Cisplatin, Docetaxel and Cetuximab (TPEx) as First-line Treatment for Patients With Recurrent or Metastatic Head and Neck Cancer: A Multicenter Real-World Study

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Abstract

BACKGROUND

The association of platinum, taxanes, and cetuximab has proven to be an effective and safe strategy for head and neck cancer treatment. Here we present a multi-institutional real-world experience of the TPEx schema as first-line therapy in advanced squamous cell carcinoma of the head and neck (SCCHN).

METHODS

This retrospective multicenter cohort study included patients with histologically confirmed recurrent or metastatic SCCHN treated with first-line TPEx regimen at five medical centers in Argentina between January 1, 2017, and April 31, 2020. Chemotherapy consisted of four cycles of docetaxel, cisplatin, and cetuximab, followed by cetuximab maintenance. Clinical outcomes and toxicity profiles were evaluated.

RESULTS

Twenty-four patients were included. Median age at diagnosis was 58 years (range 36-77). The majority of patients (83.3%) received at least four chemotherapy cycles in the initial part. In the included group, overall response rate was 62.5%, and three patients achieved a complete response (12.5%). The median time to response was 2.4 months (95% CI 1.3-3.5). With a median follow-up of 12.7 months (95% CI 8.8-16.6), the median progression-free survival was 6.9 months (95% CI: 6.5-7.3), and the overall survival rate at 12 months was 82.4%. Two-thirds of patients reported at least one treatment-related adverse event, and 25% presented grade 3-4 toxicities.

CONCLUSIONS

TPEx was an adequately tolerated regimen in our population. Median progression-free survival and overall response rates were consistent with recent reports in clinical trials evaluating this treatment combination.

1. Introduction

Squamous cell carcinoma of the head and neck (SCCHN) represents 5% of all newly diagnosed cancers, leading to over 300,000 deaths per year[1]. Despite appropriate primary treatments, in about 50% to 60% of patients with stage III to IV disease, loco-regionally relapse is evidenced[2]. Given that a significant proportion of these cases are not suitable for surgery or radiotherapy, systemic treatments and best supportive care are the preferred therapeutic options.

Up to the early 2000s, the median overall survival (OS) of patients with metastatic disease was only 6 months[3, 4]. This poor prognosis has encouraged significant research efforts in the last 15 years for developing novel drugs. In this setting, targeted therapy against the epidermal growth factor receptor (EGFR) cetuximab has proved substantial efficacy for recurrent or metastatic (R/M) SCCHN treatment in

combination with 5-fluorouracil and platinum-based chemotherapy (EXTREME regimen)[3]. More recently, a new strategy using the immune checkpoint inhibitor pembrolizumab alone, or in combination with 5-fluorouracil and platinum, became an appropriate first-line treatment for R/M SCCHN patients[5–7].

Under these circumstances, the EXTREME regimen still represents a recommended first-line treatment option in selected scenarios, such as cases with PDL-1-negative tumors or when immunotherapy is contraindicated. Noteworthy, this treatment regimen may represent an attractive approach for patients with disease progression after first-line immune checkpoint inhibitors given as monotherapy[8].

Taxanes have maintained widespread clinical use, particularly in solid tumors, since their discovery in the early 1970s and several clinical trials have shown its antineoplastic activity against SCCHN[9–11].

The fluorouracil substitution by a taxane seeks to take advantage of the potential immunogenic and proapoptotic synergy between cetuximab and docetaxel or paclitaxel[12, 13]. Cetuximab, platinum, and taxane-based schedules were associated with promising survival results and cytoreductive properties in clinical studies[14–18]. In this context, TPExtreme was the first large, phase 3, randomized trial comparing the TPEx regimen (cetuximab, taxane, and platinum) with the EXTREME schema at first-line setting[19]. This trial demonstrated similar efficacy outcomes in 539 R/M HNSCC patients, showing a median OS of 14.5 and 13.4 months using TPEx and EXTREME regimen, respectively. Furthermore, the TPEx arm had a more favorable toxicity profile, leading to better compliance of the planned treatment (72% vs. 44%), with fewer dose interruptions (10 vs. 27%).

