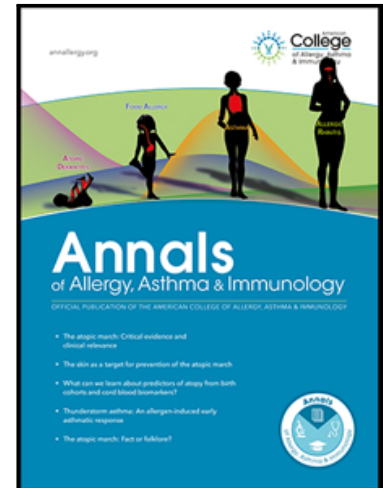


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Marina Labella MD , Mariana Castells MD, PhD

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## **HYPERSENSITIVITY REACTIONS AND ANAPHYLAXIS TO CHECKPOINT INHIBITOR-MONOCLONAL ANTIBODIES AND DESENSITIZATION**

Marina Labella, MD<sup>1,2</sup> and Mariana Castells, MD, PhD<sup>3</sup>

<sup>1</sup> Allergy Clinical Unit, Hospital Regional Universitario de Málaga, Málaga, Spain.

<sup>2</sup> Allergy Research Group, Instituto de Investigación Biomédica de Málaga-IBIMA, Málaga, Spain.

<sup>3</sup> Division of Rheumatology, Immunology, and Allergy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA.

### **Corresponding author information:**

Marina Labella

Allergy Clinical Unit

Hospital Regional Universitario de Málaga

Plaza del Hospital Civil s/n

29009, Málaga, Spain.

Tel +34 951290313

Fax +34 951290302

Email: labellaalvarezmarina@gmail.com

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**Keywords:** checkpoint inhibitors, hypersensitivity reactions, desensitization, type 1, IgE-mediated, anaphylaxis, allergy, anti-CTLA-4, anti-PD-1, anti-PD-L1, monoclonal antibodies, immune checkpoint blockade therapy.

**Abbreviations/Acronyms:**

CPIs: Checkpoint inhibitors

CTLA-4: Cytotoxic T-Lymphocyte Antigen-4

PD-1: Programmed cell death protein-1

ADRs: Adverse drug reactions

Mabs: Monoclonal antibodies

HRs: Hypersensitivity reactions

DD: Drug desensitization

PD-L1: Programmed cell death ligand-1

TCR: T-Cell Receptor

CTLs: Cytotoxic T lymphocytes

FDA: Food and Drug Administration

IrAEs: Immune-Related Adverse Events

SCARS: Severe Cutaneous Adverse Reactions

DMARDs: Disease-modifying antirheumatic drugs

TEN: Toxic epidermal necrolysis

DRESS: Drug reaction with eosinophilia and systemic symptoms

BAT: Basophil activation test

ID: intradermal

CRR: cytokine-release reaction

**Word count:** 2995

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**Tables:** 3

**Objective :** To review type-1 hypersensitivity reactions and anaphylaxis to checkpoint inhibitor-monoclonal antibodies, and its management with drug desensitization.

**Data Sources :** English language literature on Medline regarding hypersensitivity, anaphylaxis and checkpoint inhibitor-monoclonal antibodies.

**Study Selections :** References were selected based on relevance, novelty, robustness, and applicability.

**Results :** There are well known tissue toxicities associated to checkpoint inhibitors but hypersensitivity reactions and anaphylaxis have been underreported. The presentation of these reactions is based on clinical phenotypes with underlying endotypes identified by specific biomarkers. Drug desensitizations have been successfully applied to checkpoint inhibitor drugs to allow cancer patients to receive first-line therapies. This review provides current best practices for the recognition and diagnosis of hypersensitivity reactions and anaphylaxis to checkpoint inhibitors and their management using drug desensitization.

**Conclusion :** Hypersensitivity reactions and anaphylaxis have been identified as potential side effects induced by checkpoint inhibitor-monoclonal antibodies. Drug desensitization is a safe and effective treatment option for patients who suffer hypersensitivity reactions in need of these monoclonal antibodies to improve cancer outcomes.

## Key Messages

- Hypersensitivity reactions and anaphylaxis are potential side effects induced by checkpoint inhibitor-monoclonal antibodies.
- The classification based on phenotypes, endotypes, and biomarkers provides a framework for the diagnosis and management of these hypersensitivity reactions.
- Drug desensitization is a safe and effective procedure that induces a temporary tolerance to checkpoint inhibitor-monoclonal antibodies.
- Patients with hypersensitivity reactions and anaphylaxis to checkpoint inhibitor-monoclonal antibodies should be evaluated by an allergist for potential desensitization to continue on first-line therapy.

