

Six-Weekly Low-Dose Nivolumab Combined with Oral Triple Metronomic Chemotherapy for Advanced Cancers of the Head and Neck: An Open-Label, Prospective, Single-Institution Experience from Eastern India

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Abstract

Background

Pembrolizumab added to cisplatin and 5-fluorouracil (5FU) lengthens overall survival (OS) relative to chemotherapy alone in non-nasopharyngeal squamous carcinoma of head and neck origin (HNSCC) that is unresectable, relapsed or already spread. Cost restricts this option to fewer than 3% of otherwise eligible patients in India. Indian investigators have reported that an oral metronomic triplet combined with nivolumab 20 mg every three weeks achieves an OS of comparable magnitude. We set out to record what happens clinically when the same antibody is given as 40 mg once every 6 weeks alongside that triplet.

Methods

An open-label, single-arm, phase III design was adopted. Adults whose HNSCC had relapsed, spread or was inoperable received an oral metronomic triplet [TMC (Methotrexate, Erlotinib, Celecoxib)] of erlotinib 150 mg daily, celecoxib 200 mg two times a day and methotrexate 9 mg/m² weekly, to which intravenous nivolumab (N) 40 mg was added once every 6 weeks. Median PFS was the primary endpoint; OS, response rate, and response duration were secondary.

Results

Sixty-five participants received N + TMC; twenty (30.8%) had prior cisplatin exposure. Median PFS was 8.0 months, the 95% CI spanning 7.63–8.37. Complete (CR) and partial (PR) responses together yielded a 6 month response rate of 56.93%, with CR contributing 23.08%. Outcomes did not diverge appreciably by platinum status. One-year survival stood at 37.5%, with a median OS of 11.63 months [95% CI 9.73–13.53]. Median survival reached 11.67 ± 4.81 months in males against 8.72 ± 3.36 months in females ($P = 0.014$). Fatigue affected sixty-two patients (95.3%); events of grade 3 or worse comprised mucositis (9.23%), anaemia (9.23%) and rash in 4.62%. No immunologic adverse event and no treatment-attributable death occurred.

Conclusions

In relapsed, metastatic or inoperable HNSCC, N 40 mg every 6 weeks with TMC yields OS and PFS matching those of fortnightly nivolumab, of three-weekly pembrolizumab with chemotherapy, and of three-weekly N plus TMC, while requiring fewer hospital attendances, less expenditure and less disruption of the patient. Tolerability was acceptable, and the schedule was more affordable.

BACKGROUND

Head and neck malignancy ranks sixth among tumours worldwide, and economically developing countries bear a heavier burden of head and neck cancer (HNC) than industrialised ones.[1, 2] Roughly 90% of HNC diagnoses are squamous cell carcinomas, the entity abbreviated hereafter as HNSCC.[3, 4] Sites of origin are chiefly the oral cavity, the pharyngeal subsites and the larynx, all lined by the epithelium common to the aerodigestive tract.[4–6]

Once HNSCC has relapsed or spread, first-line pembrolizumab, given with a platinum agent and 5-fluorouracil, extends survival beyond that of cetuximab-based chemotherapy, a finding that has established checkpoint blockade in routine practice.[7]

NCCN (National Comprehensive Cancer Network) guidance positions immunotherapy as a preferred first-line option where relapsed or spread tumours express PD-L1 (programmed death ligand 1).[8] Guidance issued jointly under the EHNS-ESMO-ESTRO banner similarly directs that systemic treatment be considered once HNSCC lies beyond curative measures, and places checkpoint-inhibitor schedules at the core of palliative care.[9]

Standard management combines resection of the primary with neck nodal clearance, followed by radiotherapy or chemoradiation for early or locally advanced disease.[6, 10, 11] Once the disease is advanced, 5-year OS approaches 50%, and the outlook worsens further after relapse or distant spread.[12–14]

These outcomes persist despite therapeutic progress, making the search for further strategies to improve survival in HNSCC an urgent one.

Nivolumab, an immune checkpoint inhibitor (ICI), yields responses in roughly 13% of platinum-refractory cases, with a durable benefit corresponding to median PFS and OS of 2 and 8 months, respectively.[15] Its principal target is the T cell, and the conventional infusion schedule has been 3 mg/kg fortnightly (15). Interrupting this axis restores the capacity of T-cells to attack the tumour.[16] Occupancy of the PD-1 (programmed cell death protein 1) receptor still reaches 70% at reduced doses, so median PFS and OS may match those of full dosing while cost falls sharply.[17–19] Retrospective series across several tumour sites, ours among them, likewise indicate that nivolumab remains useful at low doses.[20–23]

This reflects a move towards biologically effective doses (BED) and away from the maximum tolerated dose (MTD) that phase I work yields; for antibodies and targeted compounds, the BED generally lies well beneath it.[24] Four cycles of conventionally dosed nivolumab over two months cost about Rs 400,000, whereas an effective lower dose reduces that outlay fivefold.[21] On that basis, we examined survival, safety and quality of life with reduced-dose nivolumab in advanced HNC.

