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# Mechanistic Classification of Immune Checkpoint Inhibitor Toxicity as a Pointer to minimal treatment Strategies of Selected Emergent Autoimmune Disease to further improve Survival.

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**Abstract**

Improved anti-tumour responses under immune checkpoint inhibition (ICI) are associated with concomitant autoimmune disease development termed immune related adverse events (irAEs), of which approximately 5% are rheumatic in nature. Generally, oncologists and other specialists vigorously treat irAEs in spite of the generally accepted beneficial effect of irAEs on tumour survival. Herein, we highlight mechanistic insights on how tumour responses and certain types of autoimmunity appear to be inextricably linked around CD8+ T-cell mediated responses and that strategies that interfere with such shared immunopathgenesis could impact of survival. We discuss the possible circumstances in which intensive immunosuppressive therapy for irAEs that occur with ICIs might blunt anti-tumour immunity. We also discuss potential therapeutic strategies for emergent ICI related autoimmunity and propose some treatment considerations and research questions to minimize the impact of overzealous immunosuppression strategies on tumour responses. Refraining from using powerful therapeutic armamentarium to treat irAEs, especially when these are not considered as life-threating might improve the prognosis of ICI therapy.

## Introduction

The battlefield in oncology has entered an exciting new era with the employment of immune checkpoint inhibitors (ICIs) for cancer therapy (1). The first generation of ICIs has targeted the CTLA-4 and PD-1/PD-LI pathways that remove inhibitory signals and thus stimulate adaptive immune responses (2). Not unexpectedly, ICI therapy has been linked to the development of autoimmune disease (3), which was evident in the early experimental model systems (4). In these animal models, autoimmunity was associated with better anti-tumour response but the emergent autoimmunity was not treated so an opportunity to flag potentially detrimental effects was missed (5-7).

There is an increasing recognition that systemic immune related adverse events (irAEs) are actually associated with better anti-tumour responses in man (8, 9). Recently, this has been confirmed in the rheumatological arena where polyarthritis mimicking rheumatoid arthritis (RA), polymyalgia rheumatic (PMR) and psoriatic arthritis (PsA) were collectively associated with better tumour responses and, in some other studies, a better overall survival (10, 11). The pre-eminent position of rheumatologists in the translational arena of monoclonal antibody therapy and the central role of rheumatology in the unravelling the understanding of autoimmune mechanisms place this speciality at the vanguard of deciphering potentially key future direction for ICIs triggered autoimmune disease, its cellular and molecular classification (12, 13) and optimal therapy.

In this perspective we address the key consideration that over-zealous therapy, in some circumstances, for emergent irAEs may actually detrimentally impact on patient survival. Both ICI anti-tumour efficacy and toxicities are generally adaptive immune driven which contrasts with chimeric antigen receptor T-cell (CAR) therapy where anti-tumour efficacy is adaptive immune driven but the associated immune reactions are “autoinflammatory” in nature or

mediated by innate immune mechanisms and where therapy that includes cytokine targeting does not impact on anti-cancer therapy efficacy (14) (Figure 1). We also discuss when refraining from using powerful therapeutic armamentariums to treat irAEs emergent autoimmunity in cancer patients undergoing ICIs therapy and in some settings embark on what can be considered "controlled fire burning"- at least to some degree, for a defined period, with the hope of improving cancer responses and ultimately to increase survival. This is especially relevant in the rheumatic diseases irAEs that commonly manifest as a PMR or seronegative polyarthropathy-although incapacitating diseases, unlike the cancer under therapy, these do not pose an immediate existential threat (12). The conceptual framework and emerging evidence for refraining from vigorously and aggressively treating all ICIs related autoimmunity and why such strategies should be a key part of the research agenda, are briefly set out below. We also highlight the need to define if a window of opportunity for unrestrained tumour killing exists before immunosuppression can be safely introduced.

