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Nivolumab Treatment Beyond RECIST-Defined Progression in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck in CheckMate 141: *A Subgroup Analysis of a Randomized Phase 3 Clinical Trial*

Running title: TBP with nivo in SCCHN in CheckMate 141

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PRECIS

In the randomized, open-label, phase 3 CheckMate 141 trial in patients with recurrent/metastatic squamous cell carcinoma of the head and neck post-platinum therapy, patients with stable performance status and potential for clinical benefit were permitted to receive treatment beyond RECIST-defined progression (TBP) with nivolumab; tumor burden reduction was noted in a proportion of these patients. Additional research is warranted to identify factors predictive of benefit with TBP in this population.

ABSTRACT

Background: Response patterns with immune checkpoint inhibitors may be different from those with chemotherapy. Therefore, assessment of response to immunotherapy using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 could result in premature treatment termination. The randomized, open-label, phase 3 CheckMate 141 trial (NCT02105636) evaluating nivolumab in recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN) post-platinum therapy allowed treatment beyond RECIST-defined progression (TBP) based on protocol-specified criteria.

Methods: In CheckMate 141, patients with RECIST-defined progression who had stable performance status and demonstrated clinical benefit without rapid disease progression were permitted to receive TBP with nivolumab 3 mg/kg every 2 weeks until further progression, defined as an additional ≥10% increase in tumor volume. This post hoc analysis evaluated outcomes in patients who received TBP with nivolumab.
Results: Of 240 patients randomized to nivolumab, 146 patients experienced RECIST-defined progression. Of these, 62 received TBP and 84 discontinued treatment (not TBP [NTBP]). Of 60 TBP patients evaluable for response, 15 (25%) had no change in tumor burden and 15 (25%) had reductions in target lesion size; 3 patients (5%) had reductions >30%. Median overall survival (OS) among TBP patients was 12.7 months (95% CI, 9.7-14.6). No new safety signals were observed with TBP. Exploratory analyses of immune cell biomarkers suggested a potential relationship with initial and TBP responses.
Conclusions: Tumor burden reduction was noted in a proportion of patients who received TBP with nivolumab in CheckMate 141. Additional research is warranted to identify factors predictive of TBP benefit in this population.
KEYWORDS: Immunotherapy, nivolumab, phase III clinical trials, squamous cell carcinoma of the head and neck

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INTRODUCTION

Nivolumab demonstrated significant overall survival (OS) benefit and a favorable safety profile versus investigator's choice of therapy at the primary analysis of CheckMate 141 (NCT02105636) in patients with recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN) who had experienced tumor progression or recurrence within 6 months of platinum-based chemotherapy in the adjuvant, primary (ie, with radiation), recurrent, or metastatic setting.[1] Survival and safety benefits were maintained at 1-year and 2-year follow-up.[2,3]

In CheckMate 141, tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The RECIST guidelines, which were developed for assessment of chemotherapy-treated tumors,[4] assume that early tumor growth indicates progressive disease.

With immunotherapy, however, some patients exhibit distinct response patterns including apparent increases in tumor size due to immune and inflammatory cell infiltration, and/or delayed clinical response.[5] Therefore, RECIST assessment of tumor response to immunotherapy could result in an incorrect diagnosis of disease progression and premature termination of treatment. In CheckMate 141, treatment beyond first RECIST-defined progression (TBP) with nivolumab was permitted at the discretion of investigators, based on protocol-defined criteria, for patients who were likely to benefit from continued treatment; results from this analysis are reported.

METHODS

Patients and Study Design

The full study methodology of the randomized, open-label, phase 3 CheckMate 141 study has been described previously.[1] Patients were randomized 2:1 to receive intravenous nivolumab 3 mg/kg every 2 weeks or investigator's choice, consisting of intravenous methotrexate (40-60 mg/m^2 weekly), docetaxel (30-40 mg/m^2 weekly), or cetuximab (400 mg/m^2 once, then 250 mg/m^2 weekly).Treatment was continued until the occurrence of unacceptable toxicity or disease progression, except in patients assigned to the nivolumab treatment arm who met the protocol-defined criteria for TBP. The primary end point of the study was OS; patients were followed up for survival during treatment and every 3 months after discontinuation. Objective response rate (ORR), defined as the proportion of patients with a best overall response of confirmed complete response or partial response per RECIST v1.1, was a secondary end point. Tumor response was assessed by investigators every 6 weeks beginning at week 9. Association of immune cell phenotypes with clinical response was assessed as an exploratory end point. Safety was monitored throughout treatment and for 100 days after administration of the last dose.

CheckMate 141 was approved by institutional review boards at all participating sites. Patients provided informed consent prior to enrollment.

Treatment Beyond RECIST-Defined Progression

Per protocol, TBP was permitted at the discretion of investigators, in consultation with the study monitors, if a patient demonstrated clinical benefit without rapid disease progression, tolerated nivolumab, maintained a stable performance status, and provided informed consent. Clinical benefit was assessed based on whether the patient was clinically deteriorating and unlikely to receive further benefit from continued treatment. Treatment beyond RECIST-defined

progression was not permitted if it would cause delay in an intervention to prevent serious complications from disease progression. Treatment could continue until evidence of further progression, defined as an additional ≥10% increase in tumor volume from time of first progression in all target lesions and new measurable lesions.

Patients in the nivolumab arm who received their last dose of treatment after RECIST-defined progression were included in the TBP group; patients whose last dose of nivolumab occurred prior to RECIST-defined progression were included in the not-TBP (NTBP) group.