Based on these considerations and given the scarce real-world studies including patients that underwent this schema, we retrospectively evaluated the efficacy and safety of the TPEx regimen as first-line therapy in patients with R/M SCCHN.

2. Patients And Methods

2.1 Study population and treatment characteristics.

This retrospective multicenter cohort study included patients between January 1, 2017, and April 31, 2020, with histologically confirmed diagnosis of R/M SCCHN, that received TPEx as first-line treatment at five medical centers in Argentina. Chemotherapy consisted of four cycles of docetaxel 75mg/m², cisplatin 75mg/m² every three weeks, and cetuximab (400mg/m2 on day 1 of cycle 1, then 250mg/m2 weekly), with systematic granulocyte colony-stimulating factor (GCSF) support at each cycle. Patients with controlled disease continued with weekly 250 mg/m2 or every-2-weeks cetuximab 500mg/m² maintenance until disease progression or unacceptable toxicity. Demographic and clinicopathological characteristics, including age, ECOG performance status, smoking status, alcohol consumption, primary site tumor, and previous treatments were collected from medical charts and entered in a predefined centralized database. Efficacy and safety information was also retrieved, and treatment strategies, responses, adverse events, and discontinuation were also documented.

Disease progression and treatment response were collected from medical charts. Treatment response was assessed by the investigator using CT or MRI scans in accordance with Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

2.2 Statistical analysis

Data was summarized by frequency and percentage for categorical variables and by median and range for continuous variables. Progression-free survival (PFS) and OS of TPEx as first-line treatment were calculated from the date of therapy initiation to first documented relapse or death due to any cause, respectively. Data was censored on the last follow-up if the patient was alive. The duration of response (DOR) was defined as the time from first complete response (CR) or partial response to progressive disease or death. Survival curves were performed using the Kaplan-Meier method, and differences between groups were calculated using the log-rank test. All statistical analyses were performed using SPSS software version 23.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

3.1 Patients characteristics

In this multicenter retrospective study, 24 patients with R/M SCCHN were included from five Argentinian medical centers. All patients received first-line chemotherapy with TPEx. Median age at diagnosis was 58 years (range 36-77), males represented 62.5% of the sample (n=15), and the majority had ECOG 0-1 (22, 91.7%) (Table 1). Smoking history was reported in 13 patients (54.2%), and around one-third of the cases reported alcohol consumption. Of note, only two patients (8.3%) had a body mass index (BMI) < 18.5.

Previous treatments included definitive concomitant chemoradiotherapy (33.3%), surgery (20.8%), surgery plus radiotherapy (12.5%), chemoradiotherapy (20.8%), and definitive radiotherapy alone (4.2%). Approximately half of the population had previously received cisplatin (n=13, 54.2%), and only two cases (8.3%) had metastatic disease at diagnosis. The most common reason for treatment discontinuation was disease progression (58.3%), and only two patients (8.3%) discontinued treatment prematurely due to unacceptable toxicity. Notably, most cases (83.3%) received at least four chemotherapy cycles in the induction part.

3.2 Efficacy

A total of three patients achieved a complete response (12.5%), and in half of the cases a partial response was documented (Table 2). Remarkably, most of the cases benefited from TPEx therapy since the overall response rate (ORR) and disease control rate (DCR) were 62.5 and 87.5%, respectively. The median time to response was 2.4 months (95% CI 1.3-3.5).

No statistical differences were observed in terms of ORR or DCR among patients with only locoregional recurrence prior TEPx initiation compared to the rest of the included population (ORR 50% [7/14], DCR

85.7% [12/14], and ORR 80% [8/10], DCR 90% [9/10], respectively; p=0.21 and p=1.0).

