Critical Reviews in Oncology / Hematology 144 (2019) 102816

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Current opinions in immune checkpoint inhibitors rechallenge in solid cancers

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ARTICLE INFO

Keywords:
Immune checkpoint inhibitors
Rechallenge
Efficacy
Safety

ABSTRACT

Immune checkpoint inhibitors (ICI) completely upset the therapeutic algorithm of several type of solid cancer conferring in some patients a long clinical benefit with an acceptable toxicity. ICI rechallenge is an attractive option being a palliative chemotherapy the only alternative treatment in most of cases. Despite this strategy recently entered into the clinical practice, no widely recognized recommendation is currently available to select the good candidates. Anti-Cytotoxic T Lymphocyte Antigen 4 (Anti-CTLA4) rechallenge and a sequential administration of anti-CTLA4 and anti-Programmed cell Death protein 1 (anti-PD1) or Anti-Programmed Death Ligand 1 (anti-PDL1) agents have been explored in melanoma patients in several clinical trials while the anti-PD1/anti-PDL1 rechallenge has been little investigated. Here we performed a literature revision about efficacy and tolerability of ICI rechallenge across solid tumors also focusing on inclusion criteria used into clinical trials.

1. Introduction

In the last decade, immune checkpoint inhibitors (ICI) have completely changed the treatment strategy of several solid cancer types. Though the more dramatic results have been achieved in melanoma and non-small-cell lung cancer (NSCLC), six ICIs (pembrolizumab, nivolumab, ipilimumab, durvalumab, atezolizumab and avelumab) have been approved for the treatment of melanoma, NSCLC, renal cell carcinoma, urothelial carcinoma, head and neck carcinoma and merkel carcinoma. Anti-Programmed cell Death protein 1 (anti-PD1) and Anti-Programmed Death Ligand 1 (anti-PDL1) inhibitors alone or combined with the anti-Cytotoxic T Lymphocyte Antigen 4 (anti-CTLA4) agent showed impressive survival results in advanced cancer patients. In the Keynote 024, the median overall survival (OS) for advanced PDL1 highly expressing (≥ 50%) NSCLC was 30.0 months (95% CI, 18.3 months - not reached) for those patients treated with pembrolizumab in first line (Reck et al., 2016). Recently, five-years follow-up results of Keynote 001, showed a median OS of 22.3 months (95% CI, 17.1–32.3 months) in treatment-naive NSCLC patients receiving pembrolizumab regardless of their PD-L1 score (Garon et al., 2019). Likewise, in the CheckMate 067, the median OS for advanced melanoma patients treated with nivolumab in first line was 36.9 months (95% CI, 28.3 months – not reached) while it was not reached yet for those receiving nivolumab combined with ipilimumab (Larkin et al., 2015). Patients may have to discontinue ICI due to progression disease or toxicities of course, but also because of trial designs imposing discontinuation after a given treatment period. Considering the long-term benefit provide by ICI, the treatment sequence strategy, seems a crucial issue. Mainly for those patients achieving a longer response to ICI without clinically meaningful toxicities, the rechallenge with the same or another ICI can be an attractive option. However, the potential toxicities rebound and/or new side effects onset at ICI rechallenge discourage most of physicians in joining this strategy. Despite no widely recognized recommendation is available, the National Comprehensive Cancer Network (NCCN) guidelines allows to consider the ICI re-induction in progressing patients that showed an initial response or disease stabilization lasting ≥ 3 months. However, caution is recommended when considering the resumption of immunotherapy after significant immune-related adverse events (irAEs). In this case, tumor assessment before rechallenging is suggested and, if objective response is detected, immunotherapy retreatment is not considered advisable due to risk of toxicity recurrence. In general, ICI resumption following grade II irAEs can be considered only upon resolution of toxicities to ≤ grade I (NCCN Guidelines Management of Immunotherapy-Related Toxicities, 2019). Few clinical trials investigated this issue and three strategies have been explored: retreating patients with the same agent (anti-PD1/PDL1 or

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https://doi.org/10.1016/j.critrevonc.2019.102816
Received 14 July 2019; Received in revised form 28 August 2019; Accepted 25 September 2019

Table 1
Clinical trials exploring the efficacy of immune checkpoint inhibitor rechallenge in solid tumors.

