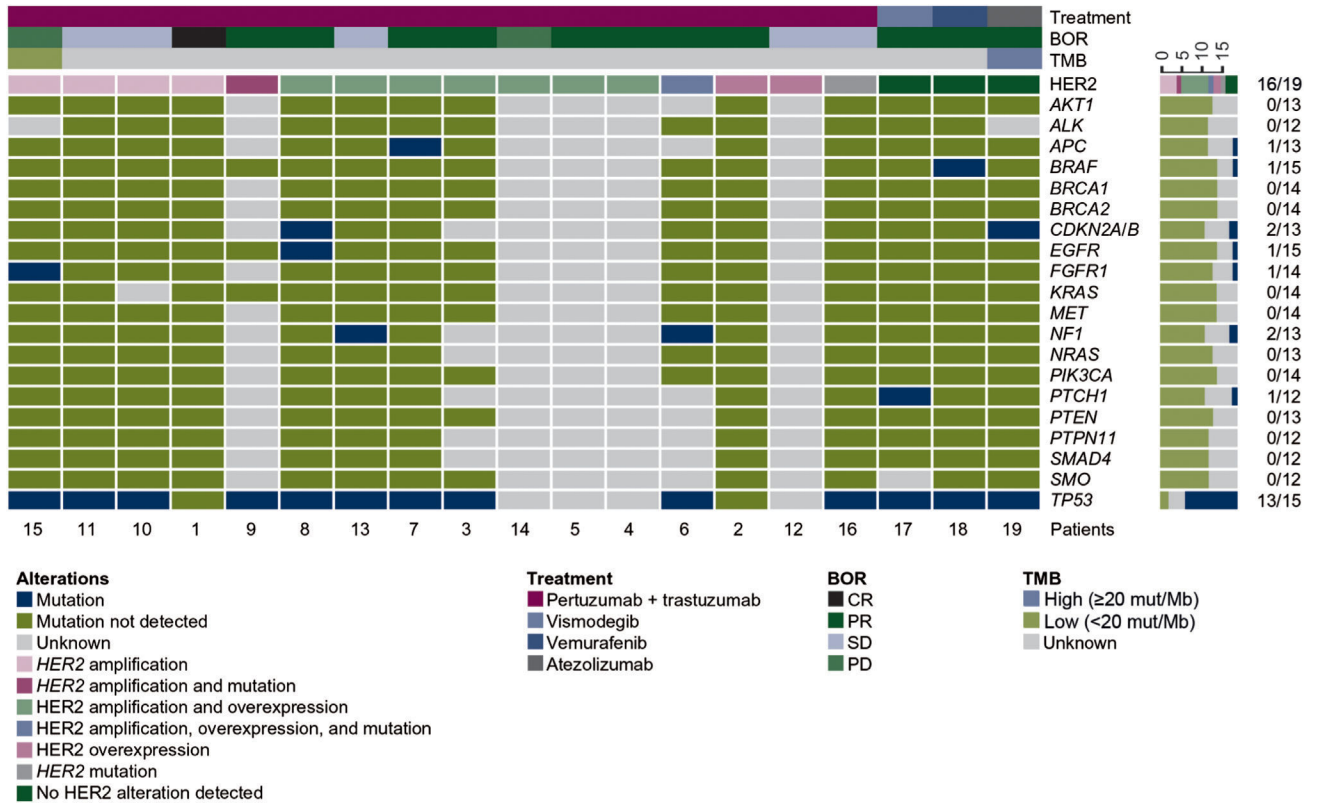


Figure 3. Mutational profile of selected oncogenic alterations in patients with advanced salivary gland carcinoma ($n = 19$).
 BOR, best overall response; CR, complete response; HER2, human epidermal growth factor receptor 2; PD, progressive disease; PR, partial response; SD, stable disease; TMB, tumor mutational burden.

Table 1.

