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Original research

Second-line therapies for steroid-refractory immune-related adverse events in patients treated with immune checkpoint inhibitors

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ABSTRACT

Background: Immune checkpoint inhibitors (ICI) induce adverse events (irAEs) that do not respond to steroids, i.e. steroid-refractory (sr) irAEs, and irAEs in which steroids cannot be tapered, i.e. steroid-dependent (sd) irAEs, in about 10% of cases. An evidence-based analysis of the effectiveness of second-line immunosuppressive agents with regard to irAE and tumor control is lacking.

Methods: The international web-based Side Effect Registry Immuno-Oncology (SERIO; http://serio-registry.org) is a collaborative initiative with the Paul-Ehrlich-Institute to document rare, severe, complex or therapy-refractory immunotherapy-induced side effects. The registry was queried on August 1, 2023 for cases of irAEs which were treated with second-line therapies.

Results: From a total of 1330 cases, 217 patients (16.3%) received 249 second-line therapies. A total of 19 different second-line therapies were employed, including TNF-alpha antagonists (46.5%), intravenous immunoglobulins (IVIG; 19.1%), mycophenolate mofetil (15.9%), and methotrexate (3.6%). Therapy choices were determined by the type of irAE. The time to onset of sr-/sd-irAEs after ICI initiation did not consistently differ from steroid-responsive irAEs. While 74.3% of sr-/sd-irAEs resolved and 13.1% had improved, 4.3% persisted, 3.9% resulted in permanent sequelae, and 4.3% in death with ongoing symptoms. Infliximab exhibited potential for earlier symptom improvement compared to mycophenolate mofetil or IVIG. Tumor response in patients with second-line treated sd-/sr-irAE was similar to patients with irAEs treated with steroids only.

Conclusion: Several second-line therapies are effective against sr-/sd-irAEs, the second-line therapies show no clear negative impact on tumor response, and infliximab shows potential for faster improvement of symptoms. However, prospective comparative data are needed.

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[1] www.serio-registry.org

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1. Introduction

Due to their effectiveness in many tumor entities immune checkpoint inhibitors (ICIs) are among the most prescribed anti-cancer therapies [1]. However, ICIs also induce immune-related adverse events (irAEs) in all organ systems. While corticosteroids are normally effective in treating irAEs [2,3], a subset of irAEs are steroid-refractory (sr) or steroid-dependent (sd). In sr-irAEs symptoms persist or worsen despite the use of corticosteroids; in sd-irAEs corticosteroids cannot be tapered or discontinued without symptom relapse. The incidence of sr-/sd-irAEs ranges from 2–7% for ICI-treated patients in general [4–6] and can be as high as 14.9% in patients receiving combination therapy with anti-PD1 and anti-CTLA4 antibodies [3] resulting in overall about 10% of cases.

To manage sr-/sd-irAEs, various immunosuppressants are used in combination with or as alternatives to corticosteroids including TNF-α inhibitors, vedolizumab (an $\alpha_4\beta_7$ integrin blocker), anti-interleukin (IL)−6 receptor antibodies (e.g., tocilizumab), anti-IL1, anti-IL17, anti-IL23 agents, anti-thymocyte globulin (ATG), rituximab (an anti-CD20 antibody), abatacept (a CTLA-4 agonist), mycophenolate mofetil, calcineurin inhibitors (e.g., cyclosporine, tacrolimus, sirolimus), cyclophosphamide, methotrexate, leflunomide, azathioprine, and janus kinase inhibitors [7,8]. Additionally, immune modulators like intravenous immunoglobulins (IVIG) and, in rare cases, extracorporeal photopheresis and immunoadsorption have been employed [9–11].

International irAE guidelines like ESMO, ASCO, NCCN or SITC guidelines provide recommendations for first- and second-line therapy of irAEs [12–15], mostly based on past use within clinical studies, retrospective analyses and case reports. Managing sd-/sr-irAEs bears similarities with the treatment of autoimmune diseases. In analogy to colitis ulcerosa treatment, irColitis is often treated with infliximab or vedolizumab, and irArthritis with methotrexate, just like rheumatoid arthritis [16,17]. However, important differences exist between the two scenarios. In autoimmune diseases, immunosuppression aims to downregulate the exaggerated immune response to self-antigens, while in irAEs, immunosuppression needs to strike a balance between controlling the autoimmune response and maintaining an effective antitumor immune response. Furthermore, it is well described that irAEs differ pathogenically from their autoimmune disease counterparts [10,11,18,19]. A more targeted approach to the treatment of irAEs that is based on the key inflammatory components and hopefully also sparing corticosteroids is desirable [7,20]. To date, there is a paucity of prospective data comparing the effectiveness of different second-line treatments for irAEs as well as their influence on tumor control.

With increasing use of ICI, there is a growing need for optimized evidence-based irAE management. We analyzed data from the Side Effect Registry Immuno-Oncology (www.serio-registry.org), an international web-based registry for irAEs that collects rare, severe or therapy-refractory irAEs [21]. By evaluating clinical characteristics, outcomes and effects on sr-/sd-irAEs and tumor response this study aims to provide insights into the use of second-line therapies. The findings of this research may lead to better tailored therapeutic approaches and thus enhance the safety and efficacy of ICI therapy.

