



Determinants of survival in advanced non-small cell lung cancer patients treated with anti-PD-1/PD-L1 therapy

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Background: The present study aimed to investigate the determinant factors of survival in patients with pretreated advanced stage non-small cell lung cancer (NSCLC) who received anti-PD-1/PD-L1 therapy.

Methods: In this observational retrospective study, the clinical profiles and laboratory parameters of patients with NSCLC treated with anti-PD-1/PD-L1 therapy were consecutively collected. Lung Immune Prognostic Index (LIPI) was calculated based on the derived neutrophil-to-lymphocyte ratio (dNLR) and lactate dehydrogenase level (LDH). Modified Glasgow Prognostic Score (mGPS) was calculated based on serum C reactive protein and albumin, and tumor mutation burden (TMB) was calculated using a targeted next-generation sequencing panel based on 422 cancer-relevant genes. The primary and secondary end points were overall survival (OS) and progression-free survival (PFS), respectively. The Cox regression model was used to identify the potential determinant factors of survival benefit. Trained oncologists at Sun Yat-sen University Cancer Center followed all of the participants through visits to doctors' offices or via telephone calls to determine their clinical status.

Results: Seventy-three patients were included in our study. With a median follow up time of 637 days, there was a significant difference in PFS between patients with high TMB compared to those with low TMB (3.7 *vs.* 2.1 months; $P=0.004$), while no significant difference was found in OS (14.0 *vs.* 16.4 months; $P=0.972$). Patients with a good LIPI score had a significantly longer OS compared to patients with a poor LIPI score (19.2 *vs.* 12.6 months; $P=0.010$). The median OS in patients with a good and a poor mGPS was 16.8 and 4.3 months, respectively ($P=0.029$). In multivariate analysis, TMB was found to be significantly associated with PFS (HR, 0.38; 95% CI: 0.21–0.69; $P=0.002$), while LIPI score was found to be significantly associated with OS (HR, 0.50; 95% CI: 0.28–0.89; $P=0.012$).

Conclusions: In the present study, LIPI score was a significant determinant of OS in patients with advanced NSCLC who received ICIs; however, TMB was only associated with PFS and not associated with OS.

Keywords: Non-small cell lung cancer (NSCLC); immune checkpoint inhibitors (ICIs); survival benefits; determinant factors; LIPI score; tumor mutation burden (TMB)

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Introduction

Recently, immunotherapy with immune checkpoint inhibitors (ICIs) has achieved excellent outcomes in the treatment of several types of cancer and was approved as the frontline treatment for patients with non-small cell lung cancer (NSCLC) (1,2). The response rate for this treatment is still unsatisfactory. In pretreated patients with NSCLC, the response rate to anti-PD-1/PD-L1 monotherapy was seen in only 14–20% of patients. When these patients were stratified by PD-L1 expression level on tumor cells, the response improved to up to 30% in patients with strong PD-L1 expression (1). Tumor mutation burden (TMB) is considered to be a potential factor that is associated with ICIs treatment outcomes (3,4). The predictive value of TMB is supported by the results from the KEYNOTE-158 trial, followed by its approval as a predictive biomarker for immunotherapy response in patients with different tumor types who were treated with pembrolizumab (5). Although PD-L1 expression and TMB have been incorporated into clinical practice as the most promising biomarkers for anti-PD-1/PD-L1 treatment outcomes, not all patients with positive PD-L1 or high TMB can attain clinical benefits from immunotherapy; therefore, their predictive values require further optimization (6).

Peripheral blood-based biomarkers, such as inflammatory and nutritional-related markers, have emerged as potential biomarkers for immunotherapy outcomes (7,8). In NSCLC, some novel prognostic scores, such as LIPI score and mGPS, have been evaluated for their association with anti-PD-1/PD-L1 therapy outcomes (9–12). These peripheral blood-based biomarkers have not been validated in large-scale prospective studies. In addition, the association between these biomarkers and TMB or PD-L1 is still not fully understood. Recent studies have demonstrated that multiple clinical factors, such as gender and smoking history, may influence the treatment outcomes of ICIs in patients with NSCLC (13,14). The current study sought to identify the determinant factor of survival benefits in advanced NSCLC patients pretreated with ICIs. We incorporated multiple factors in a multivariable analyzing model, including patient characteristics, LIPI score, mGPS, and TMB. We present the following article in accordance with the recommendations for tumor marker prognostic studies (REMARK) reporting checklist (available at <https://dx.doi.org/10.21037/atm-21-1702>).