Baseline demographics and clinical characteristics by patient

Pt	Sex	Age, years	Race	ECOG PS	Histology	Grade	Stage	Alteration	Testing platform ^a	Previous lines of therapy ^b	Sites of metastasis
HER2 amplification and/or overexpression: treated with pertuzumab + trastuzumab											
1	M	59	White	0	Salivary duct adenocarcinoma	G3	IV	HER2 amplification	NGS (copy number = 15)	1	Brain, lung, LN
2	M	80	White	1	Adenocarcinoma	G2	IVA	HER2 overexpression	IHC (3+)	1	Bone, LN
3	M	55	Black/African American	2	Unspecified carcinoma	G3	IVA	HER2 amplification + overexpression	FISH/CISH (ratio = 7.3), IHC (3+)	2	Bone, lung, LN
4	M	70	White	1	Invasive ductal carcinoma	G4	IV	HER2 amplification + overexpression	FISH/CISH (ratio = 2.4), IHC (3+)	1	Bone, liver, LN
5	M	73	White	1	Adenocarcinoma	G3	IV	HER2 amplification + overexpression	FISH/CISH (ratio = 9.9), IHC (3+)	1	Bone, LN, spleen
6	M	47	White	1	Adenocarcinoma	G3	IVC	HER2 amplification, overexpression + mutation	NGS (copy number gain: L755F and D769H mutations), IHC (3+)	0	Bone, LN
7	M	61	White	1	Unspecified carcinoma	G3	III	HER2 amplification + overexpression	NGS (copy number = 94); IHC (3+)	0	Liver, lung
8	F	54	White	0	Adenocarcinoma	G3	IV	HER2 amplification + overexpression	NGS (copy number = 104), IHC (3+)	0	Liver, LN
9	M	54	Other	1	Unspecified carcinoma	G3	III	HER2 amplification + mutation	FISH/CISH (ratio = 5.5), NGS (G776V mutation)	0	Bone, lung, LN
10	F	75	Asian	0	Adenocarcinoma	G3	IVA	HER2 amplification	NGS (copy number gain)	0	Lung
11	M	70	White	1	Unspecified carcinoma	G1	IVC	HER2 amplification	NGS (copy number = 60)	2	Bone, liver, lung, LN, intraorbital
12	M	37	White	1	Adenocarcinoma	GX	IV	HER2 overexpression	IHC (3+)	1	Bone, liver
13	M	62	American Indian or Alaska native	1	Mucoepidermoid carcinoma	G3	III	HER2 amplification + overexpression	FISH/CISH (ratio = 7.8), NGS (copy number = 20), IHC (3+)	3	Adrenal gland, liver, lung, LN
14	M	48	Asian	1	Invasive ductal carcinoma	G4	IVA	HER2 amplification + overexpression	FISH/CISH (ratio = 7.2), IHC (3+)	1	Brain, lung, LN
15	F	44	White	2	Adenocarcinoma	G3	IV	HER2 amplification	NGS (copy number = 15)	2	Brain, chest wall, left eye, liver, LN, neck

Pt	Sex	Age, years	Race	ECOG PS	Histology	Grade	Stage	Alteration	Testing platform ^a	Previous lines of therapy ^b	Sites of metastasis
HER2 mutation: treated with pertuzumab + trastuzumab											
16	M	68	White	0	Adenocarcinoma	G3	III	HER2 mutation	NGS (S310F mutation)	0	Lung, LN, mediastinum
Hh alteration: treated with vismodegib											
17	M	65	White	0	Mucoepidermoid carcinoma	G3	II	Hh alteration	NGS (PTCH-1 Q400* mutation)	0	Lung
BRAF V600 mutation: treated with vemurafenib											
18	M	51	White	1	Mucoepidermoid carcinoma	G3	IV	BRAF mutation	NGS (V600E mutation)	1	Liver, lung, LN
High TMB: treated with atezolizumab											
19	M	82	White	1	Mucoepidermoid carcinoma	G3	IVA	High TMB	NGS (31 mutations/Mb)	0	Adrenal gland, LN, skin

ECOG PS, Eastern Cooperative Oncology Group performance status; F, female; FISH/CISH, fluorescence/chromogenic in situ hybridization; HER2, human epidermal growth factor receptor 2; Hh, Hedgehog; IHC, immunohistochemistry; LN, lymph node; M, male; NGS, next-generation sequencing; Pt, patient; PTCH-1, patched homolog-1; TMB, tumor mutational burden.

