ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL RESEARCH

Early on-treatment tumor growth rate (EOT-TGR) determines treatment outcomes of advanced non-small-cell lung cancer patients treated with programmed cell death protein 1 axis inhibitor

L.-N. He[1,2,3†], S. Fu[4†], H. Ma[5,6†], C. Chen[1,2,7†], X. Zhang[1,2,3], H. Li[1,2,3], W. Du[1,2,3], T. Chen[1,2,8], Y. Jiang[1,2,8], Y. Wang[1,2,3], Y. Wang[1,2,9], Y. Zhou[1,2,10], Z. Lin[1,2,11], Y. Yang[1,2,3], Y. Huang[1,2,3], H. Zhao[1,2,11], W. Fang[1,2,3], H. Zhang[5,6*], L. Zhang[1,2,3*] & S. Hong[1,2,3*]

[1]State Key Laboratory of Oncology in South China, Guangzhou; [2]Collaborative Innovation Center for Cancer Medicine, Guangzhou; [3]Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou; [4]Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation of Sun Yat-Sen University; Department of Cellular & Molecular Diagnostics Center, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou; [5]Department of Oncology, the Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou; [6]Guangdong Provincial Key Laboratory of Clinical Research on Traditional Chinese Medicine Syndrome, Guangzhou; Departments of [7]Radiation Oncology; [8]Nuclear Medicine; [9]Endoscopy; [10]VIP Region; [11]Clinical Research, Sun Yat-sen University Cancer Center, Guangzhou, China

Available online 25 November 2022

Background: Tumor growth rate (TGR), denoted as percentage change in tumor size per month, is a well-established indicator of tumor growth kinetics. The predictive value of early on-treatment TGR (EOT-TGR) for immunotherapy remains unclear. We sought to establish and validate the association of EOT-TGR with treatment outcomes in patients with advanced non-small-cell lung cancer (aNSCLC) undergoing anti-PD-1/PD-L1 (programmed cell death protein 1/programmed death-ligand 1) therapy.

Patients and methods: This bicenter retrospective cohort study included a training cohort, a contemporaneously treated internal validation cohort, and an external validation cohort. Computed tomography images were retrieved to calculate EOT-TGR, denoted as tumor burden change per month during a period between baseline and the first imaging evaluation after immunotherapy. Kaplan—Meier methodology and Cox regression analysis were conducted for survival analyses.

Results: In the pooled cohort ($n = 172$), 125 patients (72.7%) were males; median age at diagnosis was 58 (range 28-79) years. Based on the training cohort, we determined the optimal cut-off value for EOT-TGR as 10.4%/month. Higher EOT-TGR was significantly associated with inferior overall survival [OS; hazard ratio (HR) 2.93, 95% confidence interval (CI) 1.47-5.83; $P = 0.002$], worse progression-free survival (PFS; HR 2.44, 95% CI 1.46-4.08; $P = 0.001$), and lower objective response rate (3.3% versus 20.9%; $P = 0.040$) and durable clinical benefit rate (6.7% versus 41.9%; $P = 0.001$). Results were reproducible in the two validation cohorts for OS and PFS. Among 43 patients who had a best response of progressive disease in the training cohort, those with high EOT-TGR had worse OS (HR 2.64; $P = 0.041$) and were more likely to progress due to target lesions at the first tumor evaluation (85.2% versus 0.0%; $P < 0.001$).

Conclusions: Higher EOT-TGR was associated with inferior OS and immunotherapeutic response in patients with aNSCLC undergoing anti-PD-1/PD-L1 therapy. This easy-to-calculate radiologic biomarker may help evaluate the abilities of immunotherapy to prolong survival and assist in tailoring patients' management.

Trial registration: ClinicalTrials.gov NCT04722406; https://clinicaltrials.gov/ct2/show/NCT04722406

Key words: tumor growth rate, non-small-cell lung cancer, immunotherapy, biomarker, prognosis

*Correspondence to: Prof. Shaodong Hong, Department of Medical Oncology, Sun Yat-sen University Cancer Center, 651 Dongfeng East Road, Guangzhou, Guangdong 510060, People's Republic of China. Tel: +86-20-87342480

E-mail: hongshd@sysucc.org.cn (S. Hong).

*Prof. Li Zhang, MD, Department of Medical Oncology, Sun Yat-sen University Cancer Center, 651 Dongfeng East Road, Guangzhou, Guangdong 510060, People's Republic of China. Tel: +86-20-87343458

E-mail: zhangli6@mail.sysu.edu.cn (L. Zhang).

*Prof. Haibo Zhang, Department of Oncology, the Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangdong Provincial Hospital of Chinese Medicine, 111 Dade Road, Guangzhou, Guangdong 510120, People's Republic of China. Tel: +86-20-81887233-34830

E-mail: haibozh@gzucm.edu.cn (H. Zhang).

†These authors have contributed equally to this work.

INTRODUCTION

Immune checkpoint inhibitors (ICIs), specifically programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors, have revolutionized the therapeutic landscape of advanced non-small-cell lung cancer (aNSCLC).[1-5] However, its clinical application is challenged by the low response rate and atypical response patterns such as hyperprogressive disease, pseudoprogression, dissociated response, and delayed response.[6-9] In an unselected, previously treated NSCLC population, response rates to single-agent PD-1/PD-L1 inhibitors range from 14% to 20%, with median progression-free survival (PFS) of 2-4 months and median overall survival (OS) of 10-14 months.[5,10-12] Numerous studies have proposed biomarkers to select patients likely or unlikely to respond to ICI therapy. However, even within favorable stratum, the benefit of immunotherapy is not observed for the entire population; whereas unfavorable factors could not exclude beneficial cases. Some biomarkers, such as tumor mutation burden, neoantigen burden, T-cell receptor repertoire, immune contexture, and gut microbiome are time-consuming and not cost-effective. Thus it remains urgent to explore other simple, early, and easy-to-calculate instruments to predict survival outcomes for ICI.[13]

The RECIST criteria serve as standard guidelines to assess tumor response in routine clinical practice and clinical trials.[14] However, RECIST evaluations do not take into account tumor growth characteristics. Thus the categorization of tumor response according to RECIST criteria may not sufficiently reflect the ability of an anticancer therapy to modify tumor growth and is not a good indicator of patients' survival.[15-18] To overcome such limitation, tumor growth rate (TGR), typically calculated as the change of tumor burden per unit time, was proposed.[19,20] TGR allows for quantitative assessment of tumor kinetics before or during an anticancer treatment. Several studies have suggested that TGR was associated with tumor response or survival outcomes for various carcinomas treated with different agents.[21-25] Recently, we found that pretreatment TGR was correlated with PFS but not with OS for anti-PD-1/PD-L1 monotherapy.[26] However, how tumor growth kinetics is modified by immunotherapy and its association with survival outcomes of patients remain unclear.

