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Rechallenge of immunotherapy in non-small cell lung cancer patients — navigating indications and evolving perspectives

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Abstract

Indications for immunotherapy in patients with non-small-cell lung cancer (NSCLC) are expanding, with an increasing number of patients receiving immunotherapy in the perioperative setting or as consolidation of radiochemotherapy. Immune checkpoint inhibitor (ICI)-based regimens are also being used more and more often in the first-line systemic setting. However, in many cases, the efficacy of immunotherapy is limited, and it is necessary to determine the optimal sequence of systemic treatment. There is some theoretical rationale for repeated use of immune checkpoint inhibitors, but it is debatable which subgroups of patients are likely to benefit clinically from such treatment. Currently, data on the efficacy of immunotherapy retreatment are derived mainly from retrospective analyses and reviews of small subgroups of patients treated in clinical trials, making it difficult to draw reliable conclusions. There is a need for research identifying factors that will guide clinical decision-making, such as the time from the completion of immunotherapy, the initial response achieved, the expression of PD-L1, and others. It appears that patients who discontinued immunotherapy due to disease progression should not be requalified for treatment with currently available ICIs. Treatment in controlled clinical trials is the optimal strategy in such cases.

Keywords: non-small cell lung cancer, immunotherapy, retreatment, rechallenge

Introduction

Immune checkpoint inhibitors (ICIs) have been used for several years in patients with advanced non-small-cell lung cancer (NSCLC) in first- and second-line systemic therapy. Most clinical trials were conducted with treatment for two years or until unacceptable toxicity (e.g. OAK or Checkmate017/057 trials — until disease progression) [1–4]. It should be noted that one of the exclusion criteria for patient participation in these trials was previous use of immunotherapy. Therefore, in terms of currently available treatment regimens, we do not have data to support immunotherapy use. In practice, however, immunotherapy may be withheld not only due to disease progression but also due to side effects or for reasons not related to cancer and treatment complications. The question of reinitiating ICIs can, therefore, be legitimate. A separate group of patients are those who have completed 2 years of treatment and subsequently relapsed. In Poland, treatment is usually continued until objective disease progression is documented. Furthermore, the use of immunotherapy in the treatment of patients in earlier clinical stages (perioperative management or consolidation after radical chemoradiotherapy) has recently become increasingly important. Therefore, it

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is worth discussing whether there is a rationale for reintroducing immunotherapy in patients who have relapsed.

This article presents the theoretical basis for the retreatment of immunotherapy, and it reviews the results of studies that focused on evaluating the efficacy and safety of reapplication of immunotherapy, both in patients treated originally with radical intent and in patients with advanced NSCLC, considering return to treatment after immune-related adverse events (irAE) and after a standard therapeutic interval.

Theoretical background for the rechallenge of immune checkpoint inhibitors

Immunotherapy with ICIs is widely used in many clinical settings, but unfortunately, with different clinical outcomes, not always satisfactory to clinicians. Discontinuation of ICIs is caused by two situations: immune-related adverse events or progressive disease (PD). When patients have limited therapeutic options, the question arises whether immunotherapy can be reordered. Several studies have shown that repeated ICI use could be beneficial for some patients. The justification for the immunotherapy rechallenge can be provided by immune system functioning, and, especially, the following aspects: immunological memory formation, T cell receptor antigenicity, and saturation of immune checkpoint molecules by specific antibodies [5].

Functionally active cytotoxic T lymphocytes play an essential role in the response to immunotherapy. To maintain the immune response and to obtain long-term therapeutic benefits, immunological memory should be stimulated. This means that the body has the ability to fight and destroy antigens very quickly that have previously been encountered. In patients who receive and respond to immunotherapy, there are subclones of T memory lymphocytes that should provide long-term protection against neoplastic regrowth [5]. In that case, is there a rationale for immunotherapy rechallenge since the immunological memory is already generated?