Strategy	Study	Phase	Rechallenge sample size	Cancer type	First ICI	Main Inclusion criteria	Study treatment	Grade 3-4 AEs	Endpoint	Results
Anti-PD1/PDL1 ↔ Anti-CTLA4	Keynote 002	II	361	Advanced melanoma	Ipilimumab	• ECOG PS 0-1 • PD < 24 weeks after ipilimumab • Resolution (≤ grade I) of Ipilimumab-related AEs • BRAF inhibitor received if BRAF mutant	Pembrolizumab 2mg/kg[a] and 10 mg/kg[b] versus CT	13%[a] 16%[b] vs 26%	PFS 2-year rate and OS	PFS 2y rate: 16% (HR 0.58 p< .0001)[a] 22% (HR 0.47 p< .0001)[b] vs 0.6% OS: 13.4 mo (HR 0.86 p = .1173)[a] 14.7 mo (HR 0.74 p = .0106)[b] vs 11 months (α = 0.01)
	Checkmate 037	III	272	Advanced melanoma	Ipilimumab	• ECOG PS 0-1 • PD after ipilimumab • BRAF inhibitor received if BRAF mutant • No brain metastasis • (64% had no ipilimumab benefit)	Nivolumab versus CT	14% vs 34%	ORR and OS	ORR: 27% vs 10% OS: 15.7 vs 14.4 months HR 0.95 p = .716
	Shrederes et al.	Retrospective	116	Advanced melanoma	Ipilimumab	• Ipilimumab pretreated	Pembrolizumab	NA	PFS (ipilimumab PFS ≥ 180 days vs < 45 days)	249 vs 50 Days
Anti-CTLA4 rechallenge	MDX 010-20	III	31	Advanced melanoma	Ipilimumab +/- gp100 or gp100 alone	• ECOG PS 0-1 • CR, PR with the first immunotherapy • SD ≥ 3 months with the first immunotherapy • No Grade ≥ III irAE	Ipilimumab + gp100[c] or ipilimumab[d] or gp100 alone[e]	9.9%[c] 22%[d] 0%[e] (irAEs)	DCR	65.2%[c] 75%[d] 0%[e]
	CA184-025	II	122	Advanced melanoma	Ipilimumab	• CR, PR with ipilimumab • SD ≥ 3 months with ipilimumab	Ipilimumab	29.4% to 41.7%	DCR	48.4%
	Chiarioni-Sileni et al	IV	51	Advanced melanoma	Ipilimumab	• ECOG PS 0-1 • CR, PR with ipilimumab • SD ≥ 3 months with ipilimumab • No Grade ≥ III irAE	Ipilimumab	6%	irDCR and OS	irDCR: 55% OS: 21 months
Anti-PD1/PDL1 rechallenge	Checkmate 153	II	34	Advanced NSCLC	Nivolumab	• ECOG 0-2 • CR, PR or SD after 1 year of nivolumab	Nivolumab	NA	mDuration of retreatment	3.8 months
	Keynote 010	II/III	14	Advanced NSCLC	Pembrolizumab	• PDL1 > 1% • CR, PR or SD after 35 cycles of pembrolizumab	Pembrolizumab	NA	DCR	79%

PD: Progression disease; CR: complete response; PR: partial response; SD: stable disease; CT: Chemotherapy; PFS: progression free survival; NSCLC: Non-Small-Cell Lung Cancer; Grade 3–4 AEs: adverse events of grade 3–4 over rechellange; NA: data not available.

anti-CTLA4 rechallenge) or a sequential administration of anti-CTLA4 and anti-PD1/PDL1 drugs (Table 1). Each of these strategies is detailed below.