2. Methods

The Side Effect Registry Immuno-Oncology (SERIO, www.serio-registry.org), established in partnership with the Paul-Ehrlich-Institute, serves as a comprehensive registry documenting rare, complex, or therapy-refractory side effects linked to immunotherapies including ICI therapies [21]. The registry records irAE cases since 2011. Ethical approval for analyses from the SERIO registry was granted (Erlangen Nr. 2_20 B, Erlangen Nr. 17_16 Bc).

In addition to spontaneously reported cases, seven skin cancer centers in Germany were requested to report their cases of sd-/sr-irAEs to SERIO. SERIO was queried for cases of sr-/sd-irAEs on August 1, 2023. irAEs were defined as adverse events occurring during ICI therapy and deemed immune-related by the treating clinician. The grading of irAEs followed the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Sr-/sd-irAEs encompassed those requiring second-line therapies in addition to corticosteroids. A total of 1330 cases of immune-related adverse events (irAEs) were analyzed for age, gender, tumor type, checkpoint inhibitor type, irAE type, time to irAE onset, second-line therapy type, and irAE outcome. Furthermore, time to irAE improvement, time to irAE resolution, and initial tumor response after commencing second-line immunosuppression were evaluated. The initial tumor response after commencing second-line immunosuppression was defined as the tumor response in the first staging 1–3 months after second-line treatment initiation, to reflect potential effects of second-line therapies on tumor response. Only patients with cutaneous metastatic melanoma were included in the analysis of the tumor response.

Data on time to irAE onset was available for 203/221 (91.9%) and data on irAE outcome was available for 210/221 (95.0%) of cases; time to improvement or resolution of irAEs after initiation of second-line immunosuppression was available for 82/221 (37.1%) and 51/221 (23.1%) patients, respectively. Tumor response data was available for 81 cases of patients with cutaneous metastatic melanoma and second-line therapy for irAEs, and for a control group of 41 patients with cutaneous metastatic melanoma and irAEs responsive to steroids.

Control cohorts of cases with irAEs that showed improvement after administration of steroids and did not require second-line therapies termed steroid-responsive irAEs were generated from the SERIO registry. 397 cases including patients with all tumor entities were analyzed for time to irAE response, and 41 patients with cutaneous metastatic melanoma were analyzed for tumor response.

Statistical analyses were conducted using the Mann-Whitney test for comparison of two groups and One-way Anova for comparison of three groups. MS Excel and GraphPad Prism 9 software were used for graphical representations of data.

3. Results

3.1. Patient characteristics

Out of 1330 cases, 217 patients with a total of 221 sd-/sr-irAEs treated with second-line therapies were analyzed. Among these, 57.5% (127/221) of sd-/sr-irAEs were associated with combined anti-CTLA4 and anti-PD-1 therapy, 34.4% (76/221) with anti-PD-1/PD-L1 monotherapy, and 8.1% (18/221) with anti-CTLA4 monotherapy. The majority of patients were treated for melanoma (203/217; 93.5%; including cutaneous melanoma, mucosal melanoma, conjunctival melanoma, uveal melanoma and melanoma of unknown primary), but the cohort also includes patients with cutaneous squamous cell carcinoma, Merkel cell carcinoma, renal carcinoma, hepatocellular carcinoma, gastric adenocarcinoma, endometrial carcinoma, cervix carcinoma and non-small cell lung cancer (Table 1).

3.2. 19 different second-line therapies were used, most frequently TNF inhibitors

The 217 patients analyzed received a total of 249 second-line therapies for irAEs, including 19 different types or second-line therapies. In most cases, patients were treated with a single second-line therapy, but in 15.6% of cases two subsequent, and in 2.4% of cases three different subsequent second-line therapies were used. In total, 86.4% of sd-/sr-irAE were grade 3 CTCAE or higher. We identified 14 different sd-/sr-irAE types, partly grouped by organ type (Suppl. Table 1), the most common being irColitis (48.3%), irHepatitis (15.6%), hematological irAEs (6.6%), irArthritis (6.1%), and irMyositis (5.2%; Fig. 1b). Second-line therapies included TNF-alpha antagonists (infliximab and adalimumab; 46.5%), intravenous immunoglobulins (IVIG; 19.1%), mycophenolate mofetil (15.9%), and methotrexate (3.6%); extracorporeal

Table 1
Patient characteristics.

n	217
Age – yr	
Median	66
Range	23 - 89
Sex – no. (%)	
Male	124 (57.1%)
Female	93 (42.8%)
Tumor type – no. (%)	
Melanoma	203 (93.5%)
Cutaneous melanoma	120 (55.3%)
Melanoma of unknown primary	26 (12.0%)
Mucosal melanoma	8 (3.7%)
Uveal melanoma	16 (7.4%)
Conjunctival melanoma	1 (0.5%)
Melanoma; not further defined	32 (14.7%)
Cutaneous squamous cell carcinoma	2 (0.9%)
Merkel cell carcinoma	1 (0.5%)
Renal carcinoma	4 (1.8%)
Hepatocellular carcinoma	2 (0.9%)
Gastric adenocarcinoma	1 (0.5%)
Endometrial carcinoma	1 (0.5%)
Cervix carcinoma	1 (0.5%)
Non-small cell lung cancer	2 (0.9%)
Treatment – no. (%)	
Anti-CTLA4 + anti-PD1	*127 (57.5%)*
Ipilimumab + Nivolumab	116 (52.5%)
Ipilimumab + Pembrolizumab	11 (5.0%)
Anti-CTLA4	*18 (8.1%)*
Ipilimumab	18 (8.1%)
Anti-PD-1/-PD-L1	*76 (34.4%)*
Nivolumab	34 (15.4%)
Pembrolizumab	33 (14.9%)
Cemiplimab	2 (0.9%)
Atezolizumab	3 (1.4%)
anti-PD-1; not further defined	4 (1.8%)

photopheresis was used in a minority of cases (0.2%; Fig. 1a). The type of second-line therapies used was associated with the irAE type and the organ system affected (Fig. 1c).