METHODS

This prospective observational study was run by the Department of Medical Oncology at IMS and SUM Hospital, Bhubaneswar, Odisha. Every patient with newly diagnosed or relapsed metastatic HNSCC

coming to the institution for treatment formed the target population. Enrolment spanned two years, 2023 to 2025. Because the window was fixed, all such patients attending for consultation or treatment in that period were taken up once consent had been recorded, giving a final sample of 65 and making the sampling universal.

Adults of 18 years or above with histologically proven HNSCC, newly diagnosed or relapsed, inoperable or already spread, were eligible. Also required were performance status 0 or 1 on the ECOG scale, a plan for palliative systemic therapy, haematological and biochemical indices within acceptable limits, and one or more lesions measurable under RECIST version 1.1. Platinum-sensitive and platinum-refractory disease were equally acceptable. Written consent preceded entry in every case.

Exclusion followed from concurrent investigational or immunosuppressive treatment, a history of autoimmune disease, or poorly controlled chronic illness liable to compromise participation or confound outcomes. Pregnancy or lactation, age under 18 years, and unwillingness or inability to give written consent likewise barred entry.

Data were compiled in Microsoft Excel 2007 and analysed in SPSS 27 (IBM Corp., Armonk, USA). Categorical data appear as counts with percentages and continuous data as means with standard deviations. Associations between paired categorical variables were tested by Fisher's exact or the chi-square test. Kaplan-Meier modelling supplied mean and median survival estimates. A p-value below 0.05 denotes significance.

RESULTS

Sixty-five individuals received N + TMC. Median age was 51 years, with 42 (64.6%) under 60. Median follow-up ran to 304 days (IQR 204–390). Males numbered 44 (67.7%) (Table 1). Oral cavity primaries dominated at 87.7%. Stage IV accounted for over two-thirds (70.8%); the rest had locally advanced or relapsed disease at the site of origin. Radiotherapy alone had preceded entry in 21 (32.3%), surgery alone in 32 (49%) and chemoradiation in 20 (30.8%). Every patient chewed tobacco, and 23 (35.4%) also smoked (Table 1).

Table 1
Demographic characteristics of the study
population (N = 65)

Demographic Factor	n	%
Age		
Less than 60 years	42	64.6
60 years and above	23	35.4
Gender		
Male	44	67.7
Female	21	32.3
Site of cancer		
Oral	57	87.7
Non-oral	8	12.3
Stage of cancer		
Locally Advanced	11	16.9
Recurrent	8	12.3
Stage IV	46	70.8
Previously received radiotherapy		
Yes	21	32.3
No	44	67.7
Previously undergone surgery		
Yes	32	49.2
No	33	50.8
Previously received chemoradiotherapy		
Yes	20	30.8
No	45	69.2
Chewing tobacco		
Yes	65	100.0
Smoking status		
Yes	23	35.4

Demographic Factor	n	%
No	42	64.6
Performance status score		
0	2	3.1
1	19	29.2
2	35	53.8
3	9	13.8

Insert Table 1

Haematological, hepatic and renal indices at baseline lay within reference limits. Only two (3.1%) had hypothyroidism before enrolment. Most had ECOG PS 2, as detailed in Table 1. By Kaplan-Meier estimation, OS averaged 13.34 [95% CI 11.78–14.90] with a median of 11.63 [95% CI 9.73–13.53]. PFS averaged 8.95 [95% CI 7.58–10.33], the median being 8.0 [95% CI 7.63–8.37] (Table 2, Fig. 1, Fig. 2).

Table 2
Survival among the study participants

Survival	Mean Survival	95% CI	Median survival	95% CI
Overall	13.34	11.78–14.90	11.63	9.73–13.53
Progression free	8.95	7.58–10.33	8.0	7.63–8.37

Insert Table 2; Figs. 1 and 2

Neither OS nor PFS was statistically associated with age ($p > 0.05$). Sex, however, mattered: mean OS reached 11.67 ± 4.81 months in males against 8.72 ± 3.36 months in females (P value = 0.014) (Table 3).

Table 3
Association of gender with survival

Survival in months	Male Mean (SD)	Female Mean (SD)	P value
Overall survival	11.67 (4.81)	8.72 (3.36)	0.014
Progression free survival	7.45 (2.46)	6.71 (3.04)	0.298

Insert Table 3

Platinum-refractory patients survived marginally longer, 11.32 ± 5.02 months versus 10.13 ± 4.11 months in non-refractory patients, a gap falling short of significance; corresponding median figures were 11.93months (8.73–15.13) and 11.50months (11.30–11.69), again non-significant (Table 4, Fig. 3, Fig. 4).

PFS was likewise unrelated to platinum-refractoriness. CR occurred in roughly one-fourth (15, 23.08%) and PR in one-third (33.85%), an ORR of 57% at six months (Table 5).