2. Anti-CTLA4 followed by anti-PD1/PDL1 or vice versa in melanoma

Although anti-CTLA4 and anti-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 (Pardoll, 2012). Consequently, it is not surprising that for advanced melanoma patients who progressed over ipilimumab, a subsequent anti-PD1 therapy represents a recommended option, and vice versa (NCCN Guidelines Cutaneous melanoma, 2019). Several trials actually showed an interesting clinical benefit by this strategy (Hamid et al., 2016; Larkin et al., 2018; Shreders et al., 2016; Weber et al., 2016; Ribas et al., 2015). In the phase II Keynote-002 trial, ipilimumab-refractory melanoma patients were randomized to receive two different schedules of pembrolizumab or chemotherapy (investigator choice). Notably, 55% of chemotherapy-treated patients crossed-over after disease progression. Pembrolizumab provided higher response rate (22% for pembrolizumab 2 mg/kg, 28% for pembrolizumab 10 mg/kg versus 4% for chemotherapy, $p < 1.10^{-4}$ for both pembrolizumab doses versus chemotherapy) and a longer progression free survival (PFS) (hazard ratio (HR) 0.58, $p < 1.10^{-4}$ for pembrolizumab 2 mg/kg and HR 0.47, $p < 1.10^{-4}$ for pembrolizumab 10 mg/kg compared with chemotherapy) without clear benefit in OS (13.4 months HR 0.86, $p = 1.10^{-1}$ for pembrolizumab 2 mg/kg and 14.7 months HR 0.74, $p = 1.10^{-2}$ for pembrolizumab 10 mg/kg versus 11.0 months for chemotherapy). However, pembrolizumab showed pretty lower treatment-related severe Adverse Events (AEs) compared to chemotherapy (grade III and IV AEs in 13%, 16% and 26% of patients receiving pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg and chemotherapy respectively) (Hamid et al., 2016; Ribas et al., 2015). Similarly, in the CheckMate 037 comparing nivolumab versus chemotherapy in ipilimumab-pretreated patients, despite a higher overall response rate (ORR) and median duration of response (DOR) in patients receiving nivolumab (ORR 27% versus 10% in chemotherapy arm and median DOR 31.9 versus 12.8 months in chemotherapy arm) no difference in OS could be detected (15.7 versus 14.4 months in the chemotherapy arm, $p = 7.10^{-1}$). Notably, 41% of patients included in the chemotherapy arm received an anti-PD1 as following treatment, while only 11% of nivolumab-treated ones benefited from a chemotherapy agent after progression. As expected, nivolumab-treated patients presented lower severe treatment-related AEs compared with chemotherapy (14% versus 34%) (Larkin et al., 2018). These data clearly suggested that ipilimumab-resistant patients derive a clinically significant benefit from anti-PD1 treatments with a good toxicity profile. But which is the better patient to candidate to this sequential strategy? Shreders et al, retrospectively analyzed outcomes of patients sequentially receiving ipilimumab and pembrolizumab pointing out a correlation between the PFS achieved under ipilimumab and pembrolizumab outcomes independently from the most common poor prognostic factors. Patients with a PFS ≥ 90 days with ipilimumab, showed higher clinical benefit rate (66% versus 46% for those with PFS < 90 days, $p = 3.10^{-2}$). Notably, patients achieving longer benefit from ipilimumab (PFS ≥ 180 days), presented also a longer PFS over pembrolizumab compared with rapidly progressing patients having a median PFS < 45 days (249 versus 50 days, $p = 1.10^{-2}$) (Shreders et al., 2016). Then, the PFS

achieved during the first ICI seems to be the only useful criteria for patient's selection in the sequential strategy.

