Original Article

Comparison of different maintenance regimens following first-line immunochemotherapy for advanced non-small cell lung cancer

Feng Li[1,2#], Huiting Wang[1,2#], Yang Xiang[1,2#], Run Li[1,2#], Caichen Li[1,2], Ran Zhong[1,2], Jianfu Li[1,2], Shan Xiong[1,2], Lixian Liang[3,4], Jianxing He[1,2], Wenhua Liang[1,2]

[1]Department of Thoracic Surgery and Oncology, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; [2]China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, Guangzhou, China; [3]Cancer Centre, Faculty of Health Sciences, Macau, China; [4]MoE Frontiers Science Centre for Precision Oncology, University of Macau, Macau, China

Contributions: (I) Conception and design: F Li, H Wang, Y Xiang, R Li; (II) Administrative support: J He, W Liang; (III) Provision of study materials or patients: J He, W Liang; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Wenhua Liang, MD; Jianxing He, MD. Department of Thoracic Surgery and Oncology, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, No. 151 Yanjiang Road, Guangzhou 510120, China. Email: liangwh1987@163.com; drjianxing.he@gmail.com.

Background: Immunochemotherapy is the standard first-line treatment for non-small cell lung cancer (NSCLC). However, the ideal combination strategy and maintenance regimen remain uncertain. This study aims to compare the clinical efficacy of different first-line maintenance regimens for advanced EGFR/ALK (epidermal growth factor receptor/anaplastic lymphoma Kinase) negative NSCLC and explore the eligibility of chemo-free maintenance.

Methods: We conducted a retrospective evaluation of 1,510 EGFR/ALK negative NSCLC patients who received immune checkpoint inhibitors (ICIs) treatment in our center from 2019 to 2021. Patients who had controlled disease after 2–6 cycles of first-line ICIs in combination with platinum-based doublet chemotherapy with or without anti-angiogenesis were included. Four maintenance regimens were analyzed: ICIs plus platinum-free chemotherapy with (group 1, I+C+A) or without anti-angiogenesis maintenance (group 2, I+C), single-agent ICIs maintenance (group 3, I) or ICIs plus anti-angiogenesis maintenance (group 4, I+A). For group 3–4, rechallenge with initial chemo-agents was given upon the first progression, those who achieved controlled disease were repeatedly followed by another chemo-free period. The primary outcome was progression-free survival (PFS). Notably, for group 3–4, PFS was characterized as the duration between treatment initiation and failure of rechallenge (last disease progression).

Results: In total, 140 eligible patients in the maintenance phase were analyzed, with 20, 40, 42, and 38 patients in groups 1 to 4, respectively, displaying comparable baselines. Median PFS was similar in the I+C+A maintenance group (22.6 months), I+C maintenance group (21.0 months), and I+A maintenance group (21.5 months), whereas PFS was inferior in group 4 with I maintenance alone (13.4 months). Median chemo-free duration were 6.3 months in I maintenance group, while 13.5 months in I+A maintenance group. During the maintenance period of group 1 to 4, 25%, 25%, 19%, and 42% of patients experienced partial response (PR) again, respectively. Fifty-five percent, 65%, 48% and 61% of patients sustained durable disease control at the end of follow-up. In group 4, 39% of patients received progressive disease (PD) and rechallenge initial chemo-agents. Fifty percent of patients achieved PR and resumed to chemo-free maintenance.

Conclusions: We showed that following first-line immunochemotherapy, chemo-free maintenance by ICIs plus anti-angiogenesis and on-demand chemo-rechallenge provided comparable efficacy to chemo-on maintenance in terms of PFS, thus allowing the minimization of cytotoxic drugs without compromising therapeutic effectiveness. In addition, anti-angiogenesis is essential during chemo-free maintenance.

Keywords: Non-small cell lung cancer (NSCLC); maintenance therapy; chemo-holiday regimen; immune checkpoint inhibitors (ICIs); anti-angiogenesis

Submitted Jul 28, 2023. Accepted for publication Dec 07, 2023. Published online Dec 22, 2023.
doi: 10.21037/tlcr-23-489
View this article at: https://dx.doi.org/10.21037/tlcr-23-489

Introduction

Immunochemotherapy is the standard first-line treatment for EGFR/ALK (epidermal growth factor receptor/anaplastic lymphoma kinase) wild-type advanced non-small cell lung cancer (NSCLC) (1). However, there is no consensus in clinical guidelines with respect to the combination regimen, duration, or the best maintenance strategy.

Highlight box

Key findings

- Our study demonstrated that after initial treatment with immunochemotherapy, a maintenance regimen using immune checkpoint inhibitors (ICIs) combined with anti-angiogenic agents on-demand chemo-rechallenge, achieved a progression-free survival (PFS) akin to that of continuous ICI plus chemotherapy maintenance.

What is known and what is new?

- Immunochemotherapy is the established first-line treatment for non-small cell lung cancer (NSCLC) without EGFR/ALK mutations. However, the optimal strategy for maintenance therapy after first-line treatment in NSCLC remains to be determined.
- This study compares four different maintenance regimens following first-line immunochemotherapy for advanced EGFR/ALK negative NSCLC. Chemo-free maintenance using ICIs with anti-angiogenesis drugs, and chemo-rechallenge only when needed, shows comparable PFS to maintenance regimens that include continuous chemotherapy. The addition of anti-angiogenesis agents is crucial to the effectiveness of chemo-free maintenance therapy. The study suggests that chemo-holiday regimen is possible to minimize the use of cytotoxic drugs in maintenance therapy without losing therapeutic efficacy.

What is the implication, and what should change now?

- This study's results indicate a shift toward chemo-free maintenance therapy using ICIs and anti-angiogenesis drugs for advanced NSCLC patients, which could lead to less toxic side effects while maintaining treatment efficacy. Clinically, there may be a move to update treatment protocols, offering patients a regimen that balances quality of life with disease control. Future research should focus on personalizing these strategies further and refining patient selection for this approach.

The successful discovery that programmed cell death 1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors are superior to chemotherapy leads to PD-1/PD-L1 inhibitors as a single agent treatment in advanced NSCLC patients without targetable driver mutations (2-4). The chemo-free regimen as first-line and maintenance treatment appears to be promising. However, single-agent immune checkpoint inhibitors (ICIs) may be less effective and result in treatment failure for patients with PD-L1 <1%. An indirect comparison showed that when compared to ICIs monotherapy, ICIs plus chemotherapy regimen is beneficial both in overall survival (OS) and progression-free survival (PFS), even in patients with PD-L1 expression ≥50% (5). A completely chemo-free regimen may not be an optimal selection. Combined with chemotherapy is necessary in advanced NSCLC treated with ICIs.