In this study, we hypothesized that early on-treatment TGR (EOT-TGR) based on computed tomography (CT) measurements could provide additional information on ICI efficacy and serve as a clinically relevant predictor of treatment outcomes in patients with aNSCLC.

PATIENTS AND METHODS

Definition of TGR

TGR is calculated based on an established formula: $TGR = 100 \times [\exp(TG) - 1]$; $TG = [3 \times \log(D_2/D_1)]/t$, where $t = (\text{date}_2 - \text{date}_1 + 1)/30.44$, indicating the time interval in months between two CT scans, and TG is the growth rate.[19,20] Tumor size (D) is the sum of the longest diameters of the target lesions (SLD) per RECIST version 1.1 (RECIST1.1). D_1 = tumor size at date_1; D_2 = tumor size at date_2. EOT-TGR was assessed between the baseline and the first imaging evaluation after ICI introduction (Figure 1). Follow-up imaging examinations were carried out at the physicians' discretion without a predefined interval, with an expected average time of 6-9 weeks. According to RECIST1.1, patients without measurable lesions at baseline could not be assessed for TGR. For patients who developed new lesions at the first evaluation, TGR was computed on the target lesions only.

Patients

We conducted a bicentric retrospective study (ClinicalTrials.gov identifier: NCT04722406) of a cohort of 172 aNSCLC patients (stage IIIB, IIIC, and IV) treated with single-agent anti-PD-1/PD-L1 antibody in a variety of settings covering routine clinical care, patient assistance programs, and clinical trials. In brief, patients were eligible for inclusion if they had histological confirmation of NSCLC; received treatment with single-agent anti-PD-1/PD-L1 antibody; and had baseline and at least one post-treatment CT scans. Patients with one of the following conditions were excluded: lacking available CT evaluation either at baseline or at follow-up evaluation; without measurable lesions at baseline evaluation; received maintenance treatment with single-agent ICI following immunotherapy plus chemotherapy or targeted therapy. Initially, patients from Sun Yat-sen University Cancer Center (SYSUCC) treated with PD-1/PD-L1 inhibitors between August 2016 and December 2018 ($N = 184$) were screened for eligibility and those met the inclusion criteria ($n = 146$) were randomized in a 1 : 1 ratio into a training and an internal validation cohort (Supplementary Figure S1A, available at https://doi.org/10.1016/j.esmoop.2022.100630). Clinical outcomes of the SYSUCC cohorts were followed up until 24 December 2020. The association of EOT-TGR with OS was further validated in an external validation cohort ($n = 26$) of patients treated with ICI between June 2016 and September 2020 (with follow-up completed on 29 December 2020) from Guangdong Provincial Hospital of Chinese Medicine (GPHCM;

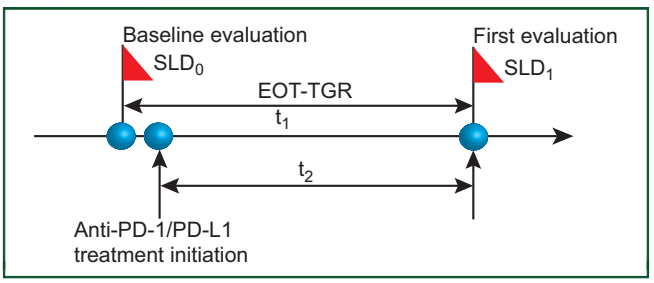

Figure 1. Diagram of computed tomography (CT) scan timepoints.
EOT-TGR, early on-treatment tumor growth rate, assessed from treatment initiation to the first imaging evaluation; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; SLD_0, SLD at baseline CT scan; SLD_1, SLD at the first CT scan; t_1, time interval between baseline and the first imaging evaluation; t_2, time interval between immunotherapy initiation and the first imaging evaluation.

Supplementary Figure S1B, available at https://doi.org/10.1016/j.esmoop.2022.100630).

The study was approved by the Institutional Review Boards of SYSUCC and GPHCM and written informed consent was waived owing to the retrospective nature of the study. This study followed the REporting recommendations for tumour MARKer prognostic studies (REMARK) guideline.[27]

Data extraction

Electronic medical records were reviewed to collect data including demographic characteristics and clinical and radiological information: sex, age; previous lines of systemic therapies, smoking status, histology, clinical stage, Eastern Cooperative Oncology Group (ECOG) performance status (PS), alterations in driver genes including epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK); date of CT scans, SLD, and status of nonmeasurable lesions and new lesions. The same assessment method and same CT technique were used at each imaging assessment point. Imaging data were extracted from a workstation (Advantage version 4.2; GE Healthcare, Chicago, IL). Missing data were recorded as not available and provided relevant interpretation if appropriate. All data were independently scrutinized by two trained physicians (L.-N.H and T.C.).

Response and endpoint evaluation

All response and outcome evaluation were determined according to RECIST1.1 by two senior radiologists (T.C. and Y.J.) blinded to patients' information, with discrepancy solved by consensus. Patients underwent tumor assessment until immunotherapy termination due to disease progression, intolerable adverse events, death, or at the decision of patients and physicians. The primary endpoint was OS, defined as the time from ICI initiation to death from any causes or end of follow-up. The secondary endpoints were PFS, objective response rate (ORR), and durable clinical benefit (DCB) rate. PFS was calculated from ICI initiation to radiologically defined progression or death from any causes. ORR was defined as the proportion of patients who had best response of complete response (CR) or partial response (PR). DCB was composed of CR, PR, or stable disease (SD) that lasted for at least 6 months.

