

Safety and Efficacy of Nivolumab in Patients With Advanced Non–small-cell Lung Cancer Treated Beyond Progression

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Abstract

The possibility of delayed immune-related responses implies that patients who experience progressive disease may benefit from treatment with immunotherapy beyond progression (TBP). Here we demonstrated that a substantial proportion of patients with non–small-cell lung cancer treated with nivolumab, who were clinically stable and judged to be eligible for TBP derive a significant survival benefit from TBP. TBP is feasible and safe, and reduction or stabilization of target lesions may occur when patients with non–small-cell lung cancer continue nivolumab after initial progression. Discontinuation of nivolumab based only on radiologic progression might be premature.

Introduction: Treatment with immune checkpoint inhibitors beyond progression is associated with improved survival in patients with melanoma and clear-cell renal carcinoma. Whether this association exists for patients with non–small-cell lung cancer (NSCLC) is currently still unclear. **Patients and Methods:** We performed a multi-institutional retrospective study based on landmark and multivariable analyses to evaluate the safety and efficacy of treatment with nivolumab beyond Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 progression in patients with advanced NSCLC. Criteria for receiving nivolumab beyond progression were investigator-assessed clinical benefit, stable performance status, tolerance of treatment, and no need of immediate intervention to prevent serious complication of progression. **Results:** Of 176 patients progressed to nivolumab according to RECIST v1.1, 60 (34.1%) were treated beyond progression (TBP) and 116 (65.9%) were not-TBP (NTBP). The median overall survival was significantly longer in the TBP group compared with the NTBP group (17.8 vs. 3.7 months; hazard ratio [HR], 0.32; 95% confidence interval [CI], 0.21–0.46; $P < .0001$). In a landmark analysis of evaluable patients beginning 6 weeks from first progression, the median overall survival for patients TBP was 10.7 months and for those NTBP, 3.4 months (HR, 0.48; 95% CI, 0.30–0.77; $P = .002$). Discontinuation of nivolumab at first progression was associated with shorter survival in multivariable analysis (HR, 2.98; 95% CI, 1.95–4.54; $P < .001$). No safety concerns emerged in patients who were in the TBP group. **Conclusion:** A subset of patients with NSCLC and progressive disease may continue to benefit from nivolumab beyond progression. Discontinuation of immunotherapy based only on RECIST v1.1 may be premature.

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Introduction

Anti-programmed cell death 1 (PD-1) and anti-programmed cell death ligand 1 (PD-L1) monoclonal antibodies are the currently recommended second-line option for patients with

advanced non–small-cell lung cancer (NSCLC) who progress to a first-line platinum doublet, having shown to improve overall survival (OS) as compared with standard cytotoxic treatments in phase III trials.^{1–4} Nivolumab is a fully human IgG4 anti-PD-1

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immune checkpoint inhibitor (ICI) antibody that selectively blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2, which is a mechanism involved in the development of immune tolerance.⁵ Emerging data have shown that patients treated with nivolumab or different ICIs might experience an atypical response pattern compared with chemotherapeutic drugs, eventually with tumor shrinkage after initial disease progression (PD).⁶⁻⁹ Mechanistically, this tumor flare preceding clinical responses is believed to reflect either transient immune cells infiltration within the tumor or momentary tumor growth during the priming of immune response triggered by ICIs.^{10,11} As tumor shrinkage induced by tumor immunotherapy can be preceded by such inflammatory changes, the assessment of response rates to tumor immunotherapy according to traditional criteria may be confounding.¹¹ To overcome the limitation of using Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 for immunotherapeutic agents, the immune-related RECIST criteria (irRECIST) and subsequently the modified immune-related RECIST (iRECIST) have been recently proposed to ensure consistent design and data collection in cancer immunotherapy trials.¹⁰⁻¹² However, they are still not widely used in clinical practice.

Although PD has always been considered to reflect the failure of treatment for non-immunotherapeutic agents, leading to treatment discontinuation, the possibility of delayed immune-related responses implies that patients who experience PD may benefit from continuing ICIs beyond PD. Accordingly, it has emerged that a subset of patients with metastatic melanoma and renal cell carcinoma might derive a survival benefit from treatment with nivolumab beyond RECIST-defined PD.¹³⁻¹⁵ More recently, in a retrospective analysis of the OAK trial, patients who received treatment with atezolizumab beyond progression experienced a significantly prolonged post-progression survival compared with those who were switched to other therapies and those who received no further treatments.¹⁶ However, there is no evidence of the potential risk and benefit of treatment with nivolumab beyond progression in patients with advanced NSCLC outside of clinical trials. Therefore, in light of uncertainty regarding whether discontinuation of ICIs based on disease progression as assessed by RECIST could be premature, we conducted this study to investigate the safety and potential benefit of treatment with nivolumab beyond first progression in patients with metastatic NSCLC.