**Anti-tumour immunity and autoimmunity**

A growing body of literature shows the multifaceted nature of the tumoural lymphocyte infiltration, neo-epitope burden load, neo-epitope therapy escape mechanisms, tumoural innate immune cell composition, regulatory molecule profiles and responses to immunotherapy (15, 16). Useful anti-tumour immune response is associated with tumour neo-epitope burden and thus likely reflects a better CD8+ T-cell immunological driven reaction against the primary tumour (17). A large body of experimental laboratory models also shows the pivotal role for CD8+ T-cells and their blockade improves anti-tumour response as reviewed previously (18). However, concomitant blockade of both effector cells and Tregs significantly improves anti-tumour immune responses (19).

In oncology, a robust response to therapy, including non-immune based therapy and adverse immune activation was well recognized prior to ICIs development, with severe innate immune driven skin inflammation being generally associated with a good tumour response following EGFR kinase inhibitor responses in lung cancer patients (20). The wealth of data linking some cancers to immunosuppression including skin cancers and animal model data also speaks to the complex interrelationship between the immune system and tumours (21). The ICIs induce irAEs more frequently in patients with pre-existing autoimmune disease (22, 23) in addition to the precipitation of a plethora of severe rheumatic irAEs or other inflammatory diseases (24). Furthermore, combination therapy with anti-CTLA-4 and anti-PD-1 is associated with both better anti-tumour therapeutic responses but also a higher prevalence of irAEs (25). The novel therapeutic pipeline in the ICI arena and the better efficacy of combinatorial ICI, with its potential to trigger autoimmunity, makes the subject under consideration of the utmost importance.

**ICI therapy autoimmunity and tumour responses.**

In the era of immunotherapy, alternative efficacy endpoints have been developed based on continuous tumour size data collected over time (tumour response) that can predict the overall survival (OS) (26). In contradistinction to tumour responses and irAEs, where a strong positive correlation exists, studies report inconsistent findings concerning the link between irAEs and long term survival (27, 28). This has been attributed to several factors such as the advanced disease stage, the patient performance status, tumour escape mechanisms and the impact of prior conventional chemotherapy (29), Crucially the impact of irAEs directed immunotherapies themselves including high dose rather than low dose immunosuppression was not considered until recently.

The prevailing view in oncology has been that irAEs directed therapy does not adversely affect survival. A retrospective analysis of 327 cancer patients who received ICIs showed that diarrhoea (a likely surrogate for colitis) was recorded in 36% of the patients and was found to be an independent predictor of a favourable OS ($P<0.001$) (30). Moreover, those who required immunosuppressant therapy (either systemic corticosteroid without or with infliximab) for colitis had a significantly better OS than those who did not have colitis or diarrhoea. However, this is not surprising as suspected untreated low grade colitis will almost certainly have a less effective anti-tumour response than those with high grade colitis and therefore a less favourable prognosis. Thus, it might be that if those patients with colitis of a higher grade were treated with a lower dose of steroids would even have a better OS. Yet, there is no sufficient data to analyse the association between the severity and type of irAEs and clinical response probably due to the heterogeneity of irAEs and the small sample sizes employed.

Until recently, there was no serious consideration of the potential detrimental effect of the therapy of emergent autoimmune/rheumatic condition and long-term cancer survival as distinct from initial responses. However, a recent study clearly showed that patients treated with low dose steroids have a much better OS and a longer time to treatment failure compared to high dose therapy for anti-CTLA-4 induced hypophysitis (31). Admittedly the study size and nuances of pituitary biology may represent confounding factors for interpreting this data which should still be viewed as preliminary (32). Acknowledging the heterogeneity of factors that may influence long term survival, there has been a paucity of consideration or of research into how aggressive immunosuppression of irAEs, with these self-same irAEs that are linked to better responses, does not equate with a better long term survival (33, 34).

**Implications for therapy**

In rheumatology where a RA-like or a PMR-like illness, although painful and sometimes frustrating, does not pose a major risk of mortality whereas, the cancer under therapy certainly does pose an imminent threat to survival. Accordingly, the question arises: should we let our patients who develop arthritis to have minimal interventions including rest, NSAIDs and local steroid injection? Should a controlled fire of ongoing immune activation be harnessed towards optimizing immune responses?