However, in the eras of immunotherapy, it is unclear whether long-term use of chemotherapy is needed as recommended in the 2021 Chinese Society of Clinical Oncology (CSCO) guidelines. Before the ICIs were approved, pemetrexed and bevacizumab played important roles in the first-line and maintenance treatment. The AVAPERL and ECOG 5508 studies showed that for advanced nonsquamous NSCLC, bevacizumab plus pemetrexed maintenance was associated with a significant PFS benefit compared with single-agent bevacizumab or pemetrexed (6,7). However, the cumulative toxicity of long-term chemotherapy, particularly in terms of neurotoxicity, nephrotoxicity, and myelotoxicity, impairs the quality of life and increases chemotherapy-associated mortality (8,9). Moreover, many older patients with advanced NSCLC have comorbid conditions and functional impairments that make long-term cytotoxic chemotherapy difficult (10).

To date, the optimal treatment in the induction and maintenance phase for advanced NSCLC has not been established. Successful induction therapy could bring a high response rate. Effective maintenance therapy could play an important role in prolonging the remission interval in the post-consolidation setting. In the Keynote-407, four cycles of pembrolizumab plus chemotherapy were

used in the induction phase, and single pembrolizumab was used in maintenance phase. Patients had significantly longer OS and PFS compared to those treated with chemotherapy (11). In the Keynote-189 study, after four cycles of pembrolizumab plus pemetrexed and platinum induction, and followed by pembrolizumab plus pemetrexed maintenance, OS and PFS were improved substantially in patients with NSCLC (12). As reported in Checkmate 9LA, there remains a need for chemotherapy (but more short-course) during the first few weeks of dual immunotherapy to enhance clinical benefit. Dual immunotherapy maintenance is another choice (13). In the IMpower 150 study, adding bevacizumab to the combination strategy in the induction and maintenance phase showed a significant benefit in PFS and OS (14). There have been no head-to-head clinical trials to demonstrate the optimal regimen of the induction and maintenance phase.

In this study, we compared the clinical efficacy of four first-line induction and maintenance regimens for non-EGFR/ALK-driven advanced NSCLC, and developed a chemo-holiday regimen that minimizes the use of chemotherapy drugs without compromising efficacy. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-489/rc).

Methods

Patients

We retrospectively evaluated 1,510 EGFR/ALK wild-type NSCLC patients who received immunotherapy in the First Affiliated Hospital of Guangzhou Medical University (Guangzhou, China) from January 2019 to September 2021 (*Figure 1*). This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (No. ES-2023-020-01). The requirement for informed consent was waived for this retrospective analysis. The study was conducted in accordance with the ethical standards of the Helsinki Declaration (as revised in 2013) and the applicable regulatory requirements.

The included criteria were as follows: (I) patients who were diagnosed with advanced or metastatic NSCLC by cytological and histological examination and confirmed without EGFR/ALK mutation by the tissue-based gene test; (II) patients treated with 2–6 cycles of first-line ICIs plus platinum-based doublet chemotherapy with or without anti-angiogenesis, and then followed by chemo-on or chemo-free maintenance. All patients had no chemotherapy or anti-angiogenesis drugs contraindications before treatment. The excluded criteria were as follows: (I) patients with neo-adjuvant/adjuvant immunotherapy; (II) patients who had disease progression or died after first-few weeks of immunochemotherapy, with no maintenance period; (III) ICIs monotherapy without chemotherapy or anti-angiogenesis; (IV) patients treated with second-line immunotherapy; (V) patients without complete clinical or imaging data.

Groups

There were four common regimens, as show in *Figure 1*: (I) chemo-on maintenance regimens: after 2–6 cycles of initial ICIs plus platinum-based doublet chemotherapy with or without anti-angiogenesis (bevacizumab/anlotinib), patients were followed by ICIs plus platinum-free chemotherapy (pemetrexed/gemcitabine) with (group 1, I+C+A) or without anti-angiogenesis maintenance (group 2, I+C); (II) chemo-free maintenance regimens: after 2–6 cycles induction of ICIs plus platinum-based doublet chemotherapy with or without anti-angiogenesis, patients were followed by single-agent ICIs maintenance (group 3, I), or ICIs plus anti-angiogenesis maintenance (group 4, I+A).

Outcomes

Clinical response was assessed by immune-related Response Evaluation Criteria in Solid Tumors (irRECIST). The primary outcome was first-line therapy PFS. For groups 1 and 2, PFS was defined as the time from the beginning of treatment until the first disease progression. For groups 3 and 4, a rechallenge with initial chemo-agents was added upon the first unconfirmed progressive disease (iuPD), those achieving controlled disease might be repeatedly followed by another chemo-free maintenance period. Notably, for groups 3 and 4, PFS was defined as the time between treatment initiation and failure of rechallenge [last progressive disease (PD)]. After the first progression, whether the patients rechallenged the initial immunochemotherapy with or without anti-angiogenesis regimen was determined by the clinician based on the patient's condition and consent.