3.3. Most irAEs resolved with second-line therapies

At the last follow-up, 74.3% of irAEs treated with second-line therapies had resolved, 3.9% had resolved with permanent sequelae (Tables 2), 13.1% had improved, 4.3% were unchanged and 4.3% of patients had died with ongoing irAE symptoms (Fig. 2a). Symptom resolution differed depending on the organ system involved and the second-line therapy used (Fig. 2b, c), with irColitis and neurological irAEs having most often sequelae (Table 2). In the case of irHepatitis, the sequelae were persistently elevated liver transaminases. In the patients who died with ongoing symptoms, 37.5% (3/8) of the deaths were due to the irAE, including 1 case of irHepatitis and 2 cases of irEncephalitis.

3.4. Time to onset of steroid-refractory or steroid-dependent irAEs does not consistently differ compared to steroid-responsive irAEs

Time to irAE onset after initiation of ICIs was compared for steroid responsive irAEs and sr-/sd-irAEs for the different irAE types. The time to onset of sr-/sd-irAEs was not significantly different from the time to onset of steroid-responsive irAEs for most irAE types, with the exception of skin-related irAEs and irArthritis. In these cases, sr-/sd-irAEs occurred later than steroid-responsive irAEs (Fig. 3).

3.5. Infliximab showed a trend towards earlier symptom improvement and symptom resolution compared to MMF and IVIG

Time to improvement was defined as the time from initiation of second-line therapy to first significant improvement of laboratory values or symptoms of irAEs. Time to resolution was defined as the time from initiation of second-line therapy to normalization of laboratory values or resolution of clinical symptoms of irAEs. At the time of resolution, some patients were still receiving second-line therapy. The analysis showed a trend towards earlier improvement and resolution of symptoms with infliximab than with mycophenolate mofetil (MMF) or intravenous immunoglobulins (IVIG). It must be noted that the vast majority of patients were treated with infliximab for irColitis and with MMF for irHepatitis (Figs. 4 and 5).

3.6. The association of second-line immunosuppression and tumor response remained inconclusive

Tumor response after second-line immunosuppression was defined as the outcome of the first staging 1–3 months after initiation of the second-line therapy. To ensure data comparability, only patients with metastatic cutaneous melanoma stage IV AJCC were included in this analysis. Progressive disease was seen in 46.1% of patients treated with infliximab and 42.9% of patients treated with MMF, for the other depicted second-line therapies n was ≤ 3. In a control cohort of patients with metastatic cutaneous melanoma stage IV AJCC with steroid-responsive irAEs, progressive disease was observed in 43.9% of patients.

4. Discussion

This study provides valuable insights into the use of second-line therapies for managing sr-/sd-irAEs in patients undergoing ICI treatment by analyzing a large cohort from the Side Effect Registry Immuno-Oncology (SERIO) and 7 additional skin cancer centers. These sr/sd-irAEs occur in 2–7% of ICI patients [4,5].

The use of the 19 different second-line therapies varied depending on the irAE type. Serious outcomes in terms of permanent sequelae or death occurred mainly for specific irAE types including neurologic irAEs, irColitis and irHepatitis. The most commonly administered second-line therapies in our cohort were TNF-alpha antagonists (infliximab and adalimumab; 46.5%), intravenous immunoglobulins (IVIG; 19.1%), mycophenolate mofetil (15.9%), and methotrexate (3.6%). This is comparable to previous studies: in a retrospective single-center study involving 2750 lung cancer patients the predominant treatments utilized were TNF inhibitors (73%) and mycophenolate mofetil (20%) [4]. Similarly, in an analysis of the Dutch Melanoma Treatment Registry TNF inhibitors were the primary treatment choice (71%) [5].

The diverse array of drugs employed in our cohort from 2011–2023 reflects an initial lack of standardized guidelines for managing sr-/sd-irAEs, and the variety recommended by today's guidelines [12,14]. For instance, current guidelines advocate for the use of infliximab or vedolizumab for irColitis, while also suggesting fecal microbiota transplantation, the JAK inhibitor tofacitinib, the IL-12/23 antagonist ustekinumab, or ECP, as these therapies demonstrated successful responses in case reports [12]. While the choice of second-line therapies is often deducted from corresponding autoimmune diseases, it has been shown that irAEs differ from spontaneous autoimmune diseases [10,11,18,19]. Moreover, considerations such as efficacy in resolving the irAE, potential side effects, and impact on anti-tumor response must be taken into account.

However, retrospective analyses are prone for bias, preclinical data are controversial and data from prospective studies on the effects of second-line immunosuppression for the treatment of sr/sd-irAEs on tumor control is lacking [22].

