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Title: Immune Checkpoint Inhibitor Rechallenge and Resumption: a systematic review

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Abstract:

Purpose of the review: The reintroduction of immune checkpoint inhibitors (ICIs) after disease progression (rechallenge) or immune-related adverse events (irAEs) recovering (resumption) raises questions in terms of efficacy and safety.

Recent findings: Here, we reviewed literature data about ICIs rechallenge/resumption in cancer patients along with their clinical characteristics to explore those factors associated with better outcomes.

Summary: Heterogenous results were pointed out across rechallenge studies with an overall response rate between 0% and 54%, a progression free survival ranged from 1,5 and 12,9 months and an overall survival between 6,5 and 23,8 months. Better outcomes have been recorded in patients with good ECOG PS, longer duration of initial ICI, discontinuation reason of initial ICI other than progression and those who received ICI sequence other than the switch between anti-PD1 and anti-PDL1. Studies about ICI resumption highlighted that certain types of irAEs were more likely to relapse at retreatment. These results suggest that ICI rechallenge / resumption can be an interesting strategy for selected patients.

Keywords: *Re-challenge, retreatment, immune checkpoint inhibitors, review, cancer*

1. Introduction

Immune checkpoint inhibitors (ICIs) aim to restore anti-tumor immunity that becomes ineffective due to the immunosuppressive microenvironment induced by cancer cells as escape mechanism(1). The expression of immune checkpoints, such as PDL1 and CTLA4, which negatively regulate the immune response directed against the tumor represents one of the best-known mechanisms and they are currently used as therapeutic targets (2). ICIs directed against the PD1/PDL1 and CTLA4 axis are now approved for many types of tumors and new inhibitors directed against other mechanisms of inhibition of the immune response (Ex. anti-LAG3, anti-TIM3, anti-NKG2A, anti-CD73 etc..) are now under investigation in order to improve the outcome of cancer patients (3,4).

However, only a small proportion of patients can achieve a long-term response from ICIs and clinical or biological characteristics clearly predicting a significant clinical benefit are not known yet (5,6). On the other hand, ICIs along with other therapeutic innovations in cancer fields in recent years, are making the survival of cancer patients even longer and therapeutic sequence strategies are becoming a critical issue. In many tumors, treatment choices after failure of immunotherapy are limited. For example, in metastatic non-oncogene-addicted non-small cell lung cancer (NSCLC), patients are supposed to receive multiple lines of chemotherapy whose efficacy remains limited beyond the second line and whose toxicity may limit their prescription. For this reason, rechallenge with ICI could be an interesting option and patients' selection became crucial.

After ICI initiation, patients can discontinue the treatment for different reasons. The first one is the achievement of a durable clinical response even then the optimal duration of treatment in these cases is not currently defined and it can depend on the histology. The second is the absence of response to treatment, or the occurrence of a disease progression after obtaining a clinical response. Finally, patients may stop treatment due to the appearance of intolerable immune-related adverse events (irAE).

The ICIs rechallenge in case of progression as subsequent or following treatment may be an option to explore but poor data are currently available to drive the choice. Conversely, more is known about the safety of ICIs resumption in patients discontinuing the treatment due to irAEs once symptoms have recovered. In case series collecting information about these patients, disease is usually still controlled, and no treatment shift is required being the choice between ICIs resumption and surveillance.

This systematic review aims to describe the efficacy and safety of ICIs rechallenge and resumption in cancer patients focusing on clinical characteristics possibly associated with a better clinical outcome.

2. Material and Method for the systematic review

The key issue was focused on the efficacy and safety of ICIs rechallenge or resumption in cancer patients. The standard reporting guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement) has been used for this literature review (Supplementary Figure 1). The terms used for the research are reported in the Appendix 1. The research was launched in Pubmed between the 12 July and the 08 August 2021. January 2010 was established as the time cut-off to searching articles. All titles and abstracts were screened individually and then collectively reviewed. Only contributions in English were accepted. Disagreements were resolved by consensus. Authors considered every abstract as eligible if all the following characteristics were identified: (1) full original paper and case series only (articles were excluded when only the abstract was available), (2) studies conducted in human only, (3) studies focused on cancer patients regardless of the histology, (4) patients included in the studies received ICIs (nivolumab, pembrolizumab, ipilimumab, atezolizumab, avelumab, durvalumab, tremelimumab), (5) first ICI treatment could be discontinued for any reason (disease progression, development of IrAEs, protocol completion) and then patients could have restart immunotherapy immediately or during their history of disease. Studies were divided into those exploring the ICIs rechallenge strategy, in which patients were retreated with ICIs once disease progression occurred (as subsequent or following treatment), and those exploring the ICIs resumption, in which patients discontinued the first ICI due to irAEs and they resumed it once symptoms recovered.

As no consensus currently exists regarding the therapeutic sequence, all lines of treatment were included, and no time interval between the two lines of immunotherapy was imposed, however publications about treatment by immune checkpoint inhibitor beyond progression were excluded. Moreover, articles that did not specify the reason for discontinuation of ICIs or that were focused on the management of a particular irAEs were excluded from the analysis. Then, full articles were individually and collectively read and validated by authors according to the previous criteria.

The following variables were extracted from the publications: (1) study design, (2) histology, (3) inclusion criteria (4) previous lines of treatment, (5) ECOG status, (6) PDL1 status, (7) number of patients included at rechallenge or resumption, (8) initial and rechallenge/resumption

ICI type (9) duration treatment by ICI (10) time interval between the two courses of ICIs (11) local or systemic treatment administered between the two ICIs, (12) grade and type irAEs when occurred (13) data about efficacy on initial ICI and rechallenge (objective response rate - ORR, disease control rate - DCR, overall survival - OS, progression free survival - PFS).

3. Results

3.1. Rechallenge with ICIs at time of progression in pre-treated cancer patients

We selected 32 studies focused on cancer patients that received a rechallenge with ICIs during their history of disease after that disease progression occurred (Supplementary Table 1) (7–38). Few prospective clinical trials were found: five studies were conducted on melanoma patients whose developed resistance to a first line of immunotherapy, two investigated the ICI rechallenge in NSCLC patients who progressed after a first line of anti-PD1, and one was conducted on HL (Hodgkin Lymphoma) patients who were treated by anti-PD1 and then experienced DP (7–10,22,23,34,38). The rest of selected articles were about retrospective observational studies on patients with melanoma (n=10), NSCLC (n=8), RCC (n=2), HL (n=1) or including multiple histology (n=2). Retrospectives studies included between 8 and 144 patients who were treated with different sequence strategies. In the following chapters, we will detail safety and efficacy of rechallenge strategy across the selected studies along with the clinical characteristics that could be associated with an improved clinical outcome.

