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Combination of immunotherapy and anti-EGFR agents in immunotherapy refractory head neck cancer recurrent and metastatic head neck squamous cell carcinoma

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Abstract

Background

Immunotherapy has become a standard treatment for recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC); however, response rates remain modest, and long-term survival is limited. Preclinical studies suggest that inhibiting the epidermal growth factor receptor (EGFR) pathway may enhance antigen presentation and augment the efficacy of immune checkpoint inhibitors. This study evaluated the real-world efficacy and safety of combining immunotherapy with anti-EGFR agents in patients with R/M HNSCC.

Methods

We conducted a retrospective study at Taipei Veterans General Hospital involving patients diagnosed with R/M HNSCC between January 2020 and July 2024 who received combination therapy comprising immunotherapy and anti-EGFR agents. The primary endpoint was the objective response rate (ORR) according to RECIST v1.1. Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), duration of response (DoR), and safety assessed by CTCAE v5.0.

Results

A total of 29 patients were included in the analysis. The cohort was characterized by a high proportion of platinum-refractory disease (59%) and 38% of patients received the combination as second-line treatment or later. The ORR was 44% (95% CI: 26%–64%), including 3 complete responses (10%) and 10 partial responses (34%). The DCR was 66%. The median PFS was 6.9 months (95% CI: 2.9–9.2), and the median OS was 15.1 months (95% CI: 8.4–not reached). Notably, in the subgroup with a PD-L1 combined positive score (CPS) < 1, the ORR was 37.5%. Treatment-related adverse events occurred in 79% of patients but were exclusively Grade 1 or 2; no Grade 3 or higher adverse events were observed.

Conclusion

The combination of immunotherapy and anti-EGFR agents demonstrated promising antitumor activity and a favorable safety profile in patients with R/M HNSCC. These findings suggest this regimen may be a viable therapeutic strategy, particularly for patients with platinum-refractory disease or low PD-L1 expression who traditionally have poor outcomes.

Introduction

Head and neck squamous cell carcinoma (HNSCC) represents a significant global health burden, contributing substantially to cancer-related morbidity and mortality, with more than 600,000 new cases

diagnosed each year worldwide [1]. Recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC) develops in over 50% of patients with locoregionally advanced disease [2]. R/M HNSCC are partially driven by immune evasion mechanisms. A key factor in this process is the expression of programmed death ligands (PD-L1), which bind to the programmed death 1 (PD-1) receptor and suppress T-cell activity through immune checkpoint pathways.

Immune checkpoint inhibitors have demonstrated significant efficacy and manageable safety profiles in HNSCC [3–5]. The pivotal CheckMate-141 and KEYNOTE-040 trials showed that anti-PD1 monoclonal antibodies improved overall survival compared to standard single-agent therapies in patients with R/M HNSCC [3, 6]. Additionally, the KEYNOTE-048 trial demonstrated that pembrolizumab monotherapy significantly improved overall survival in patients with a combined positive score (CPS) ≥ 1, exhibited non-inferiority in the overall study population, and was associated with a more favorable safety profile compared to cetuximab combined with chemotherapy [7]. Based on these findings, current guidelines recommend pembrolizumab in combination with platinum and 5-fluorouracil as the first-line treatment for unresectable R/M HNSCC [2, 8].

Despite these advancements, there is still limited number of patient can gain clinical benefit from immunotherapy, with a median overall survival (OS) about 8 months and a 1-year OS rate of about 40% [3, 6]. Resistance to immunotherapy has been attributed to mechanisms such as loss of IFNγ signaling and impaired antigen presentation [9]. Interestingly, preclinical studies have demonstrated that epidermal growth factor receptor (EGFR) pathway inhibition enhances antigen presentation and augments the efficacy of immunotherapy [10–12]. Mechanistically, cetuximab induces antibody-dependent cellular cytotoxicity (ADCC), leading to the lysis of tumor cells by natural killer (NK) cells. This process facilitates the cross-priming of cytotoxic CD8 + T cells by activated dendritic cells. Furthermore, activated NK cells secrete IFNγ alongside other proinflammatory cytokines and chemokines, thereby remodeling the tumor microenvironment to favor immune cell recruitment and activation.[13]

Several phase II studies have indicated that adding anti-EGFR agents to immunotherapy may augment efficacy and improve overall response rates in patients with platinum-refractory R/M HNSCC [13–15]. However, real-world data regarding this combination strategy remain scarce. Therefore, we conducted a retrospective study to evaluate the efficacy of combining anti-EGFR agents with immunotherapy in a real-world clinical setting.