Among the patients analyzed in this study, 59.2% received combined immunotherapy (anti-PD-1 + anti-CTLA4), in line with previous

findings suggesting higher incidences of irAEs in general [23] as well as sr-/sd-irAEs with combined immunotherapy [3,5]. The most common tumor type was melanoma, as mainly skin cancer centers report to SERIO. Differences in frequency of irAEs by tumor type have been reported, e.g. a higher incidence of irPneumonitis in ICI-treated NSCLC patients which might have contributed to the relatively low number of irPneumonitis cases [24]. Efforts to achieve a more balanced cohort across tumor entities are ongoing [21]. By leveraging the SERIO registry, primarily dedicated to rare and severe irAEs, this study provides unique insight into the use of second-line treatments for rare irAEs including hematological, neurological, and musculoskeletal irAEs. These cannot be analyzed in single-center studies [4,5].

Besides taking into account the comorbidities of the patient, the choice of second-line therapies should be based on the immunological pathways mediating the irAE [25]. For instance, the anti-CD20 antibody rituximab may be used for B-cell mediated irAEs, anti-IL10 antibodies for anti-IL10 mediated irAEs [7], and anti-IL6 antibodies such as tocilizumab for IL-6 mediated irAEs [20]. Additionally, secondline therapies should not impede tumor control. Unfortunately, the timing, dosage and complex interplay with the immune system have not yielded a uniform picture with regard to the specific effects on tumor response (nicely reviewed in Verheijden, [22]).

Table 2
Steroid-refractory and steroid-dependent irAEs with permanent sequelae and fatal outcome.

irAEs with permanent sequelae (n = 9)	Fatal irAEs (n = 3)
irColitis (4 cases; in 2: hemicolectomy) Guillain-Barré -like Syndrome (2 cases) irEncephalitis irHepatitis (2 cases)	irEncephalitis (2 cases) irHepatitis

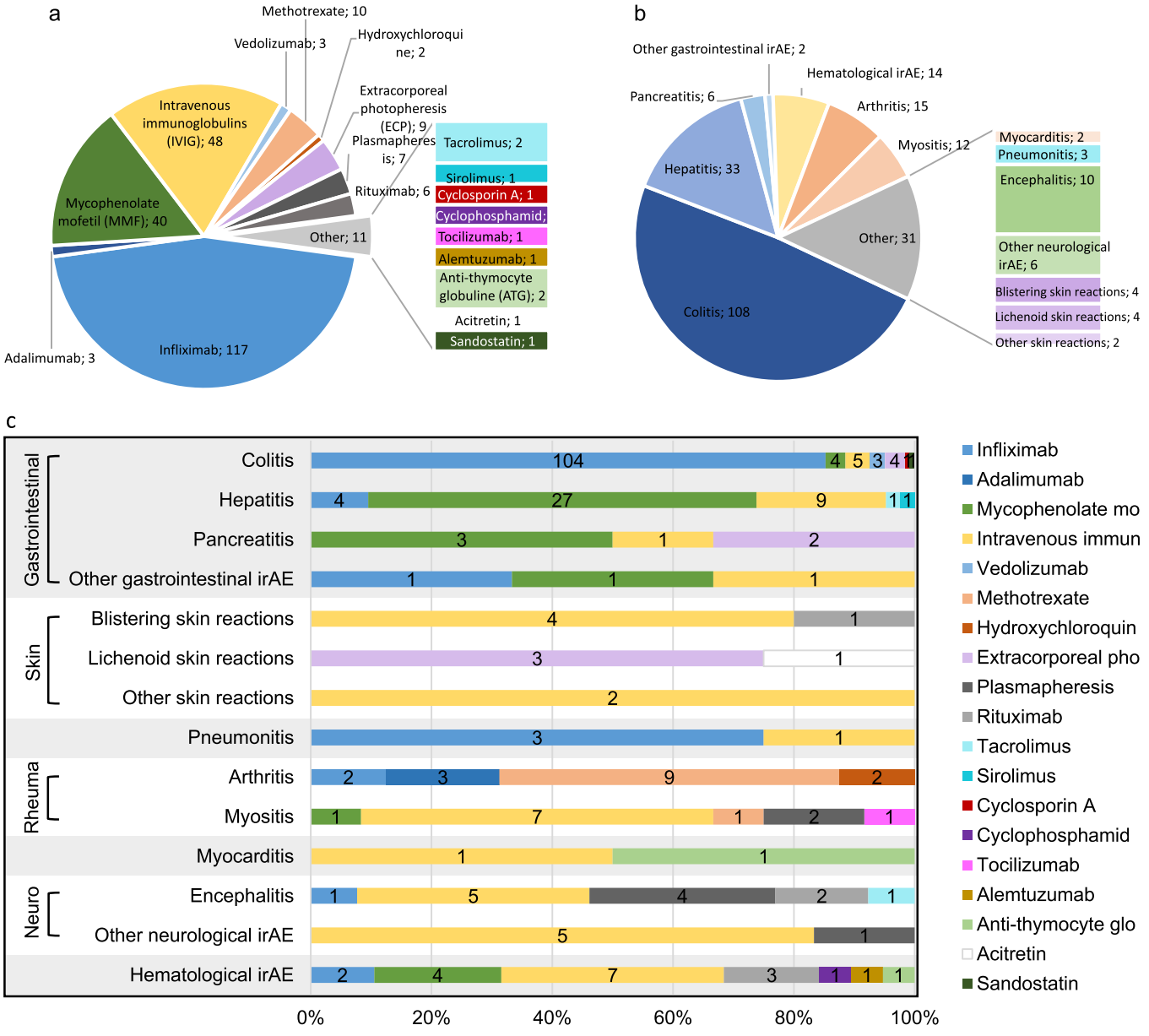


Fig. 1. (a:) Second-line therapies employed. Number of second-line therapies used for steroid-refractory / steroid-dependent immune-related adverse events in the cohort. Fig. 1b: Types of irAEs treated with second-line therapies. Number of steroid-refractory / steroid-dependent immune related adverse events (irAEs) by organ type. Fig. 1c: Second-line therapies used depending on irAE type. Number of different second-line therapies used for each type of immune-related adverse event (irAE) in the cohort.

