Editorial

Re-administration of immune checkpoint inhibitors for patients with non-small cell lung cancer

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In less than a decade, immune checkpoint inhibitors (ICIs) have completely renewed the standard of care (SoC) for patients with cancer across their primary organs and histological subtypes. For patients with advanced/metastatic non-small cell lung cancer (NSCLC), starting with anti-programmed death receptor-1 (PD-1)/programmed death ligand-1 (PD-L1) antibody monotherapy in second- or later-line settings (1-4), multiple anti-PD-1/PD-L1 antibody-containing regimens, in combination with platinum-doublet [Chemotherapy (Chemo) + anti-PD-1/PD-L1] (5-8), anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) antibody (anti-PD-1 + anti-CTLA-4) (9), or both (Chemo + anti-PD-1 + anti-CTLA-4) (10), are available as the SoC. Currently, these anti-PD-1/PD-L1 antibody-containing regimens are used mainly as the first-line treatment for most metastatic cases except for those with special circumstances. Anti-PD-L1 antibody monotherapy has also established the SoC for earlier stages as maintenance therapy after chemoradiotherapy (CRT) for locally advanced NSCLC (11) and perioperative adjuvant therapy for resectable NSCLC (12). Thus, in different scenarios, most patients with NSCLC are supposed to receive ICIs earlier in their overall clinical courses.

Despite the unquestionable clinical efficacy of ICI treatment, including tail plateau for a portion of patients, clinicians may eventually consider discontinuing ICIs for any of the following reasons: (I) progressive disease (PD) or recurrence during ICI treatment, (II) significant immune-related adverse events (irAEs), or (III) completion of a fixed-duration course of ICI treatment. For patients who experienced PD or recurrence during ICI treatment (or not long after the completion of ICI treatment), the administration of cytotoxic agents is usually considered a subsequent SoC. In later-line settings, clinicians may also consider re-administration of ICIs, especially for those who experienced certain clinical benefits from the initial ICI treatment. For those interrupted ICI treatment owing to irAEs, either permanent or temporary discontinuation is considered depending on the severity of irAEs. Most irAEs resolve after the temporary discontinuation of ICIs +/– treatment with corticosteroids, and present guidelines recommend permanent discontinuation only for severe and fatal irAEs (13). Although watchful waiting (W&W) can be an option for those with continuous disease control even after an interruption of ICI treatment, re-administration of ICIs is conceivable in many cases. For those who experienced PD after completing a fixed-duration course of ICI treatment, particularly those who experienced recurrence after ICI treatment for early (perioperative adjuvant) or locally advanced (maintenance after CRT) NSCLC, ICI re-administration would naturally be considered a treatment strategy. Thus, ICI re-administration can be attempted to improve the patient's prognosis on a case-by-case basis, although the expected

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therapeutic benefits and risk vary based on the situation. Multiple case reports/series or retrospective studies, which are mainly focused on advanced/metastatic NSCLC and melanoma, have reported the clinical utility or safety of ICI re-administration for some cases (14-18). However, because of the small number of subjects and mixed reasons for discontinuing initial ICI treatment, definitive conclusions could not be drawn from previous reports.

Cai *et al.* performed a systematic review and meta-analysis to explore the safety and efficacy of ICI re-administration based on pooled data from 18 studies (16 retrospective and two prospective) (19). In this report, the authors have provided definitions for ICI re-administration and performed subgroup analysis according to the reasons for discontinuing initial ICI treatment. They defined "ICI rechallenge" as the re-administration of ICIs in patients who experienced PD or recurrence during or within 12 weeks of terminating initial ICI treatment and "ICI resumption" as that applied to those who previously discontinued initial ICI treatment because of irAE or PD after completing a fixed-duration course of ICI treatment. In this meta-analysis, the pooled objective response rate (ORR) of ICI re-administration as ICI rechallenge and ICI resumption was 8% and 34%, respectively. In addition, ICI rechallenge showed a significantly lower ORR than the initial ICI treatment, whereas the ICI resumption presented a similar ORR to that of the initial ICI treatment. For safety, the pooled incidence of any grade and grade 2 or higher in re-administration, either as rechallenge or resumption, were similar to that in the initial treatment. Following these findings, the authors concluded that ICI re-administration, especially as ICI resumption, is feasible for patients with NSCLC considering its encouraging efficacy and tolerable safety. Despite these meta-analysis limitations, mainly the small number of subjects and retrospective nature of the studies included, the findings would provide some implications for clinicians to sensibly consider the utility of ICI re-administration based on the reasons for discontinuing the initial ICI treatment. It may be wise to focus on "ICI resumption" first rather than "ICI rechallenge" when considering ICI re-administration as a potential treatment option.