Methods

2.1 Study design and participants

We retrospectively identified patients at Taipei Veterans General Hospital diagnosed with R/M HNSCC between January 2020 and July 2024. Patients who received a combination of immunotherapy and anti-EGFR agents were selected for further analysis.

Clinical characteristics of these patients were systematically recorded, including sex, age, Eastern Cooperative Oncology Group (ECOG) performance status, smoking history, HPV status, initial tumor staging, primary tumor location, PD-L1 expression, disease status (locoregional recurrence only vs. metastatic disease), prior immunotherapy regimen, platinum-refractory status, number of prior systemic treatment lines, type of anti-EGFR agent used during combination therapy, and whether chemotherapy was included in the combination regimen. According to current clinical guidelines, human papilloma virus (HPV) status is assessed exclusively in cases of oropharyngeal cancer and is determined through immunohistochemical staining for p16 as a surrogate marker. Initial tumor staging was classified according to the American Joint Committee on Cancer (AJCC) staging system (seventh edition). Primary tumor locations were categorized as the oral cavity, oropharynx, larynx, and hypopharynx. PD-L1 expression was assessed using the PD-L1 combined positive score (CPS) via the PD-L1 28 – 8 and 22C3 immunohistochemistry assays. Based on the KEYNOTE-048 study, CPS was categorized into 3 groups: <1, 1–19, and ≥ 20. Platinum-refractory disease was defined as disease relapse occurring within six months of platinum-based therapy. This study was approved by the Institutional Review Board (IRB) and Ethics Committee of Taipei Veterans General Hospital. Details of ethics approval are provided in the Declarations section.

2.2 Outcomes

The primary endpoint of this study was the objective response rate (ORR), defined as the proportion of patients who achieved a complete response (CR) or partial response (PR), as assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Several secondary endpoints were evaluated, including the disease control rate (DCR), defined as the percentage of patients who achieved CR, PR or stable disease (SD); progression-free survival (PFS), defined as the duration from the initiation of combination therapy to disease progression (PD); Additionally, the duration of response (DoR) was assessed, defined as the time from the initiation of combination therapy to PD in patients who achieved an objective response.

Adverse events and laboratory abnormalities were systematically documented throughout the treatment period and graded according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE, version 5.0).

2.3 Statistical analysis

All statistical analyses were conducted using GraphPad Prism version 8.0.1. The ORR and DCR were reported as percentages with 95% confidence intervals (CIs). OS and PFS were estimated using the Kaplan-Meier method, with median OS, median PFS, and their respective 95% CIs presented. For OS estimation, patients who were still alive at the end of the study or lost to follow-up were censored at the time of their last medical visit. For PFS estimation, patients without disease progression at the end of the study or lost to follow-up were censored at the time of their last tumor imaging. To identify prognostic factors associated with OS, a univariate Cox proportional hazards model was applied to clinicopathologic variables, including ECOG performance status, smoking history, primary tumor site,

initial tumor staging, number of prior systemic treatments, and PD-L1 CPS. Variables with an insufficient number of cases in the comparison groups were excluded from univariate analysis.

Results

3.1 Patient characteristics

As depicted in Figure 1, between January 1, 2020, and July 31, 2024, a total of 353 and 237 patients underwent anti-EGFR therapy and immunotherapy, respectively. Cross-referencing these cohorts identified 38 individuals who received concurrent treatment. Nine patients were subsequently excluded due to mortality within one month (n=4) or loss to follow-up (n=5). Ultimately, the final cohort comprised 29 patients with R/M HNSCC treated with the combination regimen.

Figure 1. Patient Enrollment Flowchart

A total of 353 patients received anti-EGFR therapy and 237 patients received immunotherapy between January 2020 and July 2024. Among them, 38 patients had received both immunotherapy and anti-EGFR therapy. After reviewing their medical history, 4 patients were excluded due to mortality within one month and 5 patients were excluded due to lost follow up. Ultimately, 29 patients who received combination therapy were included in the study.