Statistical analysis

The concordance level of the best overall responses (BORs) assessed by the two radiologists (interobserver concordance) was examined using kappa statistics. A kappa value of >0.80 was interpreted as excellent agreement. X-tile program (Yale University School of Medicine, New Haven, CT, USA) was used to determine the optimal cut-off values for SLD at baseline (SLD_0) and EOT-TGR based on maximum OS stratification in the training cohort.[28] According to the EOT-TGR cut-off, patients were divided into two groups (high EOT-TGR and low EOT-TGR), and baseline characteristics between the two groups were compared. Continuous variables were analyzed using Mann–Whitney *U* test or independent *t*-test depending on the normality of distribution; categorical variables were analyzed using Fisher's exact test or chi-square test where appropriate. The Kaplan–Meier method and log-rank test were conducted to compare survival outcomes. Univariate Cox regression analysis was carried out to investigate association of specific factors with OS and PFS. All parameters analyzed in univariate analyses were incorporated into the final multivariate Cox regression model and a forward stepwise procedure was used to identify significant factors. Two-sided $P < 0.05$ indicated statistical significance. All statistical analyses were carried out using the R software (version 3.6.1; https://www.r-project.org/).

RESULTS

Training cohort

Patient characteristics. Baseline characteristics of the 73 patients in the training cohort are summarized in Table 1. A total of 49 (67.1%) patients were males and 44 (60.3%) were nonsmokers; median (range) age was 54 (30-74) years and median (range) SLD_0 was 73 (17-231) mm. Median follow-up was 34.9 [95% confidence interval (CI), 26.7-43.2] months. Median OS was 23.6 (95% CI 9.7-37.5) months and median PFS was 2.1 (95% CI 2.0-2.3) months.

Optimal cut-off values of SLD_0 and EOT-TGR for OS stratification. Optimal cut-off values of SLD_0 and EOT-TGR were 108 mm (χ^2=9.876, $P = 0.039$) and 10.4%/month ($\chi^2 = 9.902$, $P = 0.039$), respectively (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2022.100630). According to the EOT-TGR threshold, patients were divided into two groups (low group: EOT-TGR $\leq$10.4%/month, $n = 43$; high group: EOT-TGR $>$10.4%/month, $n = 30$). Baseline characteristics between the two groups were compared (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100630). Higher EOT-TGR was significantly associated with three or more metastatic sites ($P = 0.020$) and RECIST-defined best response ($P < 0.001$). We found no statistical difference between EOT-TGR and age, gender, ECOG PS, smoking status, histology, prior treatment lines, lung metastasis, liver metastasis, brain metastasis, pleural metastasis, SLD_0, and driver mutations (all with *P* value of >0.05).

Association of EOT-TGR with response and survival outcomes. The interobserver concordance was excellent, with a kappa value of 0.832 (95% CI 0.714-0.947) (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100630). By RECIST1.1, 10 patients (13.7%) achieved PR, 20 (27.4%) had SD, and 43 (58.9%) had progressive disease (PD) as their BOR (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2022.100630). Eleven patients (15.1%) exhibited SD that lasted for over 6 months. Hence, the ORR was 13.7% and the DCB rate was 27.4% in this cohort. The response rate was significantly higher in patients with low EOT-TGR than in patients with high EOT-TGR [9/43 (20.9%) versus 1/30 (3.3%); $P = 0.040$]. DCB rate was also higher in the low EOT-TGR group than

Table 1. Patient characteristics at baseline

Patient characteristics	Training cohort (n = 73)	Internal validation cohort (n = 73)	GPHCM cohort (n = 26)	Pooled cohort (n = 172)
Age, years				
Median (range)	54 (30-74)	58 (28-79)	66 (38-76)	58 (28-79)
<54, *n* (%)	36 (49.3)	27 (37.0)	3 (11.5)	66 (38.4)
≥54, *n* (%)	37 (50.7)	46 (63.0)	23 (88.5)	106 (61.6)
Gender, *n* (%)				
Male	49 (67.1)	57 (78.1)	19 (73.1)	125 (72.7)
Female	24 (32.9)	16 (21.9)	7 (26.9)	47 (27.3)
ECOG PS, *n* (%)				
0	30 (41.1)	29 (39.7)	7 (26.9)	66 (38.4)
1	41 (56.2)	39 (53.4)	13 (50.0)	93 (54.1)
2-3	2 (2.7)	5 (6.8)	6 (23.1)	13 (7.5)
Smoking status, *n* (%)				
Never smoker	44 (60.3)	42 (57.5)	5 (19.2)	91 (52.9)
Current or former smoker	29 (39.7)	31 (42.5)	21 (80.8)	81 (47.1)
Histology, *n* (%)				
Squamous	27 (37.0)	25 (34.2)	9 (34.6)	61 (35.5)
Adenocarcinoma	40 (54.8)	48 (65.8)	16 (61.5)	104 (60.5)
Other types	6 (8.2)	0 (0.0)	1 (3.8)	7 (4.1)
Stage, *n* (%)				
IIIB	0 (0.0)	2 (2.7)	1 (3.9)	3 (1.7)
IIIC	0 (0.0)	0 (0.0)	5 (19.2)	5 (2.9)
IV	73 (100.0)	71 (97.3)	20 (76.9)	164 (95.3)
Immunotherapy regimen, *n* (%)				
Pembrolizumab	28 (38.3)	30 (41.1)	0 (0.0)	58 (33.7)
Atezolizumab	7 (9.6)	3 (4.1)	0 (0.0)	10 (5.8)
Nivolumab	18 (24.7)	23 (31.5)	13 (50.0)	54 (31.4)
Camrelizumab	20 (27.4)	16 (21.9)	0 (0.0)	36 (20.9)
Sintilimab	0 (0.0)	0 (0.0)	8 (30.8)	8 (4.7)
Toripalimab	0 (0.0)	1 (1.4)	3 (11.5)	4 (2.3)
Tislelizumab	0 (0.0)	0 (0.0)	2 (7.7)	2 (1.2)
PD-L1 status, *n* (%)				
Positive	0 (0.0)	1 (1.4)	13 (50.0)	14 (8.1)
Negative	0 (0.0)	0 (0.0)	2 (7.7)	2 (1.2)
Not available	73 (100.0)	72 (98.6)	11 (42.3)	156 (90.7)
Number of prior treatment lines, *n* (%)				
0	4 (5.5)	10 (13.7)	7 (26.9)	21 (12.2)
1	42 (57.5)	32 (43.8)	7 (26.9)	81 (47.1)
≥2	27 (37.0)	31 (42.5)	12 (46.2)	70 (40.7)
Number of distant metastatic sites, *n* (%)				
0	0 (0.0)	2 (2.7)	6 (23.1)	8 (4.6)
1	16 (22.0)	14 (19.2)	4 (15.4)	34 (19.8)
2	25 (34.2)	30 (41.1)	6 (23.1)	61 (35.5)
≥3	32 (43.8)	27 (37.0)	10 (38.4)	69 (40.1)
EGFR mutation status, *n* (%)				
Positive	9 (12.3)	5 (6.8)	1 (3.8)	15 (8.7)
Negative	46 (63.0)	57 (78.1)	15 (57.7)	118 (68.6)
Not available	18 (24.7)	11 (15.1)	10 (38.5)	39 (22.7)
ALK translocation, *n* (%)				
Positive	3 (4.1)	2 (2.7)	0 (0.0)	5 (2.9)
Negative	47 (64.4)	50 (68.5)	15 (57.7)	112 (65.1)
Not available	23 (31.5)	21 (28.8)	11 (42.3)	55 (32.0)
SLD_0, mm				
Median (range)	73 (17-231)	71 (11-174)	73 (15-171)	73 (11-231)
≤108, *n* (%)	59 (80.8)	52 (71.2)	20 (76.9)	131 (76.2)
>108, *n* (%)	14 (19.2)	21 (28.8)	6 (23.1)	41 (23.8)
t, months				
Median (range)	2.0 (1.0-4.2)	2.0 (0.6-5.6)	2.2 (0.7-8.0)	2.0 (0.6-8.0)
EOT-TGR, %/month				
Median (range)	8.6 (−54.7 to 55.5)	3.3 (−51.8 to 47.6)	−4.2 (−28.1 to 62.7)	4.7 (−54.7 to 62.7)
≤10.4, *n* (%)	43 (58.9)	49 (67.1)	20 (76.9)	112 (65.1)
>10.4, *n* (%)	30 (41.1)	24 (32.9)	6 (23.1)	60 (34.9)

ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EOT-TGR, early on-treatment tumor growth rate, assessed from treatment initiation to the first imaging evaluation; GPHCM, Guangdong Provincial Hospital of Chinese Medicine; PD-L1, programmed death-ligand 1; SLD_0, sum of the longest diameters of the target lesions at baseline; t, time interval between baseline and the first imaging evaluation.

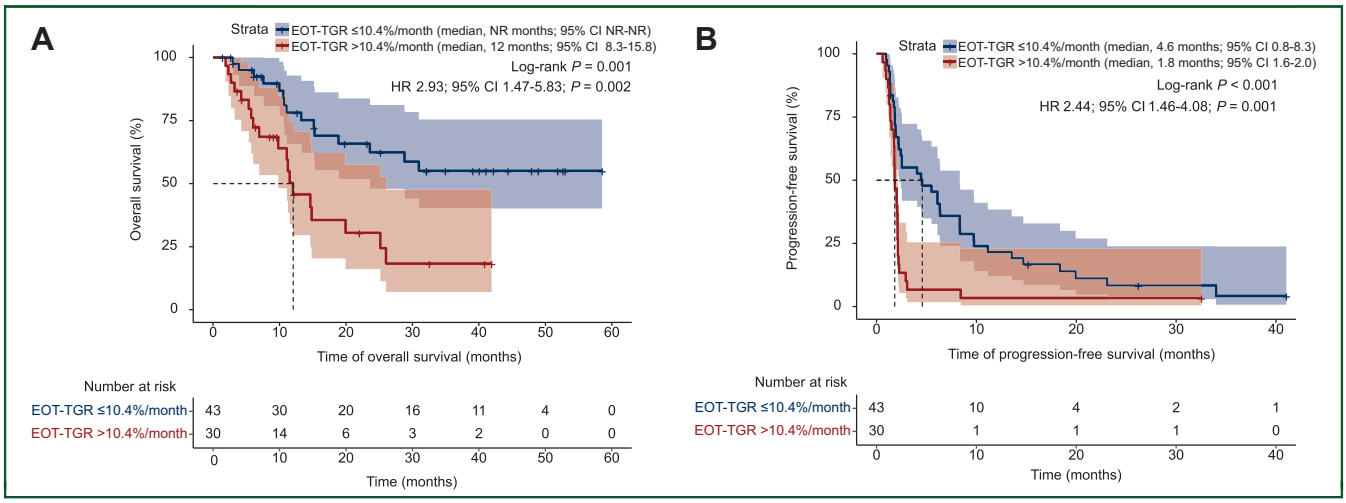

Figure 2. Overall survival (OS) and progression-free survival (PFS) according to EOT-TGR groups in the training cohort. (A) OS according to EOT-TGR groups. (B) PFS according to EOT-TGR groups.
EOT-TGR, early on-treatment tumor growth rate, assessed from treatment initiation to the first imaging evaluation; NR, not reached.

that in the high EOT-TGR group [18/43 (41.9%) versus 2/30 (6.7%); $P = 0.001$].

Patients with high EOT-TGR had significantly shorter OS than those with low EOT-TGR. Median OS was 12.0 months (95% CI 8.3-15.8 months) versus not reached [NR] months (95% CI NR-NR) for the high and low groups, respectively ($P = 0.001$; Figure 2A). EOT-TGR was also correlated with PFS ($P < 0.001$). For patients with high EOT-TGR, median PFS was 1.8 months (95% CI 1.6-2.0 months), whereas median PFS for the low EOT-TGR group was 4.6 months (95% CI 0.8-8.3 months; Figure 2B).

Cox regression analyses of survival outcomes. Univariate analysis indicated that two or more lines of prior systemic therapies [hazard ratio (HR) 1.96, 95% CI 1.00-3.87; $P = 0.050$], larger SLD_0 (HR 2.84, 95% CI 1.26-6.38; $P = 0.012$), and high EOT-TGR (HR 2.93, 95% CI 1.47-5.83; $P = 0.002$) were significantly associated with inferior OS (Table 2). In the multivariate Cox model, high EOT-TGR (HR 3.36, 95% CI 1.63-6.91; $P = 0.001$), larger SLD_0 (HR 2.98, 95% CI 1.30-6.81; $P = 0.010$), and squamous cell histology (HR 2.33, 95% CI 1.14-4.78; $P = 0.020$) were negative predictors for OS (Table 2). A consistent association of EOT-TGR with OS was observed across most subgroups (Figure 3).