Biomarkers

Blood samples were collected from patients at baseline and on day 43 of treatment in Vacutainer® sodium heparin Cell Preparation Tube (CPT™) tubes and centrifuged according to the manufacturer's recommended procedure to isolate peripheral blood lymphocytes. The cells were washed with phosphate-buffered saline (PBS) or Roswell Park Memorial Institute (RPMI)-1640 media, then resuspended in a freezing media of fetal bovine serum plus 10% dimethyl sulfoxide. The cells were immediately frozen in -70 °C for up to 72 hours, before being moved to liquid nitrogen long-term storage. Frozen PBMC samples were shipped to the analyzing laboratory in liquid nitrogen vapor shippers.

At the laboratory, vials were thawed in a water bath at 37°C for 1 minute then the sample from each vial was transferred into a 15 mL conical tube containing warm RPMI medium, washed twice by sequential centrifugation, resuspended in 5mL PBS and stained with viability dye Zombie Aqua (Biolegend, San Diego, CA) following manufacturer's protocol, and then stained for multicolor flow cytometry. Samples were stained for CD8+ T cells with the following mouse antihuman monoclonal antibodies: TCRalpha/beta AF700, CD8 APC-Cy7, CCR7-BV650, and CD45RA-BV711. Samples were stained for regulatory T cells with the following mouse antihuman antibodies: CD4-AF700, CD25-BV650, CD127-BV785, FOXP3-PerCPCy5.5, All antibodies were purchased from BD Bioscience (San Jose, CA). Mouse antihuman PD-1-APC (clone MIH4, eBIoscience), CTLA-4-PECy5 (Clone BNI3, BD Bioscience), and TIM-3-APCCy7 or PE (Clone F38-2E2, Biolegend) were also added to CD8+ T cell and regulatory T cell panels with staining performed using manufacturer protocols. Cells from each samples were analyzed using the BD Fortessa (BD Bioscience, San Diego, CA) flow cytometer and FlowJo v10 software (FlowJo, Ashland, OR).

Differences in biomarker profiles between TBP patients who had reduction in target lesions following post-progression nivolumab treatment (TBP responders) and TBP patients who had no change or increase in target lesions following post-progression treatment (TBP

nonresponders) were assessed for association with response to therapy. To serve as control, biomarker assessments were also performed in patients with RECIST-defined best response of complete or partial response who had not progressed as of data cutoff (RECIST responders) and in patients with RECIST-defined progressive disease as of data cutoff (RECIST nonresponders). In addition, immune cell phenotype expression was assessed for similarities between RECIST and TBP responders.

Statistical Analysis

Only patients from the nivolumab arm were included in the TBP analysis of clinical outcomes. Overall survival was estimated using Kaplan-Meier methodology[6]; 2-sided 95% CIs for median OS were computed using a generalization of the Brookmeyer and Crowley method.[7] Two-sided 95% CIs for ORRs were computed by the Clopper and Pearson method.[8] A 2-way analysis of variance with Šidák's multiple comparisons test correction was used to descriptively analyze the PBL biomarker data.[9,10] Database lock for efficacy and safety was September 2016, representing a minimum follow-up of 11.8 months. Database lock for biomarkers was August 2017.

The BMS policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

RESULTS

Patients

Of 240 patients randomized to nivolumab, 146 (61%) experienced RECIST-defined progression (Figure 1). Of these, 62 (42%) met the criteria for TBP and continued to receive nivolumab treatment; 84 (58%) discontinued treatment (NTBP). Of the remaining 94 of 240 patients (39%), 4 did not receive nivolumab, 11 were continuing treatment as of data cutoff, and the rest discontinued treatment primarily owing to either lack of confirmation of disease progression or adverse events.

Patient characteristics at baseline and at RECIST-defined progression are summarized in Table 1. Overall, baseline characteristics were similar between patients in both groups, although a larger percentage of TBP patients had baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0. The most common sites of metastases at baseline were similar between the TBP and NTBP groups (TBP: lung, 53% and lymph nodes 48%; NTBP: lung, 52% and lymph nodes, 54%). In both groups, RECIST-defined progression in the

majority of patients was due to increase in the size of target lesions, either with (TBP, 34%; NTBP, 39%) or without the development of new lesions (TBP, 61%; NTBP, 56%) (Table 1).

Efficacy

ORR prior to RECIST-defined progression was higher in the TBP group (16%) compared with NTBP (6%) (Table 2). Of 62 patients who underwent TBP with nivolumab, 60 were evaluable for response; 15 (25%) had no change in tumor burden and 15 (25%) had reductions in target lesion size; 3 (5%) patients had a reduction of >30% (Figure 2). Among the 15 patients with reductions in target lesion size, pharynx was the primary site of disease in 9 patients (60%) (Table 1). Five of the 15 patients with tumor reductions following TBP had previously experienced >20% increase in target lesion at RECIST-defined progression and only 1 had a pre-progression best overall response of partial response. The median time to tumor burden reduction among the 15 patients with reductions post RECIST-defined progression was 3.9 months (range, 3.1-15.8), and the median duration of tumor reduction was 3.0 months (range, <0.1-15.4+). Reductions were observed in patients with human papillomavirus (HPV)–positive and HPV-negative tumors as well as those with tumor programmed death ligand 1 (PD-L1) expression ≥1% or <1%.

Among patients receiving TBP with nivolumab, median OS was 12.7 months (95% CI, 9.7-14.6) (Figure 3a); the estimated OS rates in these patients at 12 months and 18 months were 52% and 30%, respectively. In the overall intent-to-treat population (including patients in the TBP and NTBP groups as well as those who did not experience RECIST-defined progression), median OS among nivolumab-treated patients was 7.7 months (95% CI, 5.7-8.8) (Figure 3b).[2] In a landmark analysis, median OS starting week 6 following RECIST-defined progression was 8.4 months (95% CI, 6.6-10.8) in the TBP group and 3.8 months (95% CI, 2.1-5.3) in the NTBP group (Figure 4).