Baseline demographics and disease characteristics are summarized in Table 1. The cohort had a median age of 60.8 years, with a male predominance (90%) and the majority of patients having an ECOG performance status of 0–1 (82%). A history of smoking was reported in 72% of patients. Most participants presented with stage III or IV disease (89%), and primary tumors were predominantly located in the oral cavity or oropharynx (73%). Among the five patients evaluated for HPV status, three were positive. Distant metastases were present in 9 patients (31%), and 17 patients (59%) had a PD-L1 combined positive score (CPS) of ≥1. Notably, 59% of the cohort had platinum-refractory disease, and 38% received the combination regimen as a second-line treatment. Cetuximab was the most common anti-EGFR agent (59%), and chemotherapy was not incorporated into the combination regimen in 16 patients (55%)

Table 1.

Patient characteristics

Patient characteristics	Total population (n=29)	%
Age, y/o (95% CI)	60.8 (56.4-65.2)	
Sex		
Female	3	10
male	26	90
ECOG PS		
0	17	58
1	7	24
2	5	18
Smoking		
Yes	21	72
No	8	28
HPV status		
Yes	2	40
No	3	60
Staging		
I	1	3
II	2	7
III	10	34
IV	16	55
Primary disease location		
Oral cavity	17	59
Oropharynx	4	14
Larynx	1	3
Hypopharynx	7	24
CPS		

Unknown	5	17
< 1	6	21
1-19	9	31
>= 20	8	28
Disease status		
Locoregional recurrence only	20	69
Metastasis	9	31
Platinum refractory*		
Yes	17	59
No	12	41
Lines of treatment prior receiving combination therapy		
0		
1	18	62
	11	38
Anti-EGFR agent during combined therapy		
Cetuximab		
Afatinib	17	59
	12	41
Receive chemotherapy during combination therapy		
Yes		
No	13	45
	16	55

* disease relapse within 6 months after platinum-based therapy

CI = confidence interval, CPS = combined positive score, ECOG PS = Eastern Cooperative Oncology Group Performance Status, EGFR = epidermal growth factor receptor, HPV = human papilloma virus

3.2 Efficacy

A total of 29 patients were evaluable for response. The best overall response for each patient is illustrated in the waterfall plot (Figure 2). As summarized in Table 2, 3 patients (10%) achieved CR, 10 (34%) achieved PR, 6 (22%) had stable disease (SD), and 10 (34%) experienced progressive disease (PD). The ORR was 44% (95% CI: 26%–64%), and the DCR was 66% (95% CI: 46%–82%). Objective responses

stratified by CPS group are presented in Table 3. CPS data were available for 25 patients. When stratified by CPS expression, responses were distributed as follows: in the CPS <1 group (n=8), 1 patient achieved CR and 2 achieved PR; in the CPS 1–19 group (n=8), there was 1 CR and 3 PRs; and in the CPS ≥20 group (n=9), 1 CR and 3 PRs were observed. Notably, all three patients who achieved CR had primary tumors located in the oral cavity, with CPS scores of 0, 2.3, and 82, respectively. These three patients received combination therapy with pembrolizumab and cetuximab as first-line systemic treatment for R/M HNSCC. Two of them also received concomitant chemotherapy consisting of cisplatin, fluorouracil, and leucovorin.

Figure 2. Waterfall Plot of Best Tumor Size Change from Baseline

Each bar represents an individual patient's best percentage change in tumor size from baseline. Positive values indicate tumor growth, while negative values indicate tumor shrinkage. The dotted lines represent the thresholds for progressive disease (≥20% increase) and partial response (≥30% decrease) based on RECIST v1.1 criteria. Patients with tumor progression are shown in red, those with stable disease in black, those with tumor reduction meeting the criteria for partial response in blue, and those with complete remission in green. Asterisks (*) indicate patients who had tumor progression with new lesions.

Table 2.

Treatment response

	Total population (n=29)
Best overall response, No. (%)	
CR	3 (10%)
PR	10 (34%)
SD	6 (22%)
PD	10 (34%)
Objective response rate, No. (%)	13 (44%)
95% confidence interval, %	26%-64%
Disease control rate, No. (%)	19 (66%)
95% confidence interval, %	46%-82%

CR = complete remission, PD = progressive disease, PR = partial response, SD = stable disease

Table 3

PD-L1 status and treatment response

	CR	PR	SD	PD
PD-L1 status, CPS (n= 25)				
< 1	1	2	2	3
1-19	1	3	2	2
≥20	1	3	2	3

CPS = combined positive score, PD = progressive disease, PR = partial response, SD = stable disease, TPS = tumor proportion score

At the time of data cutoff, 15 patients (51%) had died, while the remaining patients were still alive. 8 (28%) patients remained on combination therapy. Treatment was discontinued in 19 patients due to disease progression and in 2 patients due to withdrawal of patient preference. The median PFS was 6.9 months (95% CI: 2.9–9.2 months), and the median OS was 15.1 months (95% CI: 8.4 months–not reached). Kaplan-Meier curves for PFS and OS are illustrated in Figures 3 and 4. Among the 13 responders, the median DOR was 8.51 months (95% CI: 6.17–18.20 months). Univariate analysis identified no significant associations between clinicopathological factors and OS (Table 4).