Table 4
Association of platinum refractoriness with survival

Survival in months	Platinum refractory	Non-refractory	P value
	Mean (SD)	Mean (SD)	
Overall survival	11.32 (5.02)	10.13 (4.11)	0.300
Progression free survival	7.48 (2.87)	6.95 (2.46)	0.435

Table 5
Response rate of the patients to treatment at 6 months

Complete response (CR)	Frequency	%
	15	23.08%
Partial response (PR)	22	33.85%
Overall response rate (ORR)	37	56.93%
Progression of disease (PD)	28	43.07%

Insert Tables 4 and 5; Figs. 3 and 4

Some adverse event or toxicity symptom arose in every patient (100%). Fatigue headed the list at 95.38%, followed by anaemia (86.15%), hyponatremia (70%), raised SGOT (69.23%), neutropenia (64.6%) and SGPT (58.46%). At grade 3 or beyond, the events observed were mucositis (9.23%), anaemia (9.23%), and rash, the last in 4.62% (Table 6, Fig. 5). Platinum-refractory disease accounted for 49.2% of those studied. Toxicity forced five patients (7.7%) off methotrexate and one (1.5%) off erlotinib (Table 7).

Table 6
Toxicity due to therapy among the study participants (N = 65)

Toxicity	Any grade	Grade 3 or above
Any adverse event	65 (100%)	28 (43.08%)
Anaemia	56 (86.15%)	6 (9.23%)
Neutropenia	42 (64.62%)	3 (4.62%)
Thrombocytopenia	21 (32.31%)	1 (1.54%)
Raised SGOT	45 (69.23%)	
Raised SGPT	38 (58.46%)	
Raised Bilirubin	25 (38.46%)	
Raised Creatinine	4 (6.15%)	
Hyponatremia	46 (70.77%)	2 (3.08%)
Hypernatremia	4 (6.15%)	
Hypokalaemia	7 (10.77%)	
Hyperkalaemia	1 (1.54%)	
Hypothyroidism	4 (6.15%)	
Fatigue	62 (95.38%)	3 (4.62%)
Fever	2 (3.08%)	
Diarrhoea	19 (29.23%)	
Rash	39 (60.0%)	5 (7.69%)
Constipation	6 (9.23%)	
Bleeding	2 (3.08%)	
Mucositis	50 (76.92%)	6 (9.23%)
Anorexia	30 (46.15%)	
Nausea	26 (40.0%)	
Dyspnoea	10 (15.38%)	1 (1.54%)
Dryness	54 (83.08%)	
Odynophagia	16 (24.62%)	
Paronychia	2 (3.08%)	

Toxicity	Any grade	Grade 3 or above
Vomiting	20 (30.77%)	
Pneumonia	2 (3.08%)	1 (1.54%)

Table 7
Current treatment modification among the study participants (N = 65)

Treatment modification	Frequency (%)
Platinum refractory	
Yes	32 (49.2%)
No	33 (50.8%)
Discontinued methotrexate	
Yes	5 (7.7%)
No	60 (92.3%)
Discontinued erlotinib	
Yes	1 (1.5%)
No	64 (98.5%)

Insert Tables 6 and 7; Fig. 5

Table-8 Comparison of our study results with other Indian studies and Keynote-048

Outcome	Low Dose Nivo40+TMC (6-weekly) (Our study)	Low Dose Nivo20+TMC (3-weekly) (Patil et al.)	KEYNOTE-048	TMC (Patil et al.)
OS @1Yr	11..63 months; 37.5%	10.1 months; 43.4%	11.5 months; 27% (24 months)	6.7 months; 16%
PFS	8 months	6.6 months	9 months	4.6 months
ORR	57%	59.2%	16%	45%
Time to best response	2.5 months	2.5 months	2.1 months	2.1 months

DISCUSSION

This study set out to characterise median PFS, OS, response rate and toxicity when reduced-dose Nivolumab is combined with TMC (Methotrexate, Erlotinib, Celecoxib) in HNSCC that is new, relapsed, inoperable or metastatic. CheckMate 141 allocated platinum-resistant patients 2:1 to nivolumab or to treatment of the investigator's choosing. Effects of grade 3 or worse proved less frequent on nivolumab than in the comparator arm (13% vs 35%); the antibody was also ahead on median survival, 7 months against 6 months, and on response rate (ORR; 13% vs 6%). With longer observation, projected 24-month survival on nivolumab (16.9%) was close to threefold that of investigator-choice therapy (6.0%), consistent with a genuine survival gain.[24] The methodology and comparator differ from ours, yet the trial supports the same conclusion we reached: that adding Nivolumab improves response in HNSCC.

