



Published in final edited form as:

Lancet Oncol. 2025 February ; 26(2): e90–e102. doi:10.1016/S1470-2045(24)00404-2.

Management of immune checkpoint inhibitor-associated toxicities in older adults with cancer: recommendations from the International Society of Geriatric Oncology (SIOG)

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All authors formulated and defined the focus of the Policy Review, conducted scoping reviews, drafted text and recommendations, and provided critical review of the paper. CME served as chairperson of the working group and coordinated the group's activities.

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Abstract

Immune checkpoint inhibitors (ICIs) have substantially advanced the treatment landscape for a wide variety of malignancies. Older adults represent a large and rapidly growing demographic, among whom ICIs are widely prescribed. Management of ICI-associated toxicity among older adults, particularly in the presence of frailty and comorbidity, poses unique challenges. In this Policy Review, developed by the International Society of Geriatric Oncology (SIOG), we offer an evidence-based framework for health-care providers, caregivers, and policy makers for treating older adults with ICIs, focusing on unique considerations for this population that are not adequately addressed by existing guidelines, and expanding them to encompass geriatric oncology principles.

Introduction

The introduction of immune checkpoint inhibitors (ICIs) has transformed cancer treatment, offering therapy that is often more tolerable for older patients relative to historical standards of care. Older patients (defined broadly as adults aged ≥ 70 years) represent a large and growing proportion of patients seen in oncological practice, and frequently present with substantial comorbidity, frailty, and functional impairments.

Despite the therapeutic potential and advantages of ICIs, their use can expose patients to immune-related adverse events, which, even at low grades, can substantially impact the wellbeing and health-related quality of life of older patients with underlying comorbidity or frailty. The management of immune-related adverse events frequently necessitates prolonged immunomodulatory and immunosuppressive therapy (>4 weeks), posing additional risks, particularly for older patients. These factors often complicate the management of low-grade toxicity and can have a disproportionate impact on older patients' quality of life and ability to continue treatment.¹⁻³

Major immunotherapy guidelines (eg, the American Society of Clinical Oncology,⁴ the National Comprehensive Cancer Network,⁵ the European Society of Medical Oncology,⁶

and the Society of Immunotherapy of Cancer⁷) offer detailed evidence-based guidance for managing individual immune-related adverse events, organised by organ system, and focusing primarily on pharmacotherapy. In general, the principles of these guidelines apply equally to older patients. Nonetheless, despite the utility of such guidelines, organ-based approaches are not always suitable to address the specific needs of older populations.

This Policy Review addresses unique aspects in the management of ICI-associated (eg, anti-PD-1 or anti-PD-L1 [anti-PD(L)-1], and anti-CTLA-4) toxicities among older adults, defined broadly here as adults 70 years and older, in line with previous guidelines from the International Society of Geriatric Oncology (SIOG) and expert consensus. In this Policy Review, we highlight considerations for the management of the most prevalent immune-related adverse events among older patients and the use of immunosuppressive agents in this population. Additionally, we offer guidance regarding the use of comprehensive geriatric assessment (CGA) as a tool to contextualise toxicity in relation to patient-centred care among older patients, whose treatment priorities often favour quality of life and functional independence over survival alone.

Data collection and recommendation development

A multidisciplinary working group composed of subject-matter experts in internal medicine, including medical oncology, haematology, geriatric medicine, nephrology, rheumatology, pharmacology, clinical immunology, and patient advocacy, from Europe and North America, was established in December, 2022, to undertake development of this Policy Review. The working group convened between December, 2022, and March, 2024, on five occasions by teleconference, with further correspondence by email and in person.

Given the limited evidence base specifically reporting on older adults, a scoping review supplemented by expert opinion was deemed the most suitable method for this Policy Review. The method used aligns with the Institute of Medicine protocols for clinical guideline development in all aspects, except for systematic review, which we considered to be unsuitable for this Policy Review. Following consensus drafting of themes and structure, authors or author subgroups, formed from members of the working group, undertook individual scoping reviews to inform the development of key recommendations.

Authors or author subgroups, developed summary text of key recommendations and graded their recommendations according to Oxford Centre for Evidence-Based Medicine guidelines (ie, levels 1–5 or, in the absence of clear evidence, on the basis of expert consensus). Levels of evidence were defined as: Level 1—evidence obtained from systematic reviews or meta-analyses; level 2—evidence obtained from randomised controlled trials or observational studies with substantial effects; level 3—evidence obtained from non-randomised, controlled cohort studies or follow-up studies; level 4—evidence obtained from case series, case-control studies, or historically controlled studies; and level 5—mechanism-based reasoning. In the absence of clear evidence, recommendations were made on the basis of expert consensus. The inclusion and scoring of individual recommendations were subjected to a blinded voting procedure using an online voting tool. Votes were collated and analysed by the lead author. Recommendations were adopted when they met at least 75% acceptance.

Statements and recommendations provided without evidence grading were considered reasonable standard practice by the authors. A summary of key recommendations is provided in table 1.

Incidence and patterns of ICI-associated toxicity in older adults

Patterns of toxicity for ICIs are distinctive and differ substantially from other therapeutic modalities such as chemotherapy. Ageing and frailty are associated with major alterations in immune function, including T-cell anergy, exhaustion, and senescence,⁸ as well as chronic, low-grade, ageing-associated inflammation (termed inflammageing),⁹ which might affect the toxicity profile of ICIs among older adults.

Results from several pooled analyses and real-world studies suggest that the incidence of high-grade immune-related adverse events is broadly similar,^{10–13} or slightly higher,¹⁴ among older populations when compared with younger populations. The risk of low-grade immune-related adverse events might also be higher among older patients ($p=0.08$),¹⁴ and older patients who develop immune-related adverse events appear more likely to develop multisystem immune-related adverse events (32% vs 18%; $p=0.037$),¹⁴ and to require admission to hospital (54% vs 29%; $p=0.02$) than younger populations.¹⁵ ICI discontinuation due to immune-related adverse events is higher for patients aged 90 years and older (30.9% vs 15.1%; $p=0.008$) than in those aged 80–89 years,¹² indicating a diminished tolerance for low-grade immune-related adverse events with increasing age. Given these findings, older patients reporting low-grade toxicity should undergo a holistic assessment of quality of life alongside standard Common Terminology Criteria for Adverse Events (CTCAE) scoring to inform decisions relating both to initiation of immunomodulatory and immunosuppressive therapies, and discontinuation of ICI treatment.