Figure 3. Kaplan-Meier Estimates of Progression Free Survival.

Kaplan-Meier survival curves illustrating progression-free survival in patients treated with immunotherapy plus anti-EGFR therapy.

Figure 4. Kaplan-Meier Estimates of Overall survival.

Kaplan-Meier survival curves illustrating overall survival in patients treated with immunotherapy plus anti-EGFR therapy.

Table 4.

Univariate analysis

Clinicopathologic factors	Hazard ratio	95% CI	p
Smoking			
Yes	6.20	1.38-36.85	0.08
No	REF		
Primary site			
Oral cavity	1.90	0.64-5.61	0.25
Non-oral cavity	REF		
Disease status			
Metastasis	1.05	0.33-3.35	0.93
Locoregional recurrence only	REF		
Platinum refractory			
Yes	0.88	0.31-2.48	0.80
No	REF		
Previous systemic treatment			
≥ 1	0.76	0.26-2.17	0.60
0	REF		
Chemotherapy during combination therapy			
Yes			
No	1.67	0.60-4.62	0.32
	REF		
CPS			
≥ 20	0.62	0.19-2.05	0.43
< 20	REF		

3.3 Safety

As summarized in Table 5, treatment-related adverse events were reported in 23 (79%) of the 29 patients. All observed adverse events were grade 1 or 2 in severity; no grade 3 or higher events were recorded. The most common hematologic toxicity was anemia (41%), followed by leukopenia (24%). Among non-hematologic toxicities, nausea and vomiting (21%), mucositis (21%), and hyponatremia

(21%) were the most frequently observed. Grade 2 events included anemia (24%), weight loss (10%), diarrhea (10%), leukopenia (6%), mucositis (6%), and pneumonitis (3%). No treatment-related deaths occurred, and no adverse event resulted in treatment discontinuation in this study

Table 5.

Treatment related adverse events

	Total population (n = 29)		
	Grade 1	**Grade 2**	**Incidence (%)**
Blood and lymphatic system disorders			
Anemia			
Leukopenia	5	7	41.4%
Thrombocytopenia	5	2	24.1%
	2	0	6.9%
Endocrine disorders			
Hypothyroidism	1	0	3.4%
Gastrointestinal disorders			
Diarrhea	0	3	10.3%
Nausea/Vomiting	5	1	20.7%
Mucositis	4	2	20.7%
Metabolism and electrolyte			
Hypokalemia	2	0	6.9%
Hyponatremia	6	0	20.7%
Liver function impairment	3	0	10.3%
Constitutional / Others			
Weight loss	1	3	13.8%
Acne / Skin rash	4	0	13.8%
Pneumonitis	1	1	6.9%
Dysgeusia	2	0	6.9%
Decreased appetite	2	1	10.3%

Discussion

In our study, the combination regimen demonstrated promising efficacy, achieving an ORR of 44% and a DCR of 66%. The median PFS was 6.9 months, the median OS was 15.1 months, and the median DoR was 8.51 months. In comparison, the pivotal KEYNOTE-048 trial reported an ORR of approximately 17–23% and a median OS of 12 months for pembrolizumab monotherapy, while the pembrolizumab-chemotherapy arm yielded an ORR of 36–43% and a median OS of 13 months [7]. Our results compare favorably with these historical controls, demonstrating numerically higher ORR and prolonged OS.

It is worth noting that our cohort possessed less favorable baseline characteristics than the KEYNOTE-048 population. Specifically, only 59% of our patients had a PD-L1 CPS ≥ 1, compared with 85% in KEYNOTE-048. Furthermore, our study included a substantial proportion of patients with platinum-refractory disease (59%) and those receiving treatment in the second-line setting or beyond (38%)—subgroups historically associated with significantly poorer clinical outcomes.

