Management of Steroid Refractory Immune-Related Adverse Events: A Focussed Approach.

This opinion piece was written and funded by Bristol-Myers Squibb in collaboration with Dr Ricky Frazer, Consultant Medical Oncologist at the Velindre Cancer Centre and Dr Anna Olsson-Brown, Consultant Medical Oncologist at the University Hospitals Sussex NHS Foundation Trust.

Immunotherapy can cause immune-related adverse events which often require immunosuppression with corticosteroids. However, a subset of patients do not respond adequately to steroids, rendering their condition 'steroid-refractory' and requiring additional/ alternative immunosuppressive therapies which whilst used extensively in other areas of medicine are relatively novel in the oncological landscape.

Two focus groups, with oncologists from a range of different centres in the UK, were undertaken to understand the barriers and challenges of managing immune-related adverse events not responding to steroids. A particular focus of the discussion was the management approaches to patients described as steroid refractory, and the kinds of experiences oncologists are having when trying to access other treatments to treat patients experiencing different types of immune related adverse events.

It was evident from the early discussion that there is a challenge in defining the meaning of steroid 'refractory 'cases and that there are broadly two. This broad term includes patients who do not respond to steroids over an unspecified length of time, and patients who have fluctuating responses to steroids.

The discussion prompted by this underlined that while initial protocols for managing some toxicities are well-established, guidelines for steps beyond steroid use are less clear. The guidance currently lists a series of steroid-sparing immunosuppressants, both traditional agents such as mycophenolate mofetil and tacrolimus to biological agents such as infliximab. However, there is a clearly outlined urgent need for more supporting guidance including detailed protocols, information on alternative drugs, their specific contexts, and ways of solving timely access issues related to these types of treatments.

The conversation highlights significant disparities in the availability of and comfort with using advanced treatments/ biologics, with this often stemming from differences in relationships between oncologists and other specialists/ non-oncologists, as well as in local policies and resources. There was a distinct feeling of wanting to move away from a dependence upon 'who you know…or, who picks up the phone'.

The increasing complexity of treatments for immune-related adverse events means that oncologists are increasingly being asked to step outside their traditional comfort zone and it was felt that this necessitated a different approach to accessing support, advice and knowledge to help guide them with some degree of consistency. This means going beyond traditional education models, and on one hand leveraging new ways of building awareness to put this challenge and similar issues onto peoples 'radar, and the other to make it easy and efficient for clinicians to find what they need and when they need it - advice in real time without it being time consuming.

Recognising these challenges and working towards joined up solutions which support oncologists to navigate them was agreed as crucial for advancing the management of steroid refractory episodes for patients.

Job Code: ONC-GB-2300467
January 2024

Management of Steroid Refractory Immune-Related Adverse Events. A Focused Approach

This report was written and funded by Bristol-Myers Squibb following two focus groups with Oncologists that took place in July 2023.

INTRODUCTION

Background.

A feature of checkpoint inhibitor immunotherapy are the development of autoimmune side effects - Immune-Related Adverse Events (irAEs). These adverse events can range from mild skin rashes to severe, life-threatening conditions. The first line management of irAEs often involves corticosteroids. However, a subset of patients do not respond adequately to steroids, rendering their condition 'steroid-refractory' and requiring additional immunosuppression[1].

Objective of the Report.

Two focus groups were undertaken to understand the barriers and challenges of managing adverse events not responding to steroids. This report provides an overview of the discussions within two focus groups that were undertaken in July 2023 on the management of steroid-refractory Immune-Related Adverse Events (irAEs). It sought to identify key topics, challenges and barriers faced across the UK by discussing the current various pathways, local guidelines, policies, access to appropriate experts, and immunosuppressive agents available for treating these complex cases.

The main objectives of the discussion were as follows –

- Evaluate the understanding and definition of the term "steroid-refractory" in different clinical scenarios.
- Explore the types of steroid-refractory drugs commonly used, including but not confined to, infliximab, vedolizumab, and mycophenolate mofetil (MMF).
- Understand the confidence of healthcare professionals in utilising these drugs in various settings.
- Discuss the need for consultation and collaboration with other specialists in managing steroid refractory cases.
- Identify the challenges and problems faced in the use of steroid-refractory drugs, such as issues with protocols, and access to specialists.
- Highlight the variability in responsibility for monitoring and the variation in understanding among healthcare professionals.
- Discuss the needs and recommendations for improving understanding and facilitating collaboration among medical specialties in managing steroid-refractory cases.