## Introduction

Immune Checkpoint Blockade is a novel immunotherapeutic strategy that has shown extraordinary outcomes in the treatment of a variety of cancers with long-lasting anti-tumor results.<sup>1</sup> Checkpoint inhibitors (CPIs) were first approved for patients with metastatic melanoma and are currently used for renal, lung, bladder, hepatocellular cancers among others.<sup>2</sup> CPIs work by disrupting the interactions between checkpoint proteins such as Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), and Programmed cell death protein 1 (PD-1) expressed on the surface of T-Cell, with their ligands on tumor cell; thus preventing T-Cell silencing.<sup>3,4</sup> Owing to the increased use of CPIs and the dysregulation of the immune system derivated from their mechanism of action, adverse drug reactions (ADR) to this group of drugs, have raised exponentially.<sup>5,6</sup> Although many side effects are well recognized, hypersensitivity reactions (HRs) and anaphylaxis are underreported.<sup>7-10</sup> After an HR, avoidance of the culprit drug is often recommended and may negatively impact the quality of life and life expectancy of cancer patients. Drug desensitization is a safe and effective tool for

patients with first-line therapy-induced hypersensitivity and anaphylactic reactions.<sup>11,12</sup>

Therapeutic algorithms for the management of ADRs induced by CPIs have been recommended and should be updated exploring drug desensitization (DD) as an option in indicated cases. This review is focused on the identification and diagnosis of Type I HRs to CPIs, their management, and the effective and safe use of desensitization.

### **Novel immune modulators: checkpoint blockade therapy. What do CPIs do?**

This new class of cancer immunotherapy named CPIs, are monoclonal antibodies (mabs) directed against CTLA-4, PD-1, and Programmed cell death ligand-1 (PD-L1). They increase antitumor immunity by blocking intrinsic downregulating signals, providing unprecedented long-lasting anti-tumor responses.

### ***Regulation of T-cell activation Figure 1A***

Checkpoint proteins have a potent inhibitory role in regulating T-cell responses. Once checkpoint proteins bind to their ligands, they send an “off” signal to T-cells, preventing the immune system from destroying tumor cells. T-Cell activation requires recognition by the T-Cell Receptor (TCR) following antigen presentation by major histocompatibility complex-class 2- on the surface of the antigen presenting cells. Signal modulation occurs when CD80/CD86 (B7) binds to the CD28 receptor. CTLA-4 competes with CD28 for the binding of co-stimulatory molecules CD80/ CD86. This interaction induces the expression of PD-1 and the production of IFN- $\gamma$  and results in the expression of PD-L1 and inhibition of T-cell proliferation and activation, resulting in T cell exhaustion.<sup>2,3,13</sup>

***Restoring the capacity of exhausted Cytotoxic T lymphocytes (CTLs) Figure 1B***

After TCR engagement, CTLA-4 migrates to the cell surface where it outcompetes CD28 for binding with the co-stimulatory molecules and mediated inhibitory signaling into T-cells.

Anti-CTLA-4 mabs block CTLA-4/CD80 and CTLA-4/CD86 binding restoring T-cell repertoire activation and proliferation. PD-1 desphosphorylates signaling molecules downstream of TCR. Anti-PD-1 and anti-PD-L1 prevent PD-1/PD-L1 interactions, allowing T-cell activation, tumor infiltration, and inducing a cytotoxic T-cell (CTL) response. CTLs can kill cancer cells and control tumor growth.<sup>3</sup>

**Who are they?**

There are currently, one anti-CTLA-4 and six anti-PD-1/PD-L1 CPIs approved by the US Food and Drug Administration (FDA) for at least 18 cancer indications. *Table 1*

The combination of ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) has been recently approved by the FDA, with broad indications.<sup>1</sup>

***Anti CTLA-4 antibodies: Ipilimumab***

Ipilimumab is a human IgG1 anti-CTLA-4 antibody. It was the first checkpoint inhibitor approved by the FDA in 2011. The only indications for ipilimumab as a single agent, are metastatic melanoma and adjuvant treatment for melanoma. Other indications have been granted in combination with an anti-PD1 checkpoint inhibitor, nivolumab, such as advanced renal cell carcinoma, microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer, hepatocellular carcinoma, metastatic non-small cell lung cancer, and malignant pleural mesothelioma. When it is administered in combination, nivolumab is infused first, followed by ipilimumab on the same day continuing after that in monotherapy

with nivolumab until the oncologist's consideration. Another IgG class-2 anti-CTLA-4 named Tremelimumab is still under investigation.<sup>5</sup>