First, we should consider how much we know about the phenomenon of immunological memory. Previous studies have shown that memory T cells, among which we can distinguish central memory cells and effector memory cells, have a relatively short lifespan in the human body (Fig. 1) [8–10]. It was confirmed by DNA labeling techniques that memory T cells could live up to 6 months. In contrast, naïve T cells (without antigen contact) could live up to nine years. Surprisingly, immunological memory is maintained by relatively short-lived cells. The pool of memory cells could be extended in two ways: by division of existing memory T cells or by recruitment of naïve T cells to the pool [8, 10]. By measuring the Ki67 marker, Gossel et al. [9] showed that the pool of existing central memory T cells and effector memory T cells contained cells with fast and slow dynamics: short-lived cells lived three days in the pool of central memory T cells and six days in the pool of effector memory T cells, while slow-dynamic cells lived around six weeks in both groups [11]. One could ask whether a fraction of original T memory cells is maintained during therapy and in what proportion compared to initiation of therapy. More research is needed to clarify this issue.

Gossel et al. [9] found that naïve T cells replace around 10% of the population of central memory T cells every seven days. It means that these cells undergo a multistage differentiation process from naïve lymphocytes to central memory cells through stem memory cells (produced in the bone marrow) and finally effector memory cells (residues in peripheral tissue) (Fig. 1) [11]. It is not simply a one-way differentiation; this process is regulated by epigenetic and transcriptomic factors and could be disorganized when lymphocytes encounter other antigens, e.g. viruses (we are talking about *real-life*, not sterile

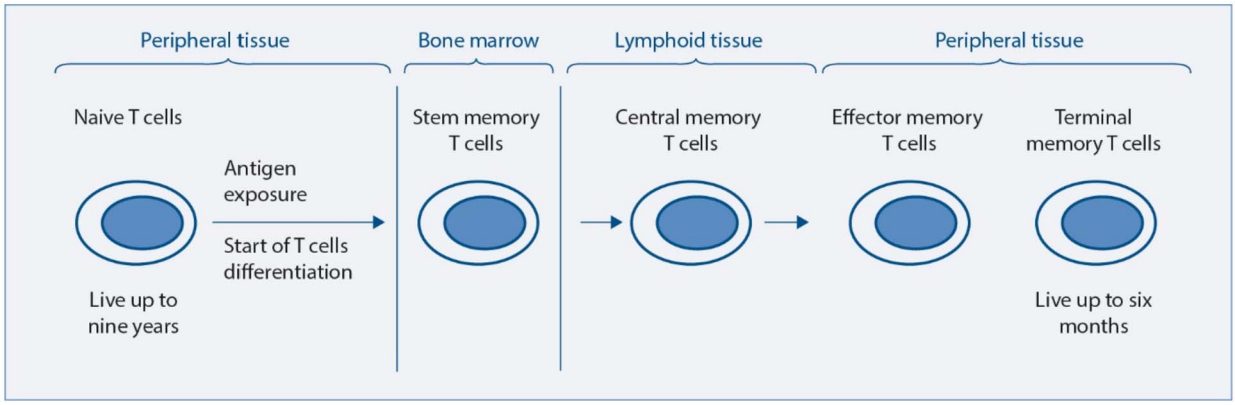

Figure 1. Schematic diagram of T-memory cell differentiation from naïve T lymphocytes into terminal memory T cells

laboratory conditions) [12]. It means that the formation and maintenance of immunological memory is a very dynamic and variable process. To illustrate this phenomenon in a simpler way, let us think about how we could store our memories. Usually, we take photos, write books, and generate other studies. Thousands of years of human experience have been written down on book pages and are stored in the world's largest libraries, such as the National Library of the United States of America or the library in the Al-Karawijjin Mosque in the Moroccan city of Fez. These creations are static, permanent, and unchanged. Unfortunately, the situation is not similar to the evolution of immunological memory. An alternative view of memory storage is provided by indigenous peoples of Africa, who preserve their memory through storytellers and singers, who pass stories from generation to generation, embellishing or retelling them in various contexts in relation to the original version [8]. This dynamic version of memory storage is like the model of immune memory formation. An effective antitumor response is based not only on the number of cells capable of attacking the tumor but also on its their quality, including the type of antigenicity of the T cell receptor (TCR) [8]. Neoplastic antigens may undergo amino acid changes to escape immune surveillance. Therefore, clonal generation of T memory cells at the time of assessment of immunotherapy effectiveness or at the time of tumor progression could be different, in terms of its antigenicity, from those induced at the beginning of therapy. To summarize, we should think about immunological memory as a variable and dynamic phenomenon.