Factors associated with worse PFS in univariate analysis included two or more lines of prior therapies (HR 2.71, 95% CI 1.57-4.65; $P < 0.001$), three or more metastatic sites (HR 2.77, 95% CI 1.65-4.64; $P < 0.001$), positive ALK rearrangement status (HR 3.96, 95% CI 1.17-13.43; $P = 0.027$), larger SLD_0 (HR 2.30, 95% CI 1.25-4.24; $P = 0.007$), and high EOT-TGR (HR 2.44, 95% CI 1.46-4.08; $P = 0.001$). In multivariate analysis, prior treatment lines ($P = 0.007$), metastatic sites ($P < 0.001$), and SLD_0 ($P = 0.001$) remained associated with PFS (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100630).

Value of TGR in patients who had PD as BOR. Among the 43 patients who had PD as their BORs, 20 (46.5%) were due to progression in nontarget lesions ($n = 1$) or occurrence of new lesions ($n = 19$). Patients in the high EOT-TGR group were more likely to progress with target lesions at the first tumor evaluation (23/27, 85.2%) versus those in the low EOT-TGR group (0/16, 0%; Fisher's $P < 0.001$; (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2022.100630**)**. For survival analyses in these 43 patients, low EOT-TGR was correlated with prolonged OS (median 31.0, 95% CI 14.0-47.9 months) compared with high EOT-TGR (median 11.3, 95% CI 8.9-13.7 months; $P = 0.034$; Supplementary Figure S5A, available at https://doi.org/10.1016/j.esmoop.2022.100630). Not surprisingly, no difference was observed in PFS regarding EOT-TGR stratum ($P = 0.380$; Figure S5B, available at https://doi.org/10.1016/j.esmoop.2022.100630).

Validation cohorts

Internal validation of association of EOT-TGR with outcomes. In the internal validation cohort, median follow-up was 31.0 months (95% CI 25.3-36.7 months). Median OS and PFS were 19.2 months (95% CI 16.1-22.2 months) and 2.6 months (95% CI 0.5-4.7 months), respectively. Baseline characteristics of this cohort are summarized in Table 1. High EOT-TGR was significantly associated with worse OS (HR 3.19, 95% CI 1.59-6.38; $P = 0.001$) and PFS (HR 5.03, 95% CI 2.76-9.19; $P < 0.001$; Supplementary Figure S6A and B, available at https://doi.org/10.1016/j.esmoop.2022.100630). In addition, patients with low EOT-TGR achieved higher ORR [13/49 (26.5%) versus 0/24 (0.0%); $P = 0.003$] and DCB rate [24/49 (49.0%) versus 0/24 (0.0%); $P < 0.001$] versus those with high EOT-TGR.

External validation of association of TGR with survivals. A total of 26 patients from the GPHCM cohort were included in the external validation cohort (Supplementary Figure S1B, available at https://doi.org/10.1016/j.esmoop.2022.100630). Baseline characteristics of this cohort are summarized in Table 1. Median follow-up was 20.1 months (95% CI 14.7-25.6 months), median OS was 25.7 months

Table 2. Univariate and multivariate analyses for overall survival in the training cohort

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, years				
<54	1 (Reference)			
≥54	1.39 (0.71-2.75)	0.338		0.260
Gender				
Male	1.00 (0.49-2.06)	0.996		0.659
Female	1 (Reference)			
ECOG PS				
0	1 (Reference)			
1-3	2.02 (0.97-4.24)	0.061		0.307
Smoking status				
Never smoker	1.17 (0.58-2.33)	0.664		0.776
Current or former smoker	1 (Reference)			
Histology				
Squamous	1.83 (0.93-3.62)	0.081	2.33 (1.14-4.78)	0.020
Nonsquamous	1 (Reference)		1 (Reference)	
Number of prior treatment lines				
<2	1 (Reference)			
≥2	1.96 (1.00-3.87)	0.050		0.088
Number of metastatic sites				
<3	1 (Reference)			
≥3	1.52 (0.77-2.99)	0.226		0.616
EGFR mutation status				
Positive	1 (Reference)			
Negative	1.83 (0.43-7.85)	0.414		0.917
Not available	4.36 (0.97-19.73)	0.056		0.257
ALK translocation				
Negative	1 (Reference)			
Positive	1.49 (0.35-6.42)	0.590		0.166
Not available	2.18 (1.05-4.50)	0.036		0.917
SLD_0, mm				
≤108	1 (Reference)		1 (Reference)	
>108	2.84 (1.26-6.38)	0.012	2.98 (1.30-6.81)	0.010
EOT-TGR, %/month				
≤10.4	1 (Reference)		1 (Reference)	
>10.4	2.93 (1.47-5.83)	0.002	3.36 (1.63-6.91)	0.001

ALK, anaplastic lymphoma kinase; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EOT-TGR, early on-treatment tumor growth rate, assessed from treatment initiation to the first imaging evaluation; HR, hazard ratio; SLD_0, sum of the longest diameters of the target lesions at baseline.

(95% CI NR-NR), and median PFS was 5.7 months (95% CI 0.5-10.8 months). Patients with high EOT-TGR had shorter OS and PFS than those with low EOT-TGR [median (95% CI) OS: 8.1 months (0.0-21.0 months) versus NR (NR-NR), $P = 0.002$; median (95% CI) PFS: 1.5 months (1.5-1.6 months) versus 6.9 months (2.8-11.0 months), $P < 0.001$; Supplementary Figure S6C and D, available at https://doi.org/10.1016/j.esmoop.2022.100630].

Association of EOT-TGR with responses and survivals in the pooled cohort. Baseline characteristics of the pooled immunotherapy cohort ($n = 172$) are summarized in Table 1. 125 patients (72.7%) were males; median age at diagnosis was 58 years (range 28-79 years). Median EOT-TGR was 4.7% (range −54.7% to 62.7%)/month. Median follow-up was 29.6 months (95% CI 23.9-35.4 months). Median OS was 24.1 months (95% CI 18.8-29.3 months) and median PFS was 2.3 months (95% CI 1.9-2.7 months). According to RECIST1.1, 28 patients (16.3%) achieved PR, 53 (30.8%) had SD, and 91 (52.9%) had PD as their best BOR. The overall response rate was 16.3% and the DCB rate was 30.8% (53/172).