^aNot all patients were tested with all testing methods. Details from testing results are included, where available.

^bPrevious regimens consisted of systemic chemotherapy in all patients.

Clinical outcomes by patient

Table 2.

Pt	Alteration	Time on treatment, months	Best response	Duration of response, months	Duration of SD, months	Best change in target lesion size from baseline, %	PFS, months	OS, months
HER2 amplification and/or overexpression: treated with pertuzumab + trastuzumab								
1	HER2 amplification	16.5 ⁺	CR	15.2 ⁺	-	-91.7 ^a	16.5 ⁺	16.5 ⁺
2	HER2 overexpression	26.1 ⁺	PR	19.7 ⁺	-	-33.3	25.2 ⁺	26.1 ⁺
3	HER2 amplification and overexpression	12.6	PR	9.2	-	-62.5	13.4	20.4
4	HER2 amplification and overexpression	8.3	PR	7.3	-	-100.0 ^b	8.6	14.9 ⁺
5	HER2 amplification and overexpression	10.6 ⁺	PR	7.2 ⁺	-	-66.7	8.5 ⁺	10.6 ⁺
6	HER2 amplification, overexpression, and mutation (L755F and D769H)	19.8	PR	4.2	-	-85.7	5.6	21.2
7	HER2 amplification and overexpression	4.1 ⁺	PR	2.8 ⁺	-	-73.0	4.0 ⁺	4.1 ⁺
8	HER2 amplification and overexpression	4.1 ^c	PR	2.7	-	-68.2	9.1	9.1
9	HER2 amplification and mutation (G776V)	3.5 ⁺	PR	1.4 ⁺	-	-55.7	2.8 ⁺	3.5 ⁺
10	HER2 amplification	11.2	SD	-	11.7	-27.9	11.7	14.0 ⁺
11	HER2 amplification	3.5	SD	-	3.9	-25.6	3.9	10.4
12	HER2 overexpression	2.9 ⁺	SD	-	2.9 ⁺	-24.3	2.9 ⁺	2.9 ⁺
13	HER2 amplification and overexpression	2.1	SD	-	2.3	1.4	2.3	8.2
14	HER2 amplification and overexpression	0.7	PD	-	-	3.6	1.5	8.3
15	HER2 amplification	0.7	PD	-	-	22.5	1.4	3.1
HER2 mutation: treated with pertuzumab + trastuzumab								
16	HER2 mutation (S310F)	10.4	SD	-	11.0	-12.8	11.0	13.7 ⁺
Hh alteration: treated with vismodegib								
17	Hh alteration (PTCH-1 Q400*)	14.4	PR	10.7	-	-55.6	14.3	17.3 ⁺
BRAF V600 mutation: treated with vemurafenib								

Pt	Alteration	Time on treatment, months	Best response	Duration of response, months	Duration of SD, months	Best change in target lesion size from baseline, %	PFS, months	OS, months
18	<i>BRAF</i> mutation (V600E) High TMB: treated with atezolizumab	16.8	PR	15.1	–	–43.4	18.5	20.1
19	High TMB (31 mutations/Mb)	5.7 ⁺	PR	0.03 ⁺	–	–56.0	5.5 ⁺	5.7 ⁺

CR, complete response; HER2, human epidermal growth factor receptor 2; Hh, Hedgehog; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; Pt, patient; PTCH-1, patched homolog-1; SD, stable disease; TMB, tumor mutational burden.

⁺ indicates measure was ongoing at the most recent assessment.

^a Patient's target lesions were both lymph nodes with a measurement of <10 mm and absent/normal status of non-target lesions following treatment cycle 12, considered a CR per RECIST v1.1.

^b Patient had a 100% reduction in the target lesion but had a remaining non-target lesion and therefore did not qualify for a CR per RECIST v1.1.

^c Patient had an ongoing tumor response but withdrew from treatment and later died.