The presence of programmed cell death protein-1 (PD-1) molecules that "unbind" is an extremely important issue in the case of immunotherapy rechallenge. Preclinical toxicology studies tested receptor occupancy (RO) for anti-PD-1 monoclonal antibodies. The mean peak occupancy for nivolumab was 85% at 4–24 hours, while the mean plateau occupancy was 72% after 57 days (8 weeks). Similar receptor occupancy saturation was reached for pembrolizumab [7]. However, we should keep in mind that stimulated T cells, which could transform into memory T cells, live only for a few weeks. This means that during each repopulation of T memory cells, we received a very variable level of PD-1 receptor occupancy on those cells. Macallan et al. analyzed time-dependent occupancy of PD-1 in patients with different cancers who had progressed on nivolumab [6]. PD-1 occupancy was measured after discontinuation of therapy. It takes approximately 32 weeks to decrease PD-1 occupancy by 50% from the initial testing value. Furthermore, two patients were rechallenged with ICIs and only one patient with a low level of PD-1 occupancy (6.6% of the total PD-1 molecules) benefited from immunotherapy reuse [6]. However, it should also be remembered that the T-memory cell repopulation process occurs with varying intensity and is very individualized.

Re-use of immunotherapy is one of the promising approaches to achieve clinical benefits in the subsequent treatment of cancer patients. Future studies should focus on clarifying the following issues: ICI rechallenge target population (biomarkers for that population would be highly recommended), the type of initial immunotherapy and rechallenge strategies (single ICI rechallenge or combination of ICIs), and finally, rechallenge timing [5].

Immunotherapy — definition of recurrence/retreatment

There are two approaches to resuming immunotherapy: retreatment or rechallenge. Retreatment denotes the clinical approach in which immunotherapy is administered without combining it with any other cancer treatments. In contrast, the ICI rechallenge strategy involves administering other treatments between the two ICI courses. This distinction is crucial, as additional treatments have the potential to affect patients' immune system equilibrium. It may change the resistance mechanism and, consequently, give a chance for a subsequent round of immunotherapy to be effective [13]. However, we can also see the use of these terms for different scenarios (Fig. 2).

One of them is retreatment in cases of disease progression after planned adjuvant or consolidating immunotherapy in an early lung cancer setting. In this case, retreatment is defined as repeated treatment with the same therapeutic class following relapse after adjuvant treatment has ended [14]. This term is used above all in melanoma therapy since adjuvant immunotherapy treatment in early lung cancer has not yet been widely implemented.

Another situation is discontinuation of immunotherapy after immune-related toxicity during primary treatment. This scenario is more frequent in the metastatic setting, where further observation of the disease is not a feasible option. No conclusions have been reached on whether ICI rechallenge should involve the initial regimen or other ICIs. 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 therapy) or locally advanced (consolidation 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 therapeutic benefits and risks vary depending on the situation.