Focus group process.

A healthcare focus group is a research method used to gather insights and opinions from a small group of individuals who share certain characteristics or experiences related to healthcare.

Two groups of 14 participants were selected to represent a cross section of medical and clinical oncologists practicing across the NHS in a variety of specialist and District General Hospital (DGH) cancer centres from across the UK.

Two experienced chairs were nominated to jointly guide the conversation and ensure that all participants were given the opportunity to express their thoughts, experiences, and opinions. The focus groups were conducted on a virtual platform with consent given to record the discussion to ensure accurate capture and reference for subsequent analysis to identify recurring themes and specific insights.

Discussions across the two groups followed broadly similar lines using a framework of standard questions supplemented by appropriate follow up questions and prompts from the chairs.

Structure of this report.

This report is structured into three sections which integrate the discussions and insights from both focus groups -

1. Discussion: Access and general use of additional immunosuppressive agents
2. Discussion: Factors influencing decision making and overall adverse event management
3. Key findings and recommendations

SECTION 1 DISCUSSION THEME: ACCESS & GENERAL USE OF STEROID-REFRACTORY MEDICINES

The following topics and issues were discussed -

The difficulty in defining what constitutes steroid resistance.

The term "refractory" was considered potentially ambiguous. It's unclear whether it refers to patients who did not respond to treatment at all or those who initially showed some benefit but then subsequently had a flair of their side effect.

Two separate clinical scenarios were identified:

- Patients who do not respond to steroids over an unspecified length of time.
- Patients who have fluctuating responses to steroids.

It was noted that treatment considerations can vary significantly depending on the type of tumour. For example, the approach for melanoma patients might differ from that for renal cancer patients and this can be dependent on alternative treatment options and prognosis.

Uncertainty over how long steroids should be administered was mentioned. There were differences in the duration of steroid treatment that should have been used before additional immunosuppression is required. The challenges around deciding that the adverse events are definitely immunotherapy related was also discussed.

Participants agreed that guidelines for steroid dosages and durations may not always be clearly defined, making treatment decisions more complicated. The introduction of second and third-line agents into the treatment regimen also poses another layer of complexity, as there may be no standardised protocol to follow.

An example was offered where one contributor suggested they were willing to administer steroids for an extended period before considering other treatments. This is because switching to steroid-resistant treatment pathways might complicate future attempts to restart or rechallenge the patient with the initial immunotherapy treatment.

Retrospective analysis of outcomes can be challenging due to the varying treatment regimens used by different medical professionals and between centres.

The conversation highlighted the need for more definitive guidelines and protocols, particularly in the use of steroids and other immunosuppressants for adverse events that are thought to be caused by checkpoint inhibitor immunotherapy.

Immunosuppressant treatment used to manage and control steroid refractory adverse events.

Please note that the medicines mentioned in this section are not licensed for the management of immune-related adverse events. Please refer to local and national guidelines when making treatment decisions.

The most commonly mentioned steroid-refractory immunotherapy adverse reactions and the drugs that may be used to manage them included:

1. Colitis: Steroid-refractory colitis is managed with:
    - Infliximab: This is a monoclonal antibody that targets tumour necrosis factor-alpha (TNF-alpha), which is involved in the inflammatory response. It can be effective in managing severe or refractory colitis[2,3].
    - Vedolizumab: This medication targets alpha-4 beta-7 integrin and is another option for refractory colitis[2,3].

2. Pneumonitis: Steroid-refractory pneumonitis may require more potent immunosuppressive agents, including:
    - Mycophenolate mofetil: This medication suppresses the immune system and is sometimes used in cases of severe pneumonitis that do not respond to steroids[2,3].
    - Cyclophosphamide: In rare cases of severe, life-threatening pneumonitis, high-dose cyclophosphamide may be considered[2,3].

3. Hepatitis: For steroid-refractory hepatitis due to immunotherapy, treatment options may include:
    - Mycophenolate mofetil: This immunosuppressive medication can be used to manage severe cases of hepatitis that do not respond to steroids[2,3].
    - Tacrolimus: Similar to pneumonitis, tacrolimus may be considered in refractory cases of hepatitis[2].
4. Dermatitis/Rash: Severe skin reactions may be managed with drugs such as:
    - Methotrexate: This medication was sometimes used for severe refractory dermatitis or rash[4].
    - Cyclosporine: In certain cases, cyclosporine was prescribed to control skin reactions that do not respond to steroids[4].