After a median follow-up of 12.7 months (95% CI 8.8-16.6), 14 progression events occurred. Median PFS and DOR were 6.9 months (95% CI 6.5-7.3) (Fig. 1) and 5.1 months (95% CI 3.0-7.2), respectively (Fig. 2). As expected, patients with documented tumor response showed a better PFS compared to the population with disease stabilization or progression (8.5 months [95% CI 5.9-11.1] and 4.5 months [95% CI 4.0-5.0], respectively; p=0.034) (Fig. 3). Notably, in the two out of three cases with documented CR a substantially longer PFS (22.3 and 18.8 months) and DOR (16.6 and 16.9) were observed. The OS rate at 12 months was 82.4%. Remarkably, among the 14 patients that experienced disease progression with TPEx, 13 received second-line treatment with immunotherapy (pembrolizumab [n=9] and nivolumab [n=4]).

3.3 Safety and adverse events

Two-third of the patients reported at least one treatment-related adverse event and 25% at least one grade 3-4 adverse event. A summary of the safety profile is listed in table 3. The most commonly reported hematological adverse events were febrile neutropenia (12.5%), anemia (12.5%), and hyponatremia/hypokalemia (12.5%). Among non-hematological events, acne-like rash was the most frequent (33.3%) related adverse event. Grade 3-4 nausea-vomiting, asthenia, and renal failure were noted in 4.2% of the cases. Only one patient experienced a grade 1 hypersensitivity reaction during taxane infusion.

Overall, serious adverse events were reported in five patients (20.8%). Three of them developed febrile neutropenia, one acute renal failure, and the remaining patient was hospitalized due to grade 3 vomiting that required intravenous hydration. All cases continued treatment after resolving the toxicity. The median duration of hospitalization among patients with severe adverse events was six days (range 2-22). Additionally, no fatal events were reported. Globally, TPEx was associated with a low rate of adverse events leading to treatment interruption (12.5%), discontinuation (8.3%), or dose reduction (8.3%).

4. Discussion

Despite substantial advances in the last decade, R/M SCCHN remains a significant clinical issue, given its associated high mortality rate. In this context, tumor response rate is an important goal in these patients given its association with symptoms improvement and better quality of life.

Over the past years, the EXTREME regimen became a preferred first-line strategy in R/M SCCHN patients[3]. While significant improvement in OS, PFS, and ORR was demonstrated in the cetuximab plus platinum–fluorouracil arm of the pivotal phase 3 trial, 82% of the included patients experienced grade 3-4 adverse events, mostly related to 5-fluorouracil continuous infusion. Of note, all these findings were observed in fit patients, hence treatment decisions in this setting should be analyzed on a case by case basis. Clinical comorbidities, performance status, nutritional assessments, access to infusion pumps, or even availability for patient hospitalization are some of the considerations made in clinical practice before treatment definition.

Given that not all patients can tolerate the EXTREME regimen, alternative treatment protocols were developed, mostly replacing 5-fluorouracil by taxanes. The phase 2 GORTEC study evaluated fifty-four patients with R/M SCCHN using cisplatin, docetaxel, and cetuximab in the first-line setting[14]. Median OS, PFS, and ORR were 14 months, 6.2 months, and 44.4%, respectively. In this selected population, only 12 patients (22.2%) experienced grade 4 adverse events. In another phase 2 trial, Bossi et al. randomized 201 patients with R/M SCCHN to first-line cetuximab plus cisplatin with or without paclitaxel[15]. Authors reported a median PFS of 7 months and an ORR of 51.7% in the cetuximab, cisplatin, and paclitaxel arm. With this regimen, 72.5% and 33% of the included patients presented grade ≥3 and 4 adverse events, respectively.

Guigay and collaborators have recently published the results of a phase 3 trials that compared TPEx with EXTREME as first-line treatment in 539 patients[19]. Overall survival, PFS and ORR were 14.5 vs. 13.4 months, 6.0 vs. 6.1 months, and 46 vs. 40%, respectively, not finding significant differences between both arms. TPEx regimen was associated with 30% grade 4 adverse events, which was significantly lower than the 43% incidence reported with the EXTREME schema. Furthermore, an exploratory analysis of this trial showed a better quality of life in patients who received TPEx, mainly in global health status, physical functioning, role functioning, and scores of appetite[20].