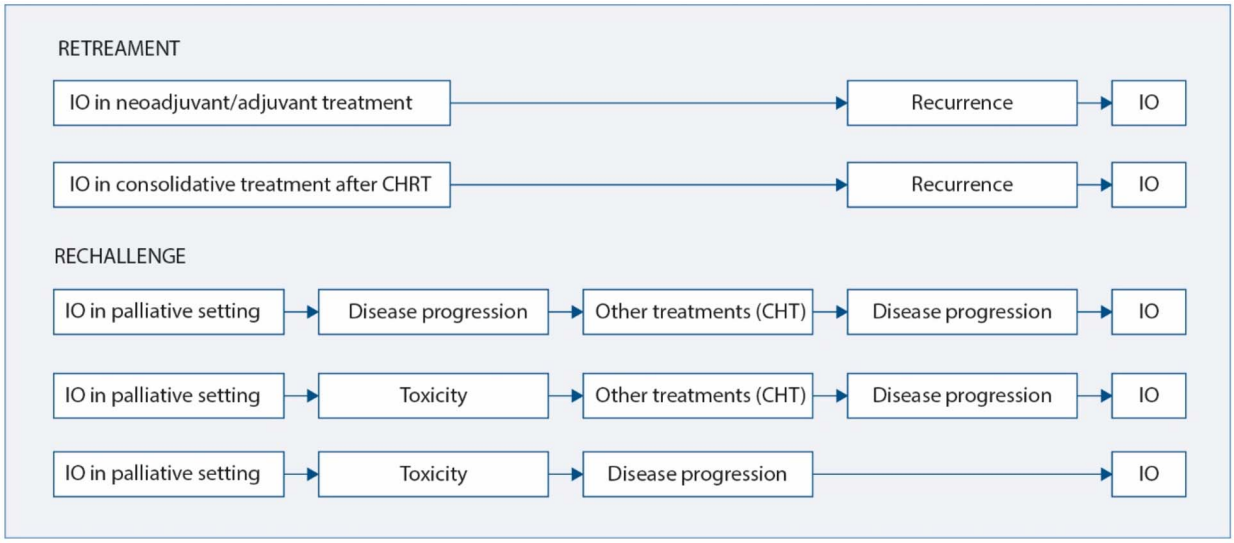

Figure 2. Possible scenarios of immunotherapy retreatment/rechallenge; CHRT — chemoradiotherapy; CHT — chemotherapy; IO — immunotherapy

However, since ICI treatments for locally advanced and resectable NSCLC have only been available as standard treatment for a short time, validation in future clinical trials will be required [15].

Immunotherapy retreatment after perioperative therapy

Despite treatment with curative intent, up to 60% of patients with resectable NSCLC still experience disease relapse. IMpower 010 is the first phase III randomized study to show a significant improvement in disease-free survival (DFS) with adjuvant immunotherapy after postoperative chemotherapy in patients with early-stage resected NSCLC. The overall survival (OS) benefit with atezolizumab versus best supportive care (BSC) was strongest in the population with stage II-IIIA PD-L1 TC (tumor cells) $\geq$ 50% [16]. Non-protocol systemic anticancer treatment following relapse was also explored, which was found to be well balanced in the 3 arms of patients who received chemotherapy, TKIs (tyrosine-kinase inhibitors) treatment, and targeted monoclonal antibody. More patients received immunotherapy in the best supportive care arm, approximately 32% of patients compared to the atezolizumab arm, in which approximately 12% of patients received immunotherapy after disease recurrence [17].

In CheckMate, 816 subsequent therapies were administered in 38 patients in the experimental arm (21.2%) and 78 (43.6%) in the chemotherapy arm. Subsequent therapy was defined as therapy started on or after the first dose date or randomization date (if the patient was never treated), outside of the adjuvant therapy specified in the protocol. Patients were permitted to receive more than one type of subsequent therapy. Immunotherapy was used in only 5.6% of the patients in the experimental arm. The results of subsequent treatment are unknown [18]. In contrast, the results of KEYNOTE-671 presented at EMSO 2023 show that immunotherapy was administered as a second-line treatment in 21.6 % of patients after progression in the experimental arm (patients receiving pembrolizumab) and in 50% of patients in the placebo arm [19].

Immunotherapy after durvalumab consolidation treatment

For many years, the standard of care for patients with unresectable stage III NSCLC was chemoradiotherapy, preferably in the form of concurrent use of both modalities. However, the results were not satisfactory. The PACIFIC trial introduced a new standard of care. In this placebo-controlled phase III trial, durvalumab consolidation treatment after concurrent chemoradiotherapy significantly improved OS and progression-free survival (PFS). Crossover was not allowed in the study. However, after the completion of the study, a total of 109 patients (10% and 27% of durvalumab and placebo patients, respectively), received subsequent immunotherapy [20]. The most common immunotherapy agents were nivolumab or pembrolizumab. Subsequent immunotherapy, administered after disease progression in the placebo or durvalumab study arm, had minimal influence on OS compared to the benefit already conferred by earlier treatment with durvalumab [21].

In daily practice, NSCLC patients diagnosed with unresectable stage III disease are usually treated with concurrent chemoradiotherapy followed by durvalumab. There is no standard-of-care treatment for