3.1.1. Efficacy of ICIs rechallenge

The set of reviewed studies have shown that rechallenge with immunotherapy in patients who experienced disease progression could have a certain clinical activity (Figure 1). Prospective studies conducted in melanoma patients reported an ORR between 12% and 54% with a DCR ranged from 39% to 77% (7–10,38) (Figure 1.a.). Two of these studies reported information about PFS and OS from rechallenge that ranged from 2.9 to 3.1 months and 13.4 to 15.7 months respectively (9,38) (Figure 1.b.). However, when looking at retrospective studies, ranges became really wide (ORR: 0%-47%, DCR: 33%-68%, PFS: 3–8.8 months, OS: 8–21.6 months) that can be probably explained by the low number of patients included in most of these studies (less than 25 patients in 8 out of 10 retrospective trials selected) but we cannot exclude some bias in clinical characteristics of selected patients or ICI sequence strategy used.

Similar results were found in NSCLC patients. In this case few prospective trials are currently available and data about outcomes are reported in the Keynote 010 post-hoc analysis only, in which the 14 patients included showed an ORR of 43% and a DCR of 79% (23). As already shown for melanoma patients, really heterogeneous results were reported in retrospective trials. In particular, we found an ORR ranged from 0% to 27% and DCR from 14% to 63.2% whereas PFS and OS from rechallenge ranged from 1.5 to 4.4 months and from 6.5 to 18 months respectively. Once again this can be partially explained by the low sample size of studies with less than 20 patients in most of cases (7 out 11 studies selected). We selected only two studies focused on RCC showing comparable results in term of ORR, being 20% and 23%, and PFS from rechallenge being 4 and 5.7 months (32,33). Finally, the greatest clinical responses during the rechallenge were demonstrated in patients with Hodgkin Lymphoma with an ORR of from 67% to 75% and a DCR from 81 to 87,5% (34,35).

In all these studies, a less important clinical benefit was achieved during rechallenge compared to the first exposition to immunotherapy suggesting that this strategy can overcome resistance mechanisms only in a certain proportion of patients. However, a small case series including 9 melanoma patients, showed higher ORR and DCR during rechallenge than during the first course of immunotherapy (33% and 67% versus 11% and 55% respectively) (16). In this study patients who became resistant to an anti-PD1 agent, were rechallenged with a combination of nivolumab + ipilimumab. These results, suggests, that a better comprehension of clinical and biological characteristics of patients achieving a significant clinical benefit from this approach is needed. Here above, we describe the different parameters that might influence the response to the rechallenge.

3.1.2. ECOG status

In clinical practice, ECOG status is an important element to consider when introducing a new line of treatment. Whether ECOG PS was often reported before the first ICI in selected articles, it was rarely detailed at the time of rechallenge (25,39–41). In the study of Gobbini et al. NSCLC patients with a good performance status (ECOG PS = 0) had a longer PFS and OS from rechallenge with anti-PD1/PDL1 agents in uni- and multi-variate analyses (ECOG 1: PFS 2.12 and OS HR 2.98; ECOG $\geq$ 2: PFS HR 2.74 and OS HR 3.97) (25). In line with this, Katayama and al. showed that poor ECOG PS status ($\geq$ 2) was associated with a decreased of PFS and OS from rechallenge in a cohort of NSCLC patients rechallenge with anti-PD1/PDL1 agents (HR

2.38 and HR 3.01 respectively) (40). These data suggested that rechallenge could not be an appropriated strategy for patients with poor performance status.

3.1.3. PDL1 status

It has been shown that patients with high PD-L1 expression present a higher rate, and longer clinical responses to immunotherapies (42–44). However, PD-L1 status is not reported in most of studies we selected and the impact of this biological feature on rechallenge efficacy was explored in only 3 of them (21,26,36). In the study of Katayama et al., NSCLC patients with PD-L1 expression between 1-49% or > 50% showed a longer PFS from rechallenge (HR 0.32 and HR 0.35 respectively) compared to PD-L1 negative ones (40). A very high expression of PD-L1 ($\geq 80\%$) was even found in all NSCLC patients who achieved a partial response or disease stabilisation under rechallenge by Fujita et al. (41). Finally, in the study of Sheth et al, including patients with different histology and PD-L1 expression above 50% a DCR of 71.4% have been highlighted. According to these results, it seems that the PDL1 status matter in the chance to achieve a significant clinical benefit from rechallenge, but controversial results can be highlighted through the studies we selected. For instance, studies that were enriched in PDL1 high NSCLC patients (50% of patients with $PDL1 \geq 50\%$) reported disappointing outcomes over rechallenge (ORR 0%, PFS 1.5 – 3.1 months) (27,28,30) .

3.1.4. Duration of first ICI treatment

The UNIVOC study was a large French register-based study focused on NSCLC patients that received at least one line of nivolumab during their disease course (45). Among them, there was a subgroup of patients who were rechallenged with an anti-PD1/PDL1 after at least one line of chemotherapy. In this group the median OS from rechallenge was 18 months and authors showed that patients who received at least 3 months of ICI during the first exposition achieved better results compared to the others (NR versus 13.1 months, respectively). Among the selected studies for this review, only one study investigated the duration of the first course of ICI as a predictive factor of the rechallenge efficacy in NSCLC patients, but no correlation was found (19). However, in some prospective studies, patients were eligible for rechallenge if they have completed 1 or 2 years of treatment according to the protocol (22,23,34,35). Interestingly, in these trials we founded the higher rate of ORR and DCR ranging from 43% to 75% and 79% to 87,5% respectively. However, it's important to

consider that two of these trials were focused on Hodgkin Lymphoma patients that might have a different response to ICI compared to solid tumors.

3.1.5. Clinical response during the first course of ICI

Most of studies did not shown a correlation between the clinical response obtained during the first ICI and that one obtained during rechallenge regardless tumor types (12,19,23,31,33,36,46). Indeed, patients who presented a disease progression as best response during the first ICI could subsequently obtain a clinical response during rechallenge and in the other way around. For instance, in the small case series of Kirchberger et al, 9 melanoma patients who had never presented a clinical response under anti-CTLA4 and then anti-PD1 showed a DCR of 30% when rechallenged with the combination of anti-PD1 and anti-CTLA4, highlighting the capacity of patients who had presented primary resistance to respond to the rechallenge (18). However, some studies which selected only patients who showed clinical benefit during the first ICI exposition highlighted better clinical outcomes compare to those studies included unselected patients. For example, in studies focused on melanoma patients with at least 15 patients included, the rechallenge lead to a DCR from 55% to 77% when patients were selected according to the response to first ICI (7,8,10,13–15) compared with 39% to 56% in studies that did not perform this kind of selection (9,11,12,47) (Figure 1.a.). In line with this, Nomura et al., showed that a PFS longer than 3 months during first course of nivolumab, was associated with a longer PFS in rechallenged patients with melanoma (39). Finally, Shreders et al. have highlighted an association between a longer PFS under ipilimumab and a reduced risk of experiencing PD during rechallenge (HR of 0.85) (11) (Figure 1.b.).

Similar results were found in NSCLC patients. The best responses recorded among the studies selected belong to the Keynote 010 trial in which only patients that completed one year of pembrolizumab and achieved at least a disease stabilization were rechallenged (23). In this study, the ORR under rechallenge was of 43% with a DCR of 79% compared to study performed on unselected patients ranging from 0% to 27% and 14% to 58.8% respectively (Figure 1.a.) (23). Contrary to what observed in melanoma patients, no correlation has been found by Fujita et al., between the PFS during the first course of ICI and the PFS from rechallenge (26) (Figure 1.b.). Finally, in RCC, an increase ORR under rechallenge was reported in patients responding to the first ICI compared to patients achieving SD or PD (29% versus 16% and 21% respectively) (28). However, studies that selected patients according to the response to the first ICI, were also liked to be enriched in patients with longer duration of treatment that, as we

detail in the previous chapter, was found to be associated with better outcome under rechallenge in some studies.