Statistical analysis

To summarize the baseline patient characteristics, means

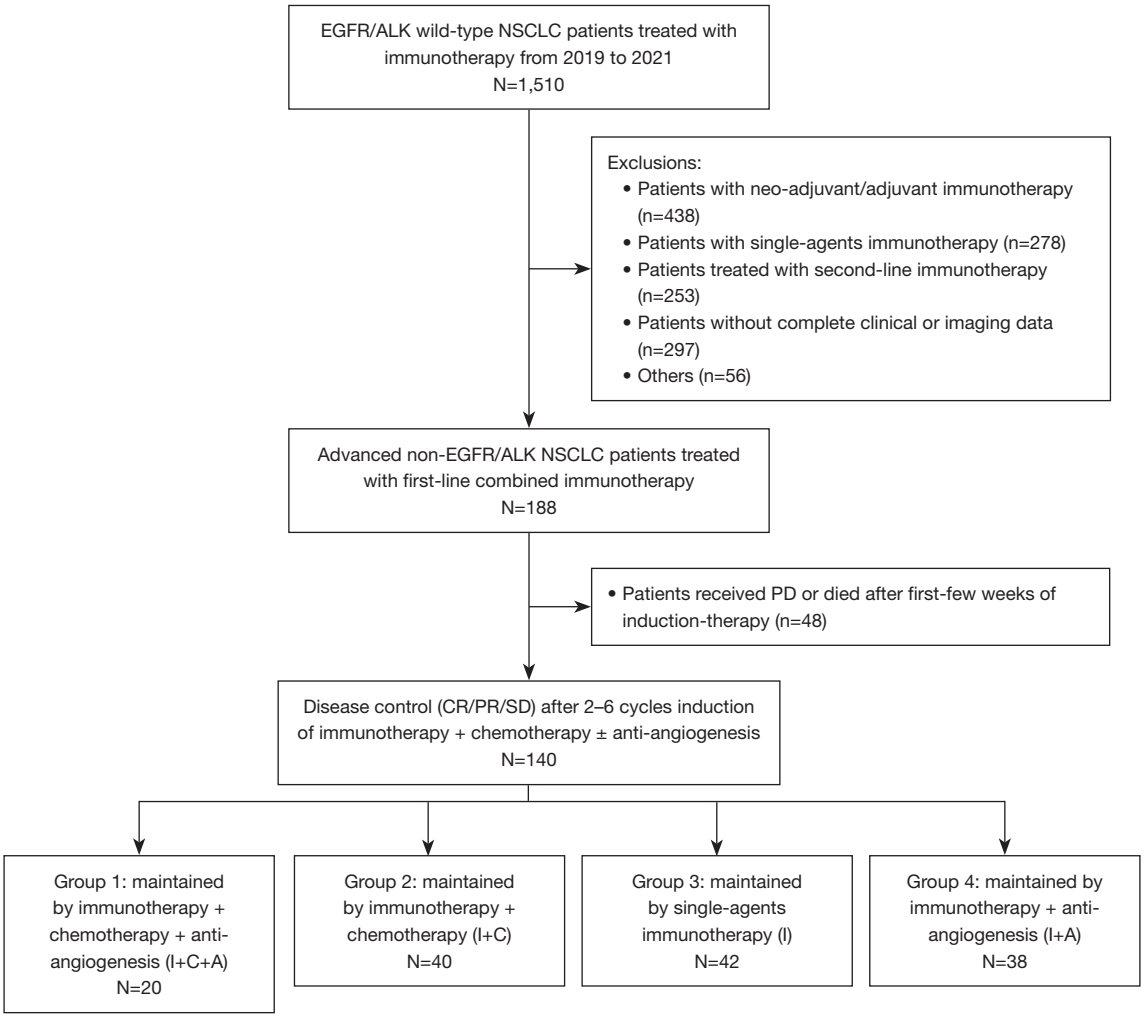

Figure 1 Flow chart of selecting eligible patients. EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; PD, progressive disease; CR, complete response; PR, partial response; SD, stable disease.

with standard deviation and medians with interquartile range (IQR) were used for normally and non-normally continuous distributed variables, respectively. Numbers reported with percentages were used for categorical variables. In order to evaluate the baseline characteristics and assess the comparability of the four groups, continuous variables were analyzed using one-way analysis of variance (ANOVA) when they were normally distributed, or the Kruskal-Wallis test for data not meeting the assumptions of normality. Categorical variables were analyzed using the Chi-square test or Fisher's exact test. Kaplan-Meier curve was used to describe the PFS, and the differences between groups were tested by log-rank method. All statistical tests were two-sided and all tests were considered significant for P values below 0.05. In addition, subgroup analyses were performed to explore hazard ratio (HR) in different groups stratified by age, sex, and smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, stage, induction cycles, histologic features and PD-L1 expression. The statistical analyses in this study were performed with R software (version 4.1.0) and SPSS statistics version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Patients' characteristics

The baseline characteristics of the included cases are summarized in *Table 1*. After 2–6 cycles of induction, a total

Table 1 Baseline characteristics of included patients

Characteristics	I+C+A maintenance (n=20)	I+C maintenance (n=40)	I maintenance (n=42)	I+A maintenance (n=38)	P value
Age (years)					0.616
Median	60	64	65	65	
Range	40–75	49–75	37–76	33–78	
Sex, n (%)					0.202
Male	13 (65.0)	34 (85.0)	36 (85.7)	32 (84.2)	
Female	7 (35.0)	6 (15.0)	6 (14.3)	6 (15.8)	
Smoking status, n (%)					0.275
Never	10 (50.0)	23 (57.5)	16 (38.1)	15 (39.5)	
Current or former	10 (50.0)	17 (42.5)	26 (61.9)	23 (60.5)	
ECOG, n (%)					0.175
0	0	9 (22.5)	4 (9.5)	5 (13.2)	
1	20 (100.0)	30 (75.0)	37 (88.1)	31 (81.6)	
2	0	1 (2.5)	1 (2.4)	2 (5.2)	
Metastases, n (%)					0.291
Liver	1 (5.0)	4 (10.0)	2 (4.8)	1 (2.6)	
Bone	7 (35.0)	13 (32.5)	4 (9.5)	16 (42.1)	
Brain	4 (20.0)	3 (7.5)	3 (7.1)	2 (5.3)	
Histologic features, n (%)					< 0.05
Adenocarcinoma	18 (90.0)	36 (90.0)	8 (19.0)	19 (50.0)	
Squamous carcinoma	0	1 (2.5)	28 (66.7)	16 (42.1)	
Other NSCLC	2 (10.0)	3 (7.5)	6 (14.3)	3 (7.90)	
Stage, n (%)					0.065
IIIB	2 (10.0)	14 (35.0)	18 (42.9)	14 (36.8)	
IV	18 (90.0)	26 (65.0)	24 (57.1)	24 (63.2)	
PD-L1 expression, n (%)					<0.05
<1%	5 (25.0)	6 (15.0)	5 (11.9)	2 (5.3)	
1–49%	6 (30.0)	8 (20.0)	12 (28.6)	5 (13.2)	
≥50%	2 (10.0)	11 (27.5)	6 (14.3)	3 (7.9)	
NA	7 (35.0)	15 (37.5)	19 (45.2)	28 (73.7)	

I, immune-checkpoint inhibitors; C, chemotherapy; A, anti-angiogenesis drugs; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death-ligand 1; NA, not available.

of 140 patients were followed by continued maintenance treatment. There were 20 (14.3%), 40 (28.6%), 42 (30.0%) and 38 (27.1%) patients in group 1 to 4, respectively. The enrolled patients ranged in age from 33 to 78. One hundred and fifteen (82.1%) were male, 76 (54.3%) were smokers, 118 (84.3%) were ECOG 1, 92 (65.7%) had distant metastasis, 18 (12.9%) had negative PD-L1 expression, and 22 (15.7%) had PD-L1expression ≥50%. The majority of baseline characteristics among participants in all four groups were similar, with the exception of histologic features and

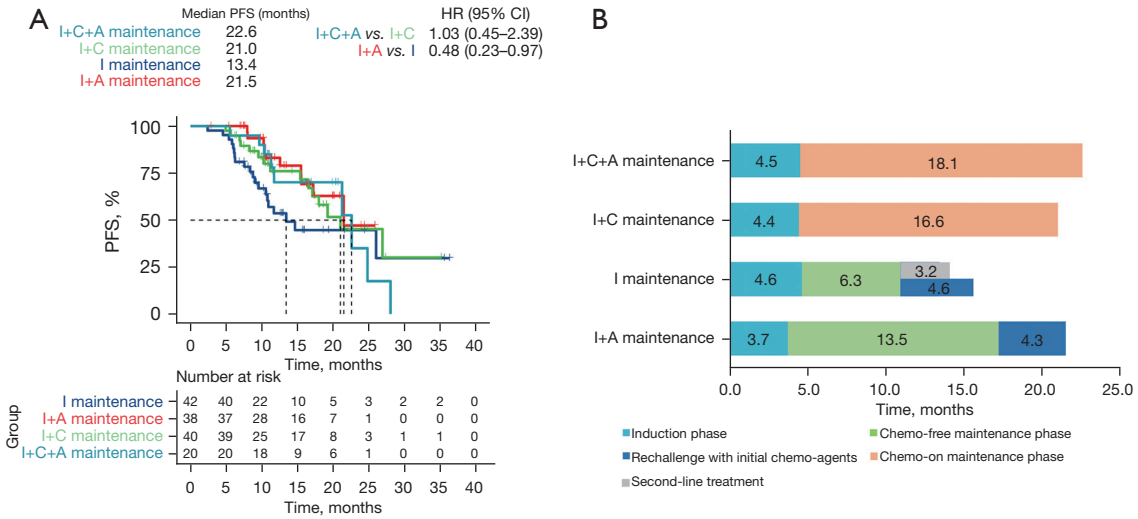

Figure 2 PFS in four groups. (A) Kaplan-Meier estimates of PFS in patients with four different maintenance regimens. (B) Median time in different treatment phase. I, immune-checkpoint inhibitors; C, chemotherapy; A, anti-angiogenesis drugs; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

PD-L1 expression.