A somewhat more radical conundrum with potential survival implications relates to whether we should let deliberately sub-optimally treat patients with ongoing arthritis (with the exception of simple analgesia and anti-inflammatories), at least for a defined period, and not immediately treat with high dose corticosteroids and biologics such as TNF blockers. This needs to be formally assessed in the research setting but we believe that suppression of the immune response, which is likely to be successfully targeting the tumour, might confer a less favourable long-term outcome for the patient in terms of prognosis (Figure 2). Although it is early days, there are worrying case reports of PsA and psoriasis that emerged under checkpoint therapy for inflammatory bowel disease (IBD) related carcinoma being treated with anti-IL-17A with rapid recrudescence of the tumours in the face of resolution of the psoriasis and PsA (35).

Clearly some rheumatic irAEs such as severe myositis and related manifestation including myocarditis need immediate potent therapy upon diagnosis (36). It would seem counterintuitive to administer anti CTLA-4 and thereafter its CTLA-4Ig "antidote" which has been reported to successfully treat severe myocarditis (37). However, the time between onset of irAEs, which may be delayed in some cases may be sufficiently long to permit a powerful "window of opportunity" for unrestrained tumour killing prior to ICI therapy irAE development is something that merits consideration (Figure 3A).

We should at least raise the question as to whether a new onset RA/PMR illness should be treated with "antiquated" rheumatological strategies such as bed rest, physical therapy, analgesic strategies and local corticosteroid injections, at least in the initial phases. (Table 1). Obviously, this will need to be carefully balanced against the potential for severe extra-articular disease or other complications such as severe myositis, myocarditis, myasthenic crisis or end organ involvement and glomerulonephritis, which require prompt more aggressive treatment, since left untreated, such complications could have a potentially worse prognosis than the tumour itself (38, 39) (Table 1) (Figure 2). Such considerations strengthen the calls for true multidisciplinary team management of these complications (13).

This has wider implications for other irAEs, some of which are more serious and some of which are less serious than the rheumatologic ones. Indeed, in most cases, dermatologic adverse events remain self-limiting and readily manageable with topical emollients and/or mild-moderate potency topical corticosteroids (40). However, colitis induced by ICIs sometimes constitutes a life-threatening event with toxic megacolon being a big challenge. Historically, elemental diet has shown comparable efficacy to steroids so scope for a gentler type of immunomodulation exists (41). Maybe, employing such strategies pre-emptively might reduce the risk of IBD flares but the implications of this strategy on ICI efficacy cannot be assumed to be neutral given the emerging knowledge that factors that alter the microbiome in experimental settings can radically affect ICIs in animal models (42) (Table 1).

**Mechanistic T-cell model basis for anti-tumour efficacy and linked autoimmunity**

It is now recognised that immune diseases sit along an immunological disease continuum of inflammation against self (43). At the innate immune end of the classification sits diseases linked to disrupted barrier function and innate immune cell dysfunction (Figure 1). In turn

dysregulation of innate immunity may trigger CD8+ T-cell responses in diseases like psoriasis. Finally, the classically recognised humoral and cell mediated CD4+ T-cell related autoimmune diseases sit at the autoimmunity boundary (Figure 1). The existing ICIs are predictably associated with the development of the autoimmune disorders but not classical innate immune disorders including autoinflammatory skin diseases (Figure 1).

The currently available ICI strategies are clearly linked to certain types of inflammation against self, with tumour efficacy also being paralleled by certain types of autoimmunity, so there is at least a degree of predictability. This might change with the implementation of strategies to specifically prime innate immunity as part of immunotherapy development (44, 45). However, in irAEs, most patients with inflammatory arthritis are not positive for RF or ACPAs and also rarely with myositis specific autoantibodies that are seen in autoimmune muscle disorders (12). This raises the issue as to whether these entities are more linked to CD8+T-cell and Tregs responses that are both critical for anti-CTLA4 mediated cancer immunity. Defining whether these irAEs were autoantibody driven would have important ramifications for a selective therapy of the emergent autoimmunity whilst keeping the anti-tumoural immune response intact (46). However, as shown in Figure 1 the knowledge of the role of CD8+ T cells in driving tumour killing and the lack of classical humoral autoimmune defined autoantibodies and known biology of conventional CD8+ T-cells in cell mediated autoimmunity mechanistically aligns anti-tumour immunity and autoimmunity for several disease complications including colitis and antibody negative rheumatic disease (Figure 1 lower panel).