Materials and Methods

Data Collection

We reviewed medical records of all patients with advanced (stage IIIB to IV) and recurrent NSCLC who had received nivolumab as second or later line of therapy at Santa Maria della Misericordia Hospital (Thoracic Oncology Unit) (Perugia, Italy), Ospedale Policlinico San Martino (Lung Cancer Unit) (Genova, Italy), and San Camillo de Lellis Hospital (Medical Oncology Department) (Rieti, Italy) between October 2013 and September 2017. We identified 195 patients who received nivolumab monotherapy as a second or subsequent line. Nivolumab was administered intravenously at the dose of 3 mg/kg every 15 days. Before the start of nivolumab and during the course of the disease, all patients were evaluated for Eastern Cooperative Oncology Group performance status (ECOG PS) as assessed by the physician, smoking history as

reported by the patient, tumor histologic type, date of diagnosis of advanced disease, disease stage, date and site of tissue collection used for both histologic diagnosis and molecular determinations, presence of central nervous system metastases, presence of oncogenic driver mutations, dates of treatments, PD, and death or last contact if death had not occurred. Never-smokers were defined as having smoked < 100 cigarettes in a lifetime. Tumor response was assessed every 6 weeks according to RECIST v1.1. As complementary evaluation, best response to treatment was also assigned according to irRECIST by a dedicated thoracic radiologist. Criteria for receiving nivolumab beyond RECIST v1.1 progression were investigator-assessed clinical benefit, stable performance status, tolerance of treatment, and no need to deliver immediate intervention to prevent serious complication of progression. Patients considered to be treated beyond progression (TBP) were defined as having received the last dose of nivolumab \geq 6 weeks after the initial progression date. Patients who received their last dose of nivolumab < 6 weeks after disease progression or discontinued the treatment before or on the date of progression were defined as not treated beyond progression (NTBP). Safety was assessed every 15 days, and adverse events (AEs) were graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical Analysis

Progression-free survival (PFS) and overall survival (OS) functions were estimated using the Kaplan-Meier method, and the log-rank test was used to assess differences between groups. The objective response rate analysis was based on best overall response, and 2-sided, 95% confidence intervals (CIs) for the response rate were computed by the Clopper and Pearson method. The Fisher exact test was applied to compare overall response rates. Univariable and multivariable Cox proportional hazard regression models were adopted to determine hazard ratios (HRs). All *P* values were based on a 2-sided hypothesis, and those < .05 were considered statistically significant. A landmark analysis of evaluable patients beginning 6 weeks after first progression was conducted to further validate the impact of treatment with nivolumab beyond progression on post-progression survival. All statistical analysis was performed with SPSS software version 24 (Chicago, IL).

Results

Patient Characteristics

Between October 2013 and September 2017, 195 patients received nivolumab as a second or later line of treatment. At data cutoff (March 2018), 176 patients had progressed to nivolumab and were included in the final analysis. The median follow up was 28.3 months (95% CI, 26.3-29.8 months), and the median duration of treatment was 2.9 months (range, 0.3-32.0 months) in patients who progressed to nivolumab. Among patients who progressed to nivolumab, 60 (34.1%) were treated beyond RECIST v1.1 progression for more than 6 weeks and 116 (65.9%) were NTBP. The median age was 62 years (range, 37-81 years) in the TBP group and 63 years (range, 30-84 years) in the NTBP group, and a similar proportion of patients with pre-treatment ECOG PS \geq 2 was present in each group. No difference in PD-L1 expression and number of prior or subsequent lines of treatment was present between patients who were TBP and those who

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Table 1 Baseline Demographic and Clinical Characteristics of Patients