Remarkably, real-world data in this setting is scarce. Before the GORTEC trial, Guigay and collaborators presented the results of 30 patients treated with TPEx at Gustave Roussy Institute between 2011 and 2013[21]. In this group of patients, median PFS and OS were 6.0 and 13.6 months, respectively. A total of eight grade 3-4 adverse events were documented, including vomiting, mucositis, skin rash, diarrhea, hypersensitivity, and neutropenia. Additionally, Fuchs et al. reported similar results in a retrospective single-institution study, including 38 R/M SCCHN patients treated with TPEx at the Medical University of Vienna[22]. In this study, the median OS, PFS, and ORR were 10.8 months, 6.3 months, and 50%, respectively.

To the best of our knowledge, our study represents the first multicenter real-world data, including South-American patients treated with the TPEx schema. Notably, PFS and ORR were consistent with the previous clinical trials. Intriguingly, two patients with complete responses were associated with longer PFS, which may support that depth of response could be studied as a prognostic factor in patients with R/M HNSCC.

In our experience, the TPEx regimen was adequately tolerated by most of the analyzed patients. The incidence of grade 3-4 adverse events was surprisingly lower than expected (25%), but it should be noted that five patients had treatment-related hospitalizations. Fortunately, no fatal toxicities were experienced.

Our experience confirms that the substitution of 5-fluorouracil by docetaxel may be a reasonable treatment strategy for R/M SCCHN patients. TPEx was incorporated as a standard regimen in our centers, considering that this regimen is associated with a lower duration of treatment infusions, lower total number of cycles, and the recent reports of safety and quality of life outcomes. These particularities are

essential in low- and middle-income countries with limited access to infusion pumps. Furthermore, the instauration of simplified regimens has become of extreme importance during the COVID-19 pandemic[23].

Our results should be interpreted with caution considering study limitations. This real-world data study was conducted in five private care centers, which can impact the high proportion of patients with access to immunotherapy after disease progression (92.9%). The low number of included patients and the study retrospective nature may also hamper the extrapolation of our results to Hispanic and Latino-American populations. Additionally, our follow-up is not long enough to adequately analyze OS in our sample.

Finally, it should also be highlighted that the landscape in R/M SCCHN is evolving. First-line treatment strategies currently include immunotherapy given alone or in combination with chemotherapy[7]. Nevertheless, TPEx represents an adequate alternative for patients with R/M HNSCC without PDL-1 expression or as a subsequent treatment after disease progression with immune checkpoint inhibitors given as a monotherapy. It should be emphasized that drugs combination regimens, such as TPEx, have proven to be associated with higher ORR, which is particularly beneficial in patients with high tumor burden.

5. Conclusions

TPEx was a well-tolerated regimen in our population. Clinical outcomes, such as PFS and ORR, were comparable to the recently reported clinical trial using the same treatment schema. This regimen may be considered an attractive therapeutic strategy due to its more simplified administration, the total number of chemotherapy cycles, treatment tolerability. In this context, quality of life, cost of hospitalizations, and adverse event management should be carefully analyzed before deciding the best therapeutic plan for patients with R/M SCCHN.

Abbreviations

R/M SCCHN: recurrent or metastatic squamous cell carcinoma of the head and neck; EGFR: epidermal growth factor receptor; PFS: Progression-free survival; OS: Overall survival; TPEx regimen: cetuximab, taxane, and platinum; CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group PerformanceStatus; HPV: Human papillomavirus; DOR: Duration of response; IQR: interquartile range, NS: not specified.