Frailty is distinct from, but related to, older age and poor performance status, and is associated with increased risk of adverse health outcomes when subjected to physiological stressors.¹⁶ One of the operationalisations of frailty is as a symptom complex including at least three of: unintentional weight loss, self-reported exhaustion, muscle weakness, low physical activity, and slow gait speed.¹⁷ Frailty, rather than age, has been identified as a risk factor for acute care use during ICI treatment,¹⁸ and further studies identify frailty and poor mobility as predictive of both survival outcomes¹⁹ and toxicity²⁰ in this setting.

Quantifying the risk of immune-related adverse events among older adults is often challenging, particularly when accounting for other age-related factors, such as comorbidity, frailty, and functional impairments. There are currently no validated predictive tools for ICI toxicity. The use of the CARG (the Cancer Aging Research Group)²¹ and CRASH (the Chemotherapy Risk Assessment Scale for High-Age Patients)²² scores, which have been validated for the prediction of toxicity among older patients undergoing chemotherapy, have not been validated in the setting of ICIs, and should not be used to guide treatment decisions in this setting.

Combination treatment

ICIs are frequently administered in combination with either a second ICI, targeted therapy, or with chemotherapy. Treatment regimens incorporating both anti-PD(L)-1 and anti-CTLA-4 show grade 3 or worse toxicity rates of up to 55% in younger and older cohorts alike.^{23,24} Observational cohort studies and an analysis of the US Food and Drug Administration Adverse Event Reporting System database show that these rates remain consistent across age groups.^{24–26} Combination ICI–tyrosine kinase inhibitor (TKI) therapy, which has a particular role among cancers prevalent among older patients (including renal cell and endometrial cancers), is associated with a high risk of severe toxicity (grade ≥ 3 in $>80\%$ of generally fit patients).^{27–29} Although age-stratified data from pivotal trials of combination chemoimmunotherapy remain scarce,³⁰ observational data suggest that grade 3 or worse toxicity of combination pembrolizumab–chemotherapy treatment increases with age,^{31,32} and that age is a strong predictor of early ICI–TKI discontinuation.³³

Given the high rates of toxicity and discontinuation observed among older patients with immunotherapy combination approaches, and the paucity of data contextualising toxicity in relation to degree of frailty or functional status, rather than chronological age, we advise considerable caution and detailed patient counselling before adopting ICI–ICI, ICI–chemotherapy, and ICI–TKI strategies in older populations with poor performance status or frailty.

Patients with pre-existing autoimmune disease

Conflicting evidence exists regarding the impact of pre-existing autoimmune disease on the toxicity of immunotherapy among older adults. A multicentre cohort study of older patients with existing autoimmune disease, including rheumatological, dermatological, gastrointestinal, and neurological conditions, who were treated with PD-1 monotherapy showed an increased risk of disease flare for pre-existing rheumatological conditions, but not gastrointestinal or neurological conditions.³⁴ A retrospective study in older patients with pre-existing inflammatory bowel disease receiving ICIs showed a higher risk of adverse gastrointestinal-related events relative to a non-inflammatory bowel disease cohort, particularly among patients receiving anti-CTLA-4 treatment.³⁵ In contrast, numerous other retrospective studies reporting on outcomes among older patients with predominantly rheumatological, dermatological, gastrointestinal, and endocrine autoimmune disease; urological cancers;³⁶ melanoma;³⁷ or non-small-cell lung cancer³⁸ showed similar rates of grade 3 or worse adverse events when compared with populations without autoimmune disease. Although CTLA-4 inhibitors probably confer a higher risk of immune-related adverse events than PD(L)-1 inhibitors in older patients with existing autoimmune disease, this observation has not been confirmed by prospective studies.

Although sparse, the available data suggest that immunotherapy can be considered for older patients with pre-existing autoimmune disease, subject to a multidisciplinary assessment of the type and severity of the underlying autoimmune disease, including consultation with organ-specific specialists.

Rechallenge following toxicity

ICI rechallenge following an immune-related adverse event is associated with a higher risk of all-grade immune-related adverse events, but not high-grade events, compared with initial treatment, and these risks seem not to differ according to age.³⁹ In a meta-analysis, longer time intervals between cessation of therapy and rechallenge have been associated with an increased risk of toxicity recurrence,³⁹ but it is unclear whether this finding is confounded by the severity and duration of initial toxicity. Given the absence of high-quality data among older adults, we recommend that the decision to reintroduce immunotherapy following severe toxicity should be individualised, taking into consideration the severity of the immune-related adverse event, the response to treatment, and the availability, expected efficacy, and toxicity of alternative treatment options, including best supportive care.

The use of concomitant immunosuppression during rechallenge has been described by guidelines including the European Society for Medical Oncology.⁶ We do not specifically endorse this approach among older adults due to their higher susceptibility to the adverse consequences of immunosuppression and the paucity of strong supporting evidence in this population.⁴⁰

Toxicity-specific recommendations in older adults

This section focuses on specific toxicities associated with ICIs that are particularly relevant to older adults with cancer. These toxicities, including dermatological conditions, diarrhoea and colitis, arthritis, endocrinopathies, fatigue, and delirium, are highlighted due to their high prevalence or substantial impact on this population.

Dermatological toxicities

Cutaneous immune-related adverse events are the most common immune-related adverse event in patients treated with ICIs, and appear to occur more frequently in older patients than in younger patients, although the evidence is variable.^{11,12,14} Between 15% and 30% of patients treated with ICIs develop any-grade cutaneous immune-related adverse events, with the lowest frequency for anti-PD(L)-1 treatments, followed by anti-CTLA-4 and combination regimens.^{11,12,14,41,42} Common clinical presentations include rash and pruritus. Although typically low-grade, cutaneous immune-related adverse event affecting instrumental activities of daily living (grade ≥ 2) can nonetheless pose serious consequences for older adults, particularly those with poor underlying skin integrity.

Evaluation of dermatological toxicity should include a full skin and oromucosal examination. Sequential clinical photography, dermatology opinion, and biopsy should be considered in cases of grade 3 (or prolonged grade 2), or worse, toxicity. Additionally, other medical causes of pruritus common among older adults, including hepatic and renal impairment, iron deficiency anaemia, polycythemia, and thyroid endocrinopathies, should be considered and excluded.