Access and method of approval

Overall, the ease of access to and approval for specialised treatments seems to be influenced by a variety of factors, including the location, the specialty involved, and whether the treatment is listed on a hospital formulary. There's a shared sentiment for the need to standardise and formalise these processes to make them easier to use.

For some drugs like infliximab, approval forms might be required, but these vary in their use and enforcement. Some cases may bypass these forms altogether, especially if there is agreement that treatment is urgently needed. Processes and the degree of administrative burden vary between centres.

Once a drug is listed on the hospital formulary, it's generally described as easier to prescribe without going through administrative approval processes.

IV Immunoglobulins were described as harder to access and considered a different case requiring multiple layers of approval due to their specialised nature. If a patient is in the critical care unit, then funding can be less of a barrier.

It was noted that the ease of obtaining treatments can sometimes depend on the specialty overseeing the care. Gastroenterologists, for example, are more accustomed to

prescribing certain medications and can expedite the process based upon their familiarity with managing these kinds of adverse events and conditions.

Variation in approaches to using Infliximab.

Overall, there was notable variability in the use and dosing of Infliximab discussed, both within the context of colitis and for other conditions. This variability often stems from evolving clinical experiences and is guided by both specialists and oncologists.

Colitis

Infliximab is not licensed for the management of immune-related adverse events. Please refer to local and national guidelines when making treatment decisions

There is variation in the way infliximab is used to manage colitis. Some oncologists described a standardised protocol recommending two doses of Infliximab for colitis. This practice evolved due to patients developing flares after just one dose. Two doses were also described as allowing for quicker steroid tapering. Others begin with one dose but find the threshold for administering a second dose is decreasing so more patients are receiving a second dose.

Another approach involves planning for three doses but making an early decision to proceed based on the patient's response to the first dose.

Use in Non-Colitis Cases -

It was shared that Infliximab has been used in treating arthritis, bone and joint issues, and skin conditions. However, its use is less standardised in these cases. There did not appear to be a standard protocol for using Infliximab across other organ toxicities; decisions tend to be made on a case-by-case basis.

Decision-Making -

Typically, the decision to use Infliximab and its dosing regime is guided by organ specialists ('ologists), though in non-colitis settings, oncologists may also push for its use.

Access to, and use of other biologics.

Overall, the discussion highlighted the challenges and considerations in accessing and using biologic drugs for example Infliximab, and Disease Modifying Anti-Rheumatic Drugs (DMARD)s. There was perhaps a tendency to stick to familiar drugs and protocols, and a collaborative approach with specialists is often favoured for less familiar or more complex cases.

Most participants appeared to rely primarily on a few drugs like Mycophenolate, Infliximab, and Vedolizumab. They described tending not to venture beyond these unless the patient is in intensive care where multiple teams are involved in decision-making.

Oncology teams prefer to use what they are most comfortable with, such as Infliximab, due to familiarity with dosing. This can create a risk of confirmation bias and limit the usage of other potentially effective drugs.

Relatively easy access to Infliximab and Vedolizumab, particularly for conditions like colitis was described.

For conditions like arthritis, the responsibility often falls to the rheumatologist, and access might be trickier due to funding streams and approval processes.

Other potential barriers to access.

Overall, the barriers discussed clearly highlighted the increasing complexity and workload associated with managing IO toxicity, pointing to a need for effective strategies and possibly specialised services to handle the growing patient volume and complexity.

Participants highlighted a significant rise in the number of patients experiencing immunotherapy toxicity (IO tox) as these treatments become more commonly used. This has led to capacity issues, putting additional pressure on the numbers seen in clinics.

Consultation times have expanded due to the complexity of managing IO toxicity. What used to be a 20-minute consultation now often approaches an hour. This issue is expected to worsen as more IO treatments are introduced.

There's anticipation of an increased pressure in the steroid-refractory treatment space in the future as more adjuvant indications for IO therapies come into play and as late toxicities from earlier treatments begin to emerge. Without effective strategies to manage these patients, it was indicated that day units and assessment services could be overwhelmed.

SECTION 2 DISCUSSION THEME: FACTORS INFLUENCING DECISION MAKING AND OVERALL ADVERSE EVENT MANAGEMENT

The following topics and issues were discussed -

Leadership in Immunotherapy and managing IO toxicities.