PFS outcome

As shown in *Figure 2A*, the median PFS were similar between I+C+A maintenance (22.6 months), I+C maintenance (21.0 months) and I+A maintenance (21.5 months), whereas PFS was relatively inferior in I maintenance alone (13.4 months). When continuous chemotherapy maintenance was given, additional anti-angiogenesis did not show a survival benefit in PFS (I+C+A *vs.* I+C, HR: 1.03, 95% CI: 0.45–2.39; P=0.95). However, in chemo-free maintenance groups, the addition of anti-angiogenesis was related to a better prognosis, with longer PFS in patients with I+A maintenance compared with those with single-agent ICIs maintenance (I+A *vs.* I, HR: 0.48, 95% CI: 0.23–0.97; P=0.045). The chemo-free period was at least 13.5 months in patients with I+A maintenance, compared to 6.3 months in those with I maintenance (P=0.038), and the effect of I+A maintenance was comparable to that of the continuous chemotherapy groups (P=0.773) (*Figure 2B*).

During the maintenance period of group 1 to group 4, 25%, 25%, 19%, and 42% of patients experienced partial response (PR) again, respectively (P=0.131). There were 55%, 65%, 48%, and 61% of patients maintained durable disease control at the end of follow-up, respectively in groups 1 to 4 (P=0.435). For patients with I+A maintenance, 39% of patients received the first iuPD, and initial ICIs plus chemotherapy with anti-angiogenesis regimen was rechallenge. Fifty percent of those patients achieved PR and returned to second chemo-free maintenance phase (*Figure 3*).

Subgroup analysis

Median time from the beginning of maintenance to disease progression was comparable among I+C+A, I+C and I+A maintenance groups, and I maintenance alone was relatively inferior (Figure S1). In the subgroup based on age, sex, smoking history, ECOG status, and stage, there was a better PFS in patients with I+A maintenance, compared with those with I maintenance (Figure S2). It seemed that patients with squamous carcinoma benefited more from I+A maintenance (Figure S2). Where stratified by induction cycles, in patients with I+A maintenance, there was a trend that a shorter-course chemo-induction (2–4 cycles) had better clinical outcome than those with 5–6 cycles of chemo-induction (Figure S2). In addition, I+A maintenance was able to improve patient outcome regardless of baseline PD-L1 expression in tumor cells (PD-L1 expression on tumor cells was detected by PD-L1 IHC 22C3 pharmDx) (Figures S2,S3). Even for patients with PD-L1 ≥50%, adding anti-angiogenesis to ICIs was beneficial in PFS. For PD-L1 negative or low expressed population, I+A maintenance still showed an advantage in PFS. Non-statistically significant HRs were found in subgroup analysis

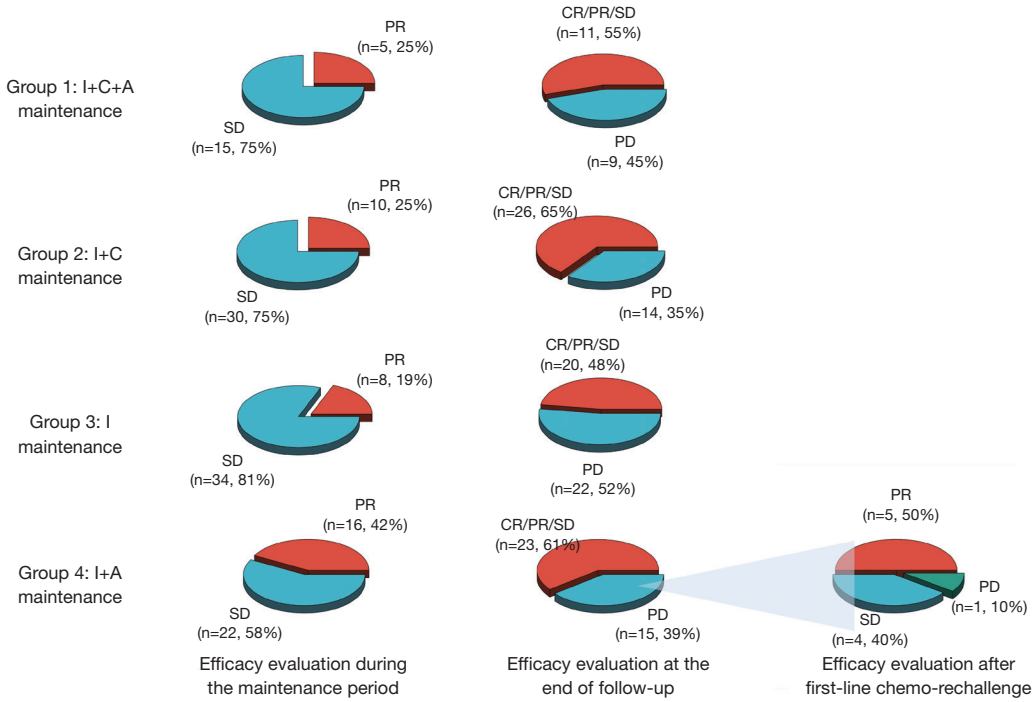

Figure 3 Clinical efficacy evaluation during maintenance period, at the end of follow-up, and after first-line chemo-rechallenge in patient who had PD after I+A maintenance. I, immune-checkpoint inhibitors; C, chemotherapy; A, anti-angiogenesis drugs; PD, progressive disease; CR, complete response; PR, partial response; SD, stable disease.

between I+A maintenance and I+C±A maintenance.

Chemo-holiday regimen

Based on the results of this study, we proposed a chemo-holiday regimen which minimizes the use of chemotherapy drugs without compromising efficacy. As shown in Figure S4: 2–4 cycles enhanced induction of ICIs plus chemotherapy with anti-angiogenesis, maintenance by ICIs plus anti-angiogenesis, and on-demand chemo-rechallenge upon PD.