Several Phase II studies have previously explored the synergy between immunotherapy and anti-EGFR blockade, demonstrating ORRs of 35–50% and median OS durations of 10–15 months [13–15]. Our real-world results align closely with these benchmarks, confirming that the efficacy observed in controlled clinical trials is reproducible in routine clinical practice.

Of particular note is the efficacy observed in the CPS < 1 subgroup, where an ORR of 37.5% and a DCR of 62.5% were achieved, consisting of one CR, two PR, and two SD. Historically, immunotherapy response rates in this population have ranged from 10% to 30%. [3, 7, 16] Consequently, our findings suggest that this combination regimen may help circumvent the limitations associated with low PD-L1 expression and offer additional clinical benefit to this subgroup.

Immunotherapy and anti-EGFR agents are generally regarded as relatively safe treatment options. Mucosal inflammation and rash are the most common adverse event related to anti-EGFR agents and most are self-limited [17]. Nonetheless, immunotherapy-related adverse events (iRAEs) represent a significant clinical concern due to its potential severity and impact on patient outcomes, especially pneumonitis. Previous studies in lung cancer have explored the potential toxicity associated with the combination of immunotherapy and EGFR tyrosine kinase inhibitors (TKIs), reporting iRAEs occurred in approximately 30% of patients [18, 19]. In another phase II study, there was one patient (3.4%) experienced a Grade 2 treatment-related pneumonitis event [14]. In our study, there was also one patient experienced grade 2 pneumonitis but no grade 3 or higher adverse event report and no adverse events led to treatment discontinuation.

This study has several limitations. First, the small sample size may have contributed to increased variability and a higher risk of false-negative findings. Larger prospective studies are warranted to validate these results. Additionally, 38% of the patients had received combination therapy as second line treatment, and 59% were platinum-refractory. Both factors are associated with poor prognosis and reduced survival outcomes. Therefore, the efficacy of combination therapy warrants further investigation in treatment-naïve or platinum-sensitive populations. Lastly, as this was a retrospective analysis, patients had undergone various treatments prior to receiving combination therapy, potentially introducing

heterogeneity and bias. A randomized controlled trial is needed to more definitively assess the efficacy of combination therapy in patients with immunotherapy-refractory RM HNSCC.

Improving overall survival in patients with R/M HNSCC remains a substantial clinical challenge. This study evaluated the efficacy of combining immunotherapy with anti-EGFR agents in patients with R/M HNSCC. The results demonstrated that an objective response can be achieved with combination therapy. Furthermore, the safety profile of the regimen was acceptable, with no severe treatment-related adverse events observed. These findings suggested that the combination of immunotherapy and anti-EGFR agents may represent a viable therapeutic strategy for patients with R/M HNSCC.

Abbreviations

- HNSCC
Head and neck squamous cell carcinoma
- R/M HNSCC
Recurrent and/or metastatic head and neck squamous cell carcinoma
- EGFR
Epidermal growth factor receptor
- ICI
Immune checkpoint inhibitor
- PD-1
Programmed cell death protein 1
- PD-L1
Programmed death-ligand 1
- CT
Computed tomography
- MRI
Magnetic resonance imaging
- RECIST
Response Evaluation Criteria in Solid Tumors
- ORR
Objective response rate
- DCR
Disease control rate
- PFS
Progression-free survival
- OS
Overall survival
- HR
Hazard ratio
- CI

Confidence interval
- AEs
Adverse events
- IRB
Institutional Review Board
- CPS
Combined positive score
- TKI
Tyrosine kinase inhibitor
- mAb
Monoclonal antibody

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Taipei Veterans General Hospital (IRB number: 2024-01-016BC). The requirement for informed consent was waived by the IRB of Taipei Veterans General Hospital due to the retrospective nature of the study.

Consent for publication

Not applicable

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Not applicable.

Author Contribution

MHY and PMHC conceived the study. THC collected and analyzed the data. YCC wrote the manuscript. All authors read and approved the final manuscript.

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Not applicable.