3.1.6. Discontinuation reason of the first ICI

In all the studies we selected, patients experienced disease progression before rechallenge but they could have discontinued the first ICI treatment to any reason. In particular 8 studies, 5 prospective and 3 retrospectives, were focused on patients which discontinued the first ICI for other reason than progression (14,15,22,23,34–37). Across these studies ORR under rechallenge ranged from 32% to 47% in melanoma and NSCLC lung cancer whereas it was between 11.4% and 25% when considering trials including multiple histology. When looking at other studies not selecting patients according to the reason of first ICI interruption ORR ranged from 12% to 47% in melanoma and from 0% to 21% in NSCLC patients (considering only studies with at least 15 patients). This question was specifically addressed in the study of Gobbini et al. in which it was shown that patients discontinuing treatment due to irAEs or medical decision had a longer PFS and OS compared to patients who discontinued for PD (PFS HR: 0.54 and 0.63 respectively, and OS HR 0.44 and 0.61, respectively)

3.1.7. Sequence of ICI in rechallenge strategy

Although anti-CTLA4 and anti-PD1/PDL1 agents are both immune checkpoints inhibitors, they are not considered the same class of agent because targeting different molecules. While CTLA4 mainly affects naïve T cells, PD1 is primarily expressed on mature T cells in peripheral tissues and the tumor microenvironment. Inhibition of CTLA4 enhances Th1 immune responses from secondary lymphoid organs primarily involving CD4+ T helper cells. In contrast to CTLA4, PD1 predominantly regulates effector T cell activity within tissues and tumors (2,48). Interesting information supporting this concept come from the study of Weber et al, in which melanoma patients were treated with different sequential strategy of ICI (49). Patients were randomized to receive nivolumab (anti-PD1) followed by ipilimumab (anti-CTLA4) or the reverse sequence. Thus, this study did not explore the rechallenge strategy since these patients did not resume immunotherapy at time of disease progression. In this study patients who received nivolumab followed by ipilimumab showed a higher clinical benefit with an ORR of 41% compared to an ORR of 20% in the group of those receiving ipilimumab followed by nivolumab. Moreover, the median OS was not reached in the nivolumab followed by ipilimumab group compared to an OS of 16.9 months in the ipilimumab followed by nivolumab

arm. These data suggest that probably the ICI sequence matters. Among the studies we selected for this review, 4 exploring a switch between anti-CTLA4 and anti-PD1, 3 explored the association of anti-PD1/PD-L1 and anti-CTLA4 after progression to anti-PD1/PD-L1, 5 investigated the switch between anti-PD1 and anti-PD-L1 whether the majority included patients that received two lines of anti-PD1/PDL1 or anti-CTLA4.

In these latter, we found 7 prospective studies focused on melanoma (7,8,10), NSCLC (22,23) or including different histology of solid tumor (36,37) that showed an ORR ranging from 12% to 54%, a DCR from 48% to 100%. Poor information was reported about survival outcome in these trials. Looking at the retrospective studies exploring the same strategy and including at least 15 patients we found similar results in term of response to rechallenge (ORR: 16%-47%, DCR: 47%-68%) with a PFS ranging from 4.4 to 8.8 (13,14,25,32).

Moreover, studies exploring the switch between anti-PD1 and anti-CTL4 agents were all focused on melanoma patients (9,11,17,50). They did not selected patients according to response to first ICI course and their ORR ranged from 22% to 42% with a DCR between 33% and 56% whereas the PFS and OS ranged from 2.9- 5.8 months and 13.4 and 15.7 months respectively. Furthermore, 2 out of 3 studies investigating the addiction of an anti-CTLA4 agent to anti-PD1 to overcome the anti-PD1 resistance were conducted on melanoma patients (12,18). In these trials results seemed to be less interesting than the other strategies in term of response ranging the ORR between 0% and 39% but PFS results were interesting being 8 and 9.9 months. The last strategy explored in the switch between anti-PD1 and anti-PDL1 agents and results were less convincing. All the 5 studies investigating this option were conducted in NSCLC patients and they showed an ORR from 0% to 21% with a PFS and OS ranging from 1.9 to 4 months (24,27–29,40).

3.1.8. Time between the two ICI courses

Among the selected studies 4 reported information about the time between the two lines of immunotherapy (14,29,31,33). Kitagawa et al. showed that 42% of NSCLC patients rechallenged after 6 months from the end of the first ICI achieved SD and this proportion improved to 50% when the rechallenge occurred after one year (29). However, one might suppose that a longer treatment interval simply reflects a more indolent disease and an outcome better than expected regardless of the type of treatment received. Indeed, other studies supported a completely different impact of the immunotherapy-free period. The study of Asher et al., failed to show a correlation between the time off treatment and clinical outcomes under

rechallenge (14), whereas in two other studies patients who were rechallenged within 3 months following discontinuation of immunotherapy, obtained better responses (31,33).

3.1.9. Impact of CT or RT between the two ICI courses

There is a strong rationale for explaining why chemotherapy or radiotherapy could facilitate ICI rechallenge efficacy. First, both chemo and radiotherapy can lead to tumor debulking, reducing *de facto* tumor-related immunosuppression and decrease intratumor hypoxia (51). Beyond their direct cytotoxic effect, both strategies are known to be able to trigger immune activation in particular conditions that is critical for reaching long lasting clinical responses (52,53). Indeed, chemotherapy is known to induce the immunogenic cell death characterized by the release of immunogenic signals promoting tumor material phagocytosis and tumor-associated antigens presentation by matured dendritic cells, generating and/or reactivating the anti-cancer immunity (54). Similarly, RT can enhance tumor neoantigen presentation through several mechanisms. RT can enhance both the expression of MHC Class I molecules and tumor-associated neoantigens generation/release, rendering the tumor cells more recognizable, immunogenic and thus more susceptible to *de novo* generated cytotoxic T cells (55,56). Moreover, RT has been shown to trigger type-I IFN production (57). Importantly, it has also been described that RT may favours the expression of PD-L1 by tumor cells (58). Altogether, these RT-induced changes might lead to a “reset” of primary or secondary acquired ICI resistance and an enhanced anti-tumor immunity, thus rationalizing the benefit of intercurrent chemotherapy and radiotherapy before ICI rechallenge.

Among the selected studies, 11 provided information about intercurrent treatments between the two ICI courses but only Gobbini et al. put that into correlation with rechallenge outcome. IN this study authors showed that NSCLC patients receiving intercalated systemic treatment between the two ICI courses had shorter PFS and OS compared to the those that were able to keep a treatment-free period (PFS HR 1.81; OS HR 1.52) (25). However, these results are not enough to make any conclusion on the impact of systemic or local treatment performed between the two courses of ICI on rechallenge efficacy.