#### *Anti-PD-1 antibodies*

The blockade of the PD-1 pathway is considered one of the most important advances in the history of cancer treatment. The Anti-PD-1 pathway has a more specific effect on antitumor T-cells, perhaps because of their chronically stimulated state, resulting in increased therapeutic activity and more limited toxicity compared to Anti-CTLA-4 mabs.<sup>6</sup>

#### *Pembrolizumab*

The first PD-1 blocking antibody approved by the FDA was Pembrolizumab in 2014. It is a humanized IgG4 mab approved currently for several indications such as melanoma, non-small cell lung cancer, small cell lung cancer, head and neck squamous cell cancer, classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, microsatellite instability-high or mismatch repair deficient cancer, microsatellite instability-high or mismatch repair deficient colorectal cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma, tumor mutational Burden-high cancer, cutaneous squamous cell carcinoma.<sup>2</sup>

#### *Nivolumab*

In 2014 an IgG4k immunoglobulin known as Nivolumab was approved by the FDA for unresectable or metastatic melanoma, adjuvant treatment of melanoma, metastatic non-small cell lung cancer, small cell lung cancer, malignant pleural mesothelioma, advanced renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck,

urothelial carcinoma, microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer, hepatocellular carcinoma, and esophageal squamous cell carcinoma.

Nivolumab is approved as a single agent, in combination with ipilimumab, with platinum-doublet chemotherapy, or both. The first drug to administer should be nivolumab, followed by ipilimumab in the case is present, and platinum-doublet at the end.<sup>6,14</sup>

### *Cemiplimab*

This human IgG4 mab was approved in 2018 for cutaneous squamous cell carcinoma.<sup>2</sup>

### *Anti-PD-L1 antibodies*

#### *Atezolizumab*

It is a humanized non-glycosylated IgG1 kappa mab approved by the FDA in 2016. The main indications are urothelial carcinoma, non-small cell lung cancer, locally advanced or metastatic triple-negative breast cancer, small cell lung cancer, and hepatocellular carcinoma.<sup>6</sup>

#### *Avelumab*

A human IgG1 lambda was approved in 2017. The indications for this PD-L1 blocking agent are advanced renal cell carcinoma, metastatic Merkel cell carcinoma, and locally advanced or metastatic urothelial carcinoma.<sup>13</sup>

#### *Durvalumab*

The approval of this human IgG1 kappa mab was granted ~~its approval~~ in 2017. Currently approved for urothelial carcinoma, non-small cell lung cancer, and small cell lung cancer.

**Pathological functions of CPIs: unleashing the immune system**

Immune checkpoint proteins are essential in preventing over-activation of the immune system and maintaining immunological homeostasis. CTLA-4 plays a role at a proximal stage of the immune response attenuating T-cell activation, whereas PD-1 is believed to inhibit T-cells at later stages. When CPI-mabs block these pathways to kill cancer cells, perturb these physiological functions inducing a dysregulation of the immune system. The main side effects derived from the mechanism of action are toxicities related to tissue-specific inflammation, termed Immune-related adverse events (irAES).<sup>14,15</sup> The different functions at distinct phases of the immune response of checkpoint proteins disclose more severe irAES in patients treated with anti-CTLA-4 than PD-1.

The incidence of side effects induced by CPIs ranges between 54% and 76% for all adverse events being greater with combinatorial therapy than for monotherapy.<sup>18,20-22</sup> In 2018, a network meta-analysis presented a safety-ranking among immune CPI-drugs based on treatment-related adverse events. Atezolizumab had the best safety profile in general, and nivolumab had the best safety profile in lung cancer when taking an integrating approach.<sup>20</sup>

A systematic review was published by the American society of clinical oncology in 2018 to increase awareness, outline strategies, and offer guidance to clinicians on the management of irAES induced by CPIs.<sup>16-18</sup> This guideline presents recommendations for specific organ-based toxicities diagnosis and management that could vary according to the organ system affected. Toxicities are classified into 4 grades with general and specific interventions. The spectrum of adverse effects derivatives of the mechanism of action of CPIs can affect multiple organs and are most commonly seen in skin, gastrointestinal, lungs, endocrine, musculoskeletal, renal, nervous system, hematological, cardiovascular, and ocular. The main

interventions included corticosteroids, immunosuppressive therapy, dose modification or discontinuation, hormone replacement, disease-modifying antirheumatic drugs (DMARDs), plasmapheresis, consultation to subspecialties, hospitalization, and best supportive care. While delayed type IV HRs such as Steven-Johnson's syndrome, Toxic epidermal necrolysis (TEN) or Drug reaction with eosinophilia and systemic symptoms (DRESS) are widely identified and published included as skin toxicities in multiple series, type-I HRs are missing and underreported.<sup>15,19</sup> Apart from the side effects related to the mechanism of action of CPIs, anaphylaxis is an important adverse effect that could lead to an interruption of the drug administration.