Declarations

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Authors’contribution

Study concept and design: AF; Data acquisition and quality control of data: AF, ML, AB, GC, DE, FW; Data analysis and interpretation: AF, ML, AB, DE, FW; Manuscript preparation and editing: All authors; Manuscript review: All authors; All authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Alexander Fleming Institute. The requirement for written informed consent was waived owing to the retrospective nature of the study

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Clinicopathological characteristics	
Characteristics	Number of Patients (%)
Total	24
Median age (range), years	58 (36-77)
Sex	
Male	15 (62.5)
Female	9 (37.5)
ECOG at TPEx initiation	
0-1	22 (91.7)
2	2 (8.3)
Smoking History	
Never	6 (25)
Current or former	13 (54.2)
NS	5 (20.8)
Alcohol consumption	
Occasional or Regular	8 (33.3)
No	7 (29.2)
NS	9 (37.5)
Primary tumor site	
Larynx	7 (29.2)
Oropharynx	6 (25)
Oral cavity	5 (20.8)
Hypopharynx	1 (4.2)
Other	5 (20.8)
p16 status (oropharyngeal carcinoma)	
Positive	4 (66.7)
Negative	0
NS	2 (33.3)

Previous treatment	
Concomitant chemoradiotherapy only	8 (33.3)
Surgery only	5 (20.8)
Surgery + concomitant chemoradiotherapy	5 (20.8)
Surgery + radiotherapy	3 (12.5)
Radiotherapy only	1 (4.2)
No	2 (8.3)
Extent of disease at TPEx initiation	
Locoregional recurrence only	14 (58.3)
Locoregional recurrence + distant metastatic	5 (20.8)
Metastatic disease	5 (20.8)
Time from initial diagnosis to recurrence (median, IQR), months	16.2 (5.4-37.5)
Metastatic or unresectable disease at diagnosis	11 (45.8)
Abbreviations: NS, not specified; ECOG, Eastern Cooperative Oncology Group; HPV, human papilloma virus; IQR, interquartile range.	

Table 2. Summary of treatment response	
	TPEx (N = 24)
Type of response — no. (%)	
Complete	3 (12.5)
Partial	12 (50)
Stable disease	6 (25)
Progression	1 (4.2)
Non-assessable	2 (8.3)
Objective response rate - % of patients (95% CI)[a]	62.5
Disease-control rate - % of patients (95% CI)[b]	87.5
Time to response - mo[c]	
Median (95% CI)	2.4 (1.3-3.5)
Duration of response - mo[d]	
Median (95% CI)	5.1 (3.0-7.2)

a. Objective response was considered to be a confirmed complete or partial response, as assessed by investigator.

b. The disease-control rate was considered to be a confirmed complete response, a partial response, or stable disease, as assessed by investigator.

c. Time to response was calculated with the use of the Kaplan-Meier method from the date of TPEx initiation to the date of the first documentation of a partial or complete response.

d. Duration of response was calculated with the use of the Kaplan-Meier method from the date of the first documented response until the date of documented disease progression, death, or the last response assessment in the absence of disease progression.

Table 3. Adverse events of any cause during TPEx treatment.		
Event n (%)	TPEx (N = 24)	
	Any Grade	Grade 3-4
Any treatment-related adverse event[a]	18 (75)	6 (25)
Hematological		
Febrile neutropenia	3 (12.5)	3 (12.5)
Anemia	3 (12.5)	0
Hyponatremia and/or hypokalemia	3 (12.5)	2 (8.3)
Hypomagnesemia	2 (8.3)	1 (4.2)
Thrombocytopenia	1 (4.2)	0
Non-hematological		
Acne-like rash	8 (33.3)	0
Nausea - Vomiting	4 (16.7)	1 (4.2)
Asthenia	4 (16.7)	1 (4.2)
Diarrhea	2 (8.3)	0
Renal failure	1 (4.2)	1 (4.2)
Hypersensitivity	1 (4.2)	0
Oral mucositis	1 (4.2)	0
Any serious adverse event[b]	-	5 (20.8)
Treatment-related deaths	0	-
Event leading to interruption of any treatment component[c]	3 (12.5)	-
Chemotherapy	2 (8.3)	-
Cetuximab	1 (4.2)	-
Event leading to discontinuation of any treatment component[c]	2 (8.3)	-
Chemotherapy	2 (8.3)	-
Cetuximab	0	
Event leading to dose reduction	2 (8.3)	-

a. The investigators determined whether adverse events were related to the treatment.

b. Adverse events that leaded hospitalization.

c. This category includes patients who interrupted or discontinued cisplatin, docetaxel, or cetuximab because of an adverse event at any time and patients who interrupted or discontinued cetuximab maintenance for an adverse event after completing the cycles of chemotherapy. Events were attributed to the specific treatment by the investigator.