H1-antihistamines are commonly used as antipruritics and are recommended for the treatment of immune-related pruritus on ICI treatment.⁴⁻⁷ First-generation H1-antihistamines are not recommended in older patients given their undesirable toxicity

profile, which includes anticholinergic activity, glaucoma, and delirium. Given the more favourable toxicity profile of second-generation H1-antihistamines, and the lower risk of drug–drug interactions, we recommend fexofenadine as the preferred H1-antihistamine in older adults.⁴³

Other measures for grade 1–3 dermatological toxicity include initiation of topical corticosteroids, omalizumab, topical emollients, and avoidance of sun and skin irritants.^{4,6,44}

Diarrhoea and colitis

Diarrhoea is among the most common toxicities of ICI therapy and is frequently the presenting manifestation of ICI-associated colitis. In older adults with reduced reserve capacity, diarrhoea and colitis can result in dehydration, malabsorption, and nutritional deficiencies, resulting in substantial physiological strain and necessitating prompt evaluation and intervention.

Rates of ICI-associated colitis and diarrhoea are similar in the older population when compared with the overall cancer population.^{12,45} In an international, multicentre cohort of patients aged 80 years and older receiving single-agent ICI (>95% anti-PD[L]1), any-grade colitis and diarrhoea were observed in 9.2% of patients.¹² The incidence of diarrhoea with CTLA-4 inhibitors is higher than with PD(L)-1 inhibitors, is dose dependent, and, among older adults, is as high as 25%.¹²

Management of colitis in older adults should follow a stepwise approach based on severity. Abdominal imaging, such as abdominal x-ray or CT, should be considered to provide initial diagnostic information, which, in certain cases, might avoid the need for endoscopy. Gastroenterology consultation and endoscopic evaluation should be considered in circumstances where patients are fit for such assessments, both to confirm the diagnosis and to exclude other causes of diarrhoea. A lower threshold of intervention is advised for patients with evidence of frailty, particularly those with baseline bowel or bladder dysfunction, or at an increased risk of falls, as they might be at higher risk of complications even at a lower severity of diarrhoea. Older patients with persistent symptoms should additionally undergo dietetics assessment.

Infectious or malignant causes of symptoms should be considered and excluded.⁷ Concurrently, supportive care should be implemented, including antidiarrhoeals, such as loperamide, intravenous hydration, and electrolyte replacement. In cases of grade 2 or worse diarrhoea and colitis (≥ 4 episodes per day above baseline), immunotherapy should be withheld, with initiation of oral budesonide, and consideration of inpatient admission in frail patients. In severe cases, systemic corticosteroids are advised, and the TNF inhibitor infliximab or the $\alpha 4\beta 7$ integrin inhibitor vedolizumab should be considered in corticosteroid-refractory colitis.⁵ The gut-specific activity of vedolizumab is particularly advantageous for managing colitis with minimal systemic immunosuppression.

Musculoskeletal toxicities

Approximately 10% of patients treated with ICIs develop rheumatic or musculoskeletal toxicities.⁴⁶ Musculoskeletal toxicities—including arthritis, polymyalgia rheumatica-like,

and myositis⁴⁷—are more frequently reported in older patients,^{26,48} but are often underdiagnosed or underestimated in CTCAE reporting of large ICI trials due to poor investigator awareness.⁴⁶ These toxicities can occur de novo (around 85%), or as a flare of pre-existing rheumatic disorders.^{46,49}

Although musculoskeletal toxicities are typically low grade and rarely fatal (with the exception of myositis), they often cause substantial functional impairment and pain that can restrict instrumental activities of daily living, particularly in older adults.^{4,46,47,50} Musculoskeletal toxicities often take a chronic course,⁵¹ requiring long-term anti-inflammatory treatment, including systemic or articular corticosteroids, non-steroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs (DMARDs), and immunosuppressants.^{46,50}

Diagnostic investigation of musculoskeletal toxicities mirrors the evaluation of classic rheumatic and musculoskeletal disorders, and should involve consultation with a rheumatologist, preferably before commencing corticosteroid treatment. Clinical, laboratory, imaging, and histological assessments should aim to verify signs of inflammation (eg, synovitis) and to exclude important differential diagnoses (eg, non-inflammatory degenerative, metastatic, paraneoplastic, or infectious disease). Reassessment of baseline and follow-up imaging after the onset of an immune-related adverse event can occasionally reveal inflammatory findings when these are explicitly sought, and can help to distinguish pre-existing rheumatic disease from true, rheumatological, immune-related adverse events.

Prospective studies assessing ICI-associated musculoskeletal toxicities remain scarce, and there are limited data on the impact of rheumatological immune-related adverse events on quality of life, functional independence, and treatment outcomes among older adults. However, paralleling classic rheumatic and musculoskeletal disorders, higher rates of frailty, sarcopenia, disability, and consequent functional impairment are to be expected in older adults with musculoskeletal toxicities, potentially necessitating early ICI discontinuation despite good oncological response. Older patients who develop grade 2 or worse musculoskeletal toxicities should be additionally referred for assessment by physiotherapy, occupational therapy, or both, as appropriate.

Thyroid and adrenocortical endocrinopathies

ICI therapy can induce often irreversible inflammation in endocrine organs, resulting in thyroid, adrenal, or pituitary endocrinopathies. Immune-related endocrinopathies occur in 14% of older patients treated with anti-PD(L)-1 agents.¹⁴ Some reports suggest a lower incidence of endocrine dysfunction among older patients compared with those aged 70 years or younger.^{11,14}

Most ICI-associated thyroid endocrinopathies present as a transient subclinical thyrotoxicosis followed by a hypothyroid phase, which can become permanent in up to 40% of cases.⁵² Classic symptoms of hypothyroidism are often absent in older patients, who more often present with non-specific findings, such as depression, fatigue, or exacerbation of underlying (possibly undiagnosed) neurocognitive disease.⁵³ Given the frequently subtle presentation of hypothyroidism in older adults, routine thyroid-stimulating

hormone testing at baseline and every 6 weeks is recommended for older patients on ICI treatment. Testing should also be prompted in older patients exhibiting persistent changes in cognition, memory, mood, cold sensitivity, or fatigue. Unlike many other immune-related adverse events, corticosteroids typically play no therapeutic role in immune-related thyroid endocrinopathy, which is typically managed with hormone replacement therapy alone. Older patients typically require reduced levothyroxine doses.⁵⁴ In particular, older patients with a history of cardiovascular disease might be at higher risk of arrhythmia, and levothyroxine should be initiated at lower doses, increasing by 12.5–25 µg every 4–6 weeks until thyroid-stimulating hormone concentrations normalise.⁵⁴