Potential side-effects to CPIs are shown and updated by organ-affected in *Table 2*.

Various studies are evaluating strategies to reduce toxicities maintaining efficacy such as modifying dosing or incrementing infusion intervals. The main intervention for patients with type-I HRs may be desensitization.

### **Beyond CPI-induced autoimmune disorders: anaphylaxis.**

The appropriate management and prevention of anaphylaxis rely on its rapid recognition and diagnosis which is based on its clinical phenotype, underlying endotype, and biomarkers.<sup>10,23–</sup>

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### ***The utility of skin testing***

When diagnosing type-I HRs and anaphylaxis, skin testing is a useful tool that provides evidence of IgE and mast cell involvement. The elevated costs of some mabs including CPIs precluded skin testing, providing a ground for this unmet need, which could be addressed by the manufacturer with small vials with 0.1 to 0.5ml of the drug.<sup>28,29</sup> In a recent article published by Isabwe et al. skin testing was done with mabs. A positive result was associated with greater severity of initial reactions. Skin testing provides a mechanistic understanding of

the reaction, helps with risk stratification and desensitization management options. Skin testing should be done when it is feasible.<sup>11</sup>

### ***Beyond type-I phenotype***

Type-I IgE HRs to CPIs have been described in some case reports, specifically to nivolumab and atezolizumab, confirmed with positive skin tests. Besides via IgE, mast cells can be activated through various routes: via IgG-antigen interaction, via MRGPRX2 transmembrane protein, via complement cascade activation, and anaphylotoxins C3a and C5a. Publications of Non-IgE HRs to this new group of mabs are still lacking.<sup>30</sup>

Although the phenotype of anaphylaxis of type-I HRs can affect many organs with cutaneous, gastrointestinal, cardiovascular compromise, throat, and respiratory affection, other presentations with fever, lumbar pain, hypertension, rigors, and chills have been seen as in association with cytokines.<sup>30-36</sup> Tryptase can be elevated in type-I HRs but also in mixed reactions along with IL-6 biomarker when cytokine release is associated.<sup>25,26,37,38</sup>

A novel study, recently published by Baruch Jakubovic et al., has explored IL-6 as a biomarker for breakthrough reactions during DD to chemotherapeutics and mabs. Thirty-eight reactions out of 21 patients were evaluated to determine the phenotypic constellations with which elevated values of IL-6 may correlate. When reaction features were subcategorized on basis of normal or abnormal values of IL-6, significant differences were noted concerning fever and neuromuscular complaints. Furthermore, tryptase levels were also measured and compared with basal levels, but surprisingly significant rises were not observed in serum tryptase. This observation may indicate that although DD is thought to prevent mast cell

mediators release, the source of IL-6 is likely from other immune cells and DD may not block all pathways of anaphylaxis.<sup>38</sup>

### ***Cytokine release reactions versus infusion reactions to mabs: specific interventions***

Infusion-related reactions and cytokine-release reactions (CRR) can occur at first exposure and may present with mild to severe symptoms. The difference between them is the self-limiting nature of infusion-related reactions on subsequent exposures, and the response to premedication. One of the largest descriptions of HRs to mabs (Isabwe et al.) where some CPIs were included, such as pembrolizumab and nivolumab, consider CRR as candidates for desensitization. Concerning breakthrough reactions during DD, this study shows CRR as the major phenotype. Importantly, the severity of the reaction during drug desensitization when compared with the initial reaction is significantly lower, and after multiple desensitizations is decreased.<sup>11</sup>

### ***The role of excipients***

All CPIs contain inactive ingredients such as polysorbate 20 (PS20) or polysorbate 80 (PS80). There are no data on the prevalence of HRs to these excipients and anaphylaxis has been reported. A recent review article described cutaneous reactions and one case of anaphylaxis to omalizumab with positive skin tests to PS20. Another case described a patient with type-I reaction to adalimumab and ustekinumab with positive skin tests to PS80, which is common to both preparations. Whether some reactions to CPI-mabs can be attributable to excipients, such as PS20 or 80, is still unclear.<sup>39</sup>