Figures

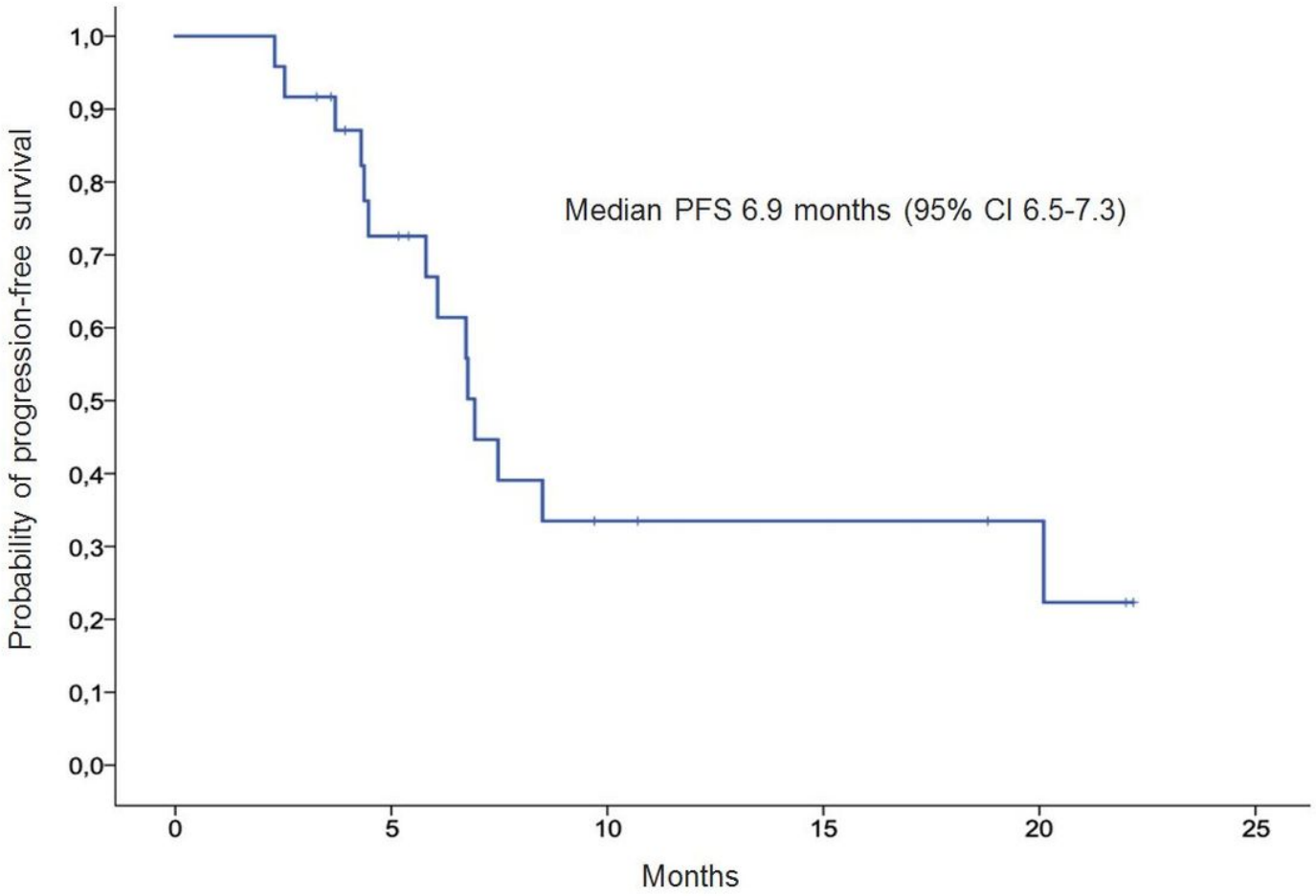

Figure 1

Kaplan–Meier curves for progression-free survival (PFS).