Currently, either pembrolizumab and nivolumab, can be prescribed as upfront treatment in melanoma patients (BRAF wild type and BRAF mutated with indolent disease) according to results of large phase III trials comparing them to ipilimumab in patient immune checkpoint inhibitors naïve (Larkin et al., 2015; Robert et al., 2015a, b). Can we suppose to keep the same benefit changing the treatment sequence order? No large trial evaluating the efficacy of ipilimumab in anti-PD1-resistant patients actually exist. However, the CheckMate 064, comparing a preplanned schedule of ipilimumab followed by nivolumab with the other way around sequence in patients without disease progression at switching time, showed similar grade III to V treatment-related AEs across the two sequence strategies (50% for nivolumab followed by ipilimumab and 43% for ipilimumab followed by nivolumab) (Weber et al., 2016). These data suggest that both of ICI sequences are safe and can be exploited in advanced melanoma patients.

3. Anti-CTLA4 rechallenge in melanoma

Anti-CTLA4 rechallenge has been more explored being ipilimumab-based clinical trials designed with only 4 cycles of induction treatment. Available data suggest that retreatment with ipilimumab upon disease progression may be a valid approach to overcome immune tolerance among eligible patients. Robert et al. firstly reported outcomes of advanced melanoma patients performing ipilimumab +/- gp100 (a synthetic peptide cancer vaccine) or gp100 alone within the phase II MDX010-20 trial that were subsequently retreated with the same protocol at progression time. Only patients achieving an objective disease control (complete response, partial response or stable disease) lasting ≥ 3 months with the assigned treatment without grade III or IV AEs were considered. Most of the 40 patients included were retreated with a combination of ipilimumab and gp100 and the median time between the first treatment and the first retreatment dose ranged from 8.9 to 11.5 months according to the different groups. The disease control rate (DCR) achieved by the rechallenge ranged from 65.2% to 75% according to different regimens and no correlation with the best response over the first immunotherapy course was shown. The frequencies of AEs observed during rechallenge were similar to those observed during the first ICI course, with no new toxicities, and most events mild-to-moderate (grade III-IV AEs ranged from 6.9% to 22%). To note, 61.3% of retreated patients survived more than 2 years from their initial randomization (Robert et al., 2013). Likewise, in the phase II CA184-025, data about advanced melanoma patients treated with different schedules of ipilimumab in six phase II trials were collected. Patients were then candidate to ipilimumab rechallenge in case of disease progression, ipilimumab extended maintenance if objective response lasting ≥ 3months achieved or surveillance. The 122 rechallenged patients showed an DCR of 48.4% with a best overall response (complete response and partial response) of 23%. Grade III-IV AEs were comparable with AEs reported by Robert et al ranging from 5.9% to 13.2% (Lebbé et al., 2014). Moreover, some real-life data are also available from the ipilimumab Italian Expanded Access Program (EAP) by Chiarion-Sileni et al. Advanced melanoma patients who achieved disease control during ipilimumab induction were retreated with ipilimumab 3 mg/kg upon progression within the EAP providing they had not experienced toxicity that precluded further dosing. Fifty-five percent patients regained disease control upon retreatment with a median OS of 21 months from the beginning of the induction therapy and 12 months from the rechallenge. In line with other reports the frequency of AEs observed during the rechallenge was similar to those observed with the induction (10% of patients presented grade III-IV AEs) and no new type of toxicity were reported (Chiarion-Sileni et al., 2014). According to these data, ipilimumab rechallenge can be effective in melanoma patients achieving a clinical benefit during the first course of ipilimumab. The good safety profile leads to the application of this strategy in the current clinical practice being the chemotherapy the only possible alternative in these frail patients. However, reported patients' survivals in these trials, clearly pointed out we are talking about selected patients probably mounting a more efficient anti-tumor immune response and achieving a more significant benefit from this strategy.