Characteristics	No. Patients (%)		
	Total	TBP	NTBP
Number	176	60 (34.1)	116 (65.9)
Median age, y (range)	63 (30-84)	62 (37-81)	64.5 (30-84)
Gender			
Male	110 (62.5)	38 (63.3)	72 (62.1)
Female	66 (37.5)	22 (36.7)	44 (37.9)
ECOG PS			
0-1	124 (70.5)	46 (76.7)	78 (67.2)
≥2	52 (29.5)	14 (23.3)	38 (32.8)
Smoking history			
Current/former	150 (85.2)	54 (90)	96 (82.8)
Never	26 (14.8)	6 (10)	20 (17.2)
Histology			
Non-squamous NSCLC	138 (78.5)	50 (83.3)	88 (75.9)
Squamous NSCLC	33 (18.7)	9 (15)	24 (20.7)
NOS	5 (2.8)	1 (1.7)	4 (3.4)
Brain metastasis prior to nivolumab			
Yes	44 (25)	16 (26.7)	28 (24.1)
No	132 (75)	44 (73.3)	88 (75.9)
EGFR mutation			
Positive	15 (8.5)	6 (10)	9 (7.7)
Negative	107 (60.8)	38 (63.3)	69 (59.5)
Not examined	54 (30.7)	16 (26.7)	38 (32.8)
ALK fusion			
Positive	1 (0.6)	0 (0.0)	1 (0.9)
Negative	69 (39.2)	28 (46.6)	41 (35.3)
Not examined	106 (60.2)	32 (53.4)	74 (63.8)
PD-L1 status			
≥ 1%	13 (7.4)	3 (5)	10 (8.6)
<1%	17 (9.6)	6 (10)	11 (9.5)
Not examined	146 (83)	51 (85)	95 (81.9)
Number of prior lines of therapy			
1	95 (54)	31 (51.7)	64 (55.2)
2	47 (27.7)	13 (21.7)	34 (29.3)
≥3	34 (19.3)	16 (26.6)	18 (15.5)
Cycles of nivolumab, median (range)	6 (1-65)	16.5 (6-65)	4 (1-47)
Number of subsequent lines of therapy			
1	20 (11.3)	6 (10)	14 (12.2)
2	4 (2.3)	2 (3.3)	2 (1.7)
≥3	4 (2.3)	1 (1.6)	3 (2.6)

Abbreviations: ALK = anaplastic lymphoma kinase; ECOG = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; NOS = not otherwise specified; NSCLC = non-small-cell lung cancer; NTBP = not treated beyond progression; PD-L1 = programmed cell death ligand 1; TBP = treated beyond progression.

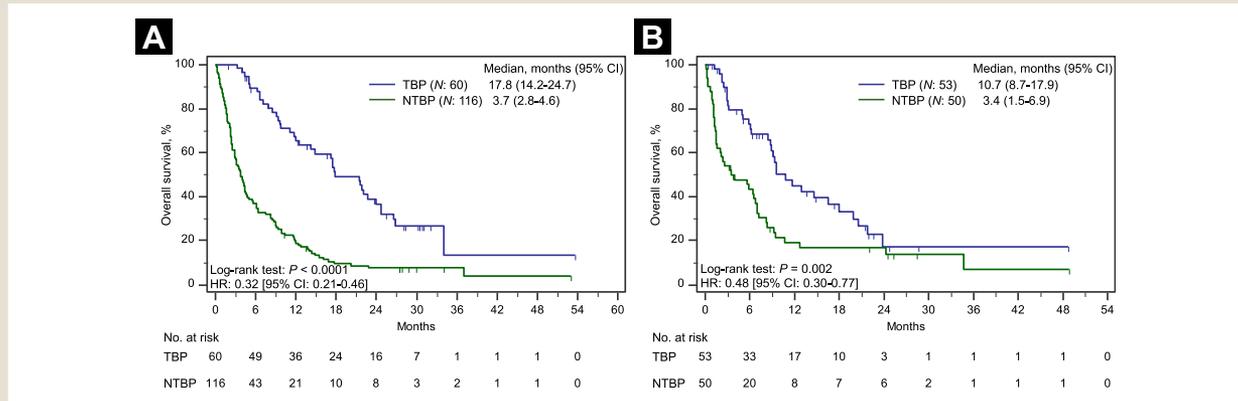
were not TBP. Baseline demographic and clinical characteristics are summarized in [Table 1](#).

Efficacy of Nivolumab Beyond RECIST v1.1 Progression

Summary of efficacy of nivolumab before first progression is summarized in [Supplemental Table 1](#) (in the online version). Among 176 patients who progressed to nivolumab, the median OS was

significantly longer in the TBP group (N = 60) compared with the NTBP group (N = 116) (17.8 vs. 3.7 months; HR, 0.32; 95% CI, 0.21-0.46; $P < .0001$) ([Figure 1A](#)). In a landmark analysis of evaluable patients beginning 6 weeks from first progression, the median OS for patients in the TBP group (N = 53) was 10.7 months and for those in the NTBP group (N = 50) was 3.4 months (HR, 0.48; 95% CI, 0.30-0.77; $P = .002$) ([Figure 1B](#)). Following initial progression,

Figure 1 A, Kaplan-Meier Curves for Overall Survival Comparing Patients TBP and Those NTBP. B, Landmark Analysis of Overall Survival Beginning 6 Weeks From First Progression



Abbreviations: CI = confidence interval; HR = hazard ratio; NTBP = not treated beyond progression; TBP = treated beyond progression.