Patil et al. randomised 151 patients to either TMC alone or TMC with Immunotherapy added (TMC-I). Introducing nivolumab at 20 mg three-weekly raised survival at one year from 16.3% to 43.4%; median OS moved from 6.7 months [95% CI 5.8 to 8.1] on TMC to 10.1 months [95% CI 7.4 to 12.6] on TMC-I (P = .0052), while events of grade 3 or beyond affected 50% and 46.1% of the arms respectively (P-value = 0.744).[25, 26] Drugs and outcomes there correspond closely to ours. The same group also followed 15 patients given palliative metronomic triplet therapy in a single-arm prospective series [27]; by 6 months, two were in complete and seven in partial remission, four had stable disease, and toxicity of grade 3 or beyond affected 40%. Harsh et al. [28] retrospectively reviewed 84 patients given oral metronomic therapy for HNC at various stages, reporting objective responses in 67%, partial responses in 11%, progression in 27% and a median survival of 6.5 months. Patil et al. had earlier audited a metronomic triplet incorporating a tyrosine kinase inhibitor in relapsed or spread disease, showing the strategy was practicable and clinically worthwhile under resource constraints, preparing the ground for pairing metronomic drugs with targeted agents.[29]

KEYNOTE-048, reported by Burtneß and colleagues as an open-label randomised phase III study across multiple centres [7], set Pembrolizumab – whose mechanism parallels that of Nivolumab – against cetuximab, and showed a survival gain of close to 4 months without a meaningful shift in PFS. The toxicity of grade 3 ran some 30% lower on Pembrolizumab alone than on cetuximab, and deaths were fewer on Pembrolizumab. Since the two antibodies share a class and a mechanism, those results serve reasonably well as a proxy for Nivolumab. Time to best response, ORR, PFS, and OS in our cohort are close to figures from other Indian series and from KEYNOTE-048 (Table 8).

Insert Table 8

CONCLUSIONS

Median OS of 11.63 months and median PFS of 8.0 months were achieved, males outliving females (11.67 ± 4.81 versus 8.72 ± 3.36 months; P = 0.014). ORR reached 57% at 6 months, with a CR of 23.08%. Fatigue dominated the toxicity profile, and events of grade 3 or beyond arose in 28 patients (43.08%), anaemia foremost among them (9.23%). So far as we are aware, no earlier study has delivered reduced-dose immunotherapy on a six-weekly cycle, with published work using fortnightly or three-weekly

intervals. Efficacy and safety matched three-weekly IO + TMC and IO + CT. For an LMIC population in which full-dose immunotherapy is unaffordable to most, this schedule represents a workable alternative standard of care.

Abbreviations

5FU

5-fluorouracil

OS

Overall Survival

HNSCC

Head & Neck squamous cell carcinoma

TMC

Triple metronomic chemotherapy

N

Nivolumab

N + TMC

Nivolumab + triple metronomic chemotherapy

CR

Complete response

PR

partial:response

HNC

Head & Neck Cancer

NCCN

National Comprehensive Cancer Network

PD-L1

programmed death ligand 1

EHNS-ESMO-ESTRO

European Head and Neck Society - European Society for Medical Oncology - European Society for Radiotherapy & Oncology

ICI

immune checkpoint inhibitor

PFS

Progression-Free Survival

PD-1

programmed cell death protein 1

BED

biologically effective doses

MTD

the maximum tolerated dose

ECOG

Eastern Cooperative Oncology Group

RECIST

Response Evaluation Criteria in Solid Tumors

SPSS

Statistical Package for the Social Sciences

IQR

interquartile range

SGOT

Serum Glutamic-Oxaloacetic Transaminase

SGPT

Serum Glutamic Pyruvic Transaminase

TMC-I

Triple metronomic chemotherapy + Immunotherapy

CI

Confidence interval

ORR

Overall Response Rate

IO

Immunotherapy

CT

Chemotherapy

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board, “INSTITUTIONAL ETHICS COMMITTEE, INSTITUTE OF MEDICAL SCIENCES (IMS) AND SUM HOSPITAL, Siksha ‘O’ Anusandhan (Deemed to be University)” (IEC/IMS.SH/SOA/2023/616; dated 10th October 2023), and patient consent was obtained. All procedures performed in our study involving human participation were in accordance with the ethical standards of the institutional and/or national research committee and in compliance with the 1964 Declaration of Helsinki and its later amendments. Consent to participate in the study and publication from all patients was informed to the institutional review board.

Consent for publication

Informed consent was obtained from all patients for both participation and the publication of their details.

Competing interests

None.

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None

Author Contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by SKS. SKS and SSP contributed to the writing of the original draft of the manuscript. SKS, SSP, and SSM contributed to writing, review, and editing. SSP provided supervision for the study. All authors did the critical revision of the final manuscript. All authors confirm that they have not used any generative AI in the writing process. All authors read and approved the final manuscript. All authors confirm that the manuscript has not been submitted elsewhere for publication

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None.

Data Availability

All data generated or analyzed during this study are included in this published article, and referenced articles are listed in the references section.