### ***Other in vitro biomarkers***

Serum drug-specific IgE is not currently available for CPI-mabs, which would confirm a type-I IgE mechanism. Nevertheless, the Basophil activation test (BAT), has been used for the diagnosis of immediate HRs and anaphylaxis to mabs.<sup>40-42</sup> González-de-Olano et al. described the case of a young woman with metastatic breast cancer, who suffered a grade-III reaction, during her second treatment with pertuzumab. Skin testing was negative, the IgE-mediated mechanism was confirmed thanks to a positive BAT. The patient underwent successful DD.<sup>43</sup>

### ***Innovative therapies and technologies***

Nanoallergen platforms have not yet been applied to the diagnosis of hypersensitivity reactions to mabs but could be potentially a tool as shown for platins. The aim would be to improve diagnosis accuracy and to avoid the risks and delays of skin testing.<sup>44</sup>

### **Treating type I reactions and anaphylaxis with drug desensitization**

DD is a robust evidence-based therapeutic procedure that induces a temporary hyporesponsive state by an incremental escalation of suboptimal doses and is drug-specific. DD In vitro models show impaired internalization of Ag/IgE-Fc3RI complexes and inhibition of extracellular calcium influx and the release of mediators.<sup>34</sup> *Figure 2.*

DD is indicated for patients with immediate reactions induced by mast cell/IgE and non-IgE activation and with certain delayed type IV reactions. Patients with type-II reactions, serum sickness, SCARS, and organ-specific toxicities as seen with CPIs, are not candidates for DD because of the risk of potentially fatal reactions on reexposure to even small amounts of the culprit medication.<sup>45</sup> *Table 2.*

Personalized premedication is based on the symptoms experienced by the patient at the initial reaction, and it is administered 30 minutes before the initiation of DD.<sup>46, 47</sup> Specific

algorithms for monoclonal antibodies based on endotypes, phenotypes, and biomarkers guide us to choose the suitable protocol.<sup>48, 49</sup>

A recent article by Fernandez J. et al. has reviewed the use of Omalizumab in drug-allergy desensitizations. They summarize that Omalizumab or other IgE targeting biologics, either a fixed dose of 300 mg Omalizumab or a dose-related total IgE and bodyweight mass, maybe an option to decrease the severity of reactions during DD in refractory patients.<sup>50</sup>

### ***Drug desensitization to CPIs in real life***

The first description of type-I HRs and desensitization to CPIs was published by Saenz de Santa Maria et al. in 2017, with an IgE-mediated reaction to nivolumab. A woman with hepatocellular carcinoma was treated with nivolumab and ipilimumab and during the third cycle, minutes after the infusion of nivolumab she presented facial flushing, hives on her neck and face, and eyelid angioedema. She tolerated ipilimumab after that. Skin testing with nivolumab was performed: prick test at a concentration of 1mg/ml (1/10) was negative; intradermal (ID) test with a concentration of 0.1 mg/ml (1/100) was positive with an 8 mm wheal. Basal tryptase was normal and anti-nivolumab IgE antibodies were measured by SDS-PAGE immunoblotting with a negative result. DD was indicated and she received premedication with oral aspirin 300mg, montelukast 10mg, intravenous dexchlorpheniramine 5 mg, ranitidine 50mg, and hydrocortisone 200mg. A 3 bags-12 steps protocol with a final rate of 160 ml/h was performed presenting grade-1 breakthrough reaction 50 minutes into the last step. The infusion was stopped, the patient was treated and after recovering the infusion was resumed, and finished with no additional issues. Protocol was modified adding steps at bag 3 (20 ml/h, 40 ml/h, 80 ml/h, 120 ml/h, 140 ml/h and 160ml/h) and intra-steps treatment with dexchlorpheniramine. Despite those modifications, the patient always had the same symptoms at 120 ml/h. Then they started treatment with antihistamine every 24 hours 3 days

before the cycle, and she did not have any reaction since the 11<sup>th</sup> desensitization until complete 20 cycles.<sup>51-55</sup>

In 2018, Isabwe et al. analyzed 524 mab-desensitizations out of 104 patients between 2014 and 2016 presenting three desensitizations to CPIs. One patient with an initial grade-I reaction to nivolumab experienced two drug desensitizations. Another patient with a grade-I initial reaction to pembrolizumab was managed with desensitization. Skin testing was not performed on CPI-drugs due to cost consideration.<sup>56</sup>