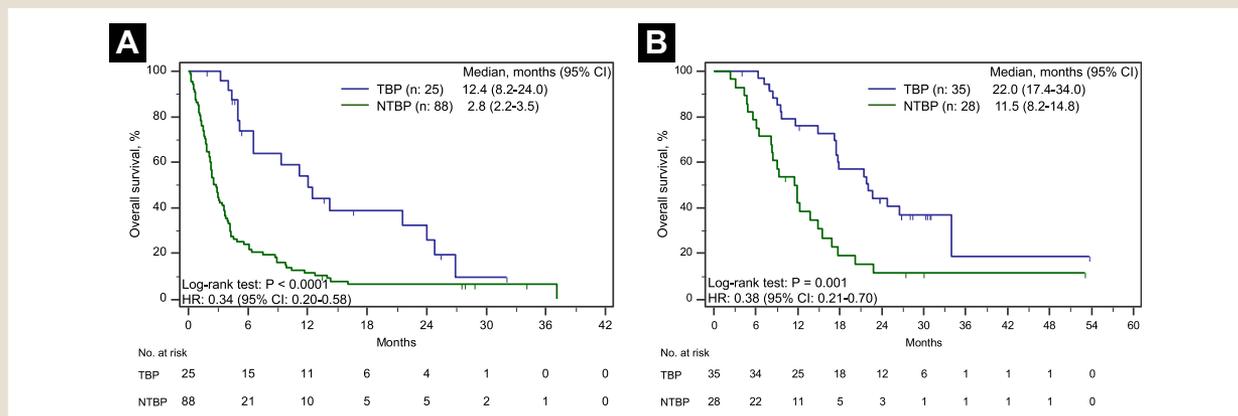
13.3% (8/60) of patients who were TBP experienced a decrease in target lesions (> 30%) compared with baseline. After excluding patients who experienced either a target lesion reduction or a stabilization after initial progression (N = 10; 16.6%), a similar survival benefit was confirmed for patients in the TBP group (see Supplemental Figure 1 in the online version). Similar results favoring TBP were obtained when survival outcomes were analyzed separately in patients who experienced PD (12.4 vs. 2.8 months; HR, 0.34; 95% CI, 0.20-0.58; $P < .0001$) or achieved disease control as best response to nivolumab (20.0 vs. 11.5 months; HR, 0.38; 95% CI, 0.21-0.70; $P = .001$) (Figure 2A, B). At the time of analysis, 52 (86.6%) of patients who were TBP had discontinued nivolumab, whereas 8 were still receiving the treatment. Among patients in the TBP group who discontinued treatment, 40 (76.9%) discontinued and died, whereas 12 (23.1%) discontinued but were still alive at data cutoff. In multivariable analysis, discontinuation of nivolumab at first progression was associated

with a shortened survival (HR, 2.98; 95% CI, 1.95-4.54; $P < .001$), with ECOG PS ≥ 2 (HR, 2.00; 95% CI, 1.29-3.11; $P = .002$), male gender (HR, 1.63; 95% CI, 1.11-2.39; $P = .03$), and PD as best overall response (HR, 2.17; 95% CI, 1.13-3.19; $P < .001$) (see Supplemental Table 2 in the online version). When survival outcomes were analyzed according to the type of post-progression management, we found a shorter survival in patients who were switched to a different regimen or did not receive any further therapy compared with patients who continued nivolumab beyond progression ($P < .0001$) (Figure 3). A summary of duration of treatment and survival in patients who were TBP is schematized in Figure 4.

Safety

The median number of cycles of nivolumab was 16.5 (range, 6-65) and 4 (range, 1-47) in patients in the TBP and NTBP groups, respectively. Following initial progression, patients who were TBP

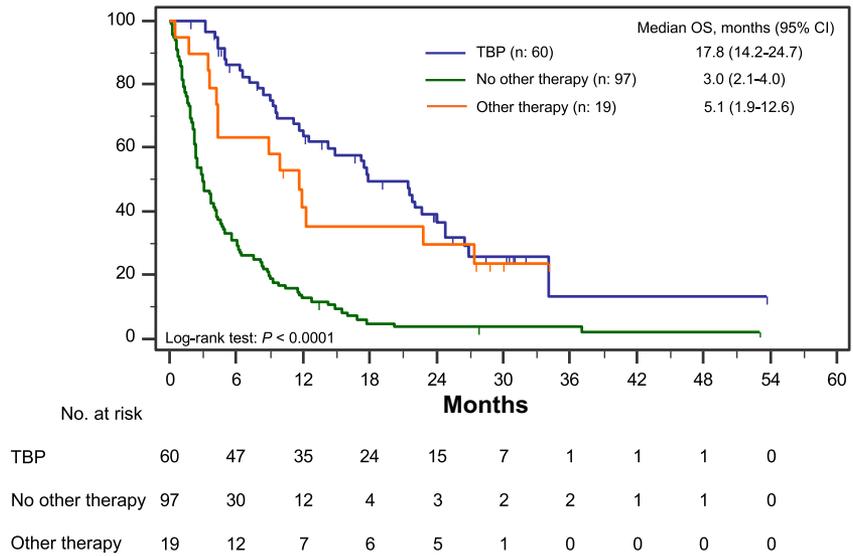
Figure 2 Kaplan-Meier Curves for Overall Survival in Patients Who had a PD (A) or Either PR/CR or SD (B) as Best Response to Nivolumab, According to Post-progression Treatment (TBP vs. NTBP)



Abbreviations: CI = confidence interval; CR = complete response; HR = hazard ratio; NTBP = not treated beyond progression; PD = progressive disease; PR = partial response; SD = stable disease; TBP = treated beyond progression.