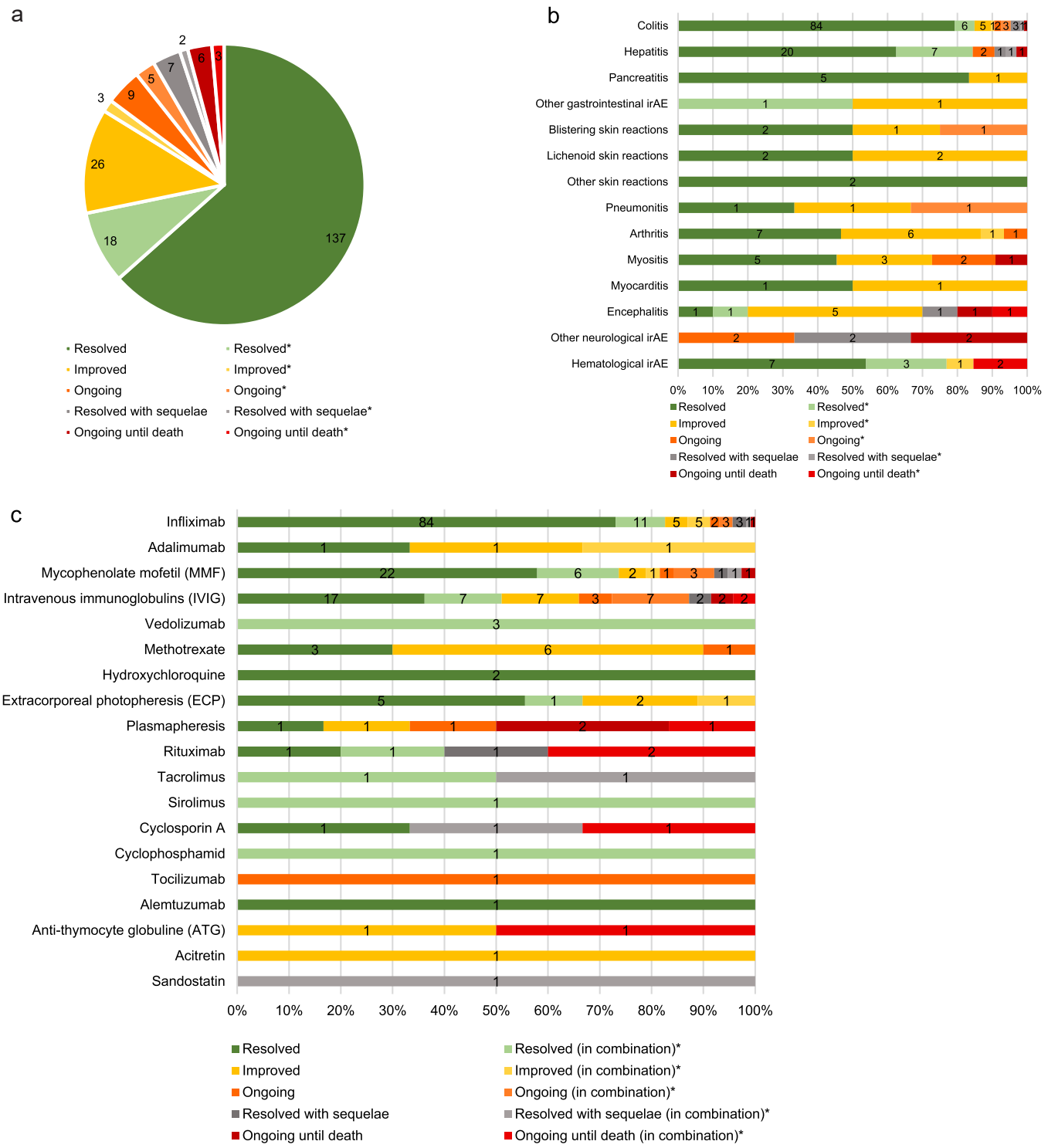


Fig. 2. (a): Outcome of irAEs treated with second-line therapies. *More than one second-line therapy was used for this outcome. irAE: immune-related adverse event; Fig. 2b: Outcome of irAEs treated with second-line therapies by irAE type. *More than one second-line therapy was used for this outcome. irAE: immune-related adverse event. Fig. 2c: Outcome of irAEs treated with second-line therapies by second-line therapy. *The second-line therapy led to the respective outcome when used in combination or sequence with another second-line therapy. irAE: immune-related adverse event.

Infliximab, an anti-TNF-alpha antibody known for its high efficacy in managing irAEs [26,27] which increases the risk of leukopenia, infections and malignancies [28], has a possible negative impact on anti-tumor response to ICI therapy [3,5]. While there have been discussions regarding the hepatotoxicity of infliximab, concrete evidence supporting this claim is lacking.