Discussion

In this study, we propose a chemo-holiday regimen featured by short-term enhanced induction of ICIs plus chemotherapy with anti-angiogenesis, maintenance by ICIs plus anti-angiogenesis, and on-demand initial chemo-rechallenge, and demonstrated its comparable efficacy to chemo-on maintenance in PFS, thus allowing the minimization of cytotoxic drugs. We highlight that on the basis of immunotherapy, chemotherapy in the maintenance phase is not necessary. ICIs plus anti-angiogenesis is essential during maintenance phase. The efficacy of single-agent ICIs maintenance is suboptimal and adding anti-angiogenesis to ICIs offers extra benefits in PFS. Chemo-holiday regimen provides equivalent efficacy and less toxicity than the continued chemo-on maintenance regimens. On-demand initial chemotherapy rechallenge can delay second-line regimens.

To our knowledge, this is the first study that answers the question of the optimal immune induction and maintenance regimens by comparing different regimens in the real world. The chemo-holiday regimen is effective and well-tolerated. It combines the concepts and advantages of immunochemotherapy in Keynote 189, short-course chemo-induction in Checkmate 9LA, and combined anti-angiogenesis in IMpower 150 (11,13,14). Short-course combined chemotherapy not only plays the sensitization effect on the immune system and avoids the super-progress caused by immune inefficiency, but also reduces the suppression of immune cells caused by excessive chemotherapy. ICIs and anti-angiogenesis exhibit a synergistic antitumor effect in the maintenance period, maximizing the anti-tumor effect, while reducing the side effects from long-term chemotherapy.

Specific immunogenic chemotherapy not only kills tumor cells but also turns "cold" tumors "hot" by inducing immunogenic cell death (ICD), allowing tumor cells sensitization to ICIs (15,16). The chemotherapy, particularly platinum-based drugs, induces tumor cell stress and death that can induce a tumor-special immune response, which leads to the recruitment of dendritic cells (DCs) to the tumor. These DCs engulf dying cancer cells and mature, while PD-L1 and PD-L2 are downregulated, resulting in enhanced tumor-specific T-cell activation (17). The number of $CD8^+$ T cells and the expression of PD-L1 in tumor site also increase after chemotherapy (18). There is evidence that chemotherapy-induced proliferation of $CD8^+$ T cells, consisting of effector cells expressing coinhibitory checkpoint molecules, offers an appropriate binding site for ICIs (19). Also, activated T cells produce interferon-γ (IFN-γ) to help further eradicate tumor cells. In addition, the combination of ICIs and anti-angiogenesis might further improve the outcome of patients with NSCLC. The use of anti-angiogenesis can normalize and remodel the tortuous tumor vasculature, enabling alleviation of hypoxia and low pH intratumorally (20). Moreover, a normalized vasculature provides a conduit for the efficient immune cells infiltration and delivery of anticancer therapeutics into tumors (21-23). In the induction phase, short-course chemo-anti-angiogenesis induction could alter the immuno-metabolism and tumor microenvironment, and increase immune sensitivity and activation, leading to a synergistic effect with ICIs (17,23-27).

Long-term immunochemotherapy maintenance regimen is not recommended in our study. Hematological, gastrointestinal and skin toxicities are frequently performed in patients with long-term chemotherapy (28,29). Grade 3 or high toxicity rate was 29%, 37%, and 50%, respectively, for bevacizumab, pemetrexed, and their combination maintenance (7). Besides the toxic side effect, long-term chemotherapy is associated with acquired tumor resistance and the emergence of chemo-resistant cancer stem cells (30-33). Cytotoxic chemotherapy also damages the immune system, prompting a suppression of the immune response and reducing the efficacy of immunotherapy (34,35). Patients had a low response rate to subsequent-line therapy once long-term immunochemotherapy had failed. A new maintenance regimen that balances the toxicity and efficacy is needed. In our study, we highlighted that a chemo-free maintenance regimen, ICIs plus anti-angiogenesis maintenance, is feasible and effective. Firstly, compared to long-term immunochemotherapy maintenance, ICI plus anti-angiogenesis maintenance provided equivalent efficacy and at least 13.5-month chemo-free periods. Secondly, it could reduce the toxicities from long-term chemotherapy. Thirdly, it could avoid immune cell suppression caused by excessive chemotherapy and maximize immune efficacy. Fourthly, patients with different histologic subsets of NSCLC can benefit from ICIs plus anti-angiogenesis maintenance. Fifth, chemo-holiday regimen showed significant clinical benefit regardless of PD-L1 expression.

Moreover, when chemotherapy was used as maintenance, additional anti-angiogenesis did not contribute to better PFS, which is similar to the result of the AVEPERL and ECOG-ACRIN 5508 study (6,7). In the AVEPERL and ECOG-ACRIN 5508 study, single-agent pemetrexed or bevacizumab maintenance was recommended for advanced nonsquamous NSCLC, but the combination of pemetrexed and bevacizumab lacked OS benefit and had higher toxicity (6,7). Similar data were obtained in colorectal cancer, the addition of antiangiogenic treatment to standard chemotherapy did not result in an improvement in OS in any of these trials (36-40). In the LEAP-006 clinical trial, pembrolizumab plus pemetrexed with or without lenvatinib were used as maintenance regimen for advanced NSCLC. This trial is still ongoing and we look forward its results to confirm our findings (41).

Single-agent immunotherapy maintenance was also not recommended in our study. Some might view that personalized maintenance regimens should be determined by PD-L1 expression. For patients with PD-L1 expression of at least 50%, Pérol *et al.* concluded that there is no difference in PFS and OS between ICIs monotherapy and ICIs plus chemotherapy in real world (42). However, only about 30% of advanced NSCLC patients have PD-L1expression ≥50%, and single-agent ICIs maintenance is less effective, especially in patients with low or negative PD-L1 expression. In addition, a large of studies showed that the combination of ICIs and chemotherapy or anti-angiogenesis is significantly better than chemotherapy alone, as well as ICI-monotherapy, regardless of PD-L1 expression. In our study, compared to single ICIs maintenance, adding anti-angiogenesis to ICIs showed significantly longer PFS. In chemo-free maintenance period, anti-angiogenesis is essential, which plays a synergistic role with ICIs and increases the anti-tumor efficacy. The current studies also suggests that anti-angiogenesis treatment was very well tolerated, with low rates of toxicity of grade 3 or high.

In chemo-free maintenance group, initial chemo-regimen were added to rechallenge in the first iuPD. Fifty

percent of those received PR and continued to second chemo-free period. We proposed to use chemotherapy on-demand instead of long-term chemotherapy. When the patients meet first PD, on-demand initial chemotherapy can not only control the disease in time, but also delay the time of second-line medication. Initial chemotherapy may play sensitive role again and help kill tumor cells. On the other side, for patients who do not receive diseased control after initial chemo-rechallenge, second-line therapy should be given timely.