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Figure 3 Kaplan-Meier Curves for Overall Survival according to Post-progression Management of Patients Progressing to Nivolumab Monotherapy



Abbreviations: CI = confidence interval; OS = overall survival; TBP = treated beyond progression.

received a median of 9 doses (range, 4-58). The incidence of any grade AEs was higher in patients who were TBP (60% vs. 39.6%), according to the difference in nivolumab exposure between the 2 groups. However, there was no significant difference in the rate of grade

3/grade 4 AEs between patients in the TBP group and those in the NTBP group (11.6% vs. 8.6%) (Table 2). Grade 2 to 4 treatment-related toxicities leading to temporary or permanent discontinuation of nivolumab occurred in 65 (36.9%) of 176 patients. Median

Figure 4 Summary of Treatment Duration and Survival of Patients Treated Beyond Progression

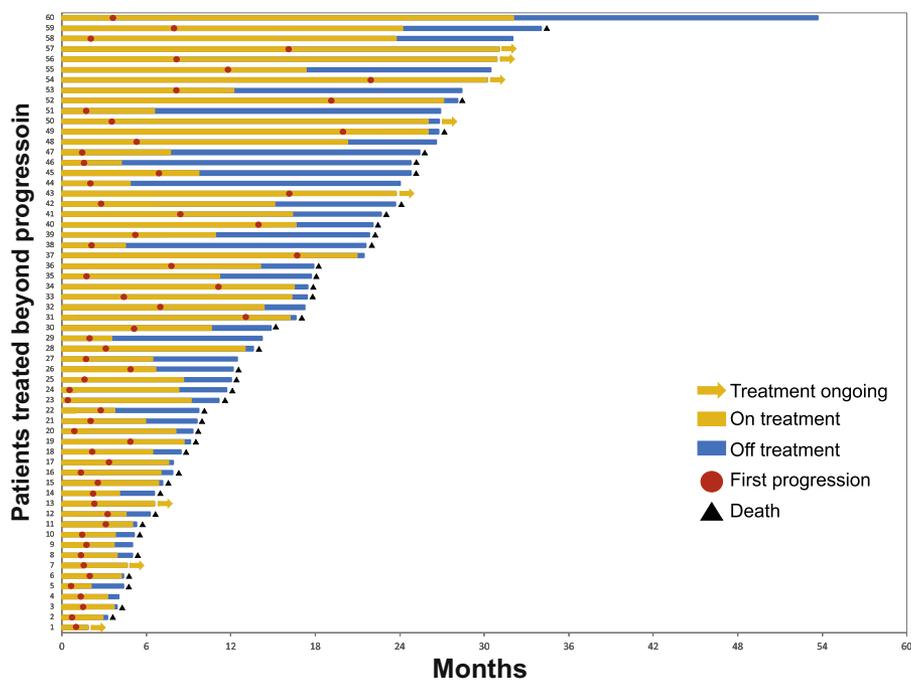


Table 2 Treatment-related Adverse Events According to Category and Grade

Category ^a	No. Patients (%)				
	Total 176	NTPB 116 (65.9)		TBP 60 (34.1)	
		Grade 1 to 2	Grade 3 to 4 ^b	Grade 1 to 2	Grade 3 to 4 ^b
Any	99 (56.2)	46 (39.6)	10 (8.6)	36 (60.0)	7 (11.6)
Hepatobiliary system	39 (22.1)	21 (18.1)	4 (3.4)	10 (16.6)	1 (1.6)
γGT increase	16 (9.0)	8 (6.9)	2 (1.7)	5 (8.3)	1 (1.6)
ALP increase	15 (8.5)	9 (7.7)	2 (1.7)	3 (5.0)	1 (1.6)
ALT increase	12 (6.8)	7 (6.0)	1 (0.8)	4 (6.7)	NA
AST increase	12 (6.8)	6 (5.1)	1 (0.8)	5 (8.3)	NA
Bilirubin increase	1 (0.5)	NA	NA	1 (1.6)	NA
Endocrine	32 (18.1)	13 (11.2)	NA	19 (31.6)	NA
Hyper/hypothyroidism	31 (17.6)	12 (10.3)	NA	19 (31.6)	NA
Hypoadrenocorticism	1 (0.5)	1 (0.8)	NA	NA	NA
Fatigue	31 (17.6)	13 (12.9)	2 (1.7)	16 (26.6)	NA
Gastrointestinal	28 (15.9)	16 (13.7)	NA	11 (18.3)	1 (1.6)
Colitis	15 (8.5)	10 (8.6)	NA	4 (6.6)	1 (1.6)
Nausea/vomiting	7 (3.9)	3 (2.5)	NA	4 (6.6)	NA
Anorexia	3 (1.7)	2 (1.7)	NA	1 (1.6)	NA
Abdominal pain	2 (1.1)	2 (1.7)	NA	NA	NA
Constipation	1 (0.5)	NA	NA	1 (1.6)	NA
Xerostomia	1 (0.5)	NA	NA	1 (1.6)	NA
Skin	27 (15.3)	12 (10.3)	2 (1.7)	11 (18.3)	2 (3.3)
Rash	17 (9.6)	8 (6.9)	2 (1.7)	5 (8.3)	2 (3.3)
Pruritus	4 (2.2)	2 (1.7)	NA	2 (3.3)	NA
Psoriasis	3 (1.7)	1 (0.8)	NA	2 (3.3)	NA
Dry skin	3 (1.7)	1 (0.8)	NA	2 (3.3)	NA
Pneumonitis	16 (9.0)	3 (2.5)	1 (0.8)	9 (15.0)	3 (5.0)
Rheumatologic	10 (5.6)	5 (4.3)	NA	5 (8.3)	NA
Arthralgias	7 (3.9)	4 (3.4)	NA	3 (5.0)	NA
Uveitis	2 (1.1)	1 (0.8)	NA	1 (1.6)	NA
Dermatomyositis	1 (0.5)	NA	NA	1 (1.6)	NA
Hematologic	4 (2.2)	NA	NA	3 (5.0)	NA
Thrombocytopenia	2 (1.1)	NA	NA	2 (3.3)	NA
Neutropenia	1 (0.5)	NA	NA	1 (1.6)	NA
Anemia	1 (0.5)	1 (0.8)	NA	NA	NA
Renal failure	1 (0.5)	NA	1 (0.8)	NA	NA

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; γGT = gamma-glutamyltransferase; NA = not applicable; NTPB = no treatment beyond progression; TBP = treatment beyond progression.

^aPercentages may add up to more than 100 because some patients experienced more than 1 event.

^bTreatment-related death was not observed in the study cohort.

time to onset with range of grade 2/grade 4 treatment-related toxicity according to post-progression management (TBP vs. NTPB) is reported in [Supplemental Figure 2](#) (in the online version).