ICI-associated adrenal insufficiency most frequently arises as a consequence of hypophysitis (secondary adrenal insufficiency), whereas primary adrenal insufficiency is less common.⁵⁵ The incidence of hypophysitis is higher with anti-CTLA-4 (6.4%) or combined ICI therapy (3.2%) compared with anti-PD-1 (0.4%) or anti-PD-L1 (0.1%) monotherapy.⁵⁵ One retrospective analysis of 154 patients with melanoma treated with ipilimumab identified older age as a risk factor for anti-CTLA-4-induced hypophysitis ($p=0.005$).⁵⁶

Older age is also a risk factor for adrenal crisis and associated mortality.^{57,58} Additionally, adrenal insufficiency (particularly primary adrenal insufficiency) can lead to orthostatic or postural hypotension, which can result in adverse outcomes in older patients, including decreased mobility, falls, and syncope. Symptoms of adrenal insufficiency are often non-specific and include fatigue, weakness, weight loss, and abdominal pain, which can be misattributed to other conditions common in older adults with cancer. The non-specificity of symptoms complicates the recognition of adrenal insufficiency among older patients, but should prompt testing of adrenocorticotrophic hormone and cortisol, particularly among patients undergoing combined ICI-containing or CTLA-4-containing regimens, and among those who report symptoms consistent with pituitary compression such as headaches, diplopia, or vomiting.

In general, steroid-replacement therapy among older adults with primary and secondary adrenal insufficiency is similar to that for younger adults, although closer monitoring of clinical symptoms is required.⁵⁷ For some older patients, prednisolone might be favoured over the more frequent dosing schedule necessitated by hydrocortisone.⁵⁷ Attention should be given to the risks of osteopenia, sarcopenia, and hypertension (particularly in primary adrenal insufficiency requiring mineralocorticoid replacement). Given potential challenges with cognition and the understanding of medication regimens in some older adults, and the higher incidence of crisis precipitants (eg, infection or acute illness) in this population, patients and their caregivers should be provided with medical identification indicating the condition, and be educated on the recognition and initial management of adrenal crisis, particularly relating to stress dosing of steroids.

Fatigue

Fatigue is a complex and multifactorial symptom that can be influenced by numerous factors, including comorbidity, polypharmacy, physical deconditioning, psychological wellbeing, the availability of social supports, and the physiological impacts of malignancy and systemic treatment.

Fatigue is a prevalent all-grade and grade 3 or worse adverse event associated with PD(L)-1 inhibitors, with an all-grade incidence of 18%.⁴⁵ Higher rates of early ICI-associated fatigue have been reported in patients with poor performance status and among patients with higher disease burden.⁵⁹

Worsening of fatigue beyond a patient's baseline following commencement of immunotherapy is common, and should prompt clinicians to exclude other causes, described previously, alongside immune-related endocrinopathies, including hypothyroidism, adrenal insufficiency, and hypophysitis. Given the high prevalence of pulmonary and cardiac comorbidities in this population, and the risk of pneumonitis and myocarditis associated with ICIs, assessment of fatigue in older adults should include evaluation for shortness of breath due to the frequent overlap of these symptoms.

In cases of grade 2 or worse fatigue (ie, fatigue affecting instrumental activities of daily living), when no identifiable cause is found, we recommend consideration of a break in therapy to assess for symptomatic improvement, alongside non-pharmacological strategies, including physical therapy, sleep-hygiene advice, psychosocial assessment, and nutritional optimisation.

Delirium

Delirium is a frequent and serious complication of almost all cancer treatments, and is defined as an acute, fluctuating, change in attention, level of alertness, cognition, and behaviour secondary to a medical condition or medications.⁶⁰ Delirium has a greater incidence among older patients, particularly among those with underlying cognitive impairment, and is associated with higher morbidity and mortality, prolonged duration of hospital stay, worse quality of life, and early treatment cessation.⁶¹

Delirium can arise directly from ICI therapy (ie, as a presenting feature of immune-related neurotoxicity), corticosteroid therapy initiated to manage ICI toxicity, or otherwise independently and unpredictably among older patients undergoing ICI treatment. Differentiating between these causes is challenging, requiring careful consideration of predisposing and precipitating factors. Predisposing factors include older age, pre-existing cognitive dysfunction, functional impairment, and substance abuse. Precipitating factors include electrolyte abnormalities, infection, pain, CNS metastatic disease, and numerous adjunctive cancer medications, including antihistamines, opiates, corticosteroids, non-benzodiazepine sleeping aids (also termed z-drugs), and benzodiazepines.

Some older patients hesitate to disclose cognitive symptoms, leading to insufficient support or awareness from health-care professionals. Pretreatment cognitive function screening (eg, the Mini-Cog assessment and Montreal Cognitive Assessment tools) and delirium screening (eg, with the Confusion Assessment Method) should be conducted for all older adults undergoing systemic cancer therapy, both for its intrinsic immediate value and as a reference for future cognitive evaluations.⁶²

Immunosuppression and immunomodulation in older adults

Corticosteroids are the primary therapy for most immune-related adverse events and are often prescribed by oncologists without multidisciplinary consultation. For patients for whom immune-related adverse events are unresponsive to corticosteroids, relapse following initial response, or where corticosteroid-related toxicities arise, it is frequently necessary to adjust the corticosteroid regimen or introduce immunosuppressive or immunomodulatory drugs (table 2). In cases in which oncologists are less experienced in the use of these drugs, multidisciplinary discussion is important to inform the best treatment choice and care.

Corticosteroid and immunomodulatory or immunosuppressive drugs are associated with substantial toxicities, to which older adults are particularly susceptible. Knowledge of the specific side-effect profiles of these drugs, careful selection of the appropriate agent and dosage, and close monitoring for adverse events and potential drug–drug interactions, is imperative in this population. Specific caution regarding the schedule and dosing of these drugs is frequently required in older patients with hepatic and renal impairment, low bodyweight, and polypharmacy. Consultation with a clinical pharmacist is advised in this setting.

Severity-based and subtype-based therapeutic algorithms are increasingly being established by interdisciplinary taskforces for most immune-related adverse event types.^{4,6,46} Due to the paucity of evidence regarding the efficacy and safety of immunomodulatory and immunosuppressive agents specifically in immune-related adverse events, their selection is often based on data from analogous, classic, immune-mediated inflammatory diseases (eg, rheumatoid arthritis for ICI-induced arthritis).⁶⁴ The paradigm of only second-line use of immunomodulatory and immunosuppressive drugs particularly in situations with expectable prolonged or higher dose corticosteroid treatment (>4 weeks) is shifting, and will be the subject of future trials.