Methods

Patients

This observational retrospective study involved 73 patients with advanced NSCLC who received either anti-PD-1 (pembrolizumab, nivolumab, or camrelizumab) or anti-PD-L1 (atezolizumab) therapy in a phase III control clinical trial at Sun Yat-sen University Cancer Center between December 2015 and August 2017. This study had a median follow up time of 637 days. All of the patients fulfilled the predefined inclusion criteria, including (I) age >18 years old; (II) performance status (ECOG) of 0–1; (III) confirmed diagnosis of recurrent or metastatic NSCLC; and (IV) assessable tumor lesion by computed tomography or magnetic resonance imaging according to Response Evaluation Criteria in Solid Tumor (RECIST, v1.1). Tumor FFPE tissue sections (n=58) or biopsy samples (n=15) were obtained before treatment and used for genetic testing. Tumor driver mutation was detected using next-generation sequencing (NGS).

TMB was calculated using a targeted next-generation sequencing panel that was based on 422 cancer-relevant genes. This was done by adding alterations in the coding region of targeted genes, including base substitutions, indels, and synonymous alterations. As previously described, known driver mutations were excluded (15) with an average coverage depth and size of 1341X and 1.4 Mb, respectively. A cut-off of 10 mutations per megabase was used to classify patients into groups defined as high and low TMB. Peripheral blood samples were obtained from all of the patients before treatment. The derived neutrophil-to-lymphocyte ratio (dNLR) was calculated as the absolute neutrophil count/ (white blood cell – absolute neutrophil). LIPI score was calculated based on dNLR >3 and LDH level > the upper limit of normal, as previously reported (11). Due to the limited number of patients with a LIPI score of 2, we stratified patients into two groups: good LIPI score [0], and poor LIPI score [1–2] (16). The mGPS scores were calculated based on serum C reactive protein and albumin with cutoffs of 10 mg/L and 35 g/L, respectively. An mGPS score of 0–1 and 2 were classified as good and poor mGPS scores, respectively (17). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center (pembrolizumab: A2016-019; camrelizumab: A2016-009; nivolumab: A2015-035; atezolizumab: A2016-021). In addition, individual consent for this retrospective analysis was waived.

Table 1 Patients baseline characteristics

Variables	Patients No.	%
Gender (female/male)	22/51	30/70
Age		
Median	54	
Range	28–73	
Pathological type		
Squamous	23	31.5
Non-squamous	50	68.5
Smoking (yes/no)	36/37	49.3/50.7
ECOG (0/1)	22/51	30.1/69.9
Line of immunotherapy		
1st	4	5.5
2nd	35	47.9
3rd	18	24.7
4th or above	16	21.9
Pretreatment metastases		
1	19	26
2	26	35.6
3	18	24.7
4 or more	10	13.7
LIPI score		
0	36	49.3
1	30	41.1
2	7	9.6
mGPS		
0	1	1.4
1	60	82.2
2	12	16.4
TMB		
High	24	33
Low	46	63
Unknown	3	4
PD-L1 expression		
Negative	14	19.2
Positive	13	17.8
Unknown	46	63

ECOG, eastern cooperative oncology group performance status; LIPI, lung immune prognostic index; mGPS, modified Glasgow Prognostic Score; TMB, tumor mutational burden.

Treatments and response assessment

All of the patients included in this study were treated as part of a phase III clinical trial. Most patients received anti-PD1/PD-L1 as their second or later line of treatment after the standard frontline treatment had failed. PFS was defined as the time from treatment initiation to the date of disease progression. OS was defined as the time from the initiation of anti-PD1/PD-L1 treatment to the date of death from any cause. Treatment response evaluation was based on RECIST evaluation criteria (RECIST, v1.1). Trained oncologists at Sun Yat-sen University Cancer Center followed all of the participants through visits to doctors' offices or via telephone calls to determine their clinical status.