Many institutions do not have a formalised role for a lead oncologist in immunotherapy toxicity (IO tox) management. Some have been unofficially tasked with IO-related responsibilities but without specific job plan time allocated for it.

Where no formal designated IO toxicity leaders are in place in most centres, collaboration with organ specialists (referred to as 'ologists') is common. Some trusts also utilise a multidisciplinary team (MDT) approach for routinely discussing IO toxicity cases.

In several centres, consultant pharmacists and senior specialty doctors have taken up roles in IO toxicity management, running clinics and overseeing protocols. Nurses specialising in this area also manage IO toxicity clinics, in some cases becoming the primary point of contact for patients.

Where cancer services have established IO toxicity clinics run by various professionals like consultant pharmacists or senior specialty doctors, these clinics focus on managing patients with acute toxicity; on a routine basis however a number expressed the need for advice and guidance to be readily available for quick decision-making without the need for waiting until the next clinic (which might be a week or more away).

In the absence of a formal role, several clinicians described having taken on de facto leadership in IO toxicity management. This includes running IO study days, overseeing protocols, and educating people across the trust.

There is a recognised need for more standardised approaches across different sites and departments. The absence of a formal leadership role in this area has led to a somewhat fragmented approach to managing IO toxicity.

Overall, while there is less formalised leadership for IO toxicity management, a collaborative and multidisciplinary approach involving various healthcare professionals has been the prevailing practice. There is, however, a noted need for standardisation and perhaps formal leadership roles to better manage the growing complexity and prevalence of IO toxicities.

Access to other specialty MDTs

Participants mentioned Liver, Gastro, and Lung MDTs have been consulted for cases of difficult or long-standing toxicity. These MDTs are not only useful for managing challenging cases but also serve as a platform for shared learning among consultants across specialties.

However others noted that they don't personally access these MDTs. In many cases, other specialists handle the MDT discussions, often without the knowledge or involvement of the referring physician. This is attributed to busy job plans and scheduling conflicts.

It was noted that specific MDT designated for immunotherapy toxicity (IO tox) were unusual, which may limit specialised discussions around cases of adverse events which are not responding to steroids.

Some believe that oncologists should be more involved in these MDTs to better engage other specialties in the care of their patients. However, clinical commitments often make it difficult for them to attend.

In the absence of a designated IO MDT, clinicians often rely on networking and colleague recommendations to decide which MDT or consultant to consult for specific issues. The choice of consultant or MDT may be influenced by who has shown interest in these cases in the past.

Access to advice from other specialties.

Participants described that they typically reach out to specific consultants within the organ of toxicity (e.g., hepatologist) for advice, but these specialists are not always available. In such cases, they speak to the consultant on call, which can lead to variability in the advice received based upon their experience and familiarity with managing these types of cases.

Advice from a specialised consultant was often considered more reliable than that from on-call teams. However, both can be variable.

There was discussion about whether oncology teams are funding organ specialists for specific advice; currently, most don't have a formal payment system or service level agreements but rely on networking and relationship-building.

Some participants noted that they prefer to consult with specialists they've worked with before, as these specialists have better understanding and experience with IO toxicities.

There was a general agreement on the need for more formal guidelines to reduce inconsistencies and variability in advice between different specialists.

Building relationships with specialists in various fields has been a lengthy process. Some centres have formal agreements with specialties like gastroenterology, cardiology, neurology, endocrinology, etc, while others do not It was felt that there is a need for more formal agreements, especially as the workload for some specialists is increasing due to the rise in IO usage.

When facing resistance from other specialties to be involved, some clinicians call upon more experienced centres for guidance. Others find that having an organ specialist who has experience of investigating and managing adverse events can support other organ specialists who are less experienced. For instance, organ specialists supporting centres outside of their local area.

In summary, while there is a general framework for consulting other specialists for IO toxicity management, the process is characterised as largely informal and built on relationships.

Managing Mild to moderate toxicities (Grade 1 and 2)

Some participants mentioned difficulties with managing lower-grade (Grade 2 or persistent Grade 1) toxicities that do not resolve despite steroids. There's hesitation to repeatedly adjust steroid doses due to potential complications. A particular challenge is patients with a moderate toxicity that doesn’t completely resolve referred to on a number of occasions as ‘grumbling grade 2 toxicity’.

Diagnosing the cause of symptoms in patients receiving IO therapy can be complicated due to multiple potential causes, such as disease progression, infection, or other toxicities. This makes treatment decisions for lower-grade toxicities particularly difficult.