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Figures

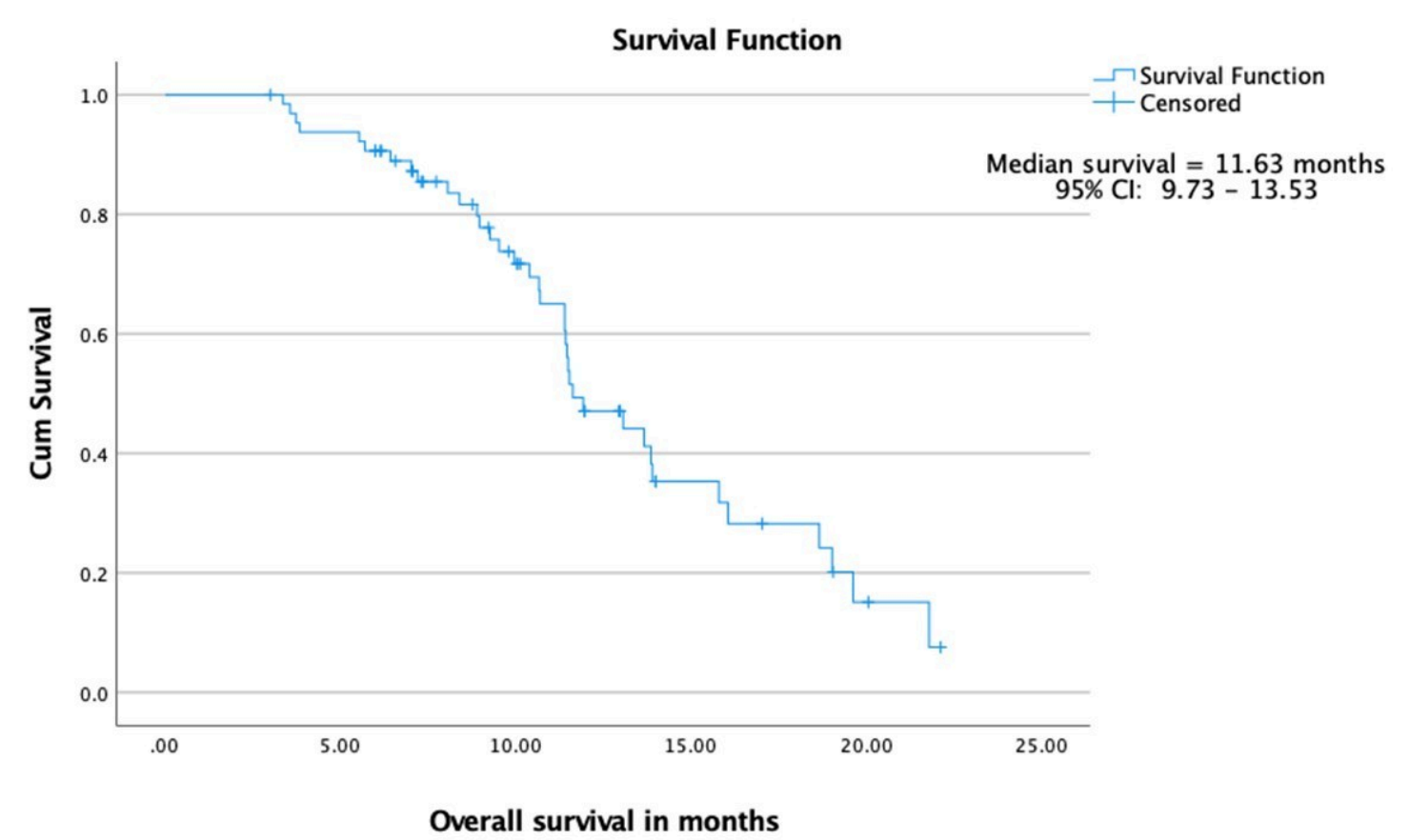


Figure 1

Kaplan-Meier survival curve for overall survival

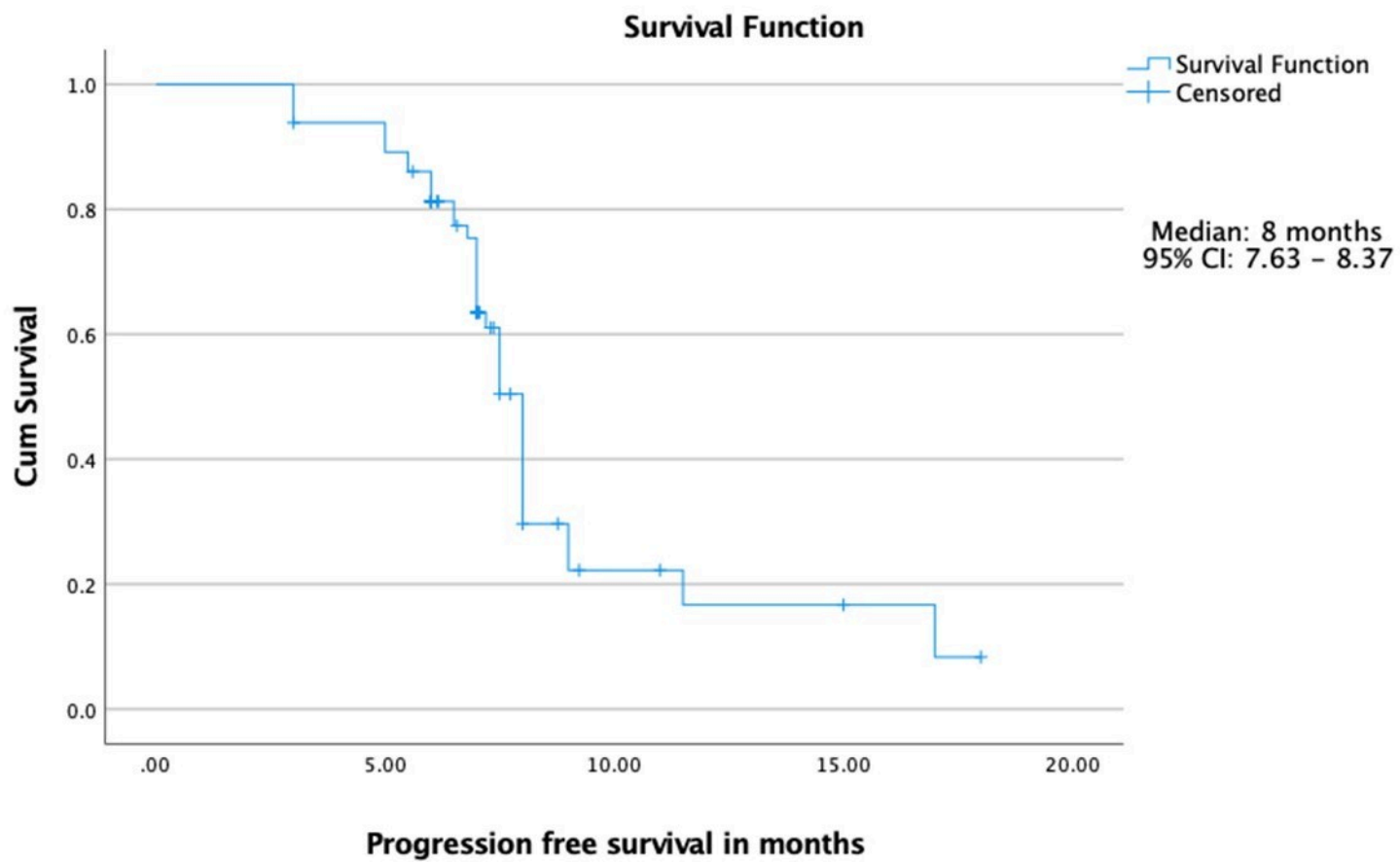