In 2020 a case-report presented a woman with metastatic clear-cell renal cancer who experienced a grade-III reaction (generalized erythema, bronchospasm, dyspnea, and oxygen saturation of 89%) 10 minutes into her 3<sup>rd</sup> infusion of nivolumab. Skin testing was negative. The patient was managed with DD. Orally premedication with cetirizine 20mg, ranitidine 300 mg, and prednisone 60mg was administered the night before the cycle. A single bag-15 steps protocol with a concentration of 1mg/ml and an increasing infusion rate every 15 minutes with a final step rate of 180 ml/h was successfully applied twice. The same protocol removing premedication with corticosteroids, and adding acetylsalicylic acid 300 mg and montelukast 10 mg instead was performed for 20 desensitizations with no reactions.<sup>57</sup>

More recently, a male patient with metastatic lung cancer suffered anaphylaxis after second-lifetime exposure to atezolizumab. Skin prick test was performed at 60mg/ml with a negative result and ID test with 0.6 mg/ml was positive with 10 mm wheal. The patient underwent a successful 4 bag-16 steps protocol desensitization and then resumed to 3 bag-12 steps protocol without reactions.<sup>58</sup>

*Table 3* summarizes-up recent publications of DD to CPIs and their clinical characteristics.

## Conclusion

Type I HRs and anaphylaxis occur with CPIs and its diagnosis requires a high index of suspicion and an appropriate management and treatment plan. Biomarkers such as skin testing, tryptase, and IL-6 can help identify the endotypes of the reactions and provide ground for DD. CPIs are essential medications that can provide long-lasting tumor responses and for which DD is indicated in allergic patients.

Clinical studies are required to further understand the mechanisms of hypersensitivity reactions to CPIs and to generate tools to standardize their diagnosis, the role of excipients, the cross-reactivity between them, and the indications and outcomes of DD.

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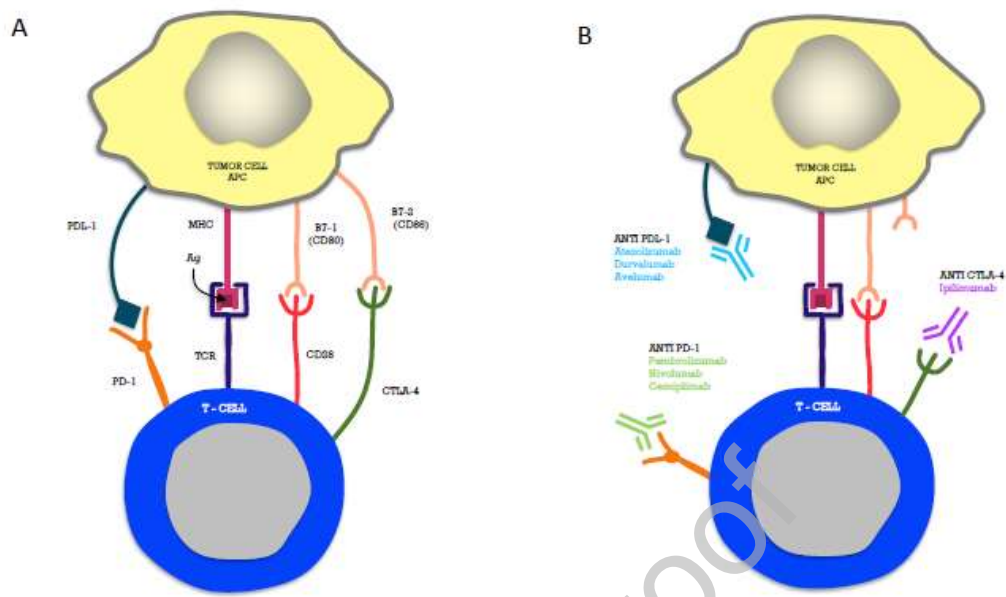


**Figure 1. Natural mechanisms of immune checkpoint proteins and Checkpoint inhibitor-monoclonal antibodies. Figure 1A:** Checkpoint proteins bind to their ligands preventing the immune system from destroying tumor cells. **Figure 1B:** Anti-CTLA-4, Anti PD-1 and Anti-PD-L1 CPI-mabs block this interaction restoring T-cell activation.