4. Anti-PD1 and anti-PDL1 rechallenge in NSCLC

Less is known about efficacy and safety of rechallenge with anti-PD1 and anti-PDL1 agents. To our knowledge, only two prospective clinical trials investigated this issue until now. The CheckMate 153 explored the clinical benefit of a fixed-duration (1 year) of nivolumab in second-line versus continuous treatment in patient with previously treated advanced NSCLC. Preliminary results showed a better PFS (HR 0.43, 95% confidence interval (CI) 0.25–0.76) and OS (HR 0.63, 95% CI 0.33–1.20) for patients receiving nivolumab continuously compared with those stopping after one-year treatment even if the study was not powered for outcome comparisons. Interestingly, in the nivolumab fixed-duration arm, 39 patients progressed during the surveillance period and were retreated with the same anti-PD1. The median time between progression and nivolumab reinduction was 0.6 months and the median duration of retreatment was 3.8 months. Unfortunately, no data are available yet about outcomes upon the second course of nivolumab Spiegel et al., 2017. The other prospective phase II/III trial was the Keynote-010, enrolling PD-L1 positive pretreated advanced NSCLC patients to receive pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg or docetaxel. Pembrolizumab provided a longer OS compared with docetaxel (HR 0.69; 95% CI, 0.60–0.80; $p < 1.10^{-5}$) and interestingly 11% of patients completed the 2-years treatment planned without progressing. Fourteen of these patients received a second course of pembrolizumab and the majority of them (78%) showed either partial response or stable disease according to preliminary results of a post-hoc analysis (Herbst et al., 2016, 2018). These results suggest that NSCLC patients may potentially benefit from an anti-PD1 retreatment but poor information are currently available about toxicities. Two large studies investigating safety of resuming anti-PD1 agents have been recently published. The first one was conducted on 80 advanced melanoma patients presenting irAEs during combined anti-CTLA4 and anti-PD1 treatment. Only 50% of patients experienced an irAEs (any grade) at anti-PD1 resumption and 18% presented a grade III–IV toxicity. The same irAE causing combination therapy discontinuation recurred in 18% of patients with a median time after resumption of 14 days, while 21% of patients experienced a different irAE during the retreatment. Hepatitis, pancreatitis, pneumonitis and nephritis were shown to recur more often compared to other toxicities. The duration of steroid treatment, the additional immunosuppressive agents administration and the grade of toxicities during the induction phase did not seem to predict an higher toxicity profile at reinduction time. Conversely, patients that experienced toxicities showed a shorter therapy-off period between the two ICI courses and they were more likely to remain on steroids at resumption time because symptoms were not solved (Pollack et al., 2018). The second study exploring the safety of anti-PD1 or anti-PDL1 retreatment was conducted on 40 patients receiving the first course of these drugs for melanoma, lymphoma, lung or colorectal cancer treatment. They all discontinued the ICI because of toxicity but only 55% of them experienced a grade 2 or higher irAE once rechallenged with the same molecule. The second irAEs were not found to be more severe than the first suggesting the risk-reward ratio for this strategy to be acceptable (Simonaggio et al., 2019).

According to these data anti-PD1 rechallenge seems to be safe even in those patients experienced toxicities causing ICI discontinuation but a careful verification of symptoms recovery is obviously required before retreatment starting.

Despite these encouraging data, anti-PD1 and anti-PDL1 rechallange is still debated because of lack of prospective studies specifically addressing this question. Moreover, poor data are available in literature