Biomarkers

Peripheral blood lymphocyte samples from baseline and day 43 of treatment were available for 14 TBP patients; of these, 3 were TBP responders and 11 were TBP nonresponders. In addition, samples were available for 26 patients assessed by RECIST criteria (16 responders and 10 nonresponders). Across all immune cell phenotypes, there were no significant differences in baseline biomarker levels between RECIST and TBP responders. Differences in levels of total $CD8^+$ T cells, PD-1^+ $CD8^+$ effector T cells, and exhausted PD-1^+ TIM-3^+ $CD8^+$ effector T cells, as well as PD-1^+ regulatory T cells and cytotoxic T lymphocyte antigen-4^+

(CTLA-4) regulatory T cells, were noted between responders and nonresponders (RECIST and/or TBP) at baseline and/or day 43, although all differences were not significant (Figures 5a and 5b). There was a wide variation in the levels of CTLA-4$^+$ CD8$^+$ effector T cells. Among TBP responders (n = 3), there was a significant reduction in PD-1$^+$ regulatory T-cell levels on day 43 compared with baseline; this difference was not noted in nonresponders (n = 11). In contrast, the CD8$^+$ T-cell compartment did not show any significant differences between TBP responders versus nonresponders following nivolumab treatment.

Safety

Treatment-related adverse events (TRAEs) and select TRAEs are summarized in Table 3. When adjusted for duration of therapy exposure, the incidence of TRAEs, with the exception of skin and subcutaneous tissue disorders, was lower in the TBP group compared with NTBP (Table 4).

DISCUSSION

In this post hoc analysis of CheckMate 141, tumor burden reduction was noted in 15 of 60 patients (25%) who underwent TBP with nivolumab; 3 patients (5%) experienced reduction >30%. In the context of all patients randomized to receive nivolumab in the trial, this translates to an efficacy benefit of treatment beyond progression in 1.3% (3 of 240). Median OS was 12.7 months among patients receiving TBP with nivolumab and 7.7 months in the overall intent-to-treat population.[2] In a landmark analysis, median OS starting week 6 following RECIST-defined progression was 8.4 months for the TBP group and 3.8 months for the NTBP group. No new safety signals were noted with TBP. Efficacy benefits following TBP with nivolumab have also been reported in melanoma,[11,12] non-small cell lung cancer,[13] and renal cell carcinoma.[14,15]

In CheckMate 141, ORR prior to RECIST-defined progression was higher in the TBP group compared with NTBP; this was expected based on the protocol-defined requirement that patients demonstrate investigator-assessed clinical benefit to be eligible for TBP. The characteristics of TBP and NTBP patients were similar at baseline, except for better ECOG performance status in the TBP group. These findings are similar to those reported in a recent pooled TBP analysis conducted by the US Food and Drug Administration in patients with melanoma.[12] Among the 15 TBP patients in this analysis who achieved any reduction in target lesion size post-progression, 8 (53%) had HPV-positive cancers.

It is important to note that while interesting, the small patient numbers in our study preclude us from drawing definitive conclusions about patient characteristics predictive of

clinical benefit from treatment with nivolumab beyond RECIST-defined progression. The criteria for TBP used in this analysis are similar to that used for TBP with nivolumab in reports for other tumors. Nonetheless, a key limitation of the analysis is that selection of patients for TBP with nivolumab was based on assessment of clinical benefit by investigators, and not on the basis of clearly defined, validated factors. Therefore, it is possible that the results of this analysis are confounded by selection bias, as patients with more favorable disease characteristics and better prognosis were probably selected for inclusion in the TBP group. In spite of the limitations, our analysis underscores the potential benefits of TBP with nivolumab and the need for identifying factors predictive of TBP benefit in this patient population.

Exploratory analyses of cellular immune biomarkers suggested a potential relationship with initial and TBP responses. Treatment beyond RECIST-defined progression with nivolumab appeared to diminish immunosuppressive signals from PD-1^{+} regulatory T cells. It should be noted, however, that sample sizes were small and this research should be considered hypothesis generating. Comprehensive analyses involving larger patient populations in prospective clinical trials are warranted to fully understand these effects. In this study, on-treatment PBL samples were collected on day 43 of treatment, a pre-specified time point for collection of on-treatment PBL samples. The timing was based on the assumption that 6 weeks was adequate to evaluate changes in frequencies in the adaptive immune cell compartment compared with baseline values, as well as to assess the expression of markers of activation or exhaustion. However, the timing of PBL sample collection was independent of the timing of tumor response; this could have resulted in a large variability in on-treatment biomarker levels.

Given the limitations of RECIST in accurately characterizing tumor response to immunotherapy, guidelines such as immune-related response criteria (irRC),[5] immune-related (irRECIST) and immune-modified (imRECIST) RECIST[16-19], and modified RECIST 1.1 for immune-based therapeutics (iRECIST)[20] have been developed. The goal of these guidelines is 2-fold: to ensure that treatment is not prematurely terminated for patients with tumor responses to immunotherapy that are different from responses typical of cytotoxic chemotherapy, and that treatment is discontinued in a timely manner in patients with true disease progression, as this can impact potential benefits from subsequent lines of treatment.[20]

In summary, patients with RECIST-defined progression who do not experience rapid disease progression, have stable performance status, and are able to tolerate treatment may derive clinical benefit from TBP with nivolumab for recurrent/metastatic SCCHN. Our results underscore the importance of conducting prospective trails aimed at evaluating eligibility and appropriate selection of patients who may derive benefit from TBP. Additional research is also

needed to determine whether response to TBP can be predicted based on immunologic factors or patient clinical characteristics. Our results indicate that continued TBP with nivolumab was not associated with new safety concerns.