Discussion

In this study, we demonstrated that patients with advanced NSCLC who were treated with nivolumab beyond RECIST v1.1 progression experienced a significantly longer survival as compared with those who discontinued treatment owing to PD. The criteria for considering treatment beyond progression included investigator

assessed clinical benefit, tolerance of treatment, stable ECOG PS, and no need to deliver immediate intervention to treat or prevent complication of disease progression. Although approximately 34.1% of patients were TBP, only 13.3% of them experienced a decrease in target lesions ($\geq 30\%$) after initial progression. Importantly, TBP was associated with an improvement in OS also in patients who progressed to nivolumab without experiencing neither a response nor a stabilization of tumor burden following initial progression, suggesting that TBP might also be considered in patients with immune confirmed disease progression as assessed by iRECIST. To

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further validate the impact of TBP on post-post-progression survival, we conducted a landmark analysis for OS beginning 6 weeks after first progression that confirmed a significant survival benefit for patients who were TBP. Noteworthy, stopping treatment at first progression was also associated with shorter survival in multivariable analysis.

In the context of available literature, our study is the first to provide evidence for the feasibility and safety of treatment with nivolumab beyond RECIST v1.1 progression in a real-life population of patients with NSCLC who progress on or following treatment with anti PD-1 monotherapy. The concept of treating patients with advanced NSCLC beyond progression when clinical benefit persists is well-established in patients with oncogene-addicted NSCLC.^{17,18} Similarly, recent data suggests that also immunotherapeutic agents can be safely administered beyond progression in patients with advanced melanoma and metastatic renal cell carcinoma, resulting in a significant prolongation of OS.¹³⁻¹⁵ With regard to NSCLC, Gandara and colleagues have recently examined the benefit-risk of atezolizumab TBP in a retrospective analysis of the phase III OAK study and found a post-progression prolongation of OS in patients who received atezolizumab beyond PD, with 7% of patients also experiencing a target lesion reduction after initial progression.¹⁶ However, until now, there was no data about the potential risk and benefit of continuing treatment with anti PD-1 agents beyond progression for patients with NSCLC outside of a clinical trial setting. Interestingly, a small retrospective study involving 26 patients with acquired resistance to anti PD-1 axis inhibitors showed that most of the patients experienced an oligo-progressive pattern of PD, with 58% of them receiving local radiation and other local ablative therapy, which indicates that in such scenarios, local ablative therapy can be considered along with continuing the PD-1 axis inhibition beyond radiographic progression.¹⁹