Certainly, ICI therapy is associated with the generation of many autoantibodies and this might be a marker of irAE toxicity but the full role of humoral immunity in comparison to cell mediated immunity awaits further definition (47). Cancer immunity and autoimmune disease development may share the same mechanisms (vitiligo development in successful melanoma

therapy which mechanistically equates with a good prognosis) (48, 49). However, if the tumoural immunity and irAEs have different mechanisms then suppression of an autoantibody mediated "epiphenomenological" reaction might have little impact on an unrelated cell mediated tumour reaction (Figure 1). Thus, selection of rituximab in cases with a humorally driven autoimmune irAE may have a minimal impact on anti tumoural CD8+ T cell mediated toxicity (46). Since these different mechanisms are currently not well defined whether the type of tumour and type of irAE specifically link to prognosis, there remains an unmet need for further studies in the field.

Some conditions including systemic sclerosis and dermatomyositis arise secondary to an underlying cancer. Indeed, neo-epitope formation, akin to that linked to driving CD8+ T-cell responses in the ICI therapy setting, has been linked to autoantibody formation in scleroderma, specifically anti RNA polymerase 3 antibodies. In a cohort of nearly 2500 scleroderma cases we found that cancer was more common in antibody positive and antibody negative scleroderma compared to 12000 matched controls (50). However, only the ANA negative group had a much worse survival. This suggests that humoral immunity might be linked to survival the speculation being that cell mediated immunity alone is not. Accordingly, the relative role of humoral and cellular immunity and the value of B cell depletion for irAEs need careful evaluation.

**Different Mechanistic Model for Chimeric Antigen Receptor (CAR) T-cell Therapy Immune Toxicity**

Whilst ICI therapy is predictably linked to autoimmunity development the other major developments in oncological immunotherapy namely CAR T-cell therapy and bispecific T-cell engagers (BiTEs) are associated with modified but powerful adaptive immune system tumour

killing that has been thus far shown for acute lymphoblastic leukaemia and diffuse large B-cell lymphoma, these therapies are not associated with autoimmunity development (51). However, the unrestrained T-cell proliferation and activation in these settings is associated with increased IFNγ production and a macrophage activation syndrome (MAS) that is termed cytokine release syndrome in the oncological arena (52). However, therapy of the MAS, an innate driven immunopathology or autoinflammatory disease is not associated with loss of tumour killing in the clinical or experimental setting (Figure 1) (53). This is in marked distinction from ICI therapy which is inextricably linked to autoimmunity but rarely autoinflammatory disease (Figure 1).

In conclusion, immune toxicity appears to be associated with better responses to ICIs therapy (Figure 3B). We feel that the existing literature is now sufficiently robust and strong for a re-evaluation of the desire to quickly and effectively treat emergent autoimmune/rheumatic irAEs or exacerbation of pre-existing autoimmune disease, even though a number of open questions remains to be answered. Overzealous therapy for such complications in the face of increased knowledge on immune homeostasis and suppressing this in ICI treated patients might adversely affect cancer prognosis at the population level.

Issues as the optional time for immunosuppressive therapy delay and whether the mere presence of autoimmunity is already sufficient for a tumour response or whether some months of unrestrained inflammation are needed remain to be defined. So, whether late irAEs emergence have a lesser or great consequence for its suppression is another open question but given that ICIs therapy can be associated with late clinical response then it would seem prudent to “go easy” on immunosuppression.

Viewing the unrestrained immune response as something potentially beneficial and the precise link between different types of autoimmunity and prognosis are topics that should be addressed. Such response may be organ-specific reflecting differing degrees of bystander damage in different organs that may share antigen composition may influence outcomes (31). Different ICI mechanisms of action may also be critical to types of autoimmunity. For example, T-cells suppression by dexamethasone reduced naive T-cells proliferation and differentiation by attenuating the CD28 co-stimulatory pathway and this effect was partially prevented by CTLA-4, but not PD-1 blockade (54) raising the issue of bespoke effects of different ICIs and their potential therapy on survival. Permitting controlled the "fire burning" of an activated immune response to ultimately stall cancer progression and improve long-term survival is a novel strategy, which merits consideration.