Corticosteroids

Corticosteroids are the mainstay of first-line immunosuppressive treatment for most immune-related adverse events and are given at different dose levels (intravenous methylprednisolone or oral prednisolone 10 mg per day, ≤1 mg/kg per day, 1–2 mg/kg per day, and >2 mg/kg per day) according to the severity and type of immune-related adverse event. In general, initial therapy for grade 3 or 4 immune-related adverse events consists of oral prednisolone or intravenous methylprednisolone given in doses of 1–2 mg/kg per day for 2–3 weeks, transitioning to a graduated 4–6 week dose-taper phase, provided the adverse event shows improvement. Where corticosteroids are ineffective or poorly tolerated, immunomodulatory or immunosuppressive drugs are recommended for several immune-related adverse events (eg, colitis, pneumonitis, and arthritis).^{4–7}

In the short-term, corticosteroid treatment can result in adverse events, including insomnia, agitation, disinhibition, gastritis, hyperglycaemia, and weight gain, in a dose-dependent manner. Prolonged corticosteroid use is associated with adverse events of particular importance in older adults,⁶⁵ including opportunistic infections (eg, *Pneumocystis jirovecii* and varicella zoster virus), hyperglycaemia, psychiatric symptoms, adrenal insufficiency,

sarcopenia, osteopenia, hypertension, and ocular adverse events, such as glaucoma. Clinicians should counsel older patients regarding these risks, assess viral serology, and commence prophylactic regimens, including trimethoprim–sulfamethoxazole and antiviral therapy, when prolonged corticosteroid use is anticipated. Although prospective data are scarce, older adults do not appear at greater risk of corticosteroid-associated delirium compared with younger patients.⁶⁶ Nonetheless, frail patients who develop delirium are inherently at greater risk of delirium-associated adverse events, such as falls. Older patients and their caregivers should therefore be counselled regarding potential mental status changes before initiation of corticosteroids.

Close monitoring and management of patients with diabetes and osteoporosis, which are common in older adults, are required. Patients should be commenced on calcium and vitamin D supplementation,⁶⁷ and encouraged to engage in weight-bearing exercises or physical therapy. Bisphosphonates or denosumab should be considered for older patients with known osteoporosis or osteopenia requiring extended courses of corticosteroid treatment. Long-term corticosteroid use can additionally increase the risk of sarcopenia, which can have substantial functional implications in older adults, including decreased mobility and increased risk of falls. To address these effects, it is advisable to refer such patients to physiotherapy and dietetics.

Immunomodulatory agents

Immunomodulators are widely used for immune-mediated inflammatory diseases in gastroenterology, rheumatology, dermatology, pneumology, and neurology; for immune-related adverse events that resemble diseases in these fields; or, more generally, in corticosteroid-refractory situations or when corticosteroid-sparing therapy is indicated (table 2).

Although DMARDs are occasionally referred to as immunosuppressants in oncology guidelines, there are no data on their use in the context of immune-related adverse events that show a higher risk of infection in this population to support this categorisation. Nonetheless, the risk of infection is generally higher in older patients than in younger patients, although it does not appear to increase linearly with age, but is rather associated with other risk factors, including active inflammatory disease, concomitant high-dose corticosteroid use, and the presence of certain comorbidities such as pulmonary or renal disease, which are more prevalent among older adults.^{68,69} Real-world data suggest similar response rates in older adults, compared with younger patients, for methotrexate, TNF inhibitors, the IL6R inhibitor tocilizumab, abatacept, and rituximab, although for methotrexate, lower doses seem to be required.⁷⁰

The prototypical conventional synthetic DMARD is low-dose methotrexate. Methotrexate does not have substantial immunosuppressive effect as evidenced by an only slightly increased susceptibility to infection in patients with rheumatoid arthritis, but also in patients without rheumatoid arthritis with substantial comorbidities.^{71,72} Other conventional synthetic DMARDs, including hydroxychloroquine, lefl and sulfasalazine, appear to have similar risk profile. However, organ dysfunction in older patients might lead to contraindications for

certain conventional synthetic DMARDs due to the hepatic and renal metabolism of many such drugs.⁷¹

Targeted therapies, particularly biological DMARDs, offer even greater anti-inflammatory efficacy with good toxicity profiles in the classic disease entities, as shown by the only slightly higher risk of serious infections with TNF inhibitors compared with methotrexate,⁷³ and substantially lower infection risk than high-dose corticosteroids.^{71,74} The infection risk appears to be similar for other biological DMARDs, including IL-6R inhibitors (eg, tocilizumab), IL-17A inhibitors, IL-12 and IL-23 inhibitors, abatacept, and rituximab in classic immune-mediated inflammatory diseases;^{74,75} however, the long half-life of certain agents (particularly rituximab) might be problematic when considering their use in older adults.

In contrast, although JAK inhibitors from the third class of immunomodulators (targeted synthetic DMARDs) do not result in higher overall infection rates than biological DMARDs, they are generally associated with a higher risk of varicella zoster virus, which is more pronounced in older patients.⁶⁹ Safety data from 2022 suggest that tofacitinib, a JAK1 and JAK3 inhibitor, when used in patients with rheumatoid arthritis aged 50 years or older with cardiovascular risk factors, presents a higher risk of cardiovascular events and malignancies than TNF inhibitors, potentially restricting its future use in older patients with such risk factors.⁷⁶

Immunosuppressive agents

Immunosuppressive drugs are characterised by a broader immunosuppressive effect at the cost of a substantially increased risk of serious infections and, for certain agents, malignancy.⁷⁴ Mycophenolate is commonly used in the management of immune-related adverse events, including hepatitis, pneumonitis, myocarditis, and colitis.^{4,6} Azathioprine is an alternative, which is particularly used for ICI-induced hepatitis.

Calcineurin inhibitors, including tacrolimus and ciclosporin, can be effective in the treatment of corticosteroid-refractory immune-related adverse event-induced colitis, although data for ciclosporin, particularly among older patients, are sparse. Ciclosporin, alone or in combination with intravenous immunoglobulin, has also been successfully applied in corticosteroid-resistant cases of severe cutaneous immune-related adverse events, including Stevens-Johnson syndrome and toxic epidermal necrolysis.⁶⁵ The adverse events of ciclosporin in particular, including hypertension, nephrotoxicity, and nausea, could potentially restrict its use among older adults.