We acknowledged some limitations to our study. First, it is a retrospective study and carries the potential disadvantages and bias of a retrospective study. Second, the number of each group is small and future studies with larger sample sizes are needed to strengthen our conclusions. Third, only 71 (50.7%) patients had baseline PD-L1 expression information. We did not perform a PD-L1 subgroup analysis including all patients. Fourth, the toxicities of each group were not recorded in our study. Fifth, the data on OS were immature. Sixth, in I maintenance group, most patients received second-line chemo-agents or gave up treatment at the first progression. Furthermore, some questions remain to be answered. First, it is unclear whether anti-angiogenesis is necessary in induction period. Second, whether anti-angiogenesis contributes a better clinical outcome in patients with dual ICIs maintenance is of doubts. Third, we need novel prognostic markers to identify patients who may benefit more from chemo-holiday regimens. Fourth, there are a number of anti-angiogenesis drugs that have been approved for NSCLC, such as bevacizumab, anlotinib, endostar, ramucirumab. Considering that the targets of these drugs are not the same completely, it is unclear that whether these anti-angiogenesis drugs combined with ICIs have the same efficacy in maintenance period.

Conclusions

For advanced NSCLC patients, we propose a chemo-holiday regimen instead of completely chemo-free or long-term chemotherapy. Chemo-holiday regimen is preferable as first-line treatment with good clinical effect and less side effects, regardless of PD-L1 expression and pathologic types.

Acknowledgments

The Abstract was in part presented on 2022 ESMO conference.

Funding: This study was supported by the China National Science Foundation (grant Nos. 82022048 and 81871893).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-489/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-489/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-489/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-489/coif). W.L. serves as an Associate Editor-in-Chief of *Translational Lung Cancer Research* from May 2023 to April 2024. The other 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 retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (No. ES-2023-020-01). The requirement for informed consent was waived for this retrospective analysis. The study was conducted in accordance with the ethical standards of the Helsinki Declaration (as revised in 2013) and the applicable regulatory requirements.

References

1. Planchard D, Popat S, Kerr K, et al. Metastatic non-small

cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29:iv192-237.
2. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018-28.
3. Akinboro O, Larkins E, Pai-Scherf LH, et al. FDA Approval Summary: Pembrolizumab, Atezolizumab, and Cemiplimab-rwlc as Single Agents for First-Line Treatment of Advanced/Metastatic PD-L1-High NSCLC. Clin Cancer Res 2022;28:2221-8.
4. Pai-Scherf L, Blumenthal GM, Li H, et al. FDA Approval Summary: Pembrolizumab for Treatment of Metastatic Non-Small Cell Lung Cancer: First-Line Therapy and Beyond. Oncologist 2017;22:1392-9.
5. Liang H, Liu Z, Cai X, et al. PD-(L)1 inhibitors vs. chemotherapy vs. their combination in front-line treatment for NSCLC: An indirect comparison. Int J Cancer 2019;145:3011-21.
6. Barlesi F, Scherpereel A, Gorbunova V, et al. Maintenance bevacizumab-pemetrexed after first-line cisplatin-pemetrexed-bevacizumab for advanced nonsquamous nonsmall-cell lung cancer: updated survival analysis of the AVAPERL (MO22089) randomized phase III trial. Ann Oncol 2014;25:1044-52.
7. Ramalingam SS, Dahlberg SE, Belani CP, et al. Pemetrexed, Bevacizumab, or the Combination As Maintenance Therapy for Advanced Nonsquamous Non-Small-Cell Lung Cancer: ECOG-ACRIN 5508. J Clin Oncol 2019;37:2360-7.
8. Arriagada R, Dunant A, Pignon JP, et al. Long-term results of the international adjuvant lung cancer trial evaluating adjuvant Cisplatin-based chemotherapy in resected lung cancer. J Clin Oncol 2010;28:35-42.
9. Florea AM, Büsselberg D. Cisplatin as an anti-tumor drug: cellular mechanisms of activity, drug resistance and induced side effects. Cancers (Basel) 2011;3:1351-71.
10. Ding R, Zhu D, He P, et al. Comorbidity in lung cancer patients and its association with medical service cost and treatment choice in China. BMC Cancer 2020;20:250.
11. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med 2018;379:2040-51.
12. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:2078-92.
13. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:198-211.
14. Reck M, Mok TSK, Nishio M, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. Lancet Respir Med 2019;7:387-401.
15. Galon J, Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. Nat Rev Drug Discov 2019;18:197-218.
16. Zhang D, Zhang J, Li Q, et al. Cold to Hot: Rational Design of a Minimalist Multifunctional Photo-immunotherapy Nanoplatform toward Boosting Immunotherapy Capability. ACS Appl Mater Interfaces 2019;11:32633-46.
17. Hato SV, Khong A, de Vries IJ, et al. Molecular pathways: the immunogenic effects of platinum-based chemotherapeutics. Clin Cancer Res 2014;20:2831-7.
18. Qiao M, Jiang T, Ren S, et al. Combination Strategies on the Basis of Immune Checkpoint Inhibitors in Non-Small-Cell Lung Cancer: Where Do We Stand? Clin Lung Cancer 2018;19:1-11.
19. de Goeje PL, Poncin M, Bezemer K, et al. Induction of Peripheral Effector CD8 T-cell Proliferation by Combination of Paclitaxel, Carboplatin, and Bevacizumab in Non-small Cell Lung Cancer Patients. Clin Cancer Res 2019;25:2219-27.
20. Khan KA, Kerbel RS. Improving immunotherapy outcomes with anti-angiogenic treatments and vice versa. Nat Rev Clin Oncol 2018;15:310-24.
21. Jain RK. Normalizing tumor microenvironment to treat cancer: bench to bedside to biomarkers. J Clin Oncol 2013;31:2205-18.
22. Huang Y, Yuan J, Righi E, et al. Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. Proc Natl Acad Sci U S A 2012;109:17561-6.
23. Shrimali RK, Yu Z, Theoret MR, et al. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer. Cancer Res 2010;70:6171-80.
24. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity 2013;39:1-10.
25. Zitvogel L, Apetoh L, Ghiringhelli F, et al. Immunological aspects of cancer chemotherapy. Nat Rev Immunol