**Legend for figures**

**Figure 1.** The application of the immunological diseases continuum model on the spectrum of toxicities induced by immune checkpoint inhibitors can be useful to explain the link between the cellular target of ICI and irAEs. The reported irAEs predictably fit the reported classification of inflammatory diseases with a relative absence of reporting on innate immune driven diseases following current ICI therapy (upper part of figure). Mechanistically the ICI simultaneously activate predominant autoimmune mechanisms in the tumour and also lymphoid organs and target tissues driving linked but unwanted autoimmune disease. In particular, anti-CD8+ T-cell related tumuoral responses might be linked to activation of identical, similar or completely different CD8+ T-cell clones in other organs (dotted blue line). Other mechanism of adaptive immunity against the cancers and tissue are highlighted in black dotted line. However, for Chimeric Antigen Receptor (CAR) T-cell and Bi-specific T-cell engagers (BiTEs) therapy the immune toxicity mainly triggers autoinflammatory toxicity or what is termed a macrophage activation syndrome (MAS) which is also termed cytokine release syndrome (CRS) or cytokine release encephalopathy syndrome (CRES) when neurological involvement occurs (Red dotted line). Collectively, this further highlights the disparity in immunotoxicities between different agents and also highlights that ICI efficacy and toxicity may be inextricably linked to autoimmunity

*Abbreviations: DC, dendritic cells; Treg, T regulatory cell; T eff, effector T cell; HS, hidradenitis suppurativa; MAS, macrophage activation syndrome; T1DM, type1 diabetes mellitus; AIH, autoimmune hepatitis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.*



**Figure 2.** Although the cancer patient ostensibly has normal immune-homeostasis there may be subtle perturbations including failure of CD8+ T-cells to react with tumour neo-epitopes, and dysregulated Treg function (Figure 2A). The ICI checkpoint initiation has several effects on adaptive immunity including reactivation of "exhausted" CD8+ T-cells removal of multiple Tregs inhibitory functions, leading to a myriad of pro-inflammatory effects on both humoral and cellular immunity. ICI therapy primes immunity in both lymphoid organs and the tumour target tissue. Good ICI tumour responses are associated with concomitant autoimmunity to the tumour and in lymphoid organs (Figure 2B). The use of steroid, DMARDs and even biological drugs to treat emergent autoimmunity might in some circumstances restore the overall immune homeostasis that prevailed prior to ICI initiation (Figure 2C). Therefore, the failure to show improved overall cancer survival, despite better responses under ICI, could in part be due successful autoimmune disease therapy but unrecognised adverse restoration of the initial tumour environment.

*Abbreviations: ICI, immune checkpoint inhibitors; irAES, immune related adverse events; Ag, antigen; DC, dendritic cells; Treg, T regulatory cell.*



Figure 3. (A) The window of opportunity This figure shows how refraining from aggressive therapy may permit a "window of opportunity" for powerful unrestrained tumour killing. Clearly stimulating and then blocking the CTLA-4 axis would appear detrimental. However,

factors including the interval between ICI therapy and subsequent autoimmunity, with a longer window would provide greater opportunity for tumour killing. (B) The different scenarios are presented. i) Without ICI therapy relevant tumour survival is very poor. ii) With ICI therapy the prognosis is better, iii) With ICI therapy and associated autoimmunity the prognosis is even better. iv) We propose that with careful therapy selection that the survival may be further improved (grey shaded area). Indeed, therapy is not administered for ICI induced vitiligo in melanoma where vitiligo is associated with overall substantially higher survival (55). Medical management of endocrine disorders with relevant hormone replacement therapy might represent another scenario whereby immunosuppressive drug therapy is not required. These observations may help define the limits of what is achievable in terms of survival for ICI drugs.