Statistical analysis

Predefined clinical endpoints in our analysis were PFS and OS. Normally distributed numeric variables are indicated by the mean \pm SD and categorical variables are indicated as a percentage (%). Estimation of PFS and OS was determined by Kaplan-Meier analysis and the differences were examined by log-rank test. Cox regression analysis was used to determine the adjusted hazard ratio (HR) for PFS and OS. The gender, age, pathological type, smoking history, ECOG, baseline metastases number, prior treatment lines, LIPI, mGPS, and TMB for all of the patients were included in the univariate analysis. Variables with P value of <0.10 were further assessed in multivariable analysis. A two-sided P value of <0.05 was considered to be significant. All of the analyses were conducted with the use of SPSS version 20 (IBM SPSS Statistics, RRID:SCR_019096) and GraphPad software version 8 (GraphPad Prism, RRID:SCR_002798) was used to draw the figures.

Results

Baseline characteristics of patients

The baseline characteristics of patients are shown in *Table 1*. Overall, 95 patients received anti-PD-1/PD-L1 monotherapy. After excluding patients with ineligible WES results, 73 patients were included in the final analysis with a median age of 54 years. Fifty-one patients (70%) were male and 36 (49.3%) patients were current or former smokers. Fifty patients (68.5%) were diagnosed with non-squamous NSCLC. TMB was high in 24 (33%) patients. A total of

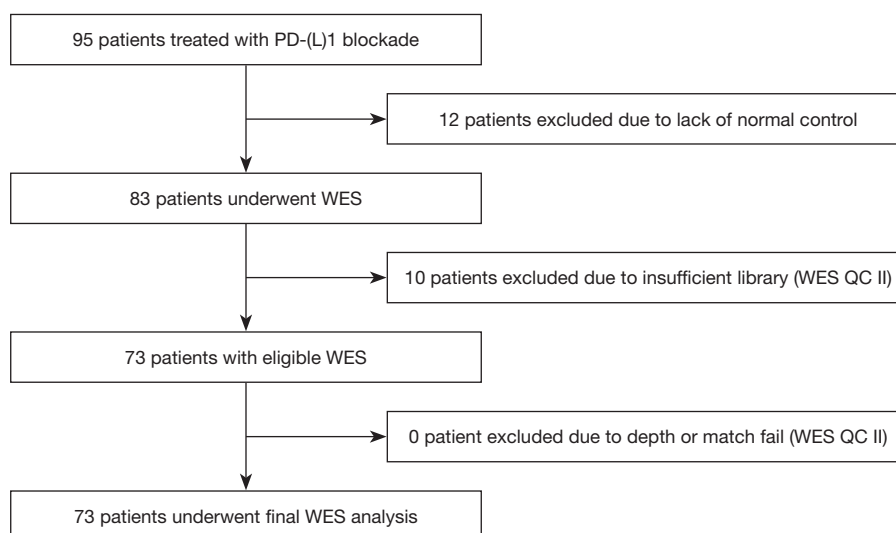


Figure 1 Flow chart illustrates the selection of eligible patients for the final analysis. WES, whole exome sequencing; QC, quality control.

36 (47%) patients received anti-PD-1/PD-L1 after failure to second line treatment, and 54 (74%) patients had 2 or more metastatic sites before treatment. Among all of the patients, 36 (49.3%) and 61 (84%) were classified as having a good score of LIPI and mGPS, respectively. The selection of eligible patients for the final analysis is illustrated with a flow chart in *Figure 1*.