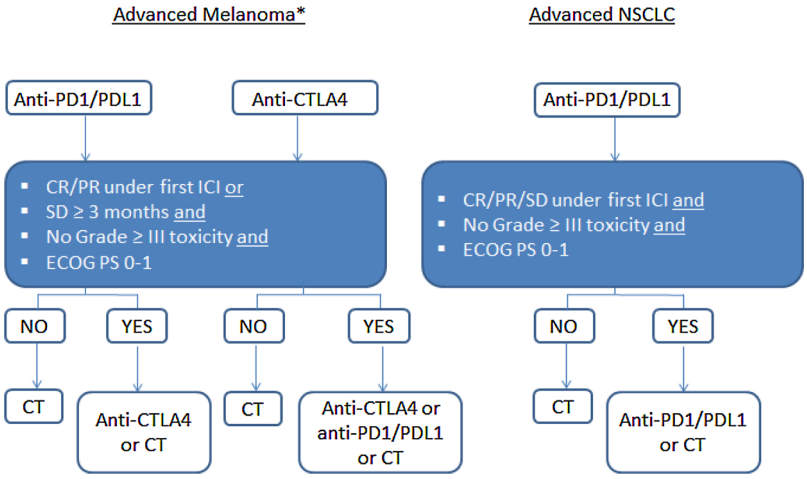

Fig. 1. Flow-chart proposition for ICI rechallenge in Melanoma and NSCLC patients.
*BRAF wild type or BRAF mutated with indolent disease progressing under BRAF inhibitor.
CR: Complete response; PR: partial response; SD : Stable disease; ICI: Immune checkpoint inhibitor; CT: Chemotherapy.

Table 2
Ongoing and not yet recruiting clinical trial investigating anti-PD1 or anti-PDL1 rechallenge strategy.

NCT number	Phase	Histology	Previous ICP	Rechallenge	Sample size	Primary EP	Status
NCT03526887	II	NSCLC	anti-PD1	pembrolizumab	110	ORR	recruiting
NCT03847649	II	Solid tumors	durvalumab	durvalumab	60	safety	not yet recruiting
NCT02743819	II	melanoma	anti-PD1 or anti-PDL1	pembrolizumab + ipilimumab	70	ORR	recruiting
NCT03262779	II	NSCLC	anti-PD1 or anti-PDL1	ipilimumab + nivolumab	50	ORR	recruiting
NCT03041181	II	NSCLC	anti-PD1 or anti-PDL1	CT +/- nivolumab	62	PFS	recruiting
NCT03334617	II	NSCLC	anti-PD1 or anti-PDL1	durvalumab versus oncogene-drived therapy	260	ORR	recruiting
NCT03469960	III	NSCLC	Ipilimumab + nivolumab	Ipilimumab +nivolumab	463	PFS	recruiting

about retrospective studies investigating factors associated to responses with anti-PD1 and anti-PDL1 retreatment. Consequently, clear clinical criteria to use in patient's selection can't be deduced.

5. Conclusions

Solid cancers can achieve a durable clinical benefit from immune checkpoint inhibitors thanks to

the effector memory T cells differentiation leading to a long-term immunological response being able to respond to tumor-antigens re-exposition (Ribas et al., 2016; Harty, 2008; Farber et al., 2014). However, patients eventually relapse because of acquired resistance mechanisms and several studies tried to infer the reasons leading to immune escape. Understanding the molecular basis behind ICI tumor resistance would be really useful to find novel strategies to optimize its efficacy and extend the therapeutic benefit to a wider cohort of cancer patients. Several non-classical immune targets are currently under evaluation with the aim to extent ICI benefit by novel combinatory strategies. Notably, the concomitant activation of multiple T cells co-stimulatory pathways (such as ICOS, CD40, OX40 and TLRs) or the shutdown of negative feedback circuits reducing the classical ICI response (by the inhibition of targets such as VISTA, CDK12, EZH2, and CD47), might overcame ICI resistances also improving the proportion of responder patients (Omar and Tolba, 2019). However, we should consider that treatment pressure can simply induce a tumor-associated neo-antigens repertoire switching, making it no more recognized by the existing memory T cells and leading to the tumor immune escape (Héninger et al., 2015; Anagnostou et al., 2017). In this case, a re-treatment with the ICI previously used may be sufficient to re-boost the expansion of T cells clones against the new neo-antigens repertoire, restoring responses. Moreover, the long-term ICI treatment can induce a tumor immune tolerance through immune suppressive cells (e.g. myeloid-derived suppressive cells and Treg), cytokines and metabolites recruitment (Highfill et al., 2014; Ngiow et al., 2015; Sharma et al., 2017; Pitt et al., 2016; O'Donnell et al., 2017). Following completion of ICI course, the balance between effector cells and tolerogenic micro-environment can be reset, potentially restoring the ICI sensibility. Immune checkpoint inhibitor rechallenge seems then an interesting approach already successfully used in advance melanoma patients. However, whereas the anti-CTLA4 rechallenge and the sequential administration of anti-CTLA4 and antiPD1/anti-PDL1 have been already explored in several clinical trials (Hamid et al., 2016; Larkin et al., 2018; Ribas et al., 2015; Robert et al., 2013; Lebbé et al., 2014; Chiarion-Sileni et al., 2014) poor data are available about efficacy and safety of anti-PD1 or anti-PDL1 retreatment.