**Figure 1. Teleological basis for link between autoimmunity and irAEs.**

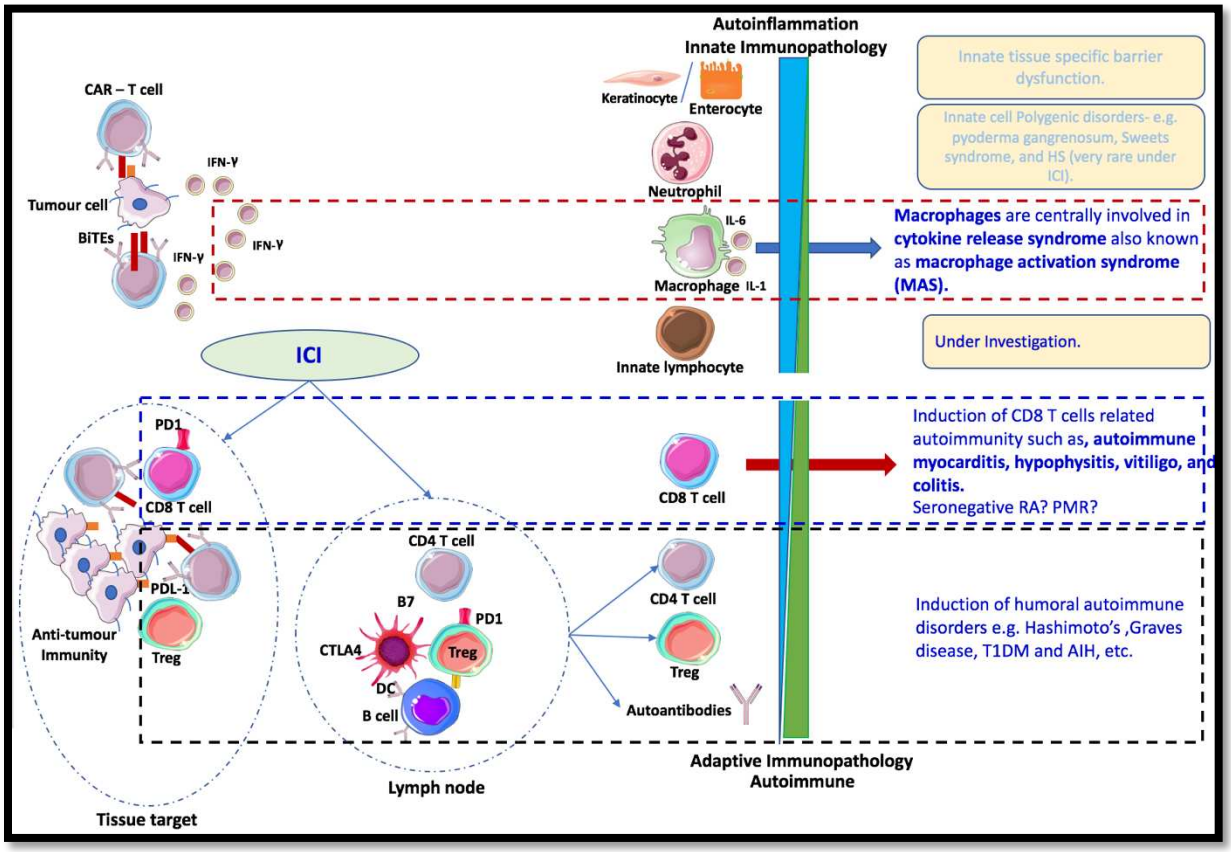

**Figure 2. Suppression of Autoimmunity following ICI and potential tumour