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Figure Legends

Figure 1. Patient subgroups for the treatment beyond RECIST-defined progression analysis. RECIST, Response Evaluation Criteria in Solid Tumors.

Figure 2. Tumor reduction in patients treated beyond RECIST-defined progression with nivolumab. HPV, human papillomavirus; PD-L1, programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors.

Figure 3. (a) OS in patients treated beyond RECIST-defined progression with nivolumab**.** OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors. **(b)** OS in the overall intent-to-treat population of patients (nivolumab arm); republished with permission of AlphaMed Press from CheckMate 141: 1-Year Update and Subgroup Analysis of Nivolumab as First-Line Therapy in Patients with Recurrent/Metastatic Head and Neck Cancer, Gillison, Oncologist 23(9), 2018, permission conveyed through Copyright Clearance Center, Inc.

Figure 4. Landmark analysis of OS starting from week 6 following first RECIST-defined progression in **(a)** the TBP group and **(b)** the NTBP group. CI, confidence interval; NTBP, not treated beyond first RECIST-defined progression OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; TBP, treated beyond first RECIST-defined progression.

Figure 5. (a) Levels of $CD8^+$ effector T cells among RECIST-defined responders, RECIST-defined Nonresponders, responders of treatment beyond RECIST-defined progression, and nonresponders of treatment beyond RECIST-defined progression. **(b)** Levels of regulatory T cells among RECIST-defined responders, RECIST-defined nonresponders, responders of treatment beyond RECIST-defined progression, and nonresponders of treatment beyond RECIST-defined progression. Dark blue bars represent baseline values; light blue bars represent day 43 values. Horizontal lines indicate the median, boxes the interquartile range, and whiskers the minimum and maximum values. $CD8^+$ effector T cells were defined as TCRalpha/beta$^+$CD8$^+$CCR7$^-$CD45RA$^+$. PD-1$^+$ TIM-3$^+$ CD8$^+$ cells were considered to be exhausted $CD8^+$ effector T cells. Regulatory T cells were defined as CD4$^+$CD25^{hi}CD127^{lo}FoxP3$^+$. * $P < .05$; ** $P < .01$; *** $P < .001$. CR/PR, complete or partial response; PD, progressive disease; TBPNR, treated beyond RECIST-defined progression with

stable or increased tumor lesion after progression; TBPR, treated beyond RECIST-defined progression with reduction in tumor lesion after progression.

Table 1. Characteristics of Patients With RECIST-Defined Progression Treated With Nivolumab

A. Baseline Characteristics			
	In Patients Treated Beyond RECIST-Defined Progression (n = 62)	In Patients Treated Beyond RECIST-Defined Progression Who Experienced Reductions in Target Lesion Size (n = 15)	In Patients Not Treated Beyond RECIST-Defined Progression (n = 84)
Age, median (range), y	59.0 (29-78)	58.0 (29-67)	61.0 (30-83)
Male, no. (%)	52 (84)	14 (93)	71 (85)
Primary site of disease, n (%)			
Oral cavity	26 (42)	3 (20)	33 (39)
Pharynx	28 (45)	9 (60)	36 (43)
Larynx	8 (13)	3 (20)	13 (15)
Other[a]	0	0	2 (2)
Number of disease sites per patient (including primary and metastatic), no. (%)[b,c]			
1	20 (32.3)	6 (40.0)	24 (28.6)
2	27 (43.5)	5 (33.3)	26 (31.0)
3	8 (12.9)	2 (13.3)	27 (32.1)
≥4	7 (11.3)	2 (13.3)	7 (8.3)
ECOG PS, no. (%)			
0	21 (34)[b]	3 (20)	17 (20)
1	41 (66)[b]	12 (80)	66 (79)
Not reported	0	0	1 (1)
HPV status, no. (%)[d]			
Positive	21 (34)	8 (53)	21 (25)
Negative	19 (31)	4 (27)	17 (20)

Unknown/not reported	22 (35)	3 (20)	46 (55)
PD-L1 expression, no. (%)			
≥1%	27 (44)	5 (33)	28 (33)
<1%	17 (27)	6 (40)	30 (36)
Not quantifiable at baseline	18 (29)	4 (27)	26 (31)
Lactate dehydrogenase			
Median (range), U/L	210.0 (97-1799)[e]	188.0 (114-919)	252.5 (94-4138)
Normal. n (%)	47 (77.0)[e]	10 (66.7)	62 (73.8)
High, n (%)	14 (23.0)[e]	5 (33.3)	22 (26.2)
Tobacco use, no. (%)			
Current/former	49 (79)	13 (87)	71 (85)
Never	12 (19)	2 (13)	10 (12)
Unknown	1 (2)	0	3 (4)

B. Characteristics at First RECIST-Defined Progression		
	In Patients Treated Beyond RECIST-Defined Progression (n = 62)	In Patients Not Treated Beyond RECIST-Defined Progression (n = 84)
ECOG PS, no. (%)		
0	22 (35)	11 (13)
1	40 (65)	32 (38)
2	0	7 (8)
Not reported	0	34 (40)
Type of RECIST progression, no. (%)		
Target lesion	38 (61)	47 (56)
New lesion	3 (5)	4 (5)
Both	21 (34)	33 (39)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; PD-L1, programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors

[a] Included patients with a tumor in more than 1 of the 3 categories (ie, larynx, oral cavity, pharynx).

[b] Patients could have had lesions at more than one site.

[c] Both target and non-target lesions are included.

[d] HPV status was assessed using p16 immunohistochemical testing, and required only for patients with oropharyngeal cancer.

[e] Data available in 61 patients; percentages are calculated with 61 as denominator.