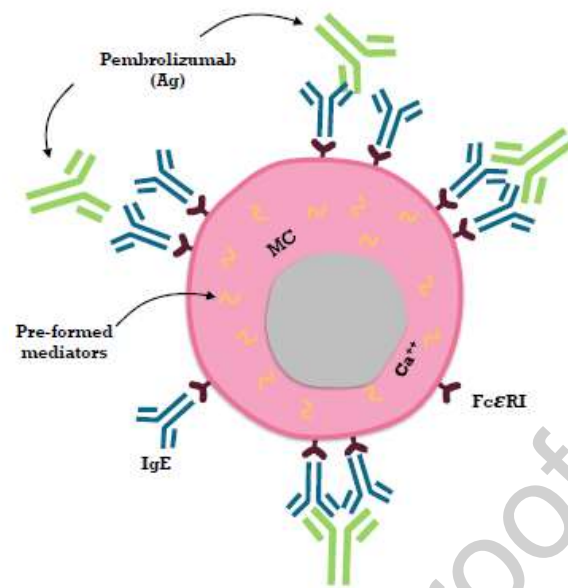


**Figure 2. Desensitized mast cell to pembrolizumab.** In vitro models show impaired internalization of Ag/IgE-Fc3RI complexes, inhibition of extracellular calcium influx, and mediators release.

**Table 1. Checkpoint inhibitors and cancer indications**

| Target             | Monoclonal antibody                       | Indications and usage                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|--------------------|-------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Anti-CTLA-4</b> | <b>Ipilimumab</b><br>Human<br>IgG1k       | <ol style="list-style-type: none"> <li>1. Unresectable or metastatic melanoma</li> <li>2. Adjuvant treatment of Melanoma</li> <li>3. Advanced Renal cell carcinoma*</li> <li>4. Microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer*</li> <li>5. Hepatocellular carcinoma*</li> <li>6. Metastatic Non-small cell lung cancer*</li> <li>7. Malignant pleural mesothelioma*</li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Anti-PD-1</b>   | <b>Pembrolizumab</b><br>Humanized<br>IgG4 | <ol style="list-style-type: none"> <li>1. Melanoma</li> <li>2. Non-small cell lung cancer</li> <li>3. Small cell lung cancer</li> <li>4. Head and neck squamous cell cancer</li> <li>5. Classical Hodgkin lymphoma</li> <li>6. Primary mediastinal large B-cell lymphoma</li> <li>7. Urothelial carcinoma</li> <li>8. Microsatellite instability-high or mismatch repair deficient cancer.</li> <li>9. Microsatellite instability-high or mismatch repair deficient colorectal cancer</li> <li>10. Gastric cancer</li> <li>11. Esophageal cancer</li> <li>12. Cervical cancer</li> <li>13. Hepatocellular carcinoma</li> <li>14. Merkel cell carcinoma</li> <li>15. Renal cell carcinoma</li> <li>16. Endometrial carcinoma</li> <li>17. Tumor mutational Burden-high cancer</li> <li>18. Cutaneous squamous cell carcinoma</li> </ol> |
|                    | <b>Nivolumab</b><br>Human<br>IgG4k        | <ol style="list-style-type: none"> <li>1. Unresectable or metastatic melanoma</li> <li>2. Adjuvant treatment of melanoma</li> <li>3. Metastatic non-small cell lung cancer</li> <li>4. Small cell lung cancer</li> <li>5. Malignant pleural mesothelioma</li> <li>6. Advanced renal cell carcinoma</li> <li>7. Classical Hodgkin Lymphoma</li> <li>8. Squamous cell carcinoma of the head and neck</li> <li>9. Urothelial carcinoma</li> <li>10. Microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer</li> <li>11. Hepatocellular carcinoma</li> <li>12. Esophageal squamous cell carcinoma</li> </ol>                                                                                                                                                                                            |
|                    | <b>Cemiplimab</b><br>Human<br>IgG4        | <ol style="list-style-type: none"> <li>1. Cutaneous squamous cell carcinoma</li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Anti-PD-L1</b>  | <b>Atezolizumab</b><br>Humanized<br>IgG1  | <ol style="list-style-type: none"> <li>1. Urothelial carcinoma</li> <li>2. Non-small cell lung cancer</li> <li>3. Locally advanced or metastatic triple-negative breast cancer</li> <li>4. Small cell lung cancer</li> <li>5. Hepatocellular carcinoma</li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                    | <b>Avelumab</b><br>Human<br>IGg1          | <ol style="list-style-type: none"> <li>1. Metastatic Merkel cell carcinoma</li> <li>2. Locally advanced or metastatic urothelial carcinoma</li> <li>3. Advanced renal cell carcinoma</li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                    | <b>Durvalumab</b><br>Human<br>IgG1k       | <ol style="list-style-type: none"> <li>1. Urothelial carcinoma</li> <li>2. Non-small cell lung cancer</li> <li>3. Small cell lung cancer</li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