3.1.10. Safety of the ICI rechallenge

Finally, concurrently with the rechallenge strategy assessment in terms of efficacy, it is also important to consider the safety of this approach. Among those selected, prospective studies

reporting this kind of information were focused on melanoma and Hodgking Lymphoma (7,8,10,35). Globally, they shown that irAEs occurring during rechallenge were not more frequent and not more severe than during the initial ICI (7,10). Within studies focusing on melanoma patients, Lebbe et al. and Chiarion-Sileni and al. showed that the safety profile of rechallenge was similar with that observed during initial treatment, with a majority of irAEs affecting skin or gastrointestinal tract (7,10). In Robert C. et al., 46% of patients presented a subsequent irAEs during pembrolizumab rechallenge, with no grade 3-4 (8). In patients with Hodgking Lymphoma, Fedorova et al., reported a decrease of grade 3-4 irAEs occurrence between initial ICI and rechallenge (45% compared to 36% respectively) (35). According to these results, the rechallenge strategy seems to be safe with a manageable toxicity profile.

3.2. ICI resumption after discontinuation because of irAEs

If irAEs under ICI are often perceived as conferring a good prognosis (5), they may lead, depending on the type and severity, to suspension or permanent discontinuation of immunotherapy. However, early discontinuation of immunotherapy may represent a loss of therapeutic chance for patients and the safety of ICI resumption in these cases is still an open question. We selected 12 studies focused on cancer patients that resumed ICIs during their history of disease (Supplementary Table 2). All of them were retrospective. 6 studies included multiple histology, 3 were performed on melanoma patients, 2 on NSCLC patients and 1 on RCC patients. Sample size of studies ranged from 21 to 180 patients that received mainly an anti-PD1/PDL1 +/- an anti-CTLA4 as first ICI and usually resumed the same ICI after irAEs recovering. The irAEs experienced during the first ICI was of moderate (grade 1-2) in 13% to 66% of patients and psevere (grade 3-4) in 34% to 86% of patients but studies were generally enriched in patients experiencing severe irAEs as per inclusion criteria.

3.2.1. Incidence, type and grade of irAEs at ICI resumption

The decision to reintroduce immunotherapy once symptoms recovered is influenced by type and grade of irAEs occurred during the first ICI. In the selected studies, results about irAEs relapse at ICI resumption were really hetereogeneous. From 37% to 78% of patients that were retreated after irAEs experienced an irAEs of any grade. This could be the same irAEs of the first ICI line (3% to 42% of cases) or a new irAEs (10% to 36% of cases) (Figure 2.a.). irAEs at resumption were severe (grade 3-4) in 18% to 62% of cases. However, these results were

really similar or even less severe than what reported during the first ICI considering study by study nothing but in the study of Simonaggio et al. reporting a numerically higher percentage of grade 3-4 irAEs at time of resumption compared to the first ICI course (Figure 2.b.)(59). The most frequent irAEs at time of resumption are colitis, pneumonitis, hepatitis and skin disorders (Figure 2.a.) but other rare events were also reported such as hematologic disorders, kidney injury or interstitial lung disease (60–62). Some studies tried to understand which could be the clinical factors associated with a higher risk of irAEs at time of resumption and we reported their results below.

3.2.2. Type of irAEs more likely to relapsed at ICI resumption

The large pharmacovigilance study of Dolalille et al showed that some irAEs are more likely to relapse at time of ICI resumption (63). In particular arthritis, skin damage, colitis, pneumonitis and hematologic injury present recurrence rate above 30%. However, this study did not provide any information about the grade of irAEs or the discontinuation reason of the first ICI. Moreover, some studies focused on a specific irAEs (haematological, colitis/diarrhea, pulmonary damage, hepatitis provided us interesting information about their risk of recurrence (60–62,64–68) (Figure 2.a). For instance, studies focusing on colitis have shown a recurrence rate ranging from 16% to 34% (65,67,68). Patrinely et al. reported a recurrence rate of 26% for Hepatitis (64). In the uncommon irAEs, recurrence rates of 30% and 43% have been shown for interstitial lung disease and hematologic irAEs respectively and a rate of 19% for acute kidney injury (60–62). Finally, Wang et al. showed a higher recurrence rate of pneumonitis compared to other studies that are not only interested in this irAEs (50% vs a maximum of 34% found by Dolladille et al.) (63,66). Among the selected studies, 3 agreed that the IrAEs most likely to recur were colitis, hepatitis, pneumonitis and skin toxicities (59,69–71). However, in the study of Kartolo et al., only pneumonitis was identified as a risk factor of recurrence, in the study of Tsui et al., hepatitis was the irAEs most frequently recorded at resumption and in the study of Santini et al., arthralgia and myalgia were the most frequent (72–74). In contrast, Pollack et al. and Menzies et al. highlighted that colitis was less at risk of recurrence (75,76). However, sample size of these studies often modest and results have to be taken with caution.

3.2.3. Severity of irAEs during the first ICI and irAEs at ICI resumption

According to most of the selected studies, the grade of the first irAEs seemed not to be predictive of irAEs recurrences (59,69,70,72,75). Moreover, there were no correlation between the use of corticosteroids or additional immunosuppressive drugs and the irAEs severity at resumption (59,75). Conversely, in the study of Kartolo et al. irAEs were more frequent in patients who presented grade 3 toxicity during the first course of ICI (74). Moreover, patients experiencing grade 3-4 irAEs at resumption were more often those who required the use of corticosteroids or immunosuppressive drugs for the first ICI management in several studies. (59,68,69,74). In line with this, patients who required hospitalization for the management of the initial irAEs had a higher risk of irAEs recurrence or the appearance of a new irAEs according to Santini et al and Alaiwi et al (70,72). Regardless of these controversial results, patients experienced high grade irAEs during the initial ICI should not be excluded from this strategy considering that, once the symptoms have recovered, toxicity during ICI resumption seems manageable.

3.2.4. Time to irAEs onset during the first ICI and irAEs at resumption

In clinical trials, it has been shown that most of irAEs occur within the first 3 months of treatment (72,75). The time to the first irAEs onset may influence the decision to retreat or not the patient once symptoms solved. Among the studies reviewed, 4 reported this kind of information (59,69,70,72). In the study of Allouchery et al., patients who presented an irAEs at resumption had a longer time to irAEs onset during the initial ICI (112 days versus 63 days) (69). Conversely, another study showed an opposite result with a higher number of patients experienced irAEs at resumption when the initial irAEs occurred within the first 3 months of treatment (72). Due to the poor data available, no conclusion can be done about the effect of the time to irAEs onset on the safety at resumption.

3.2.5. Treatment-off period before ICI resumption

Among the studies reviewed, 7 reported this kind of information (69,70,72,73,75,77,78). In the study of Santini et al. and Allouchery et al, no association was found between the irAEs rate and the time to resumption (69,72). Conversely, Pollack et al., reported a shorter interval between discontinuation of the combination nivolumab-ipilimumab and the anti-PD1 reintroduction with the risk of irAEs recurrence (median of 56 days in patients with recurrence of irAEs versus 65 days in the group without recurrence) (75). Of note, this result is surprising

because a longer delay could correspond to a longer time to resolution of the first irAEs but on the other hand, the patients who presented subsequent irAEs may have been retreated too early during irAEs course.