Figure 2

Kaplan-Meier survival curve for progression-free survival

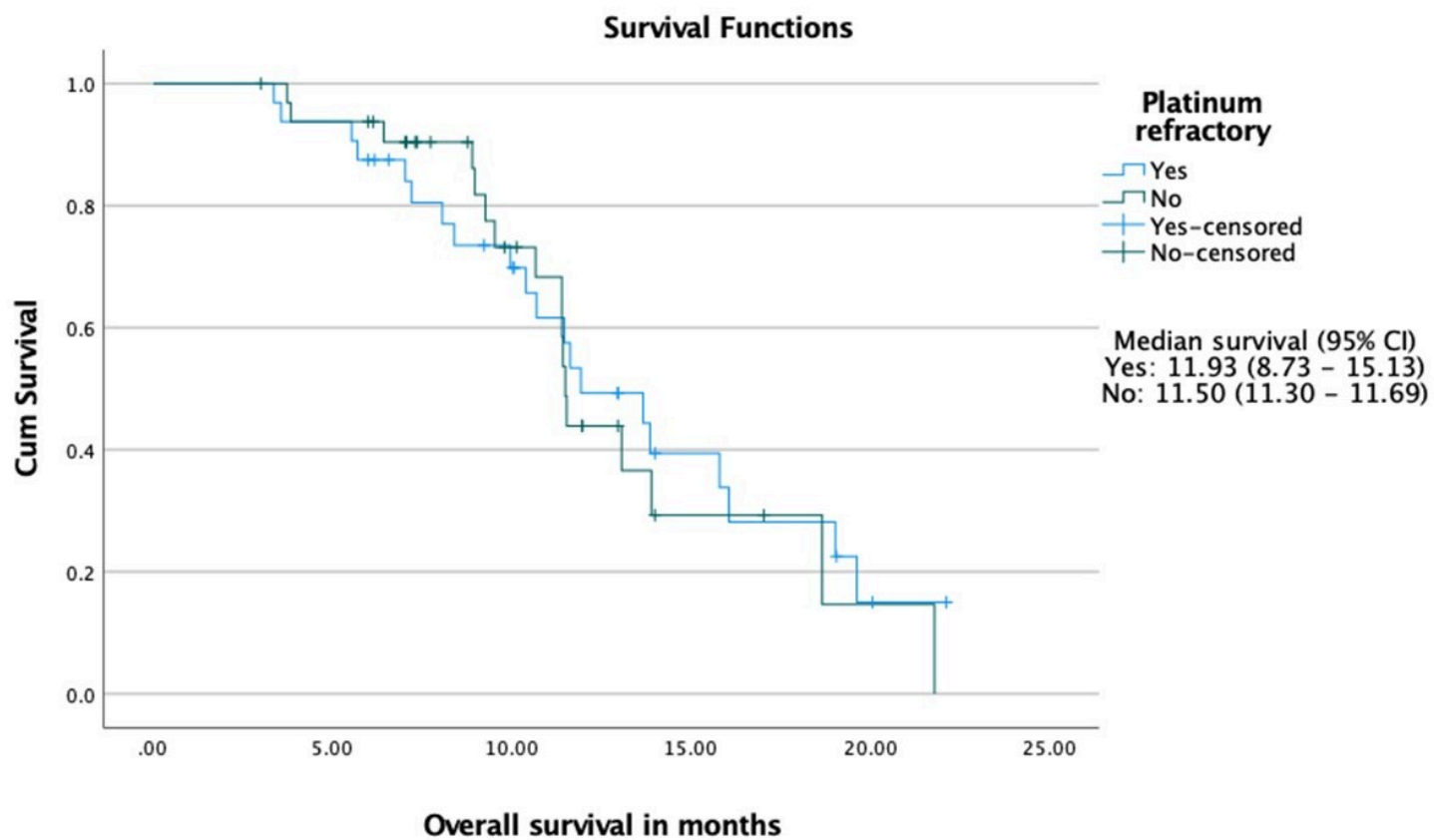


Figure 3

Comparison of the overall Kaplan-Meier survival curve for platinum refractoriness