Both the ORR and DCB rate were significantly higher for the low versus high EOT-TGR group [ORR: 24.1% (27/112) versus 1.7% (1/60); $P < 0.001$; DCB: 45.5% (51/112) versus 3.3% (2/60); $P < 0.001$]. Median OS was 31.0 months (95% CI 17.7-44.2 months) versus 11.5 months (95% CI 6.3-16.8 months) for the low and high EOT-TGR groups ($P < 0.001$), respectively (Supplementary Figure S6E, available at https://doi.org/10.1016/j.esmoop.2022.100630). Median PFS was 6.1 months (95% CI 4.1-8.1 months) versus 1.8 months (95% CI 1.6-1.9 months) for the low and high EOT-TGR group ($P < 0.001$), respectively (Supplementary Figure S6F, available at https://doi.org/10.1016/j.esmoop.2022.100630). In the multivariate Cox models, higher EOT-TGR was independently associated with worse OS (HR 3.75, 95% CI 2.32-6.05; $P < 0.001$) (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2022.100630) and PFS (HR 3.65, 95% CI 2.55-5.22; $P < 0.001$) (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2022.100630).

DISCUSSION

TGR is a practical instrument for visualizing and monitoring tumor growth kinetics.[29] Our study provided evidence that

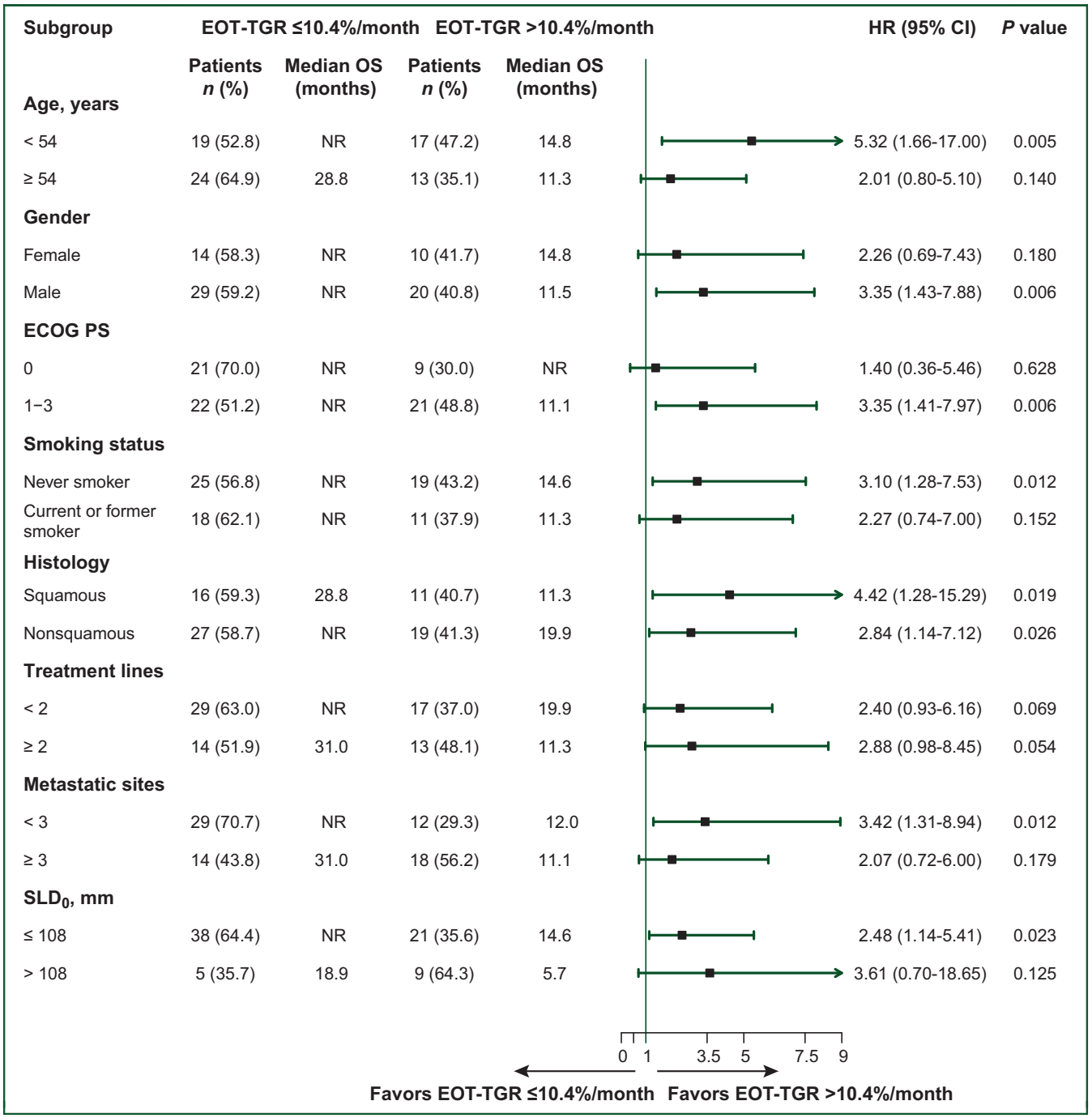

Figure 3. Overall survival (OS) in baseline characteristic subgroups. Median OS was estimated by Kaplan−Meier analysis and hazard ratios (HRs) was examined by Cox proportional hazards regression analysis.

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT-TGR, early on-treatment tumor growth rate, assessed from treatment initiation to the first imaging evaluation; NR, not reached; SLD_0, sum of the longest diameters of the target lesions at baseline.

early on-treatment tumor growth rate, or EOT-TGR, assessed between the ICI treatment onset and the first imaging evaluation, was correlated with treatment outcomes in patients with aNSCLC undergoing ICI monotherapy. The 65.1% of the population with high EOT-TGR was less likely to achieve an objective response and DCB, and had both shorter PFS and OS than those with low EOT-TGR. These results provide support that EOT-TGR can reflect clinically significant activity of the drug and might be a predictor of benefit from immunotherapy.