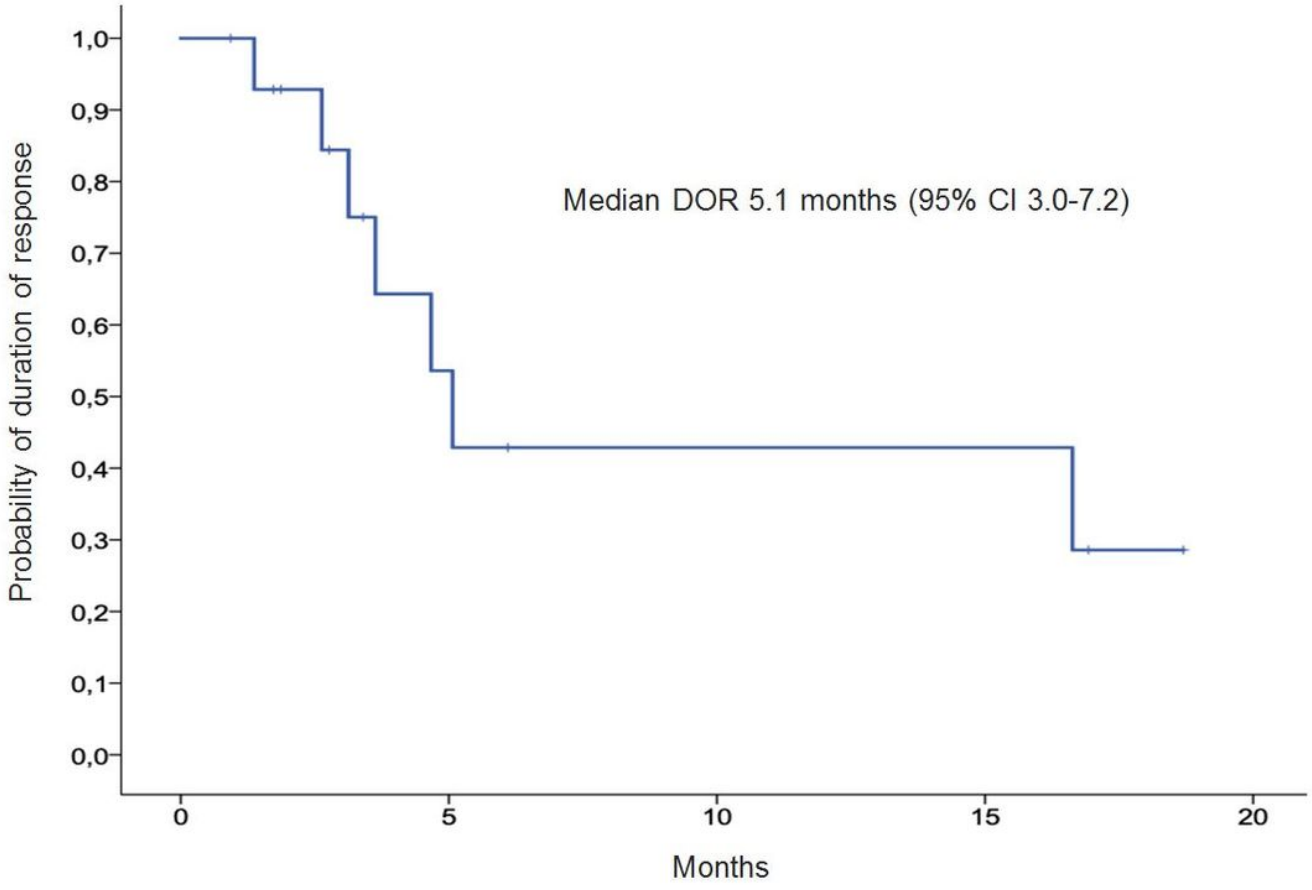

Figure 2

Kaplan–Meier curves for duration of response (DOR).