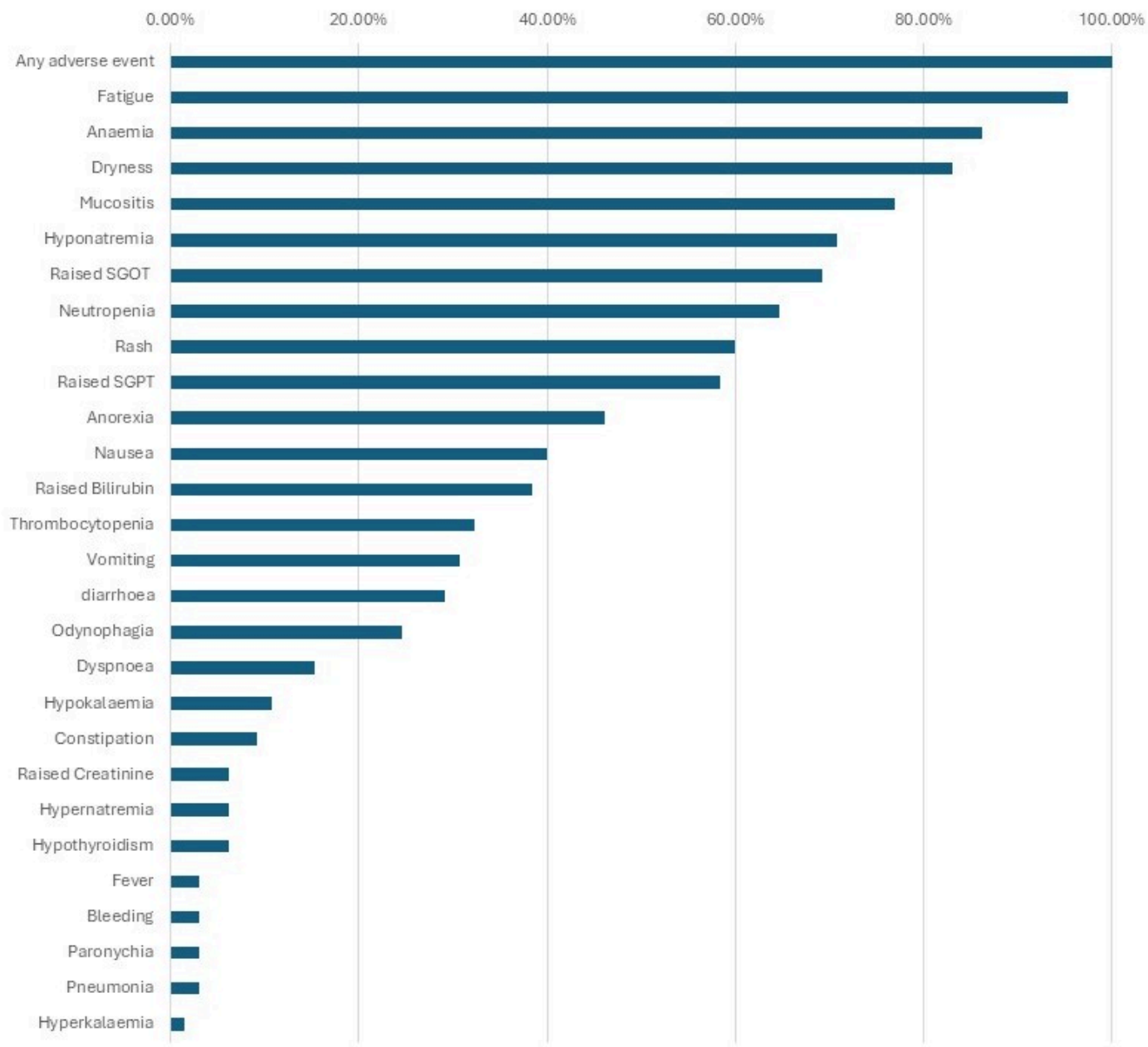


Figure 4

Comparison of progression-free Kaplan-Meier survival curve for platinum refractoriness