PFS and OS benefits analysis

Overall, the median PFS was 2.1 months (95% CI: 1.99–2.21) and median OS was 15.8 months (95% CI: 10.90–20.30). Our results showed that the variables of male sex, smoking history, and high TMB were associated with a significantly longer PFS. The median PFS (mPFS) in males compared with females was 3.6 and 1.7 months, respectively (log-rank $P=0.004$). In patients who were current or former smokers and in non-smokers, mPFS was 4.2 and 1.9 months (log-rank $P=0.003$), respectively. Patients with high TMB and low TMB had an mPFS of 3.7 and 2.1 months (log-rank $P=0.004$), respectively. These results are shown in *Figure 2A*. In patients with both good and poor LIPI scores, mPFS was 3.7 and 2.0 months (log-rank $P=0.164$), respectively. These results are shown in *Figure 2B*. OS analysis found that patients with good LIPI scores had a significantly longer OS as compared with those patients with poor LIPI scores (19.2 *vs.* 12.6 months, log-rank $P=0.010$). These results are shown in *Figure 3A*. In patients with a good mGPS, OS was significantly increased

as compared to those patients with a poor mGPS (16.8 *vs.* 4.3 months, log-rank $P=0.029$). However, the variables of patient gender, smoking history, and TMB were not associated with OS benefit. This is shown in *Figure 3B* (all $P>0.05$).

Determinants of survival benefits

Our subsequent analysis was focused on determining factors that could predict survival benefits. In univariate analysis of PFS, TMB was found to be a significant determinant of PFS (HR, 0.46; 95% CI, 0.23–0.92; $P=0.027$). LIPI score was the second determinant of PFS benefit with a margin P value of 0.064 (HR, 0.59; 95% CI, 0.34–1.03). In multivariable analysis, TMB was identified as an independent determinant factor of PFS (HR, 0.41; 95% CI, 0.23–0.73; $P=0.002$), whereas LIPI was another independent determinant factor with a marginal $P=0.081$ (HR, 0.64; 95% CI, 0.38–1.06) (*Table 2*). When considering OS benefit, only LIPI was identified as a determinant factor of OS and remained significant in multivariable analysis (HR, 0.49; 95% CI, 0.28–0.85; $P=0.012$) (*Table 3*).

Discussion

In the current study, we aimed to investigate the potential determinant factors of ICIs as well as the different treatment outcomes in pretreated advanced or metastatic NSCLC patients who received PD-1/PD-L1 blockade therapy.

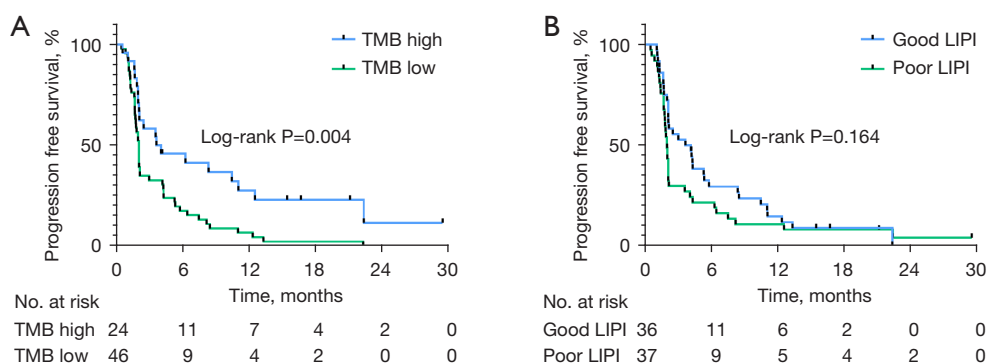


Figure 2 Kaplan-Meier estimates of PFS according to TMB (A) and LIPI score (B). PFS, progression-free survival; TMB, tumor mutational burden; LIPI, Lung Immune Prognostic Index.

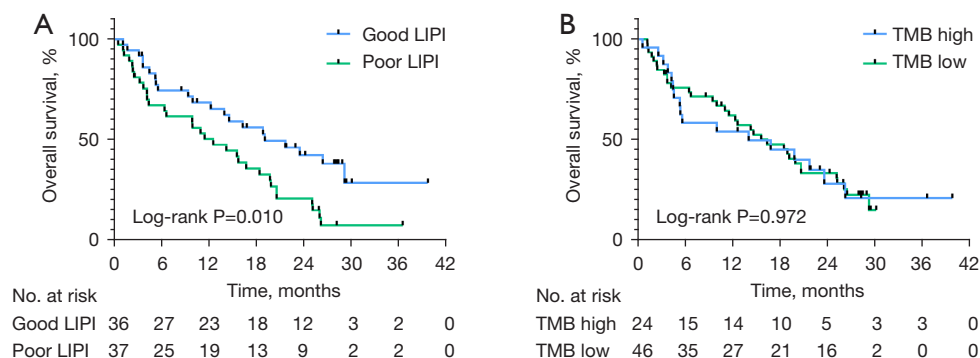


Figure 3 Kaplan-Meier estimates of OS according to LIPI score (A) and TMB (B). OS, overall survival; LIPI, Lung Immune Prognostic Index; TMB, tumor mutational burden.