2008;8:59-73.
26. Emens LA, Middleton G. The interplay of immunotherapy and chemotherapy: harnessing potential synergies. Cancer Immunol Res 2015;3:436-43.
27. Leonetti A, Wever B, Mazzaschi G, et al. Molecular basis and rationale for combining immune checkpoint inhibitors with chemotherapy in non-small cell lung cancer. Drug Resist Updat 2019;46:100644.
28. Rajeswaran A, Trojan A, Burnand B, et al. Efficacy and side effects of cisplatin- and carboplatin-based doublet chemotherapeutic regimens versus non-platinum-based doublet chemotherapeutic regimens as first line treatment of metastatic non-small cell lung carcinoma: a systematic review of randomized controlled trials. Lung Cancer 2008;59:1-11.
29. Islam KM, Anggondowati T, Deviany PE, et al. Patient preferences of chemotherapy treatment options and tolerance of chemotherapy side effects in advanced stage lung cancer. BMC Cancer 2019;19:835.
30. Gupta RA, Dubois RN. Colorectal cancer prevention and treatment by inhibition of cyclooxygenase-2. Nat Rev Cancer 2001;1:11-21.
31. Dalerba P, Dylla SJ, Park IK, et al. Phenotypic characterization of human colorectal cancer stem cells. Proc Natl Acad Sci U S A 2007;104:10158-63.
32. O'Brien CA, Pollett A, Gallinger S, et al. A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. Nature 2007;445:106-10.
33. Ricci-Vitiani L, Lombardi DG, Pilozzi E, et al. Identification and expansion of human colon-cancer-initiating cells. Nature 2007;445:111-5.
34. Zitvogel L, Kepp O, Kroemer G. Immune parameters affecting the efficacy of chemotherapeutic regimens. Nat Rev Clin Oncol 2011;8:151-60.
35. Kroemer G, Galluzzi L, Kepp O, et al. Immunogenic cell death in cancer therapy. Annu Rev Immunol 2013;31:51-72.
36. Hecht JR, Trarbach T, Hainsworth JD, et al. Randomized, placebo-controlled, phase III study of first-line oxaliplatin-based chemotherapy plus PTK787/ZK 222584, an oral vascular endothelial growth factor receptor inhibitor, in patients with metastatic colorectal adenocarcinoma. J Clin Oncol 2011;29:1997-2003.
37. Van Cutsem E, Bajetta E, Valle J, et al. Randomized, placebo-controlled, phase III study of oxaliplatin, fluorouracil, and leucovorin with or without PTK787/ZK 222584 in patients with previously treated metastatic colorectal adenocarcinoma. J Clin Oncol 2011;29:2004-10.
38. Siu LL, Shapiro JD, Jonker DJ, et al. Phase III randomized, placebo-controlled study of cetuximab plus brivanib alaninate versus cetuximab plus placebo in patients with metastatic, chemotherapy-refractory, wild-type K-RAS colorectal carcinoma: the NCIC Clinical Trials Group and AGITG CO.20 Trial. J Clin Oncol 2013;31:2477-84.
39. Robertson JD, Botwood NA, Rothenberg ML, et al. Phase III trial of FOLFOX plus bevacizumab or cediranib (AZD2171) as first-line treatment of patients with metastatic colorectal cancer: HORIZON III. Clin Colorectal Cancer 2009;8:59-60.
40. Hoff PM, Hochhaus A, Pestalozzi BC, et al. Cediranib plus FOLFOX/CAPOX versus placebo plus FOLFOX/CAPOX in patients with previously untreated metastatic colorectal cancer: a randomized, double-blind, phase III study (HORIZON II). J Clin Oncol 2012;30:3596-603.
41. Merck Sharp, Dohme LLC, et al. Safety and Efficacy Study of Pemetrexed + Platinum Chemotherapy + Pembrolizumab (MK-3475) With or Without Lenvatinib (MK-7902/E7080) as First-line Intervention in Adults With Metastatic Nonsquamous Non-small Cell Lung Cancer (MK-7902-006/E7080-G000-315/LEAP-006)-China Extension Study. Available online: https://clinicaltrials.gov/ct2/show/NCT04716933?term
42. Pérol M, Felip E, Dafni U, et al. Effectiveness of PD-(L)1 inhibitors alone or in combination with platinum-doublet chemotherapy in first-line (1L) non-squamous non-small-cell lung cancer (Nsq-NSCLC) with PD-L1-high expression using real-world data. Ann Oncol 2022;33:511-21.

Cite this article as: Li F, Wang H, Xiang Y, Li R, Li C, Zhong R, Li J, Xiong S, Liang L, He J, Liang W. Comparison of different maintenance regimens following first-line immunochemotherapy for advanced non-small cell lung cancer. Transl Lung Cancer Res 2023;12(12):2381-2391. doi: 10.21037/tlcr-23-489

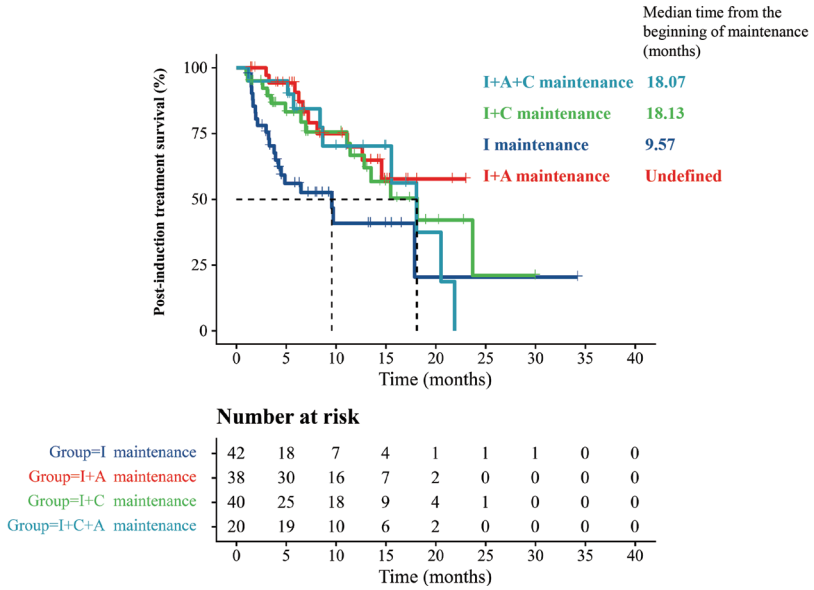

Figure S1 Median time from the beginning of maintenance in four groups. I, immune-checkpoint inhibitors; C, chemotherapy; A, anti-angiogenesis drugs.