Mycophenolate mofetil has been successfully administered for autoimmune hepatitis [29], although it carries a risk of cytopenia, infections [30] and malignancies [31,32]. The impact of MMF on ICI effectiveness and tumor control is unclear. Intravenous immunoglobulins, on the other hand, exhibit diverse immunomodulatory properties, with an exceptionally low incidence of severe adverse events and no association with infections, malignancies or a negative impact on ICI effectiveness [33].

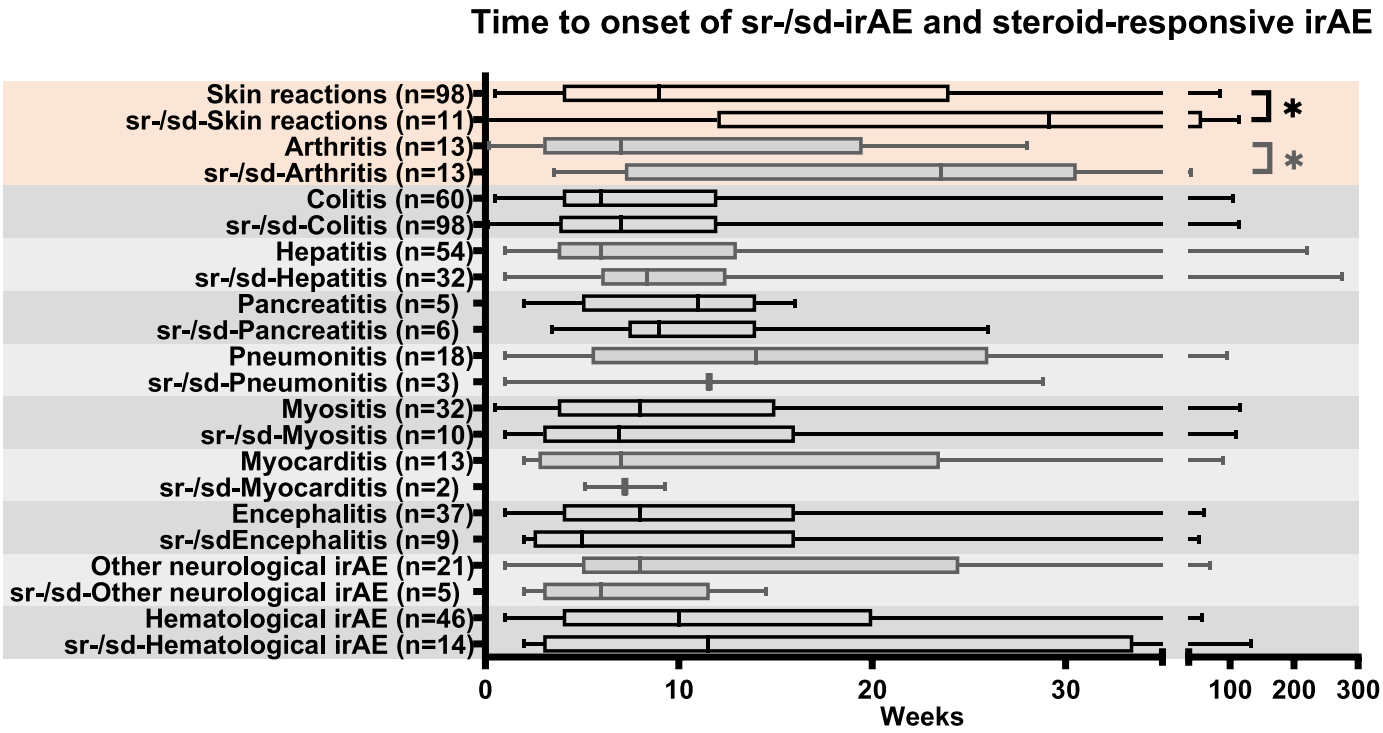
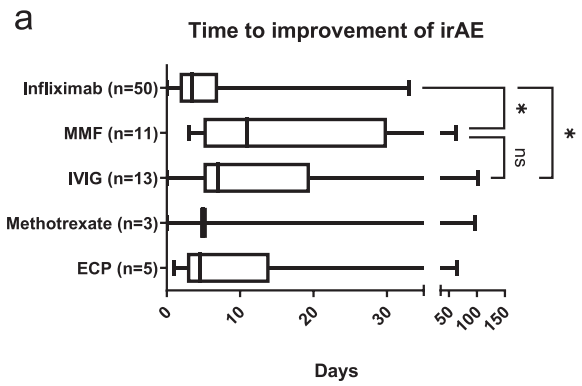
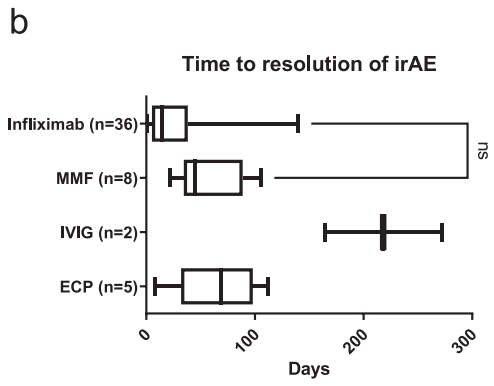


Fig. 3. Time to onset of steroid-refractory / -dependent compared to steroid-responsive immune-related adverse events. Time in weeks from initiation of immune checkpoint inhibitor therapy to onset of irAE, for each organ type compared between steroid-responsive irAEs (e.g. Colitis) and steroid-refractory or steroid-dependent irAEs (e.g. sr-/sd-Colitis). Sr-/sd-irAE: Steroid-refractory or seroid-dependent immune related adverse event.