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

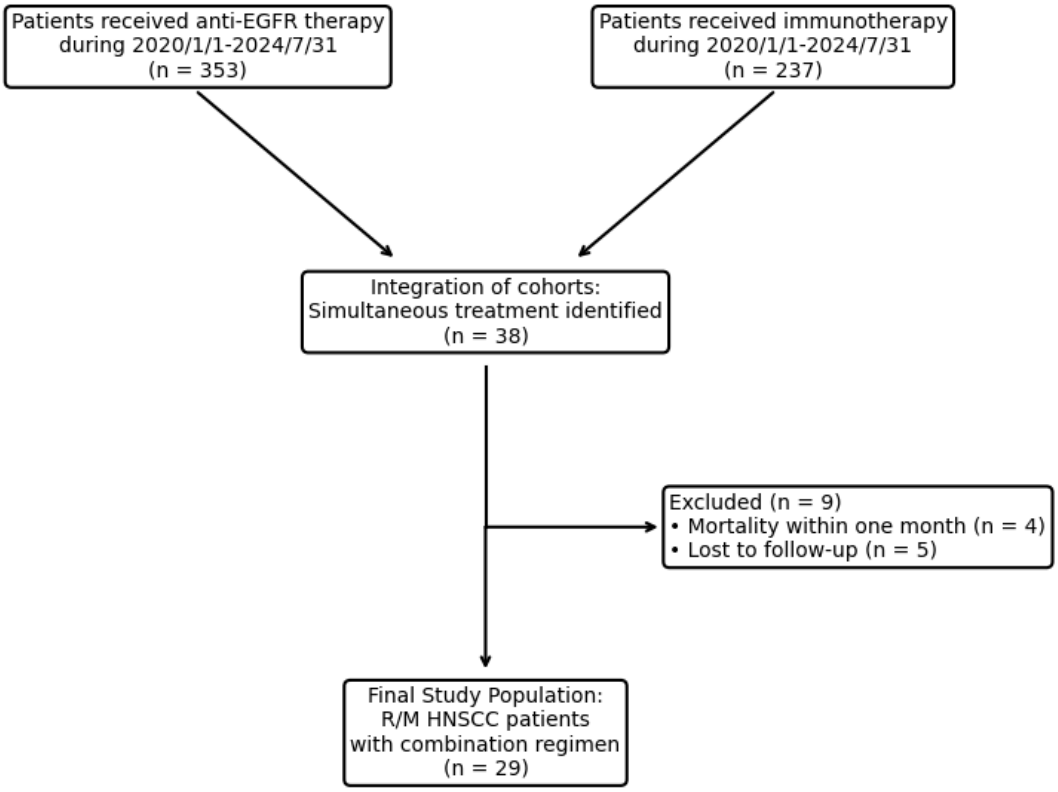


Figure 1

Patient Enrollment Flowchart

A total of 353 patients received anti-EGFR therapy and 237 patients received immunotherapy between January 2020 and July 2024. Among them, 38 patients had received both immunotherapy and anti-EGFR therapy. After reviewing their medical history, 4 patients were excluded due to mortality within one month and 5 patients were excluded due to lost follow up. Ultimately, 29 patients who received combination therapy were included in the study.