Several efforts have been made in other tumor entities to investigate predictive value of TGR upon early treatment in terms of outcomes of patients. Higher TGR during the first treatment cycle was found to be associated with shorter PFS and OS in patients with metastatic renal cell carcinoma treated with sorafenib or everolimus.[30] Low TGR_{3m} [TGR at

https://doi.org/10.1016/j.esmoop.2022.100630

3 (±1) months of study entry] could be used as an early radiological predictor of favorable PFS and objective response in patients with advanced neuroendocrine tumors initiating systemic treatment.[20,31] In our observation, EOT-TGR was significantly associated with OS, which was reproducible in two validation sets and was further identified as an independent prognosticator both in the training set and the pooled cohort. Besides, subgroup analysis could see consistent association of EOT-TGR with OS across most baseline subgroups. EOT-TGR had marginal association with PFS but failed to predict PFS in multivariate analysis in the training cohort, which, we thought, could be mainly explained by the sample size, as it was identified as an independent predictor for PFS in the pooled cohort. Together, these findings indicated that EOT-TGR has a strong potential for translation at bedside as an early risk stratification instrument and for guiding the design of future clinical trials. Worthy of note, this does not courage clinicians to determine continued treatment or to discuss other options according to the TGR profiles, but indicates a dynamic and tailored follow-up scheme. Patients with high EOT-TGR should be regularly followed up for the shorter PFS, whereas those with low EOT-TGR could have less frequent examination to reduce unnecessary radiation exposure.

Another interesting finding is that on-treatment tumor growth kinetics was able to capture a clinically significant biological effect that went unnoticed by RECIST. Owing to complicated tumor biological characteristics, progression velocity may be heterogeneous across different tumor types and across individuals suffering from the same carcinoma. As shown in our study, among 43 patients with a BOR of PD (*de novo* resistance), patients with high EOT-TGR had increased possibility of target lesion progression at the first tumor evaluation (85.2% versus 0.0%). Furthermore, among these RECIST1.1-defined progressors, OS was significantly longer in patients with low on-treatment TGR than those with high on-treatment TGR (median 31.0 versus 11.3 months). These results provided additional support that RECIST-based tumor response classification was insufficient to reflect the activity of immunotherapy. However, because a large proportion of patients had no further tumor assessments following RECIST1.1-defined progressive disease, we could not evaluate the association of EOT-TGR with pseudo-progression, nor could we explore the association of EOT-TGR with PFS calculated according to the immune response criteria in solid tumors (iRECIST). This issue should be further addressed if EOT-TGR is to be introduced into a new response assessment criterion for immunotherapy. However, we think our study is clinically relevant because RECIST criteria remain the gold metrics to define primary efficacy outcomes in clinical practice and clinical trials, whereas iRECIST is mainly used for exploratory analyses. Furthermore, the robust association between EOT-TGR and treatment outcomes indicates the significance of this instrument.

Several limitations deserve attention when interpreting our findings. The relatively small sample size, especially the external validation cohort, and the retrospective design may introduce bias. Our findings did require prospective validation with larger sample size to lower chances of bias. Meanwhile, the retrospective nature also hampered us from setting a predefined time window for radiological follow-up. We think, on the basis of median time interval presented in Table 1, the research community can carry out prospective studies in the real-world setting to capture EOT-TGR, in which the time interval between the baseline and the first imaging evaluation is uniformly set as 1 or 2 months. The strict inclusion criteria, especially from the imaging requirements, may cause potential selection bias. Most patients had unavailable PD-L1 status, which made it difficult for us to investigate the impact of PD-L1 expression on clinical outcomes. It should be noted, however, that most patients in our cohorts were treated in a second- or later-line setting and PD-L1 status was not mandatory for making treatment decisions in such setting. Patient's characteristics were not comparable between the training and validation cohorts. However, successful validation in a heterogenous population indicated that our results could be extended to a broader setting. In addition, due to the lack of comprehensive genomic data, our analyses could not be adjusted for tumor mutation burden and other specific mutation types; however, these biomarkers also were not mandatory for ICI prescription. Another limitation is the potential confounder deriving from anisotropy not included in the TGR assessment, as target lesions are presumed to be spherical.[32] Furthermore, it is unknown whether RECIST-based calculation of TGR is the optimal setting for kinetics assessment. Evaluation of target lesions may not reflect the whole tumor burden because nontarget and new lesions were not taken into account. These limitations aside, the method for TGR calculation in this study is the most widely used, easy-to-compute, and well-recognized one to evaluate tumor growth kinetics, including characterization of hyperprogressive disease in the era of immunotherapy.[19,33] Calculation of TGR is feasible, simple, and requires modest additional costs to conduct at bedside with available access to the internet calculator tool (http://www.gustaveroussy.fr/doc/tgr_calculator/index_en.html). Our findings about the predictive value of EOT-TGR had robust clinical implication, given the unpredictable fatal toxicity and crippling hospital costs of ICI therapy. Translation of TGR into clinical utility has a potential role in tailoring patient management.

In summary, EOT-TGR played a role in predicting OS and immunotherapeutic response in patients with aNSCLC treated with ICI monotherapy. Early evaluation of on-treatment TGR has promising clinical utilities in guiding patient management. Future studies in larger cohorts, most preferably prospective, are warranted to gain an in-depth understanding of this association.

ACKNOWLEDGEMENTS

We sincerely appreciate all the patients and their family who were included in this retrospective study.

FUNDING

This study was supported by National Natural Science Foundation of China [grant numbers 81972898, 8217102281]; the Natural Science Foundation of Guangdong Province [grant number 2019A1515011090], and the Outstanding Young Talents Program of Sun Yat-sen University Cancer Center [grant number 16zxyc04].

DISCLOSURE

The authors have declared no conflicts of interest.

DATA SHARING

All data and material relevant to the study are included within the article and its additional file. Raw data of this study are available from the corresponding authors upon reasonable request.

ETHICS STATEMENT

This study was approved by the Institutional Review Boards of Sun Yat-sen University Cancer Center (SYSUCC; SL-B2020-402-02) and Guangdong Provincial Hospital of Chinese Medicine (BE2020-247-01). The requirement for written informed consent was waived because of the retrospective design.