Breakdown of which irAEs were treated with each second-line therapy	
Infliximab n=50	Colitis n=49 Pneumonitis n=1
MMF n=11	Hepatitis n=8 Nephritis n=1 Myositis n=1 Other gastrointestinal irAE n=1
IVIG n=13	Hepatitis n=3 Blistering skin reactions n=3 Other skin reactions n=2 Colitis n=1 Pancreatic irAE n=1 Myositis n=1 Myocarditis n=1 Hematological irAE n=1
MTX n=3	Arthritis n=3
ECP n=5	Lichenoid skin reactions n=3 Pancreatic irAE n=2



Breakdown of which irAEs were treated with each second-line therapy	
Infliximab n=36	Colitis n=36
MMF n=8	Hepatitis n=8
IVIG n=2	Blistering skin reactions n=1 Myocarditis n=1
ECP n=5	Lichenoid skin reactions n=2 Pancreatic irAE n=2 Colitis n=1

Fig. 4. (a): Time to improvement of irAE. Time from initiation of second-line therapy to first significant improvement of clinical symptoms or laboratory values and breakdown of cases. MMF: Mycophonalete mofetil, IVIG: Intravenous immunoglobulins, ECP: Extracorporeal photopheresis, irAE: Immune-related adverse event. Fig. 4b: Time to resolution of irAE. Time from initiation of second-line therapy to final resolution of clinical symptoms or normalisation of laboratory values and breakdown of cases. MMF: Mycophonalete mofetil, IVIG: Intravenous immunoglobulins, ECP: Extracorporeal photopheresis, irAE: Immune-related adverse event.

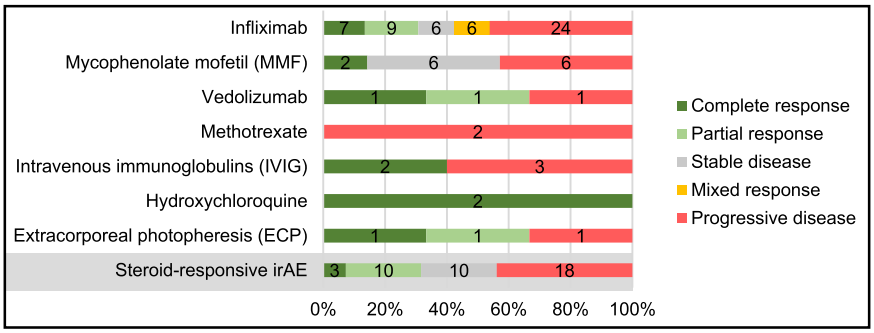


Fig. 5. Tumor response. Tumor response by second-line immunosuppression for patients with metastatic cutaneous melanoma. Only second-line therapies with reported tumor response in at least two cases are shown. The bottom row represents the tumor response of steroid-responsive irAE in patients with metastatic melanoma from the SERIO registry. irAE: immune-related adverse event.

Vedolizumab, an alpha-4-beta-6 integrin inhibitor interfering with lymphocyte trafficking to the gastrointestinal tract, was administered in three cases, all for irColitis. Remarkably, a retrospective analysis of 184 patients (62 vedolizumab, 94 infliximab, 28 combined sequentially) demonstrated that vedolizumab showed similar efficacy to infliximab in treating irColitis, but with the added benefits of better steroid sparing, fewer hospital admissions and, notably, better overall survival [34]. Vedolizumab has not been associated with an increased risk for infection [35].

Methotrexate and hydroxychloroquine were used for rheumatologic irAE such as irMyositis and irArthritis. Methotrexate is frequently employed for irArthritis [17] and does not seem to have an impact on anti-tumor response [36,37], although hepatotoxicity, hematologic toxicity and pulmonary toxicity have been described. Hydroxychloroquine modulates the immune system by hindering autophagy with no known effect on anti-tumor response, but has a slower onset of action and is less effective compared to other options [17].

The anti-IL6 antibody tocilizumab, which inhibits janus kinase (JAK) signal transducer and STAT3, was administered once in our cohort in a case of polymyalgia rheumatica. Tocilizumab has shown effectiveness in managing steroid-refractory irAE [38]. Since IL6 is associated with worse tumor outcome in melanoma patients [39] this could be improving safety and effectiveness. A phase II study is testing the combination of ipilimumab + nivolumab with tocilizumab upfront (NCT03999749) [40].

Extracorporeal photopheresis (ECP) was primarily used for lichenoid skin reactions, following guideline recommendations [41], and for irColitis, supported by a successful case report [9]. ECP has no reported severe side effects [42] and is presumed to have minimal negative impact on tumor response, as suggested by observations in lymphoma patients [43,44].

In isolated cases, rituximab, plasmapheresis, tacrolimus, sirolimus, cyclosporin A, cyclophosphamid, alemtuzumab, anti-thymocyte globuline, acitretine, and sandostatin were used.