However, in practice, the cases in which ICI re-administration, even as "ICI resumption", would be the best treatment option, are limited. In principle, for patients who discontinued initial ICI treatment because of irAE, the recommendation of guidelines should be followed to examine the validity of ICI re-administration based on the severity of irAEs and responsiveness to the interventions for irAEs. In most cases where permanent discontinuation is initially considered appropriate, W&W and treatment with other modalities, such as cytotoxic or molecular target agents, would be reasonable. Besides cases in which temporary discontinuation is applicable according to the guidelines, concerns about the safety of ICI resumption cannot be ignored. Another systematic review and meta-analysis explored the safety of ICI re-administration for multiple types of cancer, including NSCLC. A total of 789 cases showed lower safety and similar efficacy of ICI re-administration compared with the initial ICI treatment (20). The pooled incidence of any-grade and grade 3 or higher irAEs after ICI re-administration was 34.2% and 11.7%, respectively, and ICI re-administration showed a significantly higher incidence for any-grade irAEs [odds ratio (OR) =3.81; 95% confidence interval (CI): 2.15–6.74]. In addition, gastrointestinal irAEs and the time interval between initial irAEs and ICI re-administration were associated with a higher recurrence of grade 3 or higher irAEs. Although this meta-analysis has some limitations, it would be a suggestive reference in interpreting Cai *et al.*'s data. We need to be particularly careful in the differences in the definition of ICI resumption (e.g., intervals from initial irAEs) and "high grade" irAE (e.g., ≥ grade 2 or ≥ grade 3) across the meta-analysis or individual studies included in the meta-analysis. Currently, we still need to deliberate the risk-benefit of ICI resumption on a case-by-case basis for the limited cases where initial ICI was discontinued owing to significant irAEs.

Clinical scenarios that could be more feasible for "ICI resumption" would be ICI re-administration for patients who have completed a fixed-duration course of initial ICI treatment. Considering the latest SoC for patients with NSCLC, there may be room for ICI re-administration, particularly in those who relapsed after completing 1-year of anti-PD-L1 administration either as maintenance therapy after CRT or perioperative adjuvant therapy. Based on the previous reports, the duration of relapse-free survival with longstanding efficacy even after terminating the initial ICI treatment may be important. However, as these ICI treatments for locally advanced and resectable NSCLC have only been available as standard treatments for a short time, case accumulation in actual clinical practice settings and validation in future clinical trials will be required. For patients with advanced/metastatic NSCLC, no clear consensus has been reached on the duration of ICI treatment. Current guidelines require that effective

ICIs should be continuously administered unless PD or unacceptable irAEs are observed. However, even after the discontinuation of ICI treatment, long-lasting responses have been reported for advanced/metastatic NSCLC (1,21). Furthermore, economic burdens from the indiscriminate continuance of costly ICI treatment over the years, even for patients who experienced long-lasting responses, are becoming an issue of discussion (22,23). Based on these circumstances, several trials examining the optimal duration of ICI treatment for patients with metastatic/advanced cancer, such as JCOG1701 (a randomized phase III study to confirm the noninferiority of ICI discontinuation at 12 months compared to continuation) (24), are ongoing. If ICI treatment with a fixed-duration course becomes the SoC for advanced/metastatic NSCLC, the clinical utility of "ICI resumption" will gain more interest.

Regarding the efficacy of the "ICI rechallenge" for patients with advanced/metastatic NSCLC, a recently published article on a prospective trial seems suggestive. Akamatsu *et al.* reported the results of a single-arm phase II study (n=59) to explore the efficacy of "ICI rechallenge" as nivolumab in patients who progressed after response to initial ICI treatment and had an ICI-free interval of ≥60 days (25). In the cohort, "ICI rechallenge" had overall limited efficacy (ORR: 8.5%, median PFS: 2.6 months), whereas five responders had 11.1 months of median PFS. Given the available data, including current meta-analysis from Cai *et al.*, "ICI rechallenge", at least as simple re-administration of anti-PD-1/PD-L1 antibody, seems not a promising approach. If we consider using ICI treatment in later-line settings, we must first identify the underlying resistance mechanism for ICI treatment (26-28). Simultaneously, novel treatment strategies, such as combination of other agents (e.g., other ICIs, molecular targeted agents, cytotoxic agents), might need to be attempted. As a viewpoint-changing approach, some researchers have attempted to overcome resistance to ICIs by modulating the microbiota of patients with cancer. Early findings from a phase I study assessing fecal microbiota transplantation for ICI-refractory patients with melanoma may be worth casting a glance (29). Although various theoretical and clinical measures to overcome ICI resistance have been attempted, no conclusion has been drawn as to whether ICIs are "for single use only". Therefore, further research is needed.

As discussed above, the utility of ICI re-administration, either as "ICI resumption" or "ICI rechallenge", has not been determined. However, considerable knowledge has been gained than several past years when ICIs were first used for various types of cancer. Finally, in an era where ICIs are applicable even to patients with NSCLC in earlier stages, revisiting this issue with an updated SoC will be prudent.

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