Which patient should be candidate to this strategy remains the main issue to investigate. According to clinical trials detailed above, advanced melanoma patients (BRAF wild type of BRAF mutated with an indolent disease progressing over a BRAF inhibitor) achieving an objective response over the first ICI or a disease stabilization lasting ≥ 3 months without experiencing grade III or IV AEs, could be considered for the rechallenge with anti-CTLA4 or a sequential treatment with another immune checkpoint inhibitor (Fig. 1). Likewise, advanced NSCLC may be considered for anti-PD1/PDL1 rechallenge in case of objective response over the first ICI or a disease stabilization without experiencing grade III or IV AEs (Fig. 1). However, available literature data are not sufficient to give out clear recommendations about this strategy and more prospective trial are needed.

Several phase II clinical trials are currently exploring safety and efficacy of anti-PD1/anti-PDL1 rechallenge across different tumor types (even if mostly focused on NSCLC and melanoma) being really heterogeneous in term of inclusion criteria (Table 2). For instance, they may actually include all ICI progressing patients or just those achieving a long-term objective response (with different delay considered). These

latter represent a selected population possibly showing a more favorable prognosis and a more indolent disease. This selection bias should be considered interpreting the efficacy results of these studies. We thus cannot exclude the possibility that the rechallenge in this population did not specifically change their disease history, which would have been favorable even with another class of treatment. However, in the clinical practice, it seems reasonable not to propose this strategy to rapidly progressing patients or to those experiencing severe adverse events during the first ICI course. Moreover, some ongoing trials allow chemotherapy or target agents administration between the two ICI rounds whereas in some others ICI have to be the last treatment received before enrollment. Nowadays, one cannot know if systemic treatments performed between the two ICI courses may impact on rechallenge efficacy even if some evidences suggest a synergistic activity of chemotherapy and ICI agents sequentially administered (Dwary et al., 2017). In general, clinical trials about treatment sequences can be extremely challenging, due to treatment heterogeneity in current clinical practice, mostly in advanced pretreated patients. Moreover, a sequence can be studied only in patients who receive more than one line of therapy sensibly reducing the potential accrual. Finally, the primary endpoint choice can be tricky being the overall survival affected by each treatment received before the strategy under investigation. Intermediate endpoints may be considered but, even if some new endpoints such as the Durable Response Rate (DDR) or the Intermediate Response Endpoint (IME) were shown to be moderately to highly associated with OS, there is no sufficient data to support a validate surrogate endpoint in ICI-treated patients. Then, composite endpoints taking into account a duration component are encouraged (Branchoux et al., 2019). Waiting for randomized clinical trials results some retrospective real-life cohorts (mainly including NSCLC patients) are currently under evaluation. They will certainly better define the clinical benefit of this interesting strategy also helping in patients' selection and being certainly useful in future clinical trials design.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector

Declaration of Competing Interest

Authors have no conflict of interest to declare concerning the present paper

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