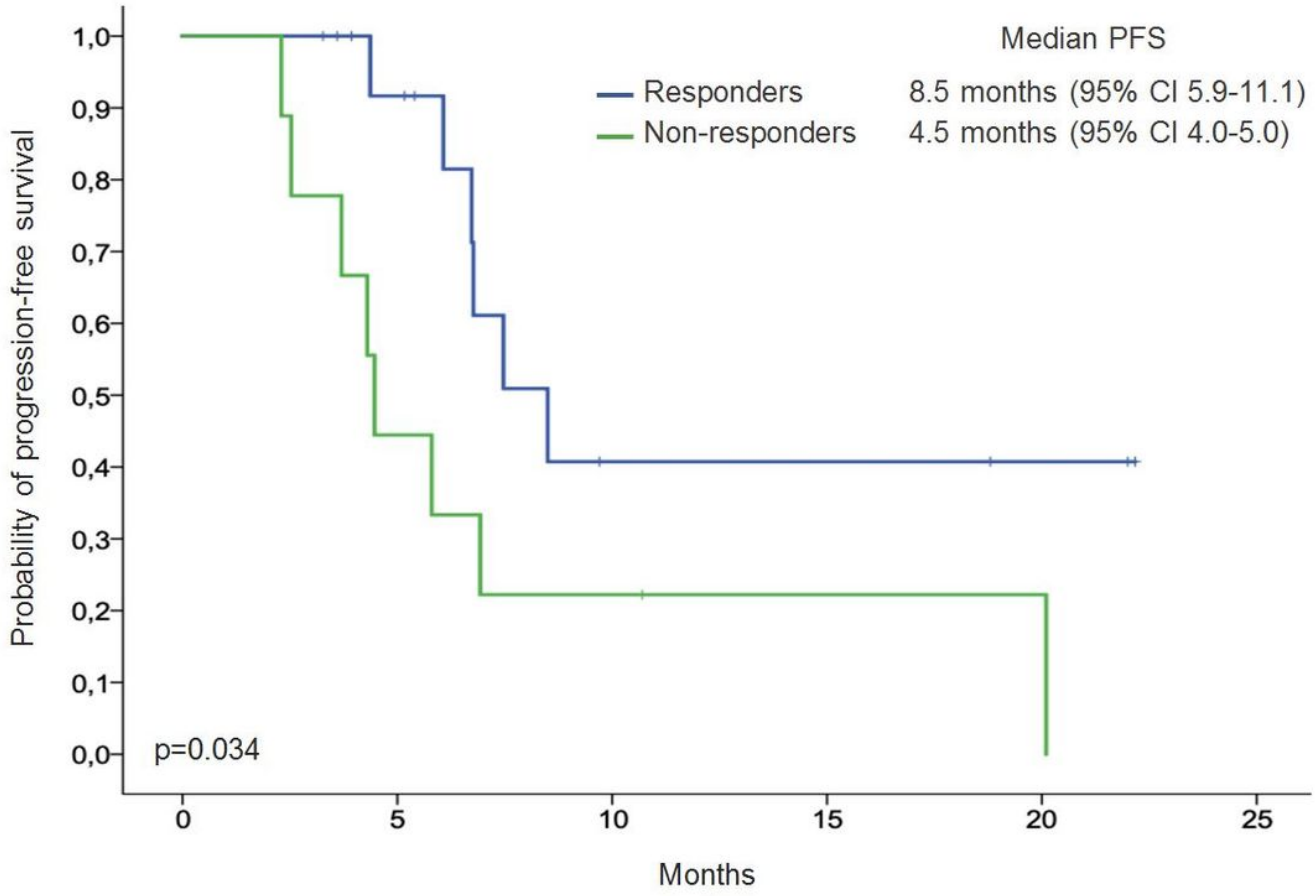

Figure 3

Kaplan–Meier curves for progression-free survival (PFS) according to response.