There's a distinction between acute refractory patients and those with "grumbling" lower-grade toxicities whose symptoms wax and wane. The latter group presents a challenge in determining when to escalate treatment or add another drug.

It was felt that current guidelines can be unclear about managing these lower-grade toxicities, especially when considering options beyond steroids. This leaves clinicians to make case-by-case decisions, which can be challenging.

Some centres have tried to develop more specific protocols to navigate this area. The aim is to bring consistency to the treatment approach and to better guide clinicians in their decision-making process.

There's a trend toward using biologics for patients who cannot be tapered off steroids. This approach is still under evaluation, but it appears to offer an alternative for long-term steroid users.

There's a general sense that specialists may not have adequate experience to manage these grumbling lower-grade toxicities, making the decision-making process even more complex. Clinicians are becoming more open to considering biologics earlier in the treatment process, although the efficacy of this approach is still under evaluation.

In summary, managing lower-grade IO toxicities presents a unique set of challenges, including unclear guidelines, complications from long-term steroid use, and diagnostic complexity. While some centres are developing protocols to handle these cases better, there is still much uncertainty, especially about when to add in additional immunosuppressants.

Involvement in reducing steroid doses and de-escalating additional immunosuppression.

It was noted that oncologists in many centres have struggled to establish de-escalation protocols with other specialists. While there has been progress, it can take significant effort to reach consensus on how to manage patients on long-term additional agents for immune related toxicities.

Different specialists within the same specialism have different approaches to de-escalating immunosuppressive agents, making it anecdotally challenging for oncologists to decide to whom they should refer patients.

In discussion it seems oncologists are not always aware of whether a patient has had their immunosuppression de-escalated/reduced until the patient returns to their clinic. This creates difficulties in planning further treatment, indicating a need for better communication between specialties.

Keeping up with de-escalation decisions across different specialties is a challenge. Clinicians often have to dig through electronic health records to understand what has been done, pointing to a need for improved information flow.

Much of the de-escalation communication occurs via email rather than in-person clinic visits. This is often faster but can result in less comprehensive oversight.

Some patients were seen in clinics months after the referral, making the consultation less relevant to the immediate treatment needs. This indicates a need for timelier engagement from specialists.

Protocols, guidelines and learning

Protocols

Clinicians feel more confident initiating treatments when they are more familiar with the immunotherapy toxicities or have specialist input. Those who are less experienced are more cautious and seek approval from specialists.

It was described that the use of drugs like tacrolimus and mycophenolate is typically guided by specific protocols available on hospital intranets. However, there is a preference for relying on specialists familiar with these drugs for patient management, especially for drugs requiring level monitoring like tacrolimus and cyclosporin.

Some centres reported not having specific oncology guidelines for drugs beyond steroids. There are specific gaps in guidelines for treating conditions like pneumonitis that don't usually require second-line immunosuppression in standard care. This results in some "freefall" scenarios where clinicians have to navigate uncharted territory.

The role of specialists like hepatologists, gastroenterologists, and rheumatologists in guideline creation and patient management is highlighted. However, the timelines of guideline updates is a concern, making it essential to consult updated guidelines and discuss challenging cases with colleagues.

There's a call for aggregating experience across cases and specialties nationally to better inform practice and fill in the gaps in existing guidelines.

In summary, the discussion suggests that while some protocols and guidelines exist, there's substantial variability and gaps. There's a general reliance on specialists for complex cases and drugs requiring specific monitoring. The need for up-to-date, comprehensive guidelines that can be widely adopted was highlighted and agreed.

Learning and access to wider knowledge & experience.

Knowledge about IO toxicities have largely been built through shared experience and education. Both generalists and specialists are learning from each other, but there's a sense that guidelines from the respective specialties hold more weight.

There was a general appetite for a centralised approach, whether it's a Multidisciplinary Team (MDT) or a repository of expertise, especially for complex or unusual cases noting that a national MDT could be potentially unwieldy, but a national repository where clinicians could access advice seems more feasible and helpful.

Running a regional MDT regularly poses logistical challenges. Complex cases often require immediate attention, making a once-a-month MDT meeting insufficient.

There's a call for better sharing of experiences from complex cases. A national repository could be a good way to collate this information and build collective experience.

Having a "friend to phone" or immediate advice system, possibly supported by a repository, could be a more effective way to manage urgent, complex cases.