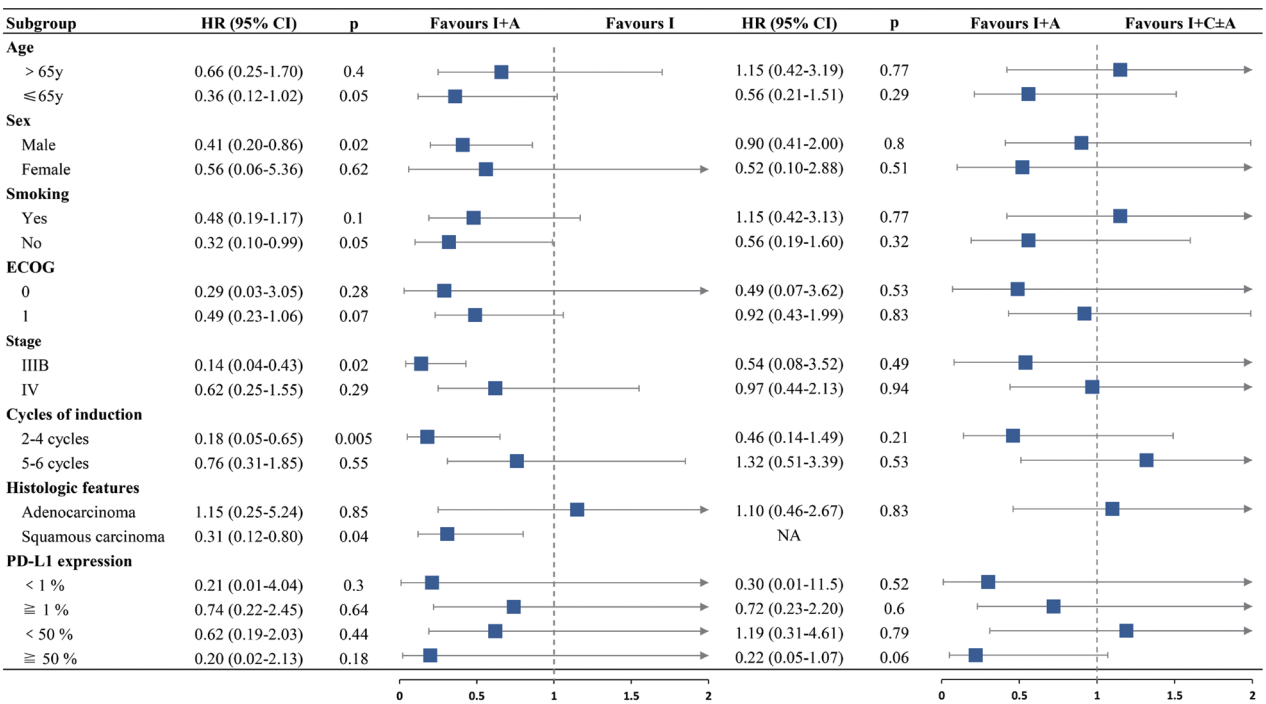

Figure S2 Forest plot HR in PFS of I+A maintenance versus I maintenance and I+A maintenance versus I+A±C in different subgroups. ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death-ligand 1; HR, hazard ratio; CI, confidence interval; I, immune-checkpoint inhibitors; C, chemotherapy; A, anti-angiogenesis drugs; NA, not available; PFS, progression-free survival.

https://dx.doi.org/10.21037/tlcr-23-489

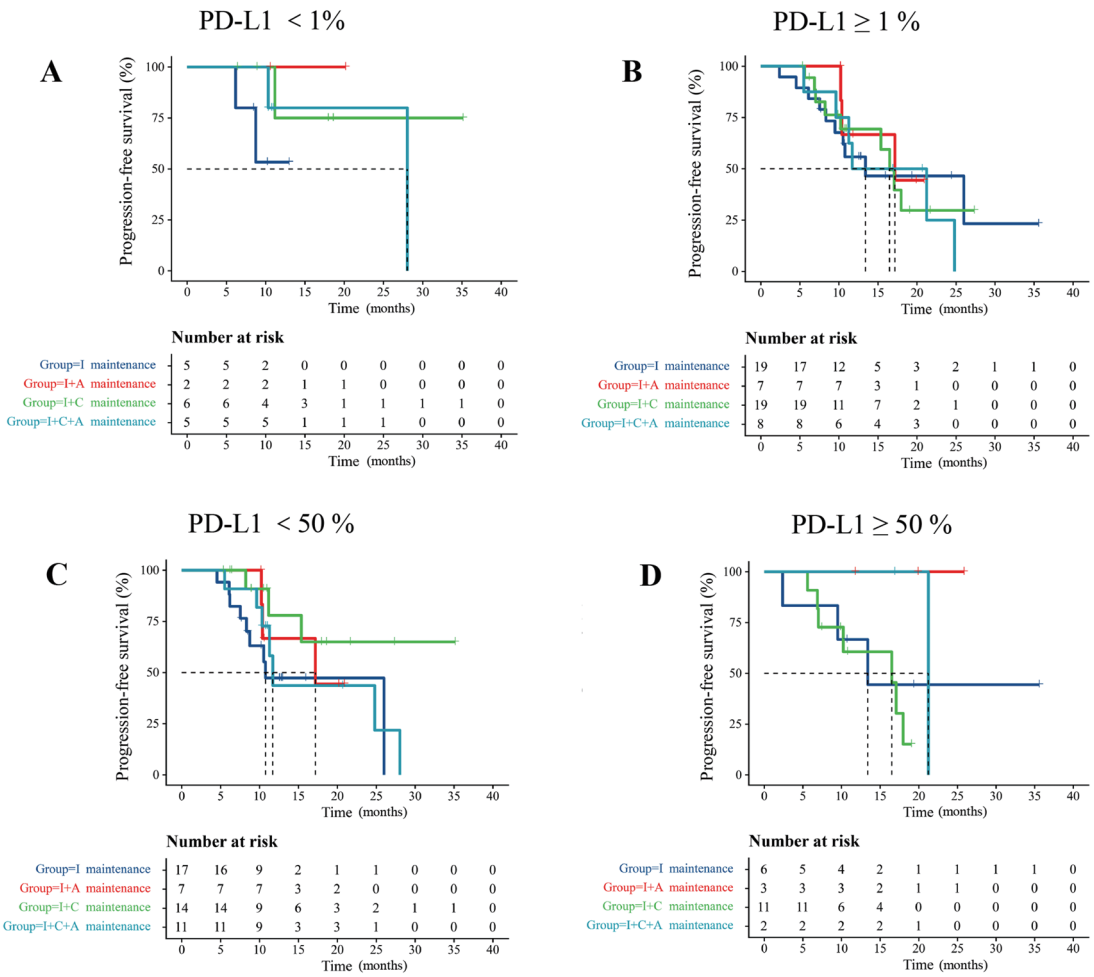

Figure S3 Progression-free survival in four groups, based on PD-L1 expression. (A) PD-L1 <1%; (B) PD-L1 ≥1%; (C) PD-L1 <50%; (D) PD-L1 ≥50%. I, immune-checkpoint inhibitors; C, chemotherapy; A, anti-angiogenesis drugs; PD-L1, programmed cell death-ligand 1.

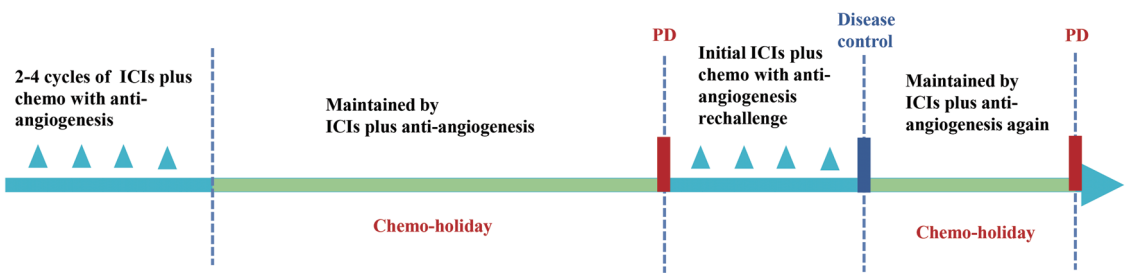

Figure S4 Schematic diagram of chemo-holiday regimen. ICIs, immune checkpoint inhibitors; PD, progressive disease.

https://dx.doi.org/10.21037/tlcr-23-489