Cyclophosphamide is a potent immunosuppressant used in the treatment of various severe immune-related adverse events, such as corticosteroid-refractory pneumonitis, interstitial lung disease, Guillain-Barré syndrome, vasculitis, and lupus nephritis.^{4-7,65} However, in the context of immune-related adverse events and the underlying malignancy, it has the advantage of antineoplastic and antiproliferative properties, caution is advised for older adults receiving cyclophosphamide at doses exceeding 1 mg/kg per day, given the potential for serious adverse events, including cytopenias and haemorrhagic cystitis. Nevertheless,

data in other settings suggest acceptable tolerability among older patients when administered at lower doses.⁷⁷

Long-term immunosuppressive therapy can lead to serious opportunistic infections. Prophylactic regimens against *P jirovecii* are recommended and, in certain situations, antifungal and antiviral prophylaxis are warranted, particularly when an extended course of highly immunosuppressive treatment is anticipated.

Intravenous immunoglobulin

Intravenous immunoglobulin can be used to treat corticosteroid-refractory immune-related adverse events, particularly haematological, neurological, and pulmonary immune-related adverse events,^{4,6,7} given its multiple anti-inflammatory effects. Although data on its safety in older adults with cancer are sparse, intravenous immunoglobulin is generally well tolerated in older adults with other conditions, including Alzheimer's disease.⁷⁸ Older adults, particularly those with cardiovascular risk factors and poor mobility, are at particularly high risk for acute kidney injury and arterial and venous thrombosis, which is not reduced by thromboprophylaxis.^{79,80} Therefore, older patients should receive adequate hydration prior to intravenous immunoglobulin treatment to minimise renal toxicity, and close monitoring of renal function.⁷⁹

The role of CGA and patient-focused care

The care of older adults with cancer is often complicated by comorbidity, functional impairments, polypharmacy, malnutrition, cognitive problems, and age-related organ dysfunction. Treatment tolerability, quality of life, and survival of older patients are affected by these geriatric variables and, in general, a higher burden of baseline impairments and comorbidity increases susceptibility to ICI toxicity.^{18,20}

Among older patients, particularly those living with frailty and comorbidity, the daily impact and lived experience of immune-related adverse events can extend beyond what is represented by CTCAE-graded toxicities. Standard reporting of immunotherapy toxicity grades, in many circumstances, only provide a partial reflection of the experiences of older patients living with frailty. For example, the development of even low-grade myalgia is likely to affect functional status more profoundly in a patient with baseline impairments relating to falls or unsteady ambulation. Low-grade chemotherapy toxicities lead to discontinuation of treatment in frail older populations.³ This finding is also suggested among patients undergoing ICI therapy in a small number of studies.^{1,2} For instance, the ELDERS study showed that although patients treated with single-agent ICI had no age-related difference in the incidence of grade^{3–5} adverse events, those with frailty had more hospital admissions and a higher risk of death than non-frail patients.²

Assessment of older adults before treatment initiation should extend beyond chronological age and performance status to include additional CGA variables, including frailty; functional independence; falls risk and mobility; cognitive, emotional, and nutritional status; polypharmacy; social support; and comorbidities.

Evidence supporting CGA in oncological care, derived from randomised controlled trials, has primarily focused on patients undergoing treatment with cytotoxic chemotherapy rather than immunotherapy.⁶² Further prospective research is needed in this setting. We recommend undertaking geriatric screening (and CGA where indicated) in patients aged 70 years or older, on the basis of consensus expert opinion and in accordance with the American Society of Clinical Oncology's guidelines recommending such assessments for all older patients commencing systemic anticancer therapy.⁶² Ideally, CGA is performed by a multidisciplinary team comprising, for instance, a geriatrician or geriatric oncologist, geriatric nurse, physiotherapist, occupational therapist, dietician, social worker, and pharmacist. Streamlined screening options, including the G8 (Geriatric-8) tool,⁸¹ can be used to triage referrals to such services.

For patients initiating ICI therapy, geriatric assessments and conversations around ageing-related concerns are imperative as a preliminary step in the process of shared decision making, and can help physicians align choice of treatment with patient preferences. Outcomes prioritised by older adults typically include avoidance of toxicity, preservation of autonomy, functional and cognitive abilities, and quality of life, alongside overall and progression-free survival.^{82,83} Geriatric assessments foster mutual understanding between the patient and physician about potential treatment outcomes and discussions around treatment goals.⁸⁴ Furthermore, the identification of frailty and the discussions that follow are important to clarify overall treatment goals and what toxicity risks are reasonable to accept. Crucially, such assessments might also help to direct individualised multidisciplinary interventions, including physiotherapy, occupational therapy, psycho-oncology, dietetics, palliative care, clinical pharmacy, and other supportive care services.

Challenges and future research needs

More research is needed in this domain. There is a well known selection bias in registration clinical trials, and frail older people are unlikely to be adequately represented in most available data. Pivotal studies of ICIs have not incorporated systematic analyses of the role of baseline comorbidity, performance status, immuno-senescence, or frailty when assessing or reporting the efficacy and toxicity of ICI treatments. Older adults are under-represented in pivotal trials in oncology, and reporting of older subgroups enrolled to such trials is often poor.³⁰ Most data on age-specific aspects of ICI therapies and toxicities are, therefore, derived from smaller prospective datasets and retrospective analyses.

Conclusion

The management of immune-related adverse events in older adults with cancer presents unique challenges and considerations that require a personalised and multidisciplinary approach, with careful consideration of individual health status, comorbidities, and potential treatment benefits. The frequency and severity of certain immune-related adverse events differ among older individuals compared to their younger counterparts, with potentially more substantial consequences in the presence of frailty or comorbidity. Even low-grade immune-related adverse events can seriously impact quality of life in older people.^{1,2} Geriatric screening, and, where indicated, CGA, should be integral components of the

decision-making process before initiating ICI therapy. Age and performance status alone should not dictate the use of ICI therapy; decisions should instead be based on a holistic evaluation of patients' overall health, personal preferences, and expected benefits.

Acknowledgments

We thank the executive and administrative staff at the International Society of Geriatric Oncology (SIOG), including Kristina Skau, Shadya Lussac, and Laurence Jocaille, for their involvement and support in coordinating the working group's activities. HW is a recipient of a grant of the Fonds Voor Wetenschappelijk Onderzoek Vlaanderen (1802211N). All authors are members of the SIOG Immunotherapy Working Group. An initial draft of this publication was circulated to an external panel of expert reviewers and patient advocates for feedback between December, 2023, and January, 2024. A final draft was circulated to all authors for approval in April, 2024.