Our analysis showed that male sex, smoking history, and TMB were associated with a significantly longer PFS; however, these factors were not associated with OS benefit. In addition, patients with a good LIPI score had a longer PFS as compared to patients who had a poor LIPI score with a marginal statistical difference. Interestingly, patients with a good LIPI score had a significantly longer OS than patients with a poor LIPI score. Similarly, patients who had a good mGPS before treatment had a longer OS compared to patients with poor mGPS. Furthermore, our analysis has confirmed the role of TMB as a significant determinant of ICIs for PFS and LIPI score as an independent determinant factor of OS benefit.

The introduction of immunotherapy with anti-PD-1/PD-L1 led to a major advancement in the treatment of NSCLC. Treatment with either ICIs in monotherapy or in combination with chemotherapy has been approved as the first-line treatment option in patients with NSCLC

without actionable tumor driver mutations (18). However, the response rate of ICIs therapies is still lower than anticipated. Several factors have been extensively evaluated to determine their roles as treatment biomarkers. These include TMB and PD-L1 expression in tumor bed (19). Consistent with previous studies, our results showed that high TMB was significantly associated with improved PFS (20,21); however, the role of TMB as a predictive marker of OS in patients treated with ICIs remains unclear. In our study, TMB was not found to be associated with OS benefit. Similar results were reported in a recent meta-analysis, which suggests that TMB was not associated with OS benefit (22). Thus, the predictive value of TMB in determining OS benefit warrants further investigation.

Although TMB has a promising predictive value for ICIs treatment outcomes, its utility in clinical practice is constrained due to several limitations, including the lack of an optimal cutoff value across different tumor types.

Table 2 Univariable and multivariable analysis of progression free survival

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender (male vs. female)	0.74 (0.36–1.52)	0.412	–	–
Age (≥ 60 vs. < 60 years)	1.36 (0.76–2.45)	0.303	–	–
Pathological type (SCC vs. non-SCC)	0.98 (0.54–1.80)	0.954	–	–
Smoking (yes vs. no)	0.65 (0.33–1.31)	0.232	–	–
ECOG (0 vs. 1)	1.26 (0.68–2.35)	0.463	–	–
Line of immunotherapy (≤ 2 nd vs. > 2 nd)	1.14 (0.65–2.03)	0.642	–	–
Pretreatment metastases (≥ 2 vs. < 2)	0.91 (0.47–1.76)	0.787	–	–
LIPI score (good vs. poor)	0.59 (0.34–1.03)	0.064	0.64 (0.38–1.06)	0.081
mGPS (good vs. poor)	0.84 (0.39–1.80)	0.648	–	–
TMB (high vs. low)	0.46 (0.23–0.92)	0.027	0.41 (0.23–0.73)	0.002

SCC, squamous cell carcinoma; non-SCC, non-squamous cell carcinoma; ECOG, eastern cooperative oncology group performance status; LIPI, lung immune prognostic index; mGPS, modified Glasgow Prognostic Score; TMB, tumor mutational burden; HR, hazard ratio; CI, confidence interval.