Table 2. Efficacy in the TBP and NTBP Patient Groups Prior to First RECIST-Defined Progression

	TBP Group (n = 62)	NTBP Group (n = 84)
Best overall response, no. (%)		
Partial response	10 (16)	5 (6)
Stable disease	20 (32)	17 (20)
Progressive disease	32 (52)	62 (74)
Objective response rate, no. (%)	10 (16)	5 (6)
(95% CI)	(8-28)	(2-13)
Maximum reduction in target lesion, %		
Median (range)	7 (−86 to 129)	23 (−85 to 162)
Time to response,[a] months		
Median (range)	2.1 (1.8-4.8)	2.0 (1.8-5.1)
Duration of response,[a] months		
Median (range)	6.4 (2.8-9.7)	5.5 (4.0-6.9)

Abbreviations: NTBP, no treatment beyond RECIST-defined progression; RECIST, Response Evaluation Criteria in Solid Tumors; TBP, treatment beyond RECIST-defined progression.

[a] For responders (n = 10 [TBP group]; 5 [NTBP group].

Table 3. Treatment-Related Adverse Events Reported in ≥10% of Patients and Select TRAEs

	Treated Beyond RECIST-Defined Progression (n = 62)		Not Treated Beyond RECIST-Defined Progression (n = 84)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any TRAE, no. (%)	48 (77)	9 (15)	51 (61)	12 (14)
Fatigue	10 (16)	1 (2)	17 (20)	2 (2)
Rash	10 (16)	0	6 (7)	0
Pruritus	9 (15)	0	3 (4)	0
Anemia	3 (5)	1 (2)	9 (11)	2 (2)
Decreased appetite	3 (5)	0	10 (12)	0
Select TRAEs, no. (%)				
Skin	19 (31)	0	10 (12)	0
Endocrine	8 (13)	0	8 (10)	0
Gastrointestinal	6 (10)	0	8 (10)	1 (1)

Hepatic	3 (5)	0	2 (2)	1 (1)
Pulmonary	2 (3)	0	3 (4)	1 (1)
Hypersensitivity/infusion reactions	1 (2)	0	1 (1)	0
Renal	1 (2)	0	0	0

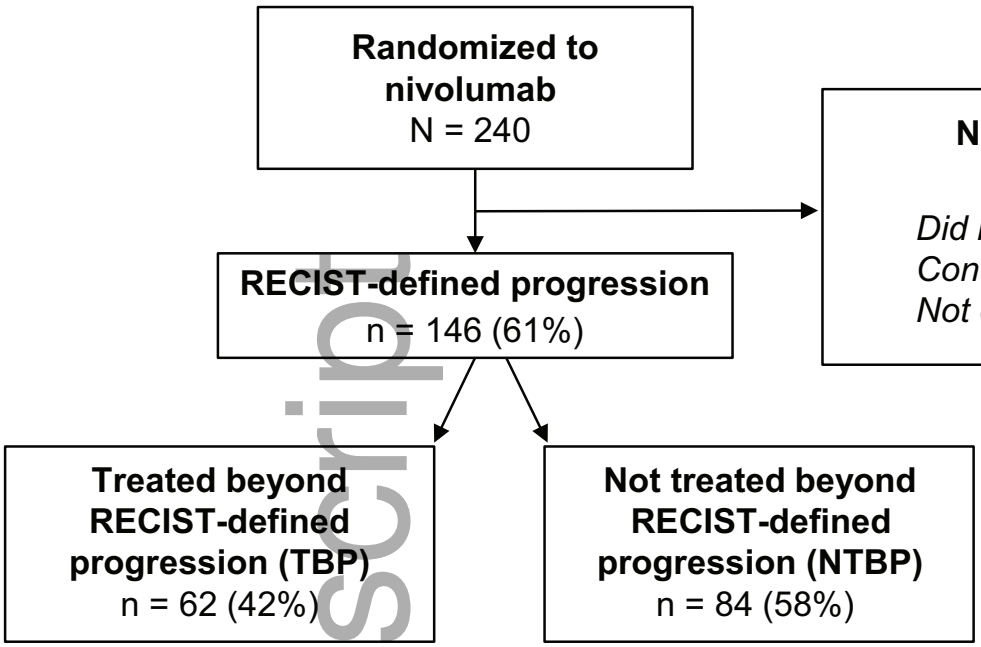
Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; TRAE, treatment-related adverse event.

Table 4. Exposure-Adjusted Incidence of Treatment-Related Adverse Events in ≥10% of Patients

	Treated Beyond RECIST-Defined Progression (n = 62) (P-Y = 37.6)		Not Treated Beyond RECIST-Defined Progression (n = 84) (P-Y = 24.3)	
	Events	Rate per 100 P-Y of Exposure	Events	Rate per 100 P-Y of Exposure
Total events	184	489	150	618
Skin and subcutaneous tissue disorders	43	114	13	54
Rash	14	37	6	25
Pruritus	9	24	4	16
General disorders and administration site conditions	26	69	29	119
Fatigue	10	27	18	74
Metabolism and nutrition disorders	17	45	19	78
Decreased appetite	5	13	11	45
Blood and lymphatic system disorders	5	13	12	49
Anemia	3	8	9	37

Abbreviations: P-Y, person-years of exposure; RECIST, Response Evaluation Criteria in Solid Tumors.

Incidence rate per 100 person-years of exposure = number of events × 100/P-Y.