Remarkably, in this cohort, the drugs vedolizumab and tocilizumab were only employed in a minority of cases (1.2% and 0.4%, respectively), despite their potential advantages in terms of anti-tumor response compared to other second-line therapies. This may be partly due to the high cost of those relatively new medications, even though in a study overall cost savings could be shown by administering tocilizumab when infliximab would have been an alternative option [38].

The major limitation of this study is its retrospective nature with voluntary reporting. Prospective data comparing second-line therapies is currently lacking, although it is highly relevant to assess the most effective treatment strategies and fully understand the impact on tumor response. However, prospective studies are ongoing to address this gap in knowledge including one at our center (NCT05700565).

Despite frequent resolution of sr-/sd-irAEs with second-line treatments, 3.9% of irAEs resulted in permanent sequelae, most commonly irColitis and neurological irAEs, and 3 sr/sd-irAEs resulted in death including 2 cases of encephalitis and 1 case of hepatitis. Our data show that sr-/sd-irAEs can affect a variety of organ systems and include rare irAEs such as hematological irAEs and neurologic irAEs. Morbidity and mortality of rare irAEs is known to be high [10,11,45], thus, identifying the most effective second-line therapy is crucial. However, since these events are rare, only single cases appear in small patient cohorts and joint efforts must be made to better analyze them.

The time to onset of sr-/sd-irAEs did not consistently differ from that of steroid-responsive irAEs within each irAE type. This suggests that rapidity of onset of irAEs is likely not a reliable predictor of irAE refractoriness or dependence on steroids.

The time to improvement or resolution of symptoms following initiation of second-line immunosuppression is a crucial consideration in managing irAEs. Our analysis demonstrated a trend towards earlier improvement and resolution of symptoms with infliximab compared to mycophenolate mofetil or IVIG, even though this may be biased since infliximab was primarily used for irColitis and mycophenolate mofetil primarily for irHepatitis. Due to data constraints, we were unable to assess concurrent steroid usage or cumulative steroid doses.

Understanding the impact of second-line therapies on tumor response is of great importance. 46.1% of infliximab-treated patients and 42.9% of mycophenolate mofetil-treated patients with metastatic cutaneous melanoma showed progressive disease 1–3 months after second-line therapy initiation. This is comparable to steroid-responsive patients which showed progressive disease in 43.9%. It is also comparable to a retrospective cohort of patients treated with steroids for irAE; here, progressive disease was observed in about 50% in patients with early steroid administration and in $< 10\%$ in patients with late steroid administration (more than 4 weeks after ICI initiation) [46]. To ensure a higher level of follow-up on tumor response data automatic reminders have been established in the SERIO database and initiatives to enlarge the non-melanoma cohort have been undertaken. In a previous study, the addition of second-line immunosuppressants to steroid therapy (TNF inhibitors $n = 67$, mycophenolate mofetil $n = 10$, tacrolimus $n = 1$, non-specified $n = 24$) compared to corticosteroids alone was linked to reduced overall survival, increased risk of tumor progression, and higher mortality in patients with advanced melanoma [3]. However, these findings are in contrast to a study involving 27 ICI-treated melanoma patients who developed irColitis and received TNF inhibitor treatment, and demonstrated a median progression-free survival of 3 months, aligning with findings from earlier studies of ICI-treated melanoma patients without TNF inhibitor treatment. Similarly, a retrospective analysis of patients with ICI-induced colitis revealed no significant disparity in overall survival between those treated solely with corticosteroids ($n = 38$) and those receiving a combination of corticosteroids and a TNF inhibitor ($n = 23$) ($p = 0.263$) [27]. First results from a prospective phase Ib clinical trial investigating the potential of combining infliximab or certolizumab with a combined immunotherapy regimen with

ipilimumab and nivolumab show safety of both combinations and a high tumor response rate in the certolizumab-treated patient cohort [47]. Further research is warranted to explore the interplay between immune-related toxicities, immunosuppression, and antitumor efficacy.

Overall, this study provides important insights into the management of sr-/sd-irAEs including rare irAEs. The findings underscore the complexity and heterogeneity of irAEs, highlighting the need for prospective studies, registries such as SERIO and individualized approaches.

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CRediT authorship contribution statement

Teresa Amaral: Writing – review & editing, Data curation. **Pia Dücker:** Writing – review & editing, Data curation. **Lucie Heinzerling:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization. **Carolin Ertl:** Writing – review & editing, Data curation. **Friedegund Meier:** Writing – review & editing, Data curation. **Lars E. French:** Writing – review & editing. **Thomas Eigentler:** Writing – review & editing, Data curation. **Lydia Reinhardt:** Writing – review & editing, Data curation. **Sarah Zierold:** Writing – review & editing, Data curation. **Ulrike Leiter:** Writing – review & editing, Data curation. **Lisa Zimmer:** Writing – review & editing, Data curation. **Rafaela Kramer:** Writing – review & editing, Data curation. **Anja Gesierich:** Writing – review & editing, Data curation. **Andrea Forschner:** Writing – review & editing, Data curation. **Ralf Gutzmer:** Writing – review & editing, Data curation. **Evelyn Dabrowski:** Data curation. **Theresa Ruf:** Writing – original draft, Visualization, Formal analysis, Data curation. **Dirk Tomsitz:** Writing – review & editing, Data curation. **Julia K. Tietze:** Writing – review & editing, Data curation.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114028.

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