relapse**

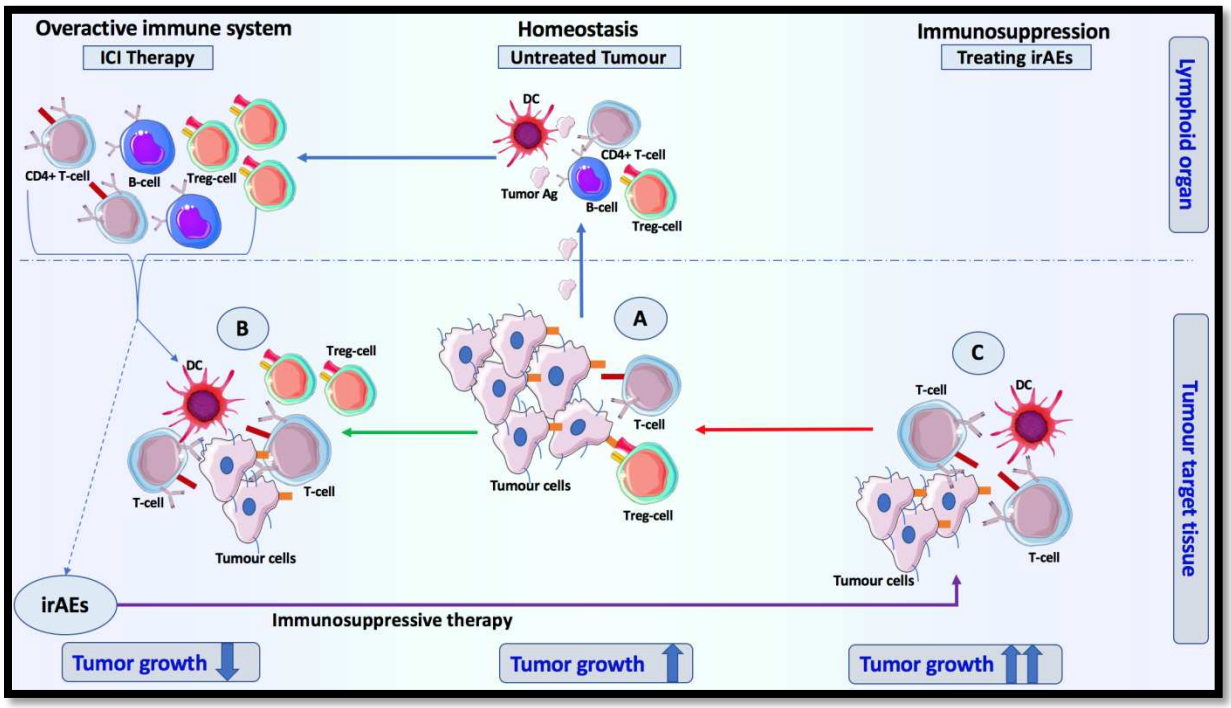


**Figure 3.** (A) **The window of opportunity for treating irAEs.** (B) **The different scenarios during ICI therapy and the related outcomes.**