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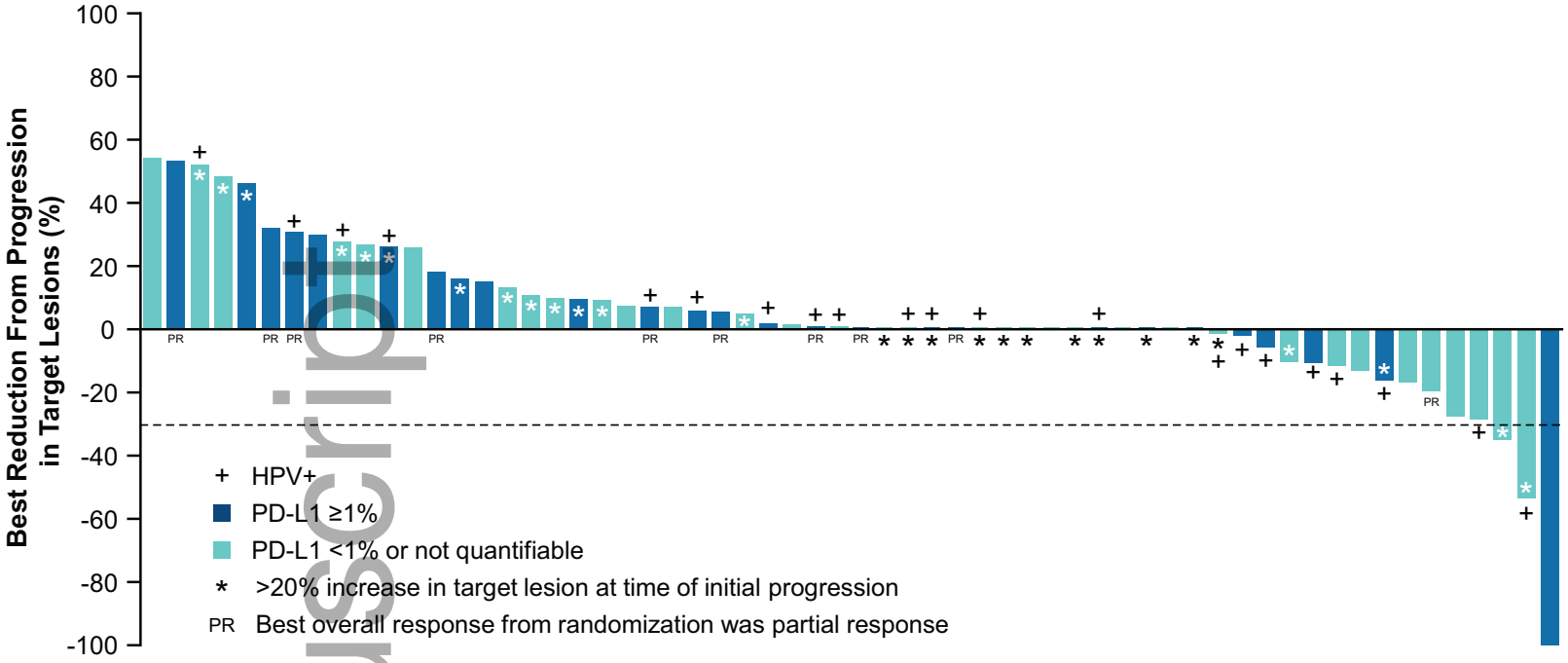

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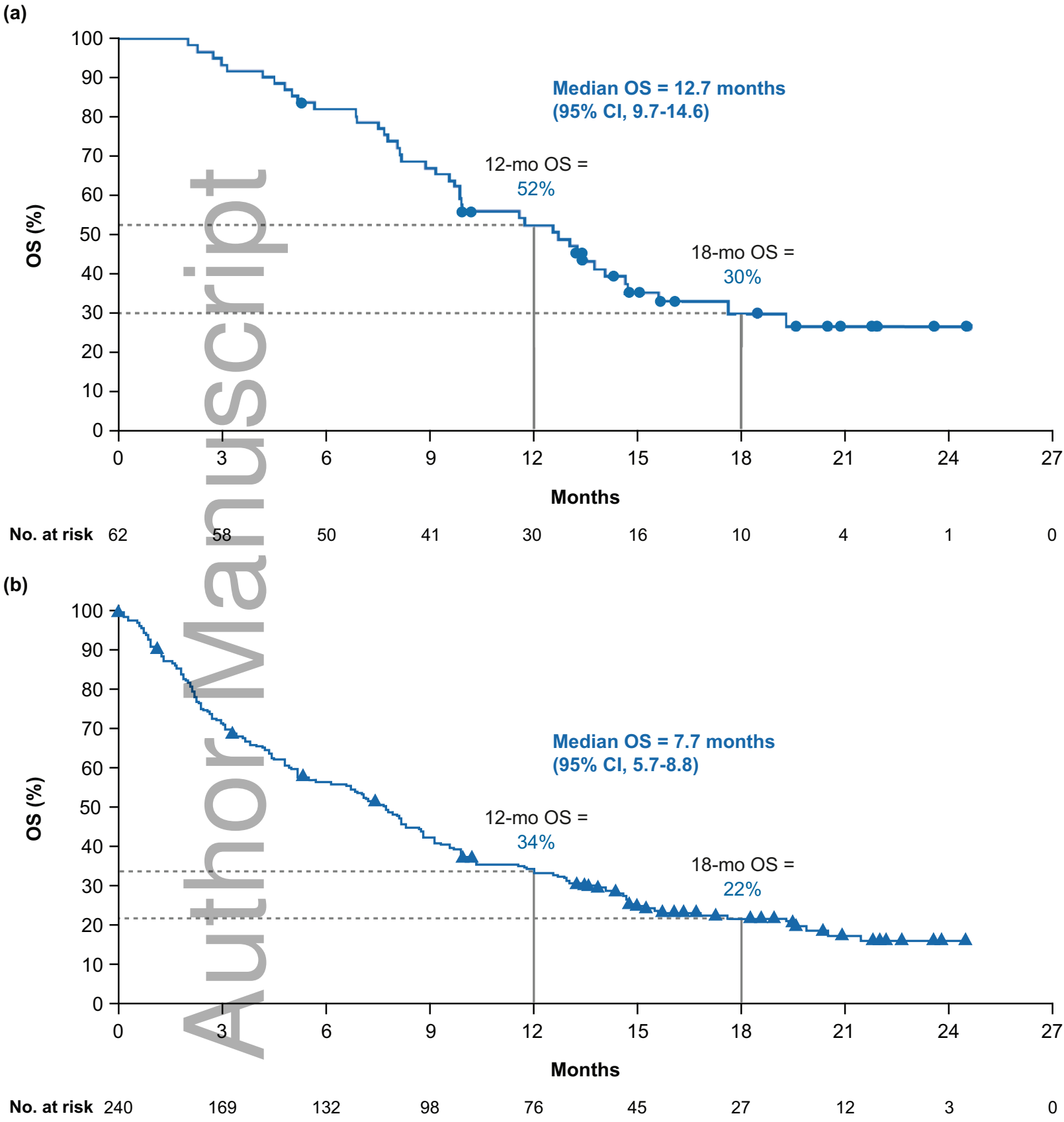