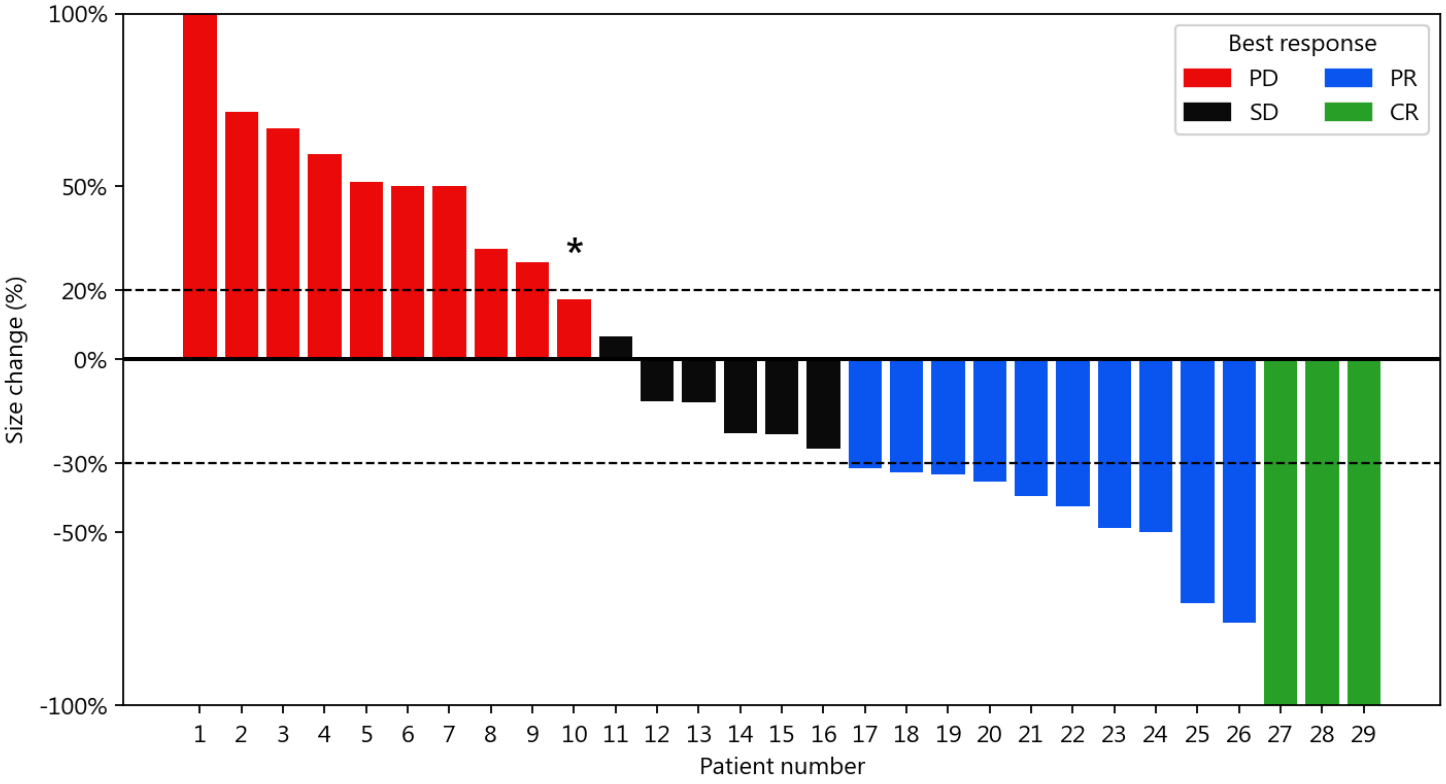


Figure 2

Waterfall Plot of Best Tumor Size Change from Baseline

Each bar represents an individual patient's best percentage change in tumor size from baseline. Positive values indicate tumor growth, while negative values indicate tumor shrinkage. The dotted lines represent the thresholds for progressive disease (≥20% increase) and partial response (≥30% decrease) based on RECIST v1.1 criteria. Patients with tumor progression are shown in red, those with stable disease in black, those with tumor reduction meeting the criteria for partial response in blue, and those with complete remission in green. Asterisks (*) indicate patients who had tumor progression with new lesions.