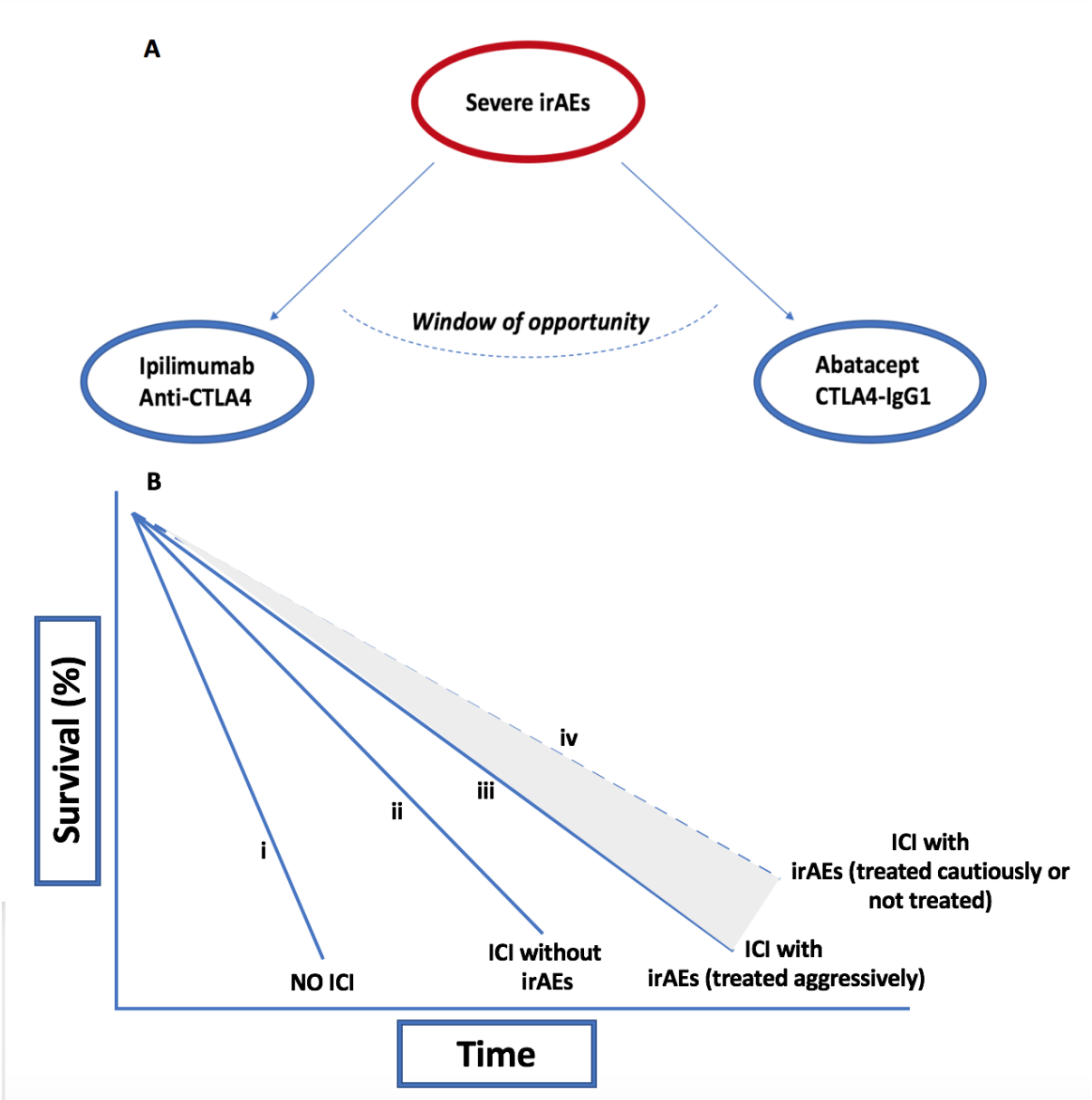


**Table 1 - The spectrum of irAEs with treatment considerations to minimize the impact immunosuppression of potentially adverse tumour responses.**

| Organ involved | Clinical feature | Classical treatment | Treatment Considerations to |
|---|---|---|---|

| | | | minimize tumour suppression |
|---|---|---|---|
| **Skin** | Rash and vitiligo, Psoriasis | Discontinue immunotherapy and systemic therapy | Topical agents |
| **Gut** | Diarrhea/Enterocolitis | Corticosteroids, TNFi | For mild forms, try gut resting strategies element diets assessment microbiome<br>For moderate forms, low dosage of steroids |
| **Joint** | Arthralgia/arthritis | Oral corticosteroids. Intra articular steroid, DMARDs | Rest, joint injections, low dose steroid |
| **Endocrine glands** | Hypothyroidism/hypophysitis TIDM, adrenal insufficiency | Replacement therapy for thyroid and DM, corticosteroids for hypophysitis | Replacement therapy and low dose of steroids |
| **Eye** | Uveitis/scleritis/ VKH | Hold ICI, topical corticosteroids, cycloplegic agents, systemic corticosteroids. | Topical or Intra-ocular steroids |
| **Heart** | Myocarditis/severe myositis | Withholding ICI, Consider corticosteroids , unavoidable early aggressive immune suppression | * |
| **Lung** | Pneumonitis, interstitial lung diseases | Start corticosteroids, consider pulmonary consultation for bronchoscopy with bronchoalveolar lavage. | * |
| **Kidney** | Nephritis, renal failure | Withholding ICI, start corticosteroids. | * |
| **Liver** | Autoimmune hepatitis | Permanently discontinue of immunotherapy and start systemic corticosteroids | * |

*No change of existing strategies due to potential gravity of disease. **Treatment considerations are dependent on the grade of immune related adverse events. Abbreviations: TNFi, TNF-α inhibitors; ICI, immune checkpoint inhibitors; DMARDs, disease modifying anti-rheumatic drugs; DM, diabetes mellitus; T1DM, type 1 diabetes mellitus; VKH, Vogt–Koyanagi–Harada disease.

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