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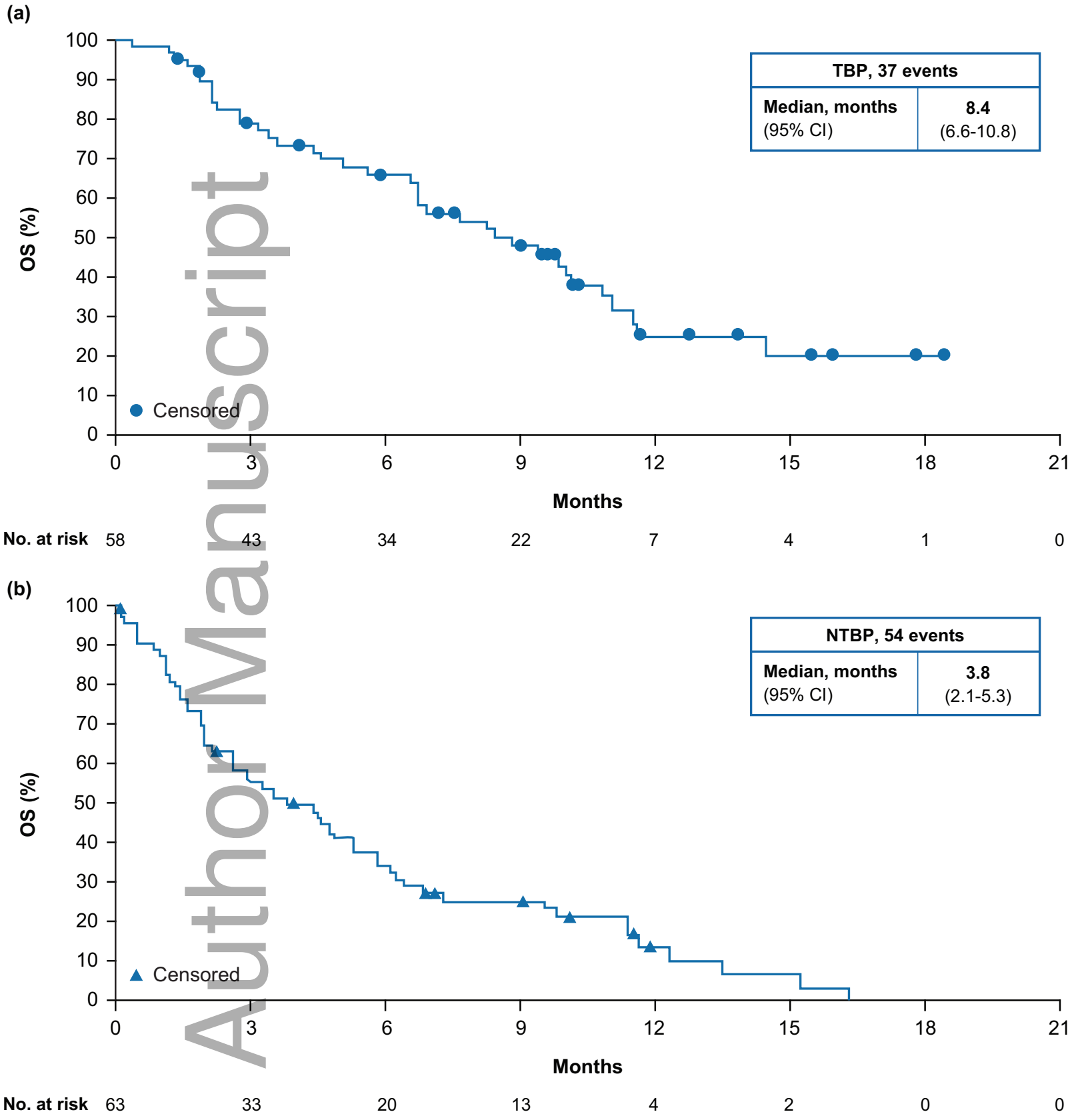