Declaration of interests

NRN declares advisory board fees and travel support from Pfi, Hexal, AbbVie, Janssen, and Novartis. KG declares grant funding and research support from the MalheuR Project (Medical Faculty and Foundations commission of University of Heidelberg), Pfi, and Novartis; and consultancy fees from AbbVie, Bristol Myers Squibb, Gilead–Galapagos, Janssen, Eli Lilly, Merck Sharp & Dohme, Sandoz, Union Chimique Belge, Viatris, Rheumaliga Baden-Württemberg, Medac, Mundipharma, Pfi, and Roche. JL declares speakers bureau fees from AbbVie, Bristol Myers Squibb, Celgene, Galapagos, Janssen-Cilag, Leo, Eli Lilly, Medac, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche–Chugai, Sanofi and Union Chimique Belge; is a member of the scientific advisory board for AbbVie, Bristol Myers Squibb, Celgene, Janssen-Cilag, Galapagos, Gilead, Leo, Eli Lilly, Novartis, PierreFabre, Roche–Chugai, Sanofi and Union Chimique Belge; and has received research support from Novartis, Pfi, AbbVie, Bristol Myers Squibb, Gilead, Janssen, and Sanofi MV declares receiving speaker fees from Pfi, Merck Sharp & Dohme, Roche, Jansen, and Domus Medica, all paid to their institution; and has received travel support from Ipsen. FG has received honoraria from MSD, AstraZeneca, Pfi, Roche, and Boehringer Ingelheim; and has received a grant from Pfi. LD declares fees for advisory boards, consultancy, research, and presentations from Bristol Myers Squibb, Merck Sharp & Dohme, Roche, AstraZeneca, Boehringer Ingelheim, and Servier, paid to their institution. NMLB is a member of the advisory board for Pfi, Abbott, Exact Sciences, Sanofi and Astellas; declares travel grants from Exact Sciences, Pfi, Eli Lilly, and Novartis; and has received speaker fees from Pfi, AbbVie, Roche, Exact Sciences, Sanofi Novartis, Servier, Gilead, and AstraZeneca. HW's institution received compensation on his behalf for consultancy fees from Immute, Merck Sharp & Dohme, AstraZeneca, Daiichi Sankyo, AbbVie, Eli Lilly, Roche, Eisai, Pfi, Sirtex, and Gilead; and he has received travel support from Pfi and Roche. All other authors declare no competing interests.

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Search strategy and selection criteria

Scoping reviews were undertaken between Jan 30, 2023, and June 30, 2023, using PubMed and Embase. The search strategy included terms related to immunotherapy toxicity, including “checkpoint inhibitor”, “ICI”, “toxicity”, “irAE”, and terms specifying older populations including “older”, “geriatric”, and “elderly”. Additionally, terms related to specific toxicities pertinent to individual subsections were incorporated (eg, “endocrinopathy”, “endocrine”, “thyroid”, “adrenal”, or “pituitary”). No date restrictions were applied to the selected publications. The search was restricted to references published in English, with final references selected based on author consensus regarding their relevance.

Table 1.

Summary of key recommendations

Empty Cell	Level of evidence
Baseline assessment	
Geriatric screening, including cognitive screening, should be undertaken among older adults before commencing ICI therapy	5
Comprehensive geriatric assessment, ideally conducted by a multidisciplinary team, should be undertaken in patients with a positive baseline geriatric screening	5
Decisions regarding use of ICI among older adults should not be based solely on patient age or performance status, but rather on geriatric screening and, where indicated, comprehensive geriatric assessment	3
Holistic assessment of toxicity	
Where toxicity (even if low grade) is reported, holistic assessment of quality of life, including reassessment of potential benefits and harms of treatment, should be undertaken alongside standard Common Terminology Criteria for Adverse Events scoring to inform decisions relating both to initiation of immunosuppressive therapies and continuation of ICI treatment	4
Combination therapy	
Considerable caution and detailed patient counselling are required before adopting combined ICI–ICI, ICI–chemotherapy, and ICI–tyrosine kinase inhibitor strategies in older populations with poor performance status or evidence of frailty	4
Pre-existing autoimmune conditions	
Immunotherapy can be considered for older patients with pre-existing autoimmune conditions, subject to a multidisciplinary assessment of the type and severity of the underlying autoimmune disease, including consultation with organ-specific specialists	3
Rechallenge	
Immunotherapy rechallenge following toxicity can be considered for older adults on an individual basis, taking account of the severity of the initial toxicity event, expected benefit of further ICI treatment, the availability and efficacy of alternative treatment options, and patients' health status, preferences, and care goals	3
Fatigue	
In cases of grade 2 or worse fatigue (defined as fatigue affecting activities of daily living), in which no identifiable cause is found, we recommend consideration of a pause in therapy to assess for symptomatic improvement alongside the use of non-pharmacological strategies	5
Management of non-endocrinopathy ICI-associated fatigue should include non-pharmacological interventions such as physical therapy, sleep hygiene, psychosocial and wellbeing assessment, and nutritional optimisation	5
Endocrinopathy	
Older patients can present with atypical symptoms of thyroid endocrinopathy; routine testing of thyroid function at baseline and every 6 weeks during ICI therapy is advised	3
Levothyroxine replacement should be commenced at a reduced dose and gradually increased, particularly in older patients with a history of cardiovascular disease	4
Pruritus	
Fexofenadine is the preferred H1-antihistamine in older adults	5
Diarrhoea and colitis	
Management of diarrhoea or colitis in older adults should follow a stepwise approach based on grade and severity; a lower threshold for intervention and inpatient admission is advised for frail patients	5
Input of a dietician is advised for older patients with prolonged diarrhoea or colitis	5
Musculoskeletal toxicity	
Diagnostic investigation of musculoskeletal toxicities parallels evaluation of classic rheumatic and musculoskeletal disorders and should involve consultation with a rheumatologist, preferably before commencement of corticosteroid treatment	4
Older patients with persistent grade 2 or worse musculoskeletal toxicities should be referred for assessment with physiotherapy or occupational therapy, or both, as appropriate	5
Considerations of immunosuppressive therapy	