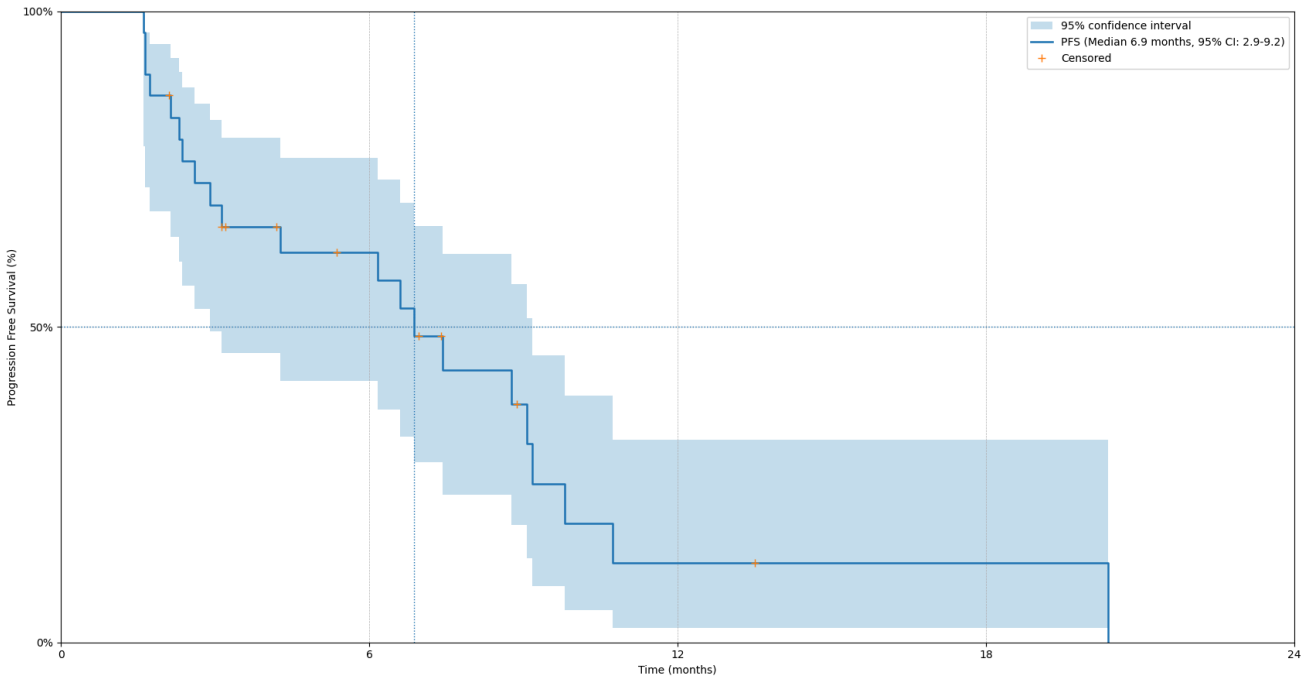


Figure 3

Kaplan-Meier Estimates of Progression Free Survival.

Kaplan-Meier survival curves illustrating progression-free survival in patients treated with immunotherapy plus anti-EGFR therapy.

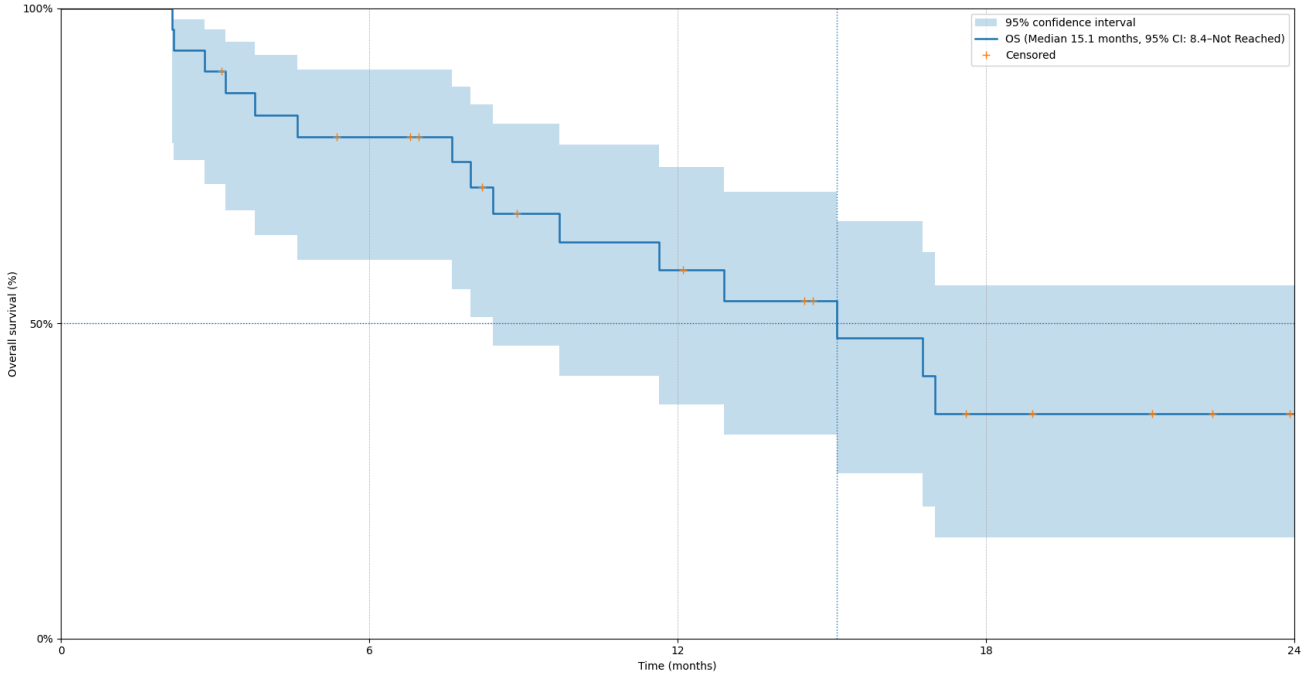


Figure 4

Kaplan-Meier Estimates of Overall survival.

Kaplan-Meier survival curves illustrating overall survival in patients treated with immunotherapy plus anti-EGFR therapy.