The fast-paced evolution in oncology treatments, particularly with new biologics, makes it challenging for individual clinicians to stay updated. Acute oncology services may need to take the lead in education and serve as a go-to resource for complex cases. There was also a recommendation for other forms of educational material and platforms such as podcasts.

A repository could serve as an invaluable resource for clinicians dealing with patients who don't neatly fit existing guidelines. It could supplement or even eliminate the need for some MDTs by providing immediate access to past cases and their management strategies.

In summary, while there is significant interest in having a centralised system for managing complex oncology cases, the form it should take—whether a formal MDT, an advice repository, or some other structure—is still under debate. Logistical challenges, the need for immediate advice, and the rapidly evolving landscape of oncology are key factors that need to be considered.

SECTION 3: KEY FINDINGS AND RECOMMENDATIONS

The following topics and issues were discussed -

Key findings

Ambiguity and Variability in Treatment

The term "refractory" lacks a universal definition, creating uncertainty in application of treatment protocols for patients resistant to steroids.

There is a high degree of variability in treatment approaches and protocols, including steroid dosages, durations, and the use of second and third-line agents.

Drug Choices and Administration

While steroids are the go-to treatment for various conditions, other medications like Infliximab, Vedolizumab, and Mycophenolate are being used for steroid-resistant cases.

Prescribing approach for treatment with commonly used biologics such as Infliximab varies from centre to centre.

Administrative and Access Barriers

Access to specialised treatments is influenced by multiple factors, including location, specialty, and hospital formulary.

Drugs like IV immunoglobulins require more layers of approval, which may complicate treatment.

Increasing Complexity and Workload

The rising use of immunotherapy has led to an increase in the number of patients experiencing toxicity, further burdening healthcare resources, especially those focused on provided unplanned response.

A lack of formal leadership in many centres to managing immunotherapy toxicity (IO tox) has led to a fragmented approach.

Decision-making and Specialty Involvement

Decision-making is largely collaborative but informal, relying on relationships and expertise rather than formal guidelines.

Mild and moderate, grades 1 and 2 side effects, present unique challenges due to unclear/ unavailable guidelines and treatment complexities when the side effect does not settle on initial steroid treatment.

Recommendations

These recommendations are focused upon positive steps to support oncologists and relevant specialties to be more uniform, consistent, and effective in the treatment response of steroid-refractory toxicity management.

Clarifying Terminologies and Guidelines

Standardise the definition of terms like "steroid-refractory" to reduce ambiguities in treatment protocols.

Develop comprehensive, evidence-based guidelines for steroid dosages, durations, and the introduction of second and third-line agents that can be used across the UK and beyond.

Streamlining Access and Administration

Simplify the process for accessing specialised treatments by streamlining approval forms and administrative procedures.

Consider introducing a fast-track approval system for urgent cases to bypass administrative delays.

Addressing Workload and Complexity

Focus on strategic approaches to manage the increasing patient volume and complexity due to the rise in IO treatments.

Consider the establishment of specialised IO tox clinics and formalise roles for healthcare professionals in managing IO toxicities.

Enhancing Decision-making and Collaboration

Formalise the consultation process between specialties and create protocols for consistent and reliable advice.

Develop more specific protocols for managing lower-grade toxicities and facilitation of early introduction of biologics in treatment where appropriate.

Information Sharing and Continuous Learning

Consider what it will take to create a centralised repository for sharing experiences, guidelines, and advice on complex cases, accessible to healthcare professionals nationwide.

Regularly update guidelines and educate healthcare professionals on the latest treatments and approaches, possibly through a central point of access and communication.

Education of other specialty groups and sharing learning about the use of immunosuppressants in this subset of patients. Consideration of further educational materials like podcasts.

References

1. Tomsitz D, Ruf T, Zierold S, French LE, Heinzerling L. Steroid-Refractory Immune-Related Adverse Events Induced by Checkpoint Inhibitors. Cancers (Basel). 2023 Apr 28;15(9):2538

2. Haanen J et al. (2022). Management of toxicities from immunotherapy: ESMO clinical Practice guideline for diagnosis, treatment and follow-up. Ann. Oncol. 33 (12), 1217–1238.

3. Schneider et al. (2021). Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO Guideline update. Journal of Clinical Oncology. 39:36, 4073-4126.

4. Phillips GS et al. J Clin Oncol. 2019; 37:2746-2758