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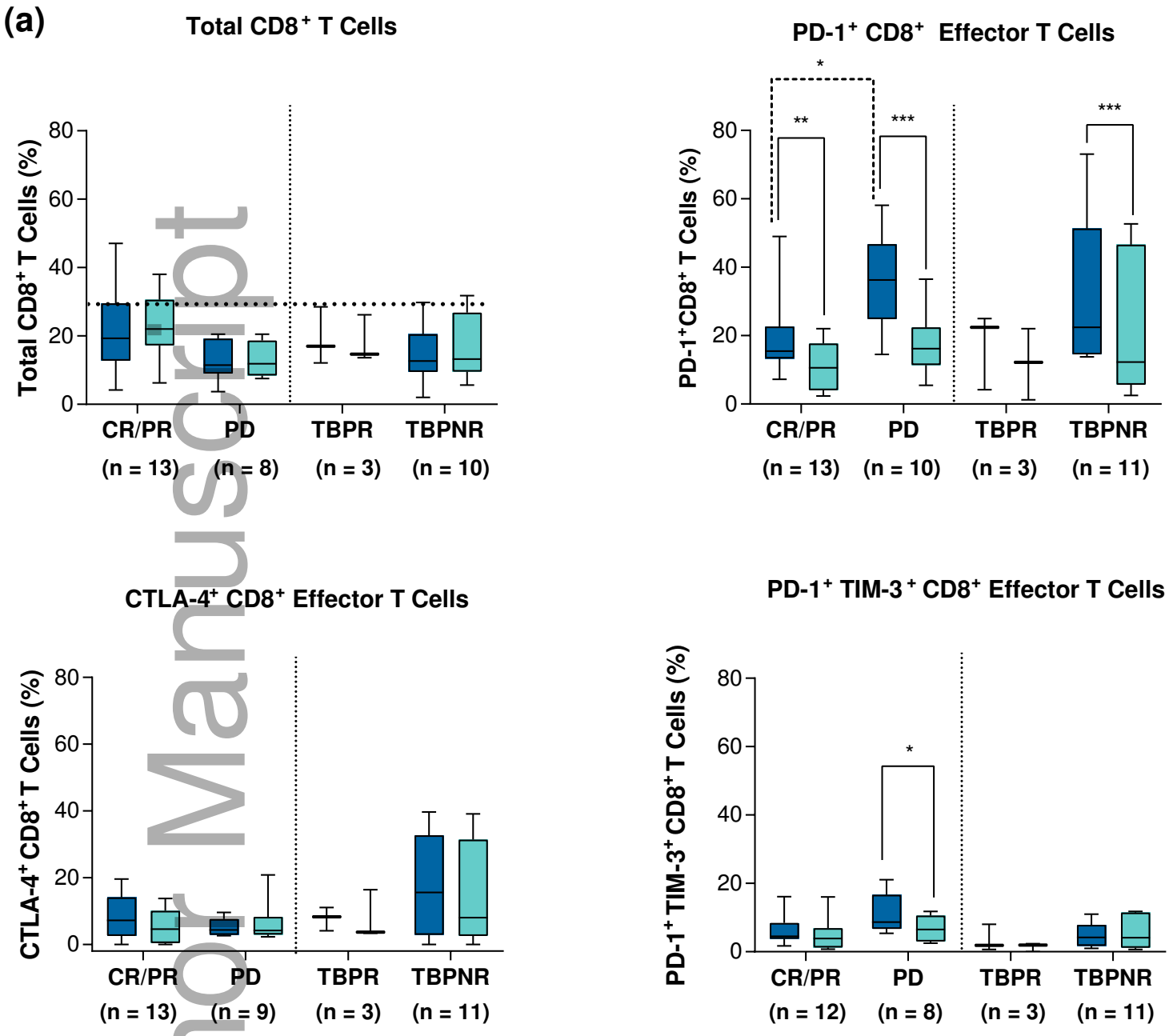

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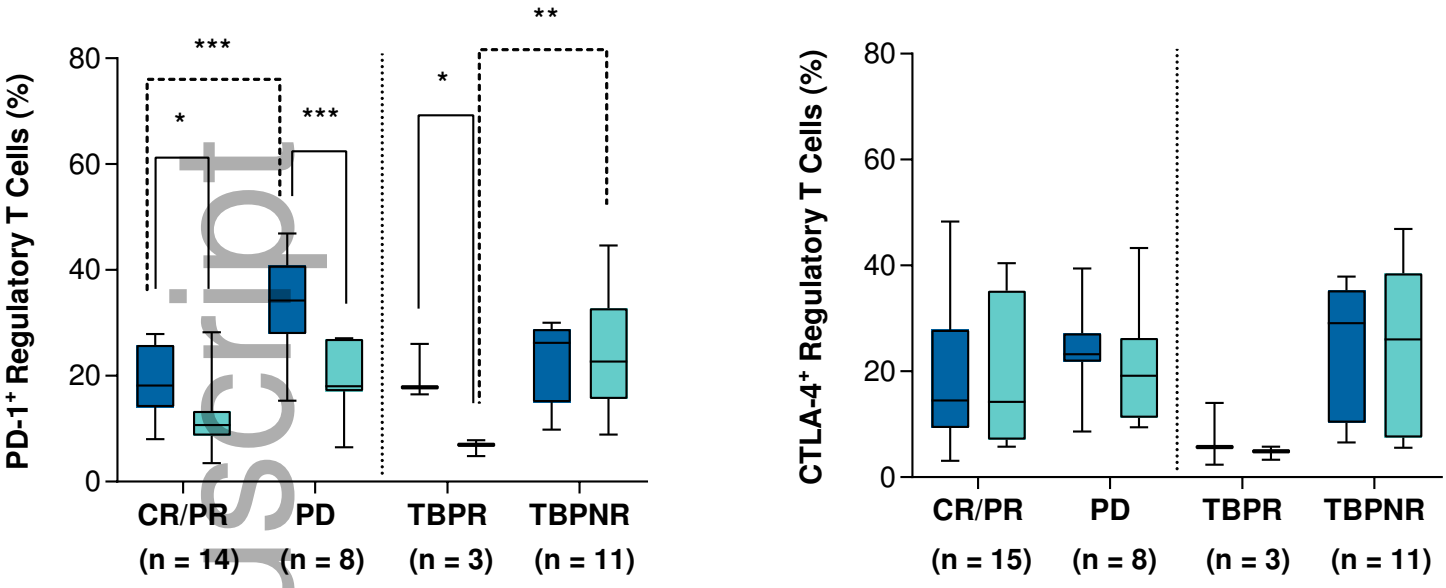

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