patients who progress on this protocol. In the real-world study of durvalumab after chemoradiotherapy in patients with unresectable stage III NSCLC (SPOTLIGHT) after discontinuation of durvalumab, 103 patients received subsequent anticancer therapy. The first subsequent therapies included chemotherapy (71/103; 68.9%), immunotherapy (39/103; 37.9%), targeted therapy (23/103; 22.3%), and/or surgery (3/103; 2.9%). The patients received immunotherapy regardless of the duration of durvalumab treatment. However, assessing the efficacy of subsequent treatment was not part of this study [22]. The study by Kutiel et al. aimed to evaluate the therapies administered to these patients and the response to immunotherapy after progression on durvalumab. The study involved 116 patients with non-resectable stage III NSCLC of whom 78 patients (67.2% of the cohort) progressed during or after durvalumab treatment. The median time to progression from durvalumab initiation was 7.1 months (range 0.1–29.1), with 21% of patients diagnosed with brain metastases. Fifty-one patients were treated for metastatic disease. Twenty-seven patients (53%) were treated with combined chemotherapy and immune checkpoint inhibitors (immunochemotherapy), 16 (31%) with chemotherapy alone, 4 (8%) with immunotherapy alone, and 4 (8%) with others. The median treatment time for chemo-immunotherapy was 5.5 months (range 1.2–19.6), for chemotherapy 4.9 months [range 0.5–21.7; nonsignificant difference (NS)], 2.4 months in immunotherapy alone (range 0.5–5.6). Most patients (79%) in the immunochemotherapy arm had PR (partial response) or SD (stable disease), compared to 60% in the chemo-only arm (NS): 4 patients in immunotherapy alone had PD. Thirty-seven patients (31.9% of the cohort) died. Based on these results, the authors concluded that in patients with unresectable stage III NSCLC who progressed after chemo-RT and durvalumab, there was no significant difference in response and time to treatment with chemo-immunotherapy *vs.* chemotherapy alone [23].

An update of this study was presented at the World Lung Cancer Conference. The shortest mPFS (5.6 months) was on anti-PD-L1/anti-CTLA-4 treatment, compared to 19.9 months on chemotherapy and bevacizumab. However, the differences were not significant. The conclusion was the same as in the previous analysis. Survival rates in patients with stage III inoperable NSCLC, who experienced disease progression after chemoradiation and durvalumab, were similar regardless of subsequent therapy [24]. Similar data from ten German sites were presented during the European Society for Medical Oncology (ESMO) Congress in 2023 [25]. The study included 122 patients who were retrospectively evaluated. In relation to all patients who underwent systemic therapy as first-line treatment (70.5%), the choice of systemic agents varied, with checkpoint inhibitors (with or without chemotherapy, 34.9%) most commonly administered, followed by platinum (30.2%) or single agent-based chemotherapy (27.9%) and targeted therapies (7.0%). Patients treated with targeted therapy or checkpoint inhibitor-based therapy benefited in terms of overall survival compared to patients who received chemotherapy alone. Additionally, performance status (ECOG) at relapse, time of relapse from first durvalumab administration, and site of relapse (intrathoracic only *vs.* extrathoracic) had a significant impact on OS. Using multivariate analysis, the main prognostic factors for OS were the type of first-line therapy after relapse, performance status at relapse after durvalumab, and site of relapse. In contrast, sex, age, PD-L1 expression level, and tumor histologic type did not have a significant impact on survival outcome [25]. It seems that there is a better chance of retreatment with immunotherapy if relapse happens long after completing treatment. In this scenario, clinical trials would include these patients, assuming there are no toxicities that would exclude them.

Immunotherapy after immune checkpoint inhibitors in the treatment of advanced disease

Immunotherapy rechallenge after completion of scheduled treatment

As mentioned above, there is a paucity of data from prospective clinical trials in patients who have completed treatment (usually 2 years) and who have been retreated with immunotherapy or immunochemotherapy after disease progression. A further challenge is the difficulty in defining the terms ‘immunotherapy resistance’ and ‘retreatment’ in the context of advanced NSCLC. The consensus proposed by Kluger et al. defines terms for primary and secondary resistance to immunotherapy, emphasizing that cases of regimens combined with chemotherapy require further evaluation. Primary resistance was defined as disease progression during the first 6 months of treatment, and secondary resistance as progression beyond 6 months in patients who have initially achieved disease control. For patients who discontinued treatment (due to AE or according to a protocol), primary resistance was defined as not achieving CR (complete response)/PR by patients, secondary resistance as progression in the first 12 weeks after completion of immunotherapy (and achievement of CR/PR) and late progression after 12 weeks [26, 27].