4. Conclusions

According to our review, ICI rechallenge seem to lead to interesting results regardless the tumor type, especially in patients with good ECOG PS, longer duration of initial ICI, discontinuation reason of initial ICI other than progression and those who received ICI sequence other than the switch between anti-PD1 and anti-PDL1. Conversely, the PDL1 expression, the radiological response to the initial ICI, the use of intercurrent chemotherapy or radiotherapy between the two ICI courses and the treatment-off period were more debated across the selected studies not allowing to make a conclusion about these features. Moreover, the resumption of ICI after resolution of an irAEs showed fewer adverse events than those experienced during the first ICI. Among studies, the irAEs more likely to recur were colitis, pneumonitis, hepatitis and skin damage. Conversely, the severity, the time to onset and the duration of irAEs during the first ICI were less frequently found as associated with a higher risk of irAEs at resumption. These results suggest that ICI rechallenge/resumption can be an interesting strategy for selected patients.

Conflict of Interest:

EG is the spouse of an Astrazeneca employee, she received personal fees from Roche, Pfizer, Merck Sharpe and Dohme and Bristol-Myers Squibb, and she received research grants form Bristol-Myers Squibb and Astrazeneca.

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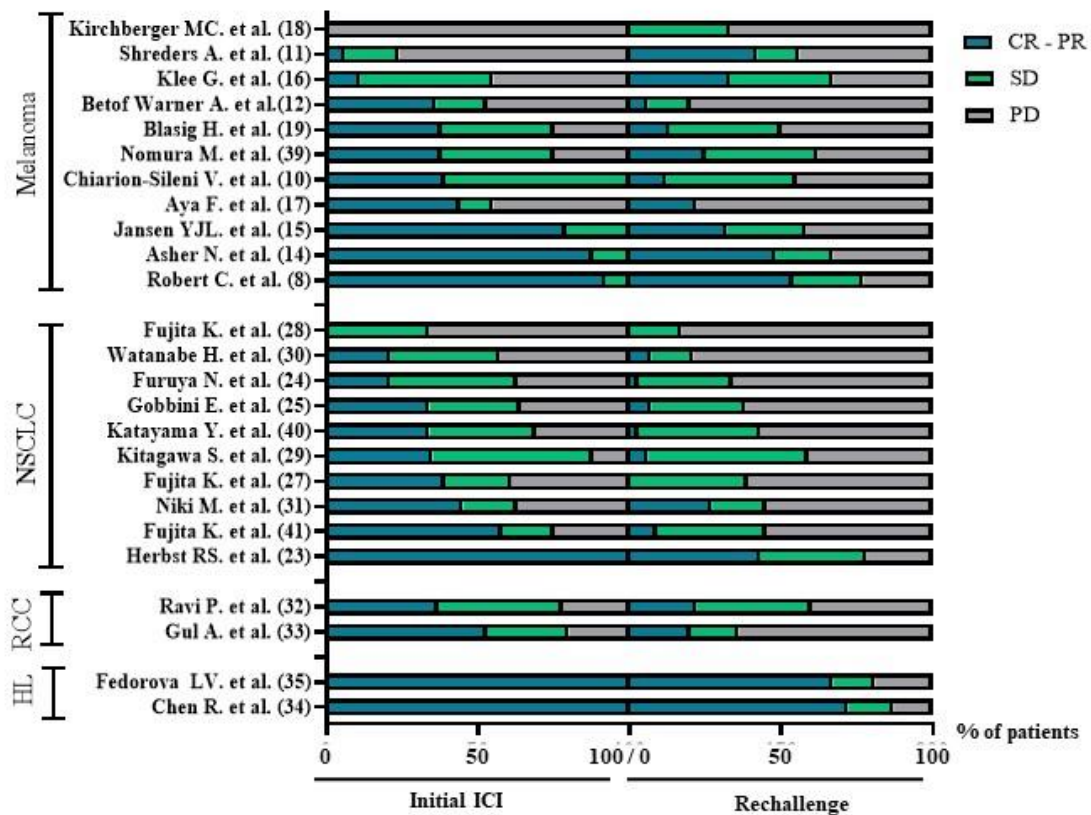
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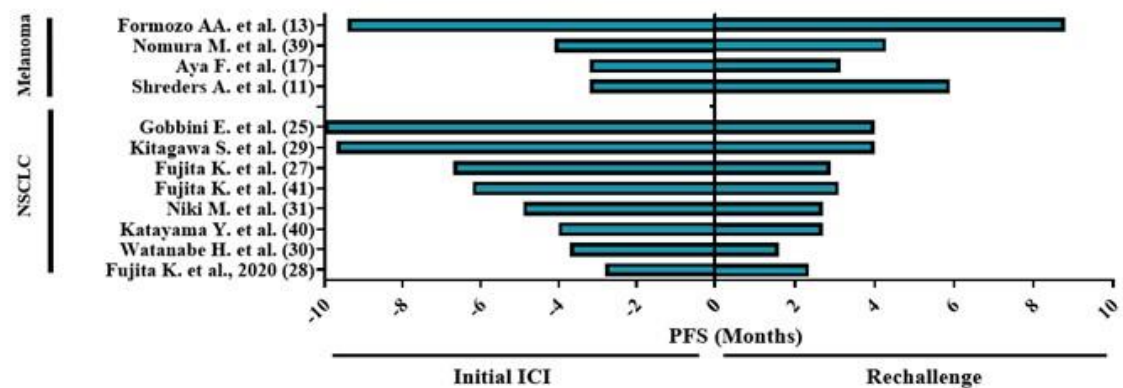
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Figure 1: Efficacy of Immune Checkpoint Rechallenge in cancer

a. Response during the first course of Immune Checkpoint Inhibitors and at rechallenge