Of note, it has been estimated that 5% of patients receiving ICIs experience an unconventional imaging pattern of tumor response where tumors show features of progression, including tumor enlargement or development of new lesions, with subsequent radiologic tumor shrinkage on serial imaging with prolonged therapy. This pseudoprogression is a raising concern in NSCLC as most of the patients with suspected pseudoprogression ultimately have a true progressive disease.²⁰ In our cohort, the incidence of pseudoprogression was 4.5% in the entire cohort and was in line with previous data.²⁰ Together, this evidence further underscores the need for novel criteria for assessing tumor response in patients with NSCLC treated with immunotherapy.

Some limitations affect this study including the retrospective design and the relatively small number of patients TBP. Detractors may argue that, prior to first progression, patients who were TBP had a higher objective response rate and a slightly longer median PFS. However, TBP resulted in a prolonged OS also in patients who had a PD as best response to treatment. It may also be speculated that patients treated beyond PD had better clinical features at the time of first progression and that the difference in survival observed might reflect this unbalance. However, by including in the landmark analysis only patients who were alive 6 weeks after initial progression, we excluded most of the patients who rapidly

progressed and died in the NTBP group, which might have impacted, at least partly, the difference in survival we initially observed. Therefore, the persistence of a survival benefit in the TBP group in the 6-week landmark analysis further corroborates our results, and suggests that the administration of nivolumab beyond PD accounts for the difference in survival, rather than the difference in baseline feature at the date of initial PD.

Whether continuing to boost the immune system with PD-1 axis inhibition after initial PD is mechanistically responsible for the survival benefit reported in patients who were TBP is currently unclear. It is rather likely that the current evaluation criteria (RECIST v1.1) are not adequate to accurately estimate response to ICIs. However, the evidence that patients who experience a PD as their best response to treatment argues in favor of the hypothesis that a sustained inhibition of the PD-1 axis might contribute to keep cancer under control in a subset of patients, even when neither a response nor a stabilization of disease to immunotherapy is observed. This aspect is certainly still in need further investigation.

Lastly, it can be speculated that prolonged treatment with nivolumab might be associated with an increase in time-dependent toxicities. However, although patients who were TBP had a higher incidence of any grade AEs, in our study there was no difference between the TBP and the not TBP groups in terms of development of serious AEs. In addition, the TBP group was preselected for those who were tolerating therapy, which makes the difference in the higher incidence of any grade AEs in this group not clinically relevant.

Conclusion

This study demonstrated that treatment with nivolumab beyond progression is feasible and safe, and that reduction or stabilization of target lesions may occur when patients continue nivolumab after initial progression in advanced NSCLC. Treatment beyond PD can be considered in patients who perform well at the time of initial PD. Decision about the discontinuation of ICIs should be cautiously considered on an individual basis, as stopping treatment based solely on radiologic progression as could be premature.

Clinical Practice Points

- Although disease progression has historically reflected the failure of treatment for non-immunotherapeutic agents, the possibility of delayed immune-related responses implies that patients who experience disease progression may benefit from continuing ICIs beyond progression.
- In this study, we demonstrated that a substantial proportion of patients with NSCLC treated with nivolumab, who were clinically stable and judged to be eligible for treatment beyond RECIST v1.1-defined progression by the treating investigators, derived a significant survival benefit from TBP.
- Our results indicate that treatment with nivolumab beyond progression is feasible and safe, and that reduction or stabilization of target lesions may occur when patients continue nivolumab after initial progression in advanced NSCLC.
- Decision about the discontinuation of ICIs should be cautiously considered on an individual basis as stopping treatment based solely on radiologic progression could be premature.

Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

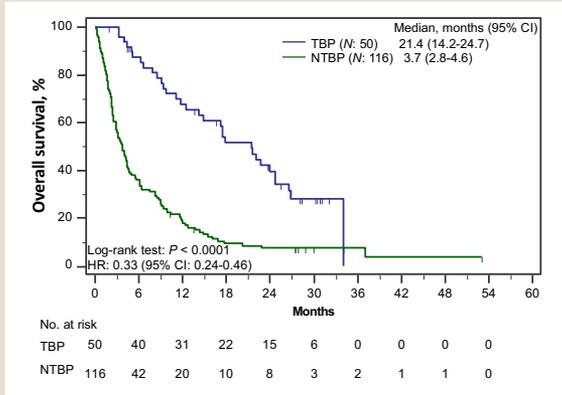
Supplemental tables and figures accompanying this article can be found in the online version at <https://doi.org/10.1016/j.clc.2019.02.001>.