Repeated use of immune checkpoint inhibitors after failure of first-line systemic immunotherapy

The results of a pooled analysis of patients treated with pembrolizumab were presented in five clinical trials, KEYNOTE-024, KEYNOTE-042, and

KEYNOTE-598, as well as KEYNOTE-189 and KEYNOTE-407. Those patients completed the duration of treatment defined in the protocol (2 years) and then experienced disease progression [28]. In cohort 1, of the 148 patients who completed 35 cycles of pembrolizumab and experienced PD, 58 patients received pembrolizumab again, while in cohort 2, 16 of 55 patients were included in the analysis. The median time between first- and second-line immunotherapy was 11.7 (3.8–35.6) months in cohort 1 and 6.3 (0.9–18.2) months in cohort 2. The median duration of repeat immunotherapy was 8.3 and 7.3 months in cohorts 1 and 2, respectively. Overall response rates (ORRs) were 19% and 6% in cohorts 1 and 2, respectively [28]. The authors conclude that pembrolizumab retreatment provides clinical benefit although slightly better results were observed in patients with high expression of PD-L1 (originally treated with monotherapy). In addition, the analyzed patients represent a small proportion of the total number of patients originally enrolled in these clinical trials.

Reimmunotherapy after immunotherapy failure in second-line systemic treatment

The CheckMate-153 study evaluated the efficacy of nivolumab in second-line systemic treatment of advanced NSCLC [29]. The analysis included 252 patients (of 1428 patients initially enrolled) without disease progression after the first 12 months of therapy. After this time, patients were randomly assigned to continue treatment with nivolumab 3 mg/kg every 2 weeks (n = 127) or to discontinue treatment with the option of returning to nivolumab if progressive disease (PD) was documented (n = 125). In the group of patients who discontinued treatment after 12 months, 47 patients (55.35) subsequently experienced progression, and 39 (83.0%) were retreated with nivolumab. At the time of database closure (with a minimum follow-up of 13.5 months post-randomization), 10.2% of the patients who received nivolumab (4/39) were still receiving treatment and 35.9% (14/39) were still alive [29]. In particular, differences in PFS were observed between study groups; longer PFS was observed in patients who remained on treatment compared to those who stopped treatment at 12 months — 24.7 *vs.* 9.4 months [hazard ratio (HR) = 0.56; 95% confidence interval (CI) 0.37–0.84]. Median OS after random assignment was longer with continuous treatment versus 1-year fixed duration — not reached *vs.* 28.8 months (HR = 0.62; 95% CI 0.42–0.92). At the same time, a higher incidence of adverse events (32.3% *vs.* 15.2%), treatment-related adverse events (TRAEs; 48.0% *vs.* 26.4%), and TRAEs leading to discontinuation (9.4% *vs.* 1.6%) was observed in the continuous immunotherapy group. The authors of this study conclude that despite responses in several patients in the fixed 1-year treatment arm, the greatest benefit of immunotherapy was observed in patients who did not discontinue treatment and that a duration of 12 months appears to be too short in patients diagnosed with advanced NSCLC. It is worth knowing that the authors of another retrospective analysis of 1091 patients treated in daily practice indicated that there were no statistically significant differences in OS between patients who stopped immunotherapy after 2 years (with confirmed clinical benefit) and those who continued it for longer (HR = 1.26; 95% CI 0.77–2.08; p = 0.36) [30]. This observation warrants further analysis, with a focus on the fate of patients who develop disease progression.

Levra et al. [31] presented the results of a cohort study that included a total of 10 452 patients diagnosed with advanced NSCLC who were eligible for nivolumab treatment after failure of chemotherapy. The purpose of the analysis was to identify the subgroup of patients who would benefit from immunotherapy retreatment — 14.5% of patients (1517/10 452) were eligible for this treatment — in most cases, no chemotherapy was administered between immunotherapy lines (defined as retreatment), 390 patients (representing 25.7% of the 1517 group) received chemotherapy between ICI regimens (defined as rechallenge). In the overall population analyzed, median OS after nivolumab withdrawal was 15.0 months (13.9–16.7) in patients who did not recover after nivolumab and 18.4 months (14.8–21.9) in the group that recovered. Median OS was significantly longer in patients who received nivolumab for a shorter time (less than 6 months) [31]. In the 1127 patients in the immunotherapy restart arm, the median interval between discontinuation of initial nivolumab treatment and restart of PD-1 inhibitor treatment was 9 weeks, and the median duration of the second treatment with the PD-1 inhibitor was 4.0 months. Median OS after restarting immunotherapy was 14.8 months. The authors did not report the reasons for discontinuation of upfront immunotherapy. In the 390 patients who received chemotherapy before restarting immunotherapy, the median time to restart immunotherapy was 11 weeks, median PFS — 3.0 months, and median OS — 18.1 months (95% CI 14.6–21.6). Details of the reasons for discontinuation of immunotherapy were not provided; it is assumed that this was due to disease progression, due to which chemotherapy was started [31]. The authors highlight the results of the multivariate analysis. The time to respond to primary treatment was considered a favorable prognostic factor (greatest benefit in patients with response > 6 months) [31]. It should be underlined that the incomplete clinical data collected by the authors of the cited article make it difficult to formulate reliable conclusions, and it should also be noted that