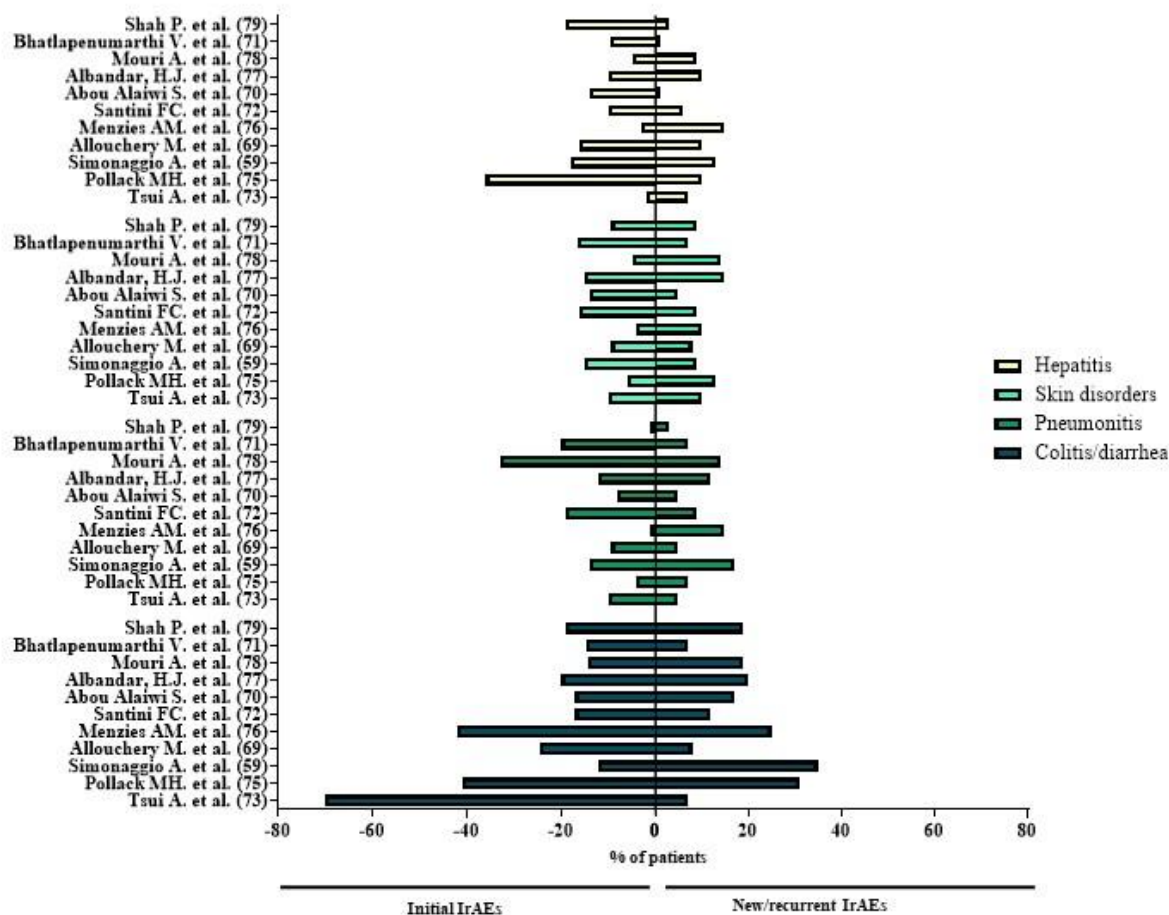
b. Progression Free Survival over the first course of Immune Checkpoint Inhibitors and at rechallenge



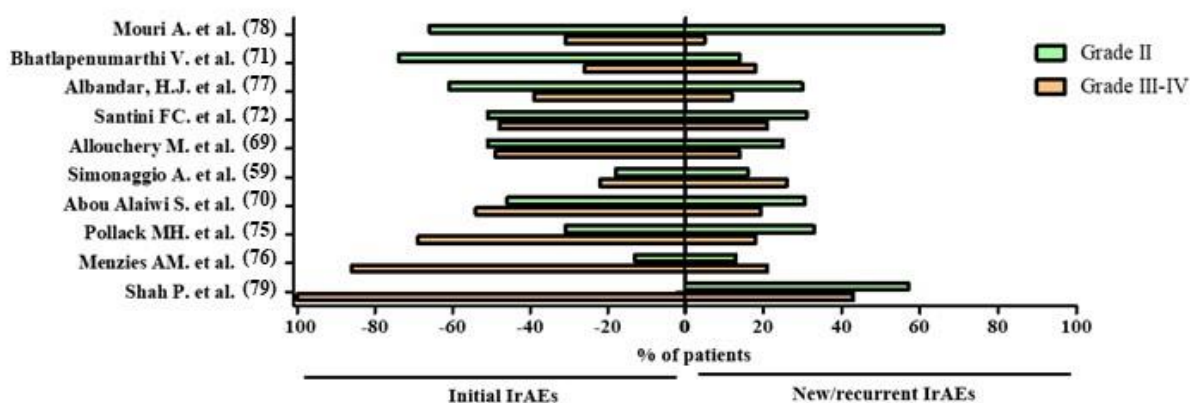
DCR: disease control rate, PD: progression disease, NSCLC: Non-Small-Cell-Lung Cancer, RCC: Renal Cell Carcinoma, HL: Hodgkin Lymphoma.

Figure 2: Type and Grade of irAEs at immune checkpoint inhibitors resumption

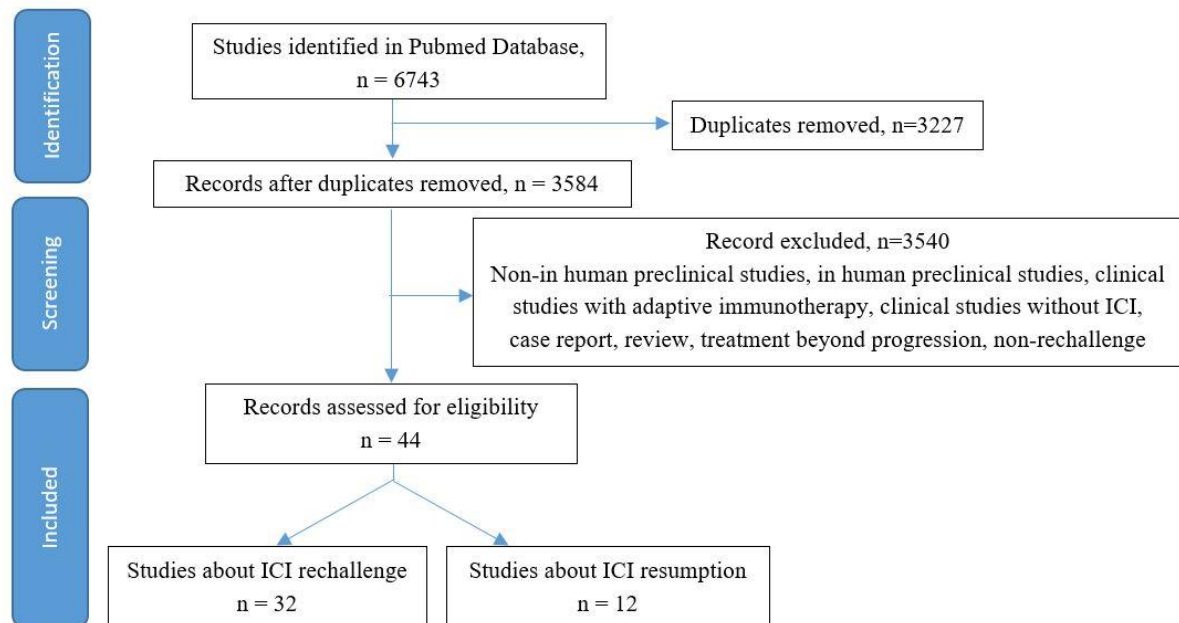
a. Proportion of irAEs during initial immune checkpoint inhibitors and at resumption