Table 3 Univariable and multivariable analysis of overall survival

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender (male vs. female)	1.671 (0.75–3.75)	0.213	–	–
Age (≥ 60 vs. < 60 years)	1.33 (0.69–2.57)	0.395	–	–
Pathological type (SCC vs. non-SCC)	1.35 (0.68–2.67)	0.386	–	–
Smoking (yes vs. no)	0.56 (0.27–1.17)	0.12	–	–
ECOG (0 vs. 1)	1.22 (0.60–2.49)	0.575	–	–
Line of immunotherapy (≤ 2 nd vs. > 2 nd)	1.51 (0.81–2.82)	0.196	–	–
Pretreatment metastases (≥ 2 vs. < 2)	0.82 (0.39–1.70)	0.589	–	–
LIPI score (good vs. poor)	0.48 (0.26–0.88)	0.018	0.49 (0.28–0.85)	0.012
mGPS (good vs. poor)	0.63 (0.28–1.40)	0.253	–	–
TMB (high vs. low)	0.83 (0.41–1.69)	0.616	–	–

SCC, squamous cell carcinoma; non-SCC, non-squamous cell carcinoma; ECOG, eastern cooperative oncology group performance status; LIPI, lung immune prognostic index; mGPS, modified Glasgow Prognostic Score; TMB, tumor mutational burden; HR, hazard ratio; CI, confidence interval.

In addition, its significance as a single biomarker for ICI treatment outcomes might be sub-optimal (6,23). Recently, the association of LIPI score with ICI treatment outcomes has been investigated in the setting of multiple cancers, including NSCLC (24). In NSCLC patients who received ICIs as the first-line therapy, LIPI score was identified as an

independent prognostic factor (25,26). In the present study, we found that LIPI score was a significant determinant of OS irrespective of TMB; however, due to the limited number of patients with a LIPI score of 2, we classified patients into two groups: good LIPI score [0], and poor LIPI score [1–2].

Of note, the mechanism for anti-tumor activity of ICIs may be due to these inhibitors breaking the inhibitory signals of T-cell activation against tumors (27). TMB can serve as a surrogate of anti-tumor immunity that is elicited by tumor neoantigens, whereas immune reaction may be reflected by a specific immune cell that is in abundance in the tumor microenvironment or peripheral blood. Our analysis results showed that the prognostic value of LIPI was independent of TMB. A combination of TMB with LIPI score might be used as surrogate biomarkers to more significantly identify patients with survival benefits as compared with either TMB or LIPI score as a single predictor (28,29). Interestingly, when we compared patients with high TMB and good LIPI score versus patients with low TMB and poor LIPI score, a more statistically significant difference was seen in mPFS compared with patients stratified by TMB alone. However, there were only a limited number of patients in each group. These results indicate that the combination of TMB and LIPI score as a potential biomarker for ICI response is worth further investigation.

Our study has some limitations, since it is retrospective in nature and was conducted with a relatively small patient population. However, the patients included in our analysis were enrolled in a controlled clinical trial, which reduced the bias of patient selection. PD-L1 expression was available only for a small number of patients, so this was not included in the multivariable analysis of treatment determinant factors. A recent study has shown that the prognostic value of LIPI score is independent of PD-L1 expression (30). Another limitation is that our analysis included some patients with EGFR mutation (n=5) or ALK rearrangement (n=1). Patients with these features have been shown to respond poorly to ICIs.

To the best of our knowledge, this is the first study to include mGPS, LIPI score, and TMB in a multivariable analysis of survival benefit in patients with NSCLC who have previously received ICI therapy. Although the prognostic value of LIPI score and mGPS have been reported previously, earlier studies did not include TMB in their multivariable analysis model of outcomes. This may affect the prognostic role of LIPI score or mGPS. Our study showed that the prognostic value of LIPI score was independent of TMB. Although TMB is a promising biomarker for immunotherapy outcomes, it still presents several limitations. In the present study, LIPI score was a promising biomarker of overall survival (OS) in patients with advanced NSCLC who received ICIs. TMB was

associated with progression-free survival (PFS), but not OS. LIPI score represented a readily available biomarker for immunotherapy outcomes; however, the role of LIPI score as a prognostic biomarker for ICIs treatment outcomes requires further validation in future studies.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at <https://dx.doi.org/10.21037/atm-21-1702>

Data Sharing Statement: Available at <https://dx.doi.org/10.21037/atm-21-1702>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/atm-21-1702>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center (pembrolizumab: A2016-019; camrelizumab: A2016-009; nivolumab: A2015-035; atezolizumab: A2016-021), and individual consent for this retrospective analysis was waived.

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