Table 1. Efficacy of immunotherapy after failure of previous immunotherapy in patients with advanced non-small-cell lung cancer (NSCLC)

First author	Number of pts	ICIs	Treatment before the second ICIs	ORR [n]	DCR [n]	mPFS [months]
Fujita 2018 [36]	12	Pembrolizumab	–	1	4	3.1
Fujita 2020 [37]	18	Atezolizumab	–	–	7	2.9
Katayama 2019 [38]	35	Different (monotherapy)	Chemotherapy Radiation therapy	1	15	2.7
Fujita 2020 [39]	15	Atezolizumab	–	–	5	2.8
Sternschuss 2020 [40]	15	Ipilimumab + anti-PD-1	–	–	5	2
Kuruya 2020 [41]	38	Atezolizumab	–	1	13	2
Watanabe 2019 [42]	14	Different (monotherapy)	–	1	3	1.6
Niki 2018 [43]	11	Nivolumab	–	3	5	2.7

DCR — disease control ratio; ICI — immune checkpoint inhibitor; n — number of patients; ORR — overall response ratio; PD-1 — programmed cell death protein 1; PFS — progression free survival; pts — patients

ICI retreatment was used in a negligible proportion of patients included in the overall analysis.

Gobbini et al. [32] conducted a single-center retrospective analysis of 144 patients with advanced NSCLC who were retreated with ICIs 12 weeks after discontinuation of the drug. A lower rate of clinical benefit was observed with ICI retreatment (36% *vs.* 76%) than originally observed. Median PFS1 and PFS2 (after re-initiation of immunotherapy) were 13 (10–16.5) and 4.4 (3–6.5) months, respectively. Median OS was 3.3 and 1.5 years, respectively. Clinical benefit was observed in patients who discontinued ICIs due to toxicity or a physician's decision, in patients who did not receive additional chemotherapy, and in patients with good performance status. Patients who discontinued first-line therapy because of PD did not benefit from retreatment with ICIs. In a multivariate analysis, only performance status influenced the prognosis for patients who received immunotherapy retreatment [32].

The TAIL study was an open-label, single-arm phase III/IV study that evaluated the efficacy of atezolizumab in a patient population broader than the registration trial. Eligibility criteria included intermediate performance status [Eastern Cooperative Oncology Group (ECOG 2)] and prior treatment with ICIs [33]. In the overall analyzed population, median OS was 11.2 (95% CI 8.9–12.7) months, and median PFS was 2.7 (95% CI 2.3–2.8) months [33]. On the contrary, median OS in the repeat immunotherapy arm (n = 40) was only 5.8 months (95% CI 3.3–11.5). This outcome is supported by the observations of Akamasu et al. [34]. A group of 61 patients with an objective response to treatment, a response time of at least six months, and an interval of at least 60 days between discontinuation of immunotherapy and retreatment were included in the analysis. Regression with nivolumab resulted in an ORR of 8.5% and median PFS of 2.6 months (95% CI 1.6–2.8 months). In multivariate analysis, the time from completion of first-line immunotherapy was the only factor associated with PFS (HR = 2.02; $p < 0.02$), while the prior efficacy or irAE were not significant [34].

Additional data are provided by subgroup analyses from the clinical trials — these refer to patients who completed the study protocols for 2-year treatment. In KEYONOTE-010, 691 patients were enrolled in the pembrolizumab arm. Only 71 patients (8%) completed two years of treatment, of whom 23 patients experienced disease progression. In 14 cases, pembrolizumab was given again; 11 patients achieved clinical benefit; details of duration were provided [35].

Table 1 [36–42] summarizes selected reports showing the limited efficacy of immunotherapy in patients who progressed during treatment. Some of these studies attempted to overcome resistance to PD-L1 inhibitors with anti-PD-L1 or anti-CTLA-4 drugs. Only SD was achieved (in 20–30% of the patients) and median PFS did not exceed 3 months. The authors highlight that the efficacy of repeat immunotherapy (in terms of PFS) was lower.