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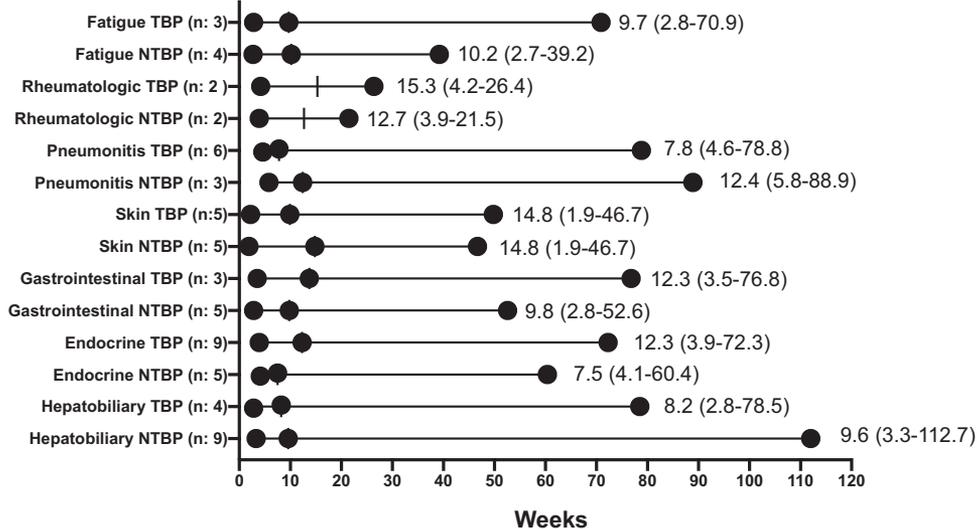
Nivolumab Beyond Progression in NSCLC

Supplemental Figure 1 Kaplan Meier-Curves for Overall Survival After Excluding Patients Who Experienced Either a Reduction $\geq 30\%$ or a Stabilization of Target Lesions After Initial Progression



Abbreviations: CI = confidence interval; HR = hazard ratio; NTBP = no treatment beyond progression; TBP = treatment beyond progression.

Supplemental Figure 2 Median Time to Onset (Range) of the Most Common Grade 2 to Grade 4 Treatment-related Adverse Events Leading to Treatment Temporary Discontinuation or Definitive Interruption According to Post-Progression Management (TBP vs. NTBP)



Abbreviations: NTBP = no treatment beyond progression; TBP = treatment beyond progression.

Supplemental Table 1 Summary of Efficacy of Nivolumab Before First Progression			
	TBP (N = 60)	NTBP (N = 116)	P Value
Objective response rate, N (%) [95% CI]	28/60 (46.6) [0.33-0.60]	7/116 (6.03) [0.02-0.12]	<.0001
Disease control rate, N (%) [95% CI]	35/60 (58.3) [0.44-0.70]	28/116 (24.1) [0.16-0.32]	<.0001
Best overall response, N (%)			
Progressive disease	25 (41.6)	88 (75.8)	
Stable disease	7 (11.6)	21 (18.1)	—
Partial response	24 (40)	7 (6.03)	
Complete response	4 (6.6)	0 (0.0)	
Progression-free survival, median (95% CI), mos	3.5 (2.2-4.8)	2.0 (1.7-2.3)	.002

Abbreviations: CI = confidence interval; NTBP = no treatment beyond progression; TBP = treatment beyond progression.

Supplemental Table 2 Univariate and Multivariate Analysis for Overall Survival				
	Univariate Hazard Ratio (95% CI)	P Value	Multivariate Hazard Ratio (95% CI)	P Value
Nivolumab discontinuation at first PD (yes vs. no)	3.29 (2.24-4.82)	<.0001	2.98 (1.95-4.54)	<.001
Gender (male vs. female)	1.52 (1.06-2.48)	.02	1.63 (1.11-2.39)	.03
Smoking status (yes vs. no)	1.15 (0.73-1.88)	.53	1.20 (0.67-1.72)	.43
ECOG PS (≥ 2 vs. 0-1)	3.52 (2.37-5.23)	<.001	2.00 (1.29-3.11)	.002
Age (≥ 70 vs. < 70)	1.28 (0.90-1.84)	.16	1.30 (0.89-1.90)	.17
Baseline brain metastasis (yes vs. no)	1.20 (0.82-1.75)	.33	1.59 (0.98-2.24)	.09
Best response to treatment (PD vs. SD/PR/CR)	2.77 (1.94-3.96)	<.001	2.17 (1.13-3.19)	<.001

Abbreviations: CI = confidence interval; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; NTBP = no treatment beyond progression; PD = progressive disease; PR = partial response; SD = stable disease; TBP = treatment beyond progression.