Empty Cell	Level of evidence
Older patients and caregivers should be counselled regarding potential mental status changes before initiation of corticosteroid treatment	5
Older patients receiving corticosteroids should be commenced on calcium and vitamin D supplementation and encouraged to engage in weight-bearing exercises or physical therapy	1
Older patients with, or at risk of, sarcopenia receiving corticosteroids should be encouraged to engage in weight-bearing exercises or physical therapy and referred for nutritional assessment	5
Older patients commencing prolonged immunosuppressive therapy (>4 weeks), including high-dose corticosteroid treatment, should receive prophylaxis against opportunistic infections for <i>Pneumocystis jirovecii</i> , and, for selected indications, against fungal infections and varicella zoster virus	1
Older patients receiving intravenous immunoglobulin should receive adequate hydration before intravenous immunoglobulin infusion to minimise renal toxicity, have careful monitoring of renal function, and be counselled regarding the risk of thromboembolic events	4

Level 1 evidence obtained from [systematic reviews](#) or meta-analyses. Level 2 evidence obtained from randomised controlled trials or observational studies with substantial effects. Level 3 evidence obtained from non-randomised, controlled cohort studies or follow-up studies. Level 4 evidence obtained from case series, case-control studies, or historically controlled studies. Level 5 evidence based on mechanism-based reasoning. In the absence of clear evidence, recommendations were made on the basis of expert consensus. ICI=immune checkpoint inhibitor.

Table 2.
Immunomodulatory and immunosuppressive drugs for immune-related adverse events

Empty Cell	Mode of action	Applicable immune-related adverse events [*]	Infection risk [†]	Special considerations in older adults
Corticosteroids				
Prednisolone and methylprednisolone	Pleiotropic, transcriptional regulation of multiple inflammatory and stress-related molecules on cellular and systemic level	All but endocrinopathies, in which hormone substitution (including hydrocortisone in adrenal insufficiency) is usually the treatment of choice; dexamethasone might be preferably used in CNS immune-related adverse events	Dose dependent; in higher doses exceeding risk of other listed substances	Osteoporosis, hypertension, diabetes, delirium, and sarcopenia
Immunosuppressants				
Alemtuzumab	Anti-CD52	Myocarditis, pericarditis, arrhythmia, and heart failure	Moderate risk	NA
Azathioprine	Inhibition of purine ribonucleotide synthesis	Hepatitis, rheumatological toxicity, myositis, and nephritis	Moderate risk	Interaction with allopurinol (severe bone marrow toxicity)
Cyclophosphamide	DNA crosslinking	Neuromuscular toxicity, pneumonitis, nephritis, and acquired haemophilia A	High risk	Cytopenias and haemorrhagic cystitis
Ciclosporin and tacrolimus	Calcineurin inhibition and T-cell proliferation	Hepatitis, neuromuscular toxicity or myositis, severe cutaneous adverse reactions, nephritis, and haemolytic anaemia	High risk	Frequent hypertension, nephrotoxicity, and nausea
Mycophenolate	Inhibitor of IMPDH enzyme important for purine synthesis in proliferating lymphocytes	Hepatitis, ILD, rheumatological toxicity, neuromuscular toxicity or myositis, pneumonitis, myocarditis, pericarditis, arrhythmias, heart failure, and haemolytic anaemia	High risk	NA
Immunomodulators				
Abatacept	CTLA-4-Ig and T-cell costimulation blockade	Myocarditis, pericarditis, arrhythmia, heart failure, and colitis	Low risk	NA
Dupilumab	IL-4Ra blockade	Rash or inflammatory dermatitis	Low risk	NA
Guselkumab	IL-23 inhibition	NA	Low risk	NA
Hydroxychloroquine	Interference lysosomal activity and autophagy	Musculoskeletal	Minimal risk	Drug-induced QT interval prolongation, multiple drug interactions, and ophthalmological toxicity
Infliximab, adalimumab, and etanercept	TNF inhibition	Musculoskeletal or myositis; maculopapular rash; colitis; hepatitis; ILD; neuromuscular toxicity; pneumonitis; nephritis; myocarditis or pericarditis; arrhythmias or heart failure; haemolytic anaemia; and uveitis, iritis, or episcleritis	Moderate risk	Infection risk; infliximab is greater than adalimumab, which is greater than etanercept
Leflunomide	Inhibition of pyrimidine synthesis	Musculoskeletal	Low risk	Frequent liver enzyme increase, hypertension, diarrhoea, and nausea
Methotrexate	Interference with nucleoside synthesis and increase in adenosine	Musculoskeletal arthritis, polymyalgia rheumatica-like, myositis, neuromuscular, uveitis, or iritis	Low risk	Lower dose due to kidney and bone marrow toxicity; interaction with non-steroidal anti-inflammatory drugs

Empty Cell	Mode of action	Applicable immune-related adverse events [*]	Infection risk [†]	Special considerations in older adults
Rituximab	Anti-CD20 and CD20 B-cell depletion	Myositis, myasthenia gravis, encephalitis, bullous dermatoses, haemolytic anaemia, acquired thrombotic and idiopathic thrombocytopenic purpura, and acquired haemophilia A	Moderate risk	Long half-life; hypogammaglobulinaemia in long-term use; vaccinations preferably before infusion
Secukinumab	IL-17A inhibition	NA	Low risk	NA
Sulfasalazine	Unknown	Musculoskeletal	Low risk	Potential kidney and bone marrow toxicity; multiple drug interactions (eg, anticoagulants)
Tocilizumab	IL-6R inhibition	Musculoskeletal, myositis, maculopapular rash, hepatitis, ILD, and myocarditis	Moderate risk	Normal C-reactive protein concentrations even in severe infections
Tofacitinib	JAK1 and JAK3 inhibition	Colitis, diarrhoea, and enterocolitis	Moderate risk	Increased varicella zoster virus; malignancy and cardiovascular risks
Ustekinumab	IL-12 and IL-23 inhibition	Colitis	Low risk	NA
Vedolizumab	$\alpha 4\beta 7$ integrin blockade	Colitis	Low risk	NA

ILD=interstitial lung disease. IMPDH=inosine-5'-monophosphate dehydrogenase. Use for certain immune-related adverse events also derived from Henderson et al.⁶³

^{*} According to guidelines for corticosteroid-refractory immune-related adverse events from the American Society of Clinical Oncology or European Society for Medical Oncology, or both.

[†] Infection risk extrapolated from classic, immune-mediated, [inflammatory diseases](#) and based on consensus expert opinion.