Immunotherapy resumption after discontinuation due to immune-related adverse events

Immunotherapy-related side effects may be an indication for temporary discontinuation of treatment and, in some patients, for permanent discontinuation of treatment. Although most recommendations do not see a chance for resumining immunotherapy in the case of grade 3 toxicities, the question of reusing immunotherapy in cases of less severe side effects is valid [44]. The main concern is the safety of this type of treatment. Santini et al. [45] analyzed a group of 482 patients with NSCLC treated with anti-PD-L1. Sixty-eight (14%) developed severe irAE that required discontinuation of treatment [45]. Of these, 38 (56%) received retreatment and 30 (44%) discontinued treatment. In the retreatment cohort, 18 (48%) patients did not have additional irAEs, 10 (26%) had a recurrence of the initial irAEs, and

10 (26%) had a new type of irAEs, most commonly G1–2. The risk of irAE recurrence was higher in patients hospitalized at the time of the first episode; for patients who achieved ORR before irAE, PFS and OS were similar in both cohorts, whether or not immunotherapy was restarted. For patients who did not initially achieve an ORR, the prognosis was better for those who resumed immunotherapy. Taken together, the data suggest that retreatment may benefit patients with irAE who did not respond to treatment before irAE [45]. Data from a pharmacovigilance cohort study were published from the VigiBase database of the World Health Organisation, which contains case reports from more than 130 countries [46]. Case reports for all cancers and all available ICIs were extracted from the inception of the database (1967) to 1 September 2019. A total of 24 079 cases of irAE were identified. Patients who received immunotherapies were more likely to have colitis [odds ratio (OR) = 1.77; 95% CI 1.14–2.75; p = 0.01], hepatitis (OR = 3.38; 95% CI 1.31–8.74; p = 0.01), and pneumonia (OR = 2.26; 95% CI 1.18–4.32; p = 0.01) [46]. A meta-analysis of 789 cases estimated the risk of irAE after re-administration of immunotherapy at 34.2% (≥ G3 11.7%). The overall incidence of irAEs was higher in patients receiving retreatment than in those receiving first-line therapy (OR = 3.81; 95% CI 2.15–6.74; p < 0.0001) [47].

Conclusions

The indications for immunotherapy in patients with NSCLC without abnormalities in the *EGFR, ALK*, and *ROS1* genes are expanding, with an increasing number of patients receiving immunotherapy in the perioperative setting or as consolidation after radiochemotherapy. Immune checkpoint inhibitor-based regimens are also increasingly being used in the first-line systemic setting. Therefore, it is necessary to determine the value of ICI retreatment after failure of previous therapy. This review is based on prospective clinical trials and information from retrospective analyses. A limitation of these data is the heterogeneous nature of patient populations of varying sizes, making it difficult to draw reliable conclusions and identify subgroups of patients who may benefit clinically from such treatment. However, immunotherapy rechallenge seems to continue to be a challenge in the future.

It appears that in patients who receive ICIs for perioperative or consolidation management, re-application of immunotherapy could be considered if long-term clinical benefits from initial treatment are documented. However, there is a lack of data clearly indicating a criterion for timing of re-application after primary treatment completion, as well as a lack of clearly defined additional predictive factors. In the case of advanced NSCLC patients who had failed on immunotherapy, currently available ICIs do not appear to be superior to chemotherapy [48, 49]. Responses to immunotherapy have been observed primarily in patients who have maintained a good performance status and had a long-term objective benefit from primary treatment, although the time criteria recognized by different authors differ [50, 51]. Patients who discontinued primary therapy due to disease progression had a significantly lower clinical benefit than those who discontinued due to irAEs or physician decisions [52]. Currently, there is no basis for implementing this type of treatment in clinical practice. There is a need for new drugs that act on other immunotherapy targets or combine known molecules with antiangiogenic drugs [53–56]. It is optimal to qualify patients for clinical trials with new drugs.

Article Information and Declarations

Author contributions

M.K.-W.: conceptualization, literature review, writing of the manuscript draft; I.Ch.: literature review, writing of the manuscript draft; K.W.-K.: conceptualization, literature review, writing of the manuscript draft; M.K.: conceptualization, supervising.

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Supplementary material

None.

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