\*In combination with nivolumab

**Table 2. Potential side effects and toxicities induced by checkpoint inhibitor-mabs**

| Potential side effects and toxicities induced by Checkpoint inhibitor-mabs |                                                                                                                                                                                   | Indication for drug desensitization                                                                                                                      |
|----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>SKIN</b>                                                                | Rash inflammatory dermatitis; Bullous dermatoses; SCARS (TEN, DRESS, Steven's Johnson syndrome).                                                                                  | Selected cases.<br>It is indicated for maculopapular exanthema and delayed urticaria without involving other organs.<br>DD is contraindicated for SCARS. |
| <b>GASTROINTESTINAL</b>                                                    | Enterocolitis; Hepatitis; Lymphocytic gastritis; Pancreatitis.                                                                                                                    | No                                                                                                                                                       |
| <b>LUNG</b>                                                                | Interstitial lung disease (Pneumonitis; Pulmonary fibrosis; Pulmonary hemorrhage)                                                                                                 | No                                                                                                                                                       |
| <b>ENDOCRINE</b>                                                           | Primary hypothyroidism; Hyperthyroidism; Primary adrenal insufficiency; Hypophysitis; Diabetes. Mellitus; Hypogonadism.                                                           | No                                                                                                                                                       |
| <b>MUSCULOSKELETAL</b>                                                     | Inflammatory arthritis; Myositis, Polymyalgia-like syndrome.                                                                                                                      | No                                                                                                                                                       |
| <b>RENAL</b>                                                               | Nephritis                                                                                                                                                                         | No                                                                                                                                                       |
| <b>NERVOUS SYSTEM</b>                                                      | Myasthenia gravis; Guillain- Barré syndrome; Peripheral neuropathy; Autonomic neuropathy; Aseptic meningitis; Encephalitis; Transverse myelitis.                                  | No                                                                                                                                                       |
| <b>HEMATOLOGIC</b>                                                         | Autoimmune hemolytic anemia; Acquired thrombotic thrombocytopenic purpura; Hemolytic uremic syndrome; Aplastic anemia; Lymphopenia; Immune thrombocytopenia; Acquired hemophilia. | No                                                                                                                                                       |
| <b>CARDIOVASCULAR</b>                                                      | Myocarditis; Pericarditis; Arrhythmias; Impaired ventricular function with heart failure; Vasculitis; Venous thromboembolism.                                                     | No                                                                                                                                                       |
| <b>OCULAR</b>                                                              | Uveitis; Iritis; Conjunctivitis; Episcleritis; Blepharitis; Vogt-Koyanagi-Harada syndrome.                                                                                        | No                                                                                                                                                       |
| <b>TYPE-I REACTIONS</b>                                                    | Hypersensitivity reactions and Anaphylaxis.                                                                                                                                       | Yes                                                                                                                                                      |

**Table 3. Drug desensitization to CPIs**

| Year/ Ref | Case report (n/drug) | Underlying disease       | Grade of initial reaction | Lifetime exposures prior to reaction | Skin tests                                             | Protocol           | Desensitizations/ Outcome      |
|-----------|----------------------|--------------------------|---------------------------|--------------------------------------|--------------------------------------------------------|--------------------|--------------------------------|
| 2017/ 53  | 1/Nivolumab          | Hepatocellular carcinoma | I                         | 2                                    | Prick test 1mg/ml: negative<br>ID 0.1 mg/ml: positive  | 3 bags<br>12 steps | 20/ 10 grade I, 10 no reaction |
| 2018/ 55  | 1/Pembrolizumab      | Ovarian cancer           | I                         | NA                                   | NA                                                     | 3 bags<br>12 steps | 1/NA                           |
| 2018/ 55  | 1/Nivolumab          | Melanoma                 | I                         | NA                                   | NA                                                     | 3 bags<br>12 steps | 2/NA                           |
| 2020/ 56  | 1/Nivolumab          | Metastatic renal cancer  | III                       | 2                                    | Negative*                                              | 1 bag<br>15 steps  | 20/ No reaction                |
| 2020/ 57  | 1/Atezolizumab       | Metastatic lung cancer   | III                       | 1                                    | Prick test 60mg/ml: negative<br>ID 0.6 mg/ml: positive | 4 bags<br>16 steps | 3/No reaction                  |

NA: Not available

\* Concentrations for skin tests NA