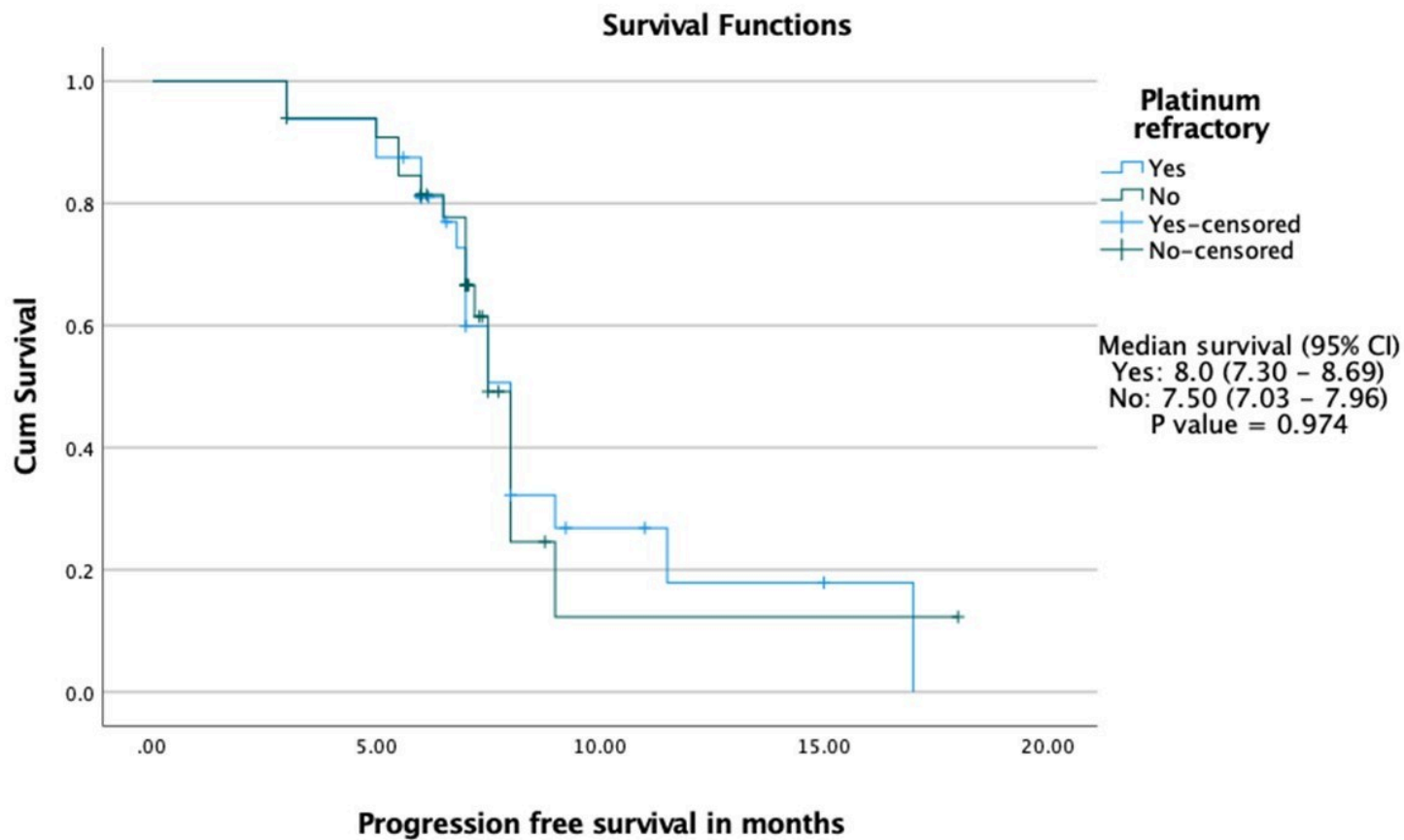


Figure 5

Toxicity irrespective of severity due to therapy among the study participants (N=65)