b. Grade of irAEs during initial immune checkpoint inhibitors and at resumption



Supplementary Figure 1: PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



Study	Type of study	Histology	Inclusion criteria	ECOG	PDL1	N° of pts	N° of previous lines (median)	Initial ICI type	Median duration of initial ICI (months)	Treatment between ICI (median n° of lines)	Rechallenge ICI type	Median duration of rechallenge (months)
Larkin et al 2018 (38)	Prospective	Melanoma	PD after anti-CTLA4, ECOG 0-1, BRAFi if BRAF mutated, No Grade IV irAES with ipilimumab, No active brain metastasis	0: 60%, 1: 40%	>1%: 49%	272	2	ipilimumab	NA	NA	nivolumab	5,3
Ribas et al. 2015 (9)	Prospective	Melanoma	PD after anti-CTLA4, ECOG 0-1, BRAFi if BRAF mutated, irAEs recovered to ≤ grade 1, No brain metastasis	0: 54%, 1: 44%	NA	361	2	ipilimumab	NA	No	pembrolizumab 2mg/kg or 10mg/kg	3,7-4,8
Chiarion-Sileni et al. 2014 (10)	Prospective	Melanoma	PD after anti-CTLA4, ECOG 0-2, SD under ipilimumab ≥ 3 months or CR/PR under ipilimumab, No irAEs requiring ipilimumab stop	0: 71%, 1: 29%	NA	51	2	ipilimumab	NA	NA	ipilimumab	3
Lebbe et al., 2014 (7)	Prospective	Melanoma	PD after anti-CTLA4, SD under ipilimumab ≥ 3 months or CR/PR under ipilimumab	NA	NA	122	NA	ipilimumab	NA	No	ipilimumab	NA
Robert C. et al., 2019 (8)	Prospective	Melanoma	PD after anti-PD1, at least SD during 24months or CR during 6 months	NA	NA	13	NA	pembrolizumab	NA	NA	pembrolizumab	NA
Shreders et al., 2016 (11)	Retrospective	Melanoma	PD after anti-CTLA4	NA	NA	116	0	ipilimumab	NA	Yes (49%)	pembrolizumab	NA
Warner et al., 2020 (12)	Retrospective	Melanoma	PD after anti-PDL1	NA	NA	78	NA	anti-PD1	NA	No	anti-PD1 +/- ipilimumab	1,6
Formozo et al, 2021 (13)	Retrospective	Melanoma	PD after anti-CTLA4, SD under ipilimumab ≥ 6 months or CR/PR under ipilimumab, irAEs < Grade III under ipilimumab	NA	NA	22	1	ipilimumab	NA	Yes (91%)	ipilimumab	NA
Asher et al., 2021 (14)	Retrospective	Melanoma	ICI discontinuation without PD	0-1: 94%	NA	21	0	anti-PD1 +/- ipilimumab	15,2	No	anti-PD1 +/- ipilimumab	7
Jansen et al., 2019 (15)	Retrospective	Melanoma	ICI discontinuation whitout PD or treatment limiting toxicity	0: 82%, 1: 15%	NA	19	NA	anti-PD1	12	NA	anti-PD1	NA
Klee et al., 2021 (16)	Retrospective	Melanoma	PD after anti-PD1 and rechallenge with anti-PD1 + anti-CTLA4	NA	>1%: 44%	9	NA	anti-PD1+/-anti-CTLA4	5,3	NA	anti-PD1+/-anti-CTLA4	NA

Aya et al., 2016 (17)	Retrospective	Melanoma	PD after anti-PD1 and rechallenge with anti-CTLA4	0-1: 100%	NA	9	0	anti-PD1	NA	Yes (44%)	ipilimumab	3
Kirchberger et al., 2016 (18)	Retrospective	Melanoma	PD after anti-PD1 and anti-CTLA4 (sequentially administered) and rechallenge with anti-PD1 + anti-CTLA4	0:44%, 1:33%	NA	9	3	anti-PD1 and anti-CTLA4 (sequence)	anti-PD1: 5,2 anti-CTLA4: 3	NA	anti-CTLA4 + anti-PD1	NA
Blasig et al., 2017 (19)	Retrospective	Melanoma	PD after anti-PD1 and rechallenge with anti-PD1	NA	NA	8	NA	anti-PD1	5,5	Yes (75%)	pembrolizumab	2,5
Nomura et al., 2017 (39)	Retrospective	Melanoma	PD after nivolumab and rechallenge with nivolumab	0:50%, 1:25%	NA	8	0	nivolumab	4,1	Yes (88%)	nivolumab	4,3
Waterhouse et al., 2020 (22)	Prospective	NSCLC	CR, PR or SD afer 1 year of nivolumab ECOG 0-2	0:36%, 1:62%*	≥50%: 11%* ≥1%: 36% <1%: 13%	39	2	nivolumab	NA	NA	nivolumab	3,8
Herbst et al., 2020 (23)	Prospective	NSCLC	CR, PR or SD after 35 cycles of pembrolizumab PDL1 ≥ 1%	0:34%, 1:66%*	≥50%: 42%*, 1-49%: 58%	14	1	pembrolizumab	NA	No	pembrolizumab	NA
Katayama et al., 2019 (40)	Retrospective	NSCLC	PD after anti-PD1/PDL1 and rechallenge with anti-PD1/PDL1	0-1:65%	≥50%: 40% 1-49%: 22,9% <1%: 20%	35	2	Anti-PD1: 89% Anti-PDL1: 11%	NA	NA	Anti-PD1: 34% Anti-PDL1: 66%	NA
Furuya et al., 2020 (24)	Retrospective	NSCLC	Patients received atezolizumab (subgroup analysis on those previously treated with anti-PD1)	0-1: 71%*	≥50%: 9,2%*, 1-49%: 16,4% <1%: 57,9%	38	2	anti-PD1	NA	NA	atezolizumab	2,2
Gobbini et al., 2020 – (25)	Retrospective	NSCLC	PD after anti-PD1/PDL1 and rechallenge with anti-PD1/PDL1	0-1:81%	≥50%: 40% >1%: 83%	144	2	anti-PD1: 88% anti-PDL1: 12%	NA	Yes (43%)	anti-PD1: 94% anti-PDL1: 6%	5,8
Fujita et al., 2019 (27)	Retrospective	NSCLC	PD after anti-PD1 and rechallenge with atezolizumab	NA	≥50%: 50%, 1-49%: 16,7% <1%: 16,7%	18	1	anti-PD1	4,7-7,5	NA	atezolizumab	2,2
Kitagawa et al. 2020 – (29)	Retrospective	NSCLC	anti-PD1 and anti-PDL1 during disease course	0-1: 82,4%	≥50%: 17,7%, 1-49%: 23,5% <1%: 20,4%	17	2	anti-PD1 88% anti-PDL1 12%	NA	NA	anti-PD1 12% anti-PDL1 88%	NA
Fujita et al., 2020 (28)	Retrospective	NSCLC	PD after anti-PDL1 and rechallenge with anti-PD1	0-1: 87%	≥50%: 0%, 1-49%: 33,3% <1%: 33,3%	15	NA	anti-PDL1	3,7	Yes (33%)	anti-PD1	02-mars
Watanabe et al., 2019 (30)	Retrospective	NSCLC	PD after anti-PD1/PDL1 and rechallenge with anti-PD1/PDL1	0:21%, 1:50%	≥50%: 50%, 1-49%: 7% <1%: 29%	14	2	anti-PD1: 86% anti-PDL1: 14%	3,7	Yes (100%)	anti-PD1	2