ROLE OF THE FUNDING SOURCE

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Antonia SJ, Borghaei H, Ramalingam SS, et al. Four-year survival with nivolumab in patients with previously treated advanced non-small-cell lung cancer: a pooled analysis. *Lancet Oncol*. 2019;20(10):1395-1408.
2. Blumenthal GM, Zhang L, Zhang H, et al. Milestone analyses of immune checkpoint inhibitors, targeted therapy, and conventional therapy in metastatic non-small cell lung cancer trials: a meta-analysis. *JAMA Oncol*. 2017;3(8):e171029.
3. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393(10183):1819-1830.
4. Gettinger S, Horn L, Jackman D, et al. Five-year follow-up of nivolumab in previously treated advanced non-small-cell lung cancer: results from the CA209-003 study. *J Clin Oncol*. 2018;36(17):1675-1684.
5. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017;389(10066):255-265.
6. Tazdait M, Mezquita L, Lahmar J, et al. Patterns of responses in metastatic NSCLC during PD-1 or PDL-1 inhibitor therapy: comparison of RECIST 1.1, irRECIST and iRECIST criteria. *Eur J Cancer*. 2018;88:38-47.
7. Sheng Z, Zhu X, Sun Y, Zhang Y. The efficacy of anti-PD-1/PD-L1 therapy and its comparison with EGFR-TKIs for advanced non-small-cell lung cancer. *Oncotarget*. 2017;8(34):57826-57835.
8. Seto T, Sam D, Pan M. Mechanisms of primary and secondary resistance to immune checkpoint inhibitors in cancer. *Med Sci (Basel)*. 2019;7(2):14.
9. Kim JY, Lee KH, Kang J, et al. Hyperprogressive disease during anti-PD-1 (PDCD1)/PD-L1 (CD274) therapy: a systematic review and meta-analysis. *Cancers (Basel)*. 2019;11(11):1699.
10. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373(17):1627-1639.
11. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373(2):123-135.
12. Wu YL, Lu S, Cheng Y, et al. Nivolumab versus docetaxel in a predominantly Chinese patient population with previously treated advanced NSCLC: CheckMate 078 randomized phase III clinical trial. *J Thorac Oncol*. 2019;14(5):867-875.
13. Havel JJ, Chowell D, Chan TA. The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy. *Nat Rev Cancer*. 2019;19(3):133-150.
14. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.
15. Blumenthal GM, Karuri SW, Zhang H, et al. Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non-small-cell lung cancer: US Food and Drug Administration trial-level and patient-level analyses. *J Clin Oncol*. 2015;33(9):1008-1014.
16. Mushti SL, Mulkey F, Sridhara R. Evaluation of overall response rate and progression-free survival as potential surrogate endpoints for overall survival in immunotherapy trials. *Clin Cancer Res*. 2018;24(10):2268-2275.
17. Maitland ML, Schwartz LH, Ratain MJ. Time to tumor growth: a model end point and new metric system for oncology clinical trials. *J Clin Oncol*. 2013;31(17):2070-2072.
18. Champiat S, Ferrara R, Massard C, et al. Hyperprogressive disease: recognizing a novel pattern to improve patient management. *Nat Rev Clin Oncol*. 2018;15(12):748-762.
19. Ferte C, Fernandez M, Hollebecque A, et al. Tumor growth rate is an early indicator of antitumor drug activity in phase I clinical trials. *Clin Cancer Res*. 2014;20(1):246-252.
20. Lamarca A, Crona J, Ronot M, et al. Value of tumor growth rate (TGR) as an early biomarker predictor of patients' outcome in neuroendocrine tumors (NET)-the GREPONET study. *Oncologist*. 2019;24(11):e1082-e1090.
21. Stein WD, Wilkerson J, Kim ST, et al. Analyzing the pivotal trial that compared sunitinib and IFN-alpha in renal cell carcinoma, using a method that assesses tumor regression and growth. *Clin Cancer Res*. 2012;18(8):2374-2381.
22. Gomez-Roca C, Koscielny S, Ribrag V, et al. Tumour growth rates and RECIST criteria in early drug development. *Eur J Cancer*. 2011;47(17):2512-2516.
23. Dromain C, Pavel ME, Ruszniewski P, et al. Tumor growth rate as a metric of progression, response, and prognosis in pancreatic and intestinal neuroendocrine tumors. *BMC Cancer*. 2019;19(1):66.
24. Purcell Y, Sartoris R, Paradis V, Vilgrain V, Ronot M. Influence of pretreatment tumor growth rate on objective response of hepatocellular carcinoma treated with transarterial chemoembolization. *J Gastroenterol Hepatol*. 2020;35(2):305-313.
25. Ten Berge D, Hurkmans DP, den Besten I, et al. Tumour growth rate as a tool for response evaluation during PD-1 treatment for non-small cell lung cancer: a retrospective analysis. *ERJ Open Res*. 2019;5(4):00179-2019.
26. He LN, Zhang X, Li H, et al. Pre-treatment tumor growth rate predicts clinical outcomes of patients with advanced non-small cell lung cancer undergoing anti-PD-1/PD-L1 therapy. *Front Oncol*. 2020;10:621329.

27. McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM. REporting recommendations for tumour MARKer prognostic studies (REMARK). *Eur J Cancer.* 2005;41(12):1690-1696.
28. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. *Clin Cancer Res*. 2004;10(21):7252-7259.
29. Nagase M, Aksenov S, Yan H, Dunyak J, Al-Huniti N. Modeling tumor growth and treatment resistance dynamics characterizes different response to gefitinib or chemotherapy in non-small cell lung cancer. *CPT Pharmacometrics Syst Pharmacol*. 2020;9(3):143-152.
30. Ferte C, Koscielny S, Albiges L, et al. Tumor growth rate provides useful information to evaluate sorafenib and everolimus treatment in metastatic renal cell carcinoma patients: an integrated analysis of the TARGET and RECORD phase 3 trial data. *Eur Urol*. 2014;65(4):713-720.
31. Lamarca A, Ronot M, Moalla S, et al. Tumor growth rate as a validated early radiological biomarker able to reflect treatment-induced changes in neuroendocrine tumors: the GREPONET-2 study. *Clin Cancer Res*. 2019;25(22):6692-6699.
32. Schiavon G, Ruggiero A, Bekers DJ, et al. The effect of baseline morphology and its change during treatment on the accuracy of Response Evaluation Criteria in Solid Tumours in assessment of liver metastases. *Eur J Cancer.* 2014;50(5):972-980.
33. Champiat S, Dercle L, Ammari S, et al. Hyperprogressive disease is a new pattern of progression in cancer patients treated by Anti-PD-1/PD-L1. *Clin Cancer Res*. 2017;23(8):1920-1928.