Fujita et al., 2018 (41)	Retrospective	NSCLC	PD after nivolumab and rechallenge with pembrolizumab	0-1:84%	≥50%: 50%, 1-49%: 50% <1%: 0%	12	2	nivolumab	6,2	Yes (66,7%)	pembrolizumab	2,6
Niki et al., 2018 (31)	Retrospective	NSCLC	PD after nivolumab and rechallenge with anti-PD1	0:55%, 1:45%	NA	11	4	nivolumab	NA	Yes (91%)	anti-PD1	NA
Ravi et al., 2020 (32)	Retrospective	RCC	ICI rechallenge during the disease course	NA	NA	69	NA	anti-PD1/PD1/CTLA4 alone or combined with other agents	NA	NA	anti-PD1/PD1/CTLA4 alone or combined with other agents	NA
Gul et al., 2020 (33)	Retrospective	RCC	PD after anti-PD1/PDL1 and rechallenge with nivolumab + ipilimumab	0:33%, 1:53%	NA	45	3	anti-PD1/PDL1	13	NA	nivolumab + ipilimumab	NA
Chen et al., 2019 (34)	Prospective	Hodgkin Lymphoma	Refractory Hodgkin Lymphoma (subgroup analysis on patients experiencing PD after pembrolizumab and rechallenge with pembrolizumab)	NA	NA	10	4	pembrolizumab	NA	No	pembrolizumab	NA
Fedorova et al., 2021 (35)	Retrospective	Hodgkin Lymphoma	PD after CR under nivolumab	0-1:43%	NA	11	NA	nivolumab	NA	No	nivolumab	NA
Sheth et al., 2020 (36)	Prospective	Cross tumor	durvalumab discontinuation without PD	0:47%, 1:52,9%	high: 62,9% low: 31,4%	70	3	durvalumab	NA	NA	durvalumab	NA
Bernard Tessier et al. 2018 (37)	Prospective	Cross tumor	anti-PD1/PDL1 discontinuation without PD then rechallenge with anti-PD1/PDL1	NA	NA	8	2	anti-PD1/PDL1	12	No	anti-PD1/PDL1	NA

Supplementary Table 1: Studies about Immune Checkpoint Inhibitors rechallenge

NSCLC: Non-Small-Cell-Lung Cancer, RCC: Renal Cell Carcinoma, irAEs: immune-related adverse events, PD: progression disease, CR: complete response, PR: partial response, SD: stable disease, ICI: immune checkpoint inhibitors, NA: Not available

*Percentages calculated on the entire study population.

Study	Type of study	Type of tumor / IrAEs	Inclusion criteria	Nb of patients	Initial ICI	Median duration first ICI (months)	irAEs during initial ICI grade %	Systemic steroid use%	Time to irAEs onset (months)	Median duration of TFT (weeks)	Nb of patients resuming ICI	Resumed ICI
Simonaggio et al, 2019 (59)	Retro-spective	Cross-tumor	Grade ≥ 2 irAES	93	anti-PD1/PDL1	2,5	G2: 46% G3: 39% G4:15%	53%	2,75	3,8	40	anti-PD1/PDL1
Allouchery et al., 2020 (69)	Retro-spective	Cross-tumor	Grade ≥ 2 irAES and discontinuation ≥ 2 cycles	180	anti-PD1/PDL1 +/- anti-CTLA4	2,5	G2: 51% G3-4: 49%	54%	2,1	8	180	anti-PD1/PDL1 +/- anti-CTLA4
Tsui et al., 2021 (73)	Retro-spective	Cross-tumor	irAEs treated with corticosteroids	81	anti-PD1/PDL1 +/- anti-CTLA4	NA	Na	100%	NA	8,7	54	anti-PD1/PDL1 +/- anti-CTLA4
Albandar, et al., 2021 (77)	Retro-spective	Cross-tumor	irAEs ≥ 1	133	anti-PD1/PDL1 +/- anti-CTLA4	10	G2: 61% G3-4: 39%	25%	NA	4	98	anti-PD1/PDL1 +/- anti-CTLA4
Kartolo et al 2021 (74)	Retro-spective	Cross-tumor	irAEs ≥ 2	40	anti-CTLA4 anti-PD1 anti-PD1 + anti-CTLA4	NA	G2: 75% G3-4: 25%	44%	2,1	NA	40	anti-CTLA4 anti-PD1 anti-PD1 + anti-CTLA4
Bhatlape-numarthi et al., 2021 (71)	Retro-spective	Cross-tumor	anti-PD1/PDL1 treated patients	465	anti-PD1/PDL1	NA	NA	NA	NA	NA	27	anti-PD1/PDL1
Menzies et al., 2016 (76)	Retro-spective	Melanoma	anti-PD1/PDL1 treated patients, irAEs ≥ 2 with ipilimumab	67	ipilimumab	NA	G2: 13% G3: 76% G4: 10%	NA	NA	NA	67	anti-PD1
Pollack et al., 2018 (75)	Retro-spective	Melanoma	Discontinuation of ICI due to irAEs	80	anti-PD1 + anti-CTLA4	0,5	G2: 31% G3: 61% G4:8%	96%	NA	5	80	anti-PD1
Shah et al., 2021 (79)	Retro-spective	Melanoma	irAEs ≥ 3 and retreatment	32	Anti-PD1 Anti-CTLA4 Anti-PD1 + anti-CTLA4	NA	G3: 75% G4: 25%	97%	1,5	10	32	anti-PD1 anti-CTLA4 anti-PD1 + anti-CTLA4
Santini et al, 2018 (72)	Retro-spective	NSCLC	Discontinuation of ICI due to irAEs	68	anti-PD1/PDL1 +/- anti-CTLA4	2,8	G1-2: 66% G3-4: 34%	76%	2,3	4,6	38	anti-PD1/PDL1 +/- anti-CTLA4
Mouri et al. 2019 (78)	Retro-spective	NSCLC	Discontinuation of nivolumab due to irAEs	49	nivolumab	NA	G1-2: 66% G3-4: 33%	71%	NA	4	21	nivolumab
Alaiwi et al., 2020 (70)	Retro-spective	RCC	Discontinuation of ICI due to irAEs	80	anti-PD1/PDL1	NA	G1-2: 52,8% G3-4: 47,2%	55,60%	2,8	3,6	36	anti-PD1/PDL1

Supplementary Table 2: Studies about retreatment after irAEs in patient treating by ICI.

NSCLC: Non-Small-Cell-Lung Cancer, RCC: Renal Cell Carcinoma, irAEs: immune-related adverse events, PD: progression disease, CR: complete response, PR: partial response, SD: stable disease, ICI: immune checkpoint inhibitors, NA: Not available.

Appendix 1: Search methods for systematic review on Pubmed database

The extraction of all the publications was performed on Pubmed, using the following terms: « rechallenge », « retreatment », « re-administration », « reintroduction », « resumption », « discontinuation » followed by « immunotherapy », « immune checkpoint inhibitor », « nivolumab », « pembrolizumab », « ipilimumab », « atezolizumab », « durvalumab », « avelumab », « tremelimumab ».

Graphical abstract: (create by Biorender)

