Appendix. Supplementary data

Persistent immune-related adverse events after cessation of checkpoint inhibitor therapy: Prevalence and impact on patients' health-related quality of life

Thomas U. Schulz, Sarah Zierold, Michael M. Sachse, Giulia Pesch, Dirk Tomsitz, Katharina Schilbach, Katharina C. Kähler, Lars E. French, Lucie Heinzerling

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LMU KLINIKUM
Department of
Dermatology and Allergology

Effects of Autoimmunity

Questionnaire for Patients after Immunotherapy

Dear patient,

Even after the end of therapy, immune-checkpoint inhibitors can still lead to persistent and sometimes very distressing side effects that can significantly impair the quality of life. By means of the following questionnaire, we would like to find out more about how you feel and how you deal with possible impairments caused by these long-term effects.

Please make sure you meet all of the following criteria:

- You are at least 18 years old.
- You have received at least one dose of an immune-checkpoint inhibitor / immunotherapeutic agent in the context of a cancer disease (e.g., atezolizumab, avelumab, cemiplimab, durvalumab, ipilimumab, nivolumab, pembrolizumab).
- The last administration of the immune-checkpoint inhibitor was at least 12 weeks ago.

Please read the questions carefully and mark the answers as follows: [only for outpatient clinics]

- Boxes are marked by ticking: ☐☐☒
  If you wish to change an answer, please black out the incorrectly made cross and check another box:
  ☐☒■
- If there is an answer bar, please tick the expression that suits you:

The information is recorded and evaluated anonymously. Please make sure that you do not enter (e.g. in free text) any personal data such as name, address or date of birth. It is not possible to draw any conclusions about your person.

Thank you very much for your participation!

This survey is conducted by:

Prof. Dr. med. Lucie Heinzerling, MPH
- Head of Dermatooncology -
Dr. med. Sarah Zierold
Thomas Schulz
(thomas.schulz@med.uni-muenchen.de)

University Hospital, LMU Munich
Department of Dermatology and Allergology
Dermatooncology
Frauenlobstr. 9-11
80337 Munich, Germany

A. Information about the survey

1. Please provide today's date:

_____ (dd.mm.yyyy)

2. Is this your first time taking part in this survey?
☐ Yes ☐ No

B. Personal Information

1. Your gender: ☐ female ☐ male ☐ diverse

2. Your Age: _____ (in years)

3. Your highest educational level:
☐ no degree (yet)
☐ lower secondary school certificate (or equivalent)
☐ secondary school certificate (or equivalent)
☐ general qualification for university entrance (or equivalent)
☐ university degree (or equivalent)
☐ postgraduate (or equivalent)

4. Your marital status:
☐ living alone
☐ living with partner
☐ married / in a civil partnership
☐ divorced / civil partnership annulled
☐ widowed / life partner deceased

C. Information about your Disease and Therapy

1. Which cancer do you suffer from?
☐ Melanoma ☐ Squamous cell carcinoma ☐ Merkel cell carcinoma
☐ Lung carcinoma (NSCLC) ☐ Renal cell carcinoma ☐ Bladder cancer
☐ Hodgkin lymphoma ☐ Other cancer type: _____

2. Do you have (had) metastases?
☐ Yes ☐ No

> If yes, please answer the following question:
>
> 2a. How well has the cancer responded to treatment?
> ☐ Metastases are gone
> ☐ Metastases are smaller
> ☐ Metastases are stable
> ☐ Metastases are larger or more

3. With which immunotherapeutic agents / immune-checkpoint inhibitors have you been treated so far?

☐ Combi: Ipilimumab + nivolumab ☐ Atezolizumab ☐ Avelumab
☐ Cemiplimab ☐ Durvalumab ☐ Ipilimumab
☐ Nivolumab ☐ Pembrolizumab
☐ other immunotherapeutic agents: _____

4. When was the last administration of immunotherapy?

_____ (dd.mm.yyyy)

5. How burdened did you feel by the cancer before immunotherapy?

not at all very much

(please mark on the left bar )

6. How burdened did you feel by the cancer during immunotherapy?

not at all very much

(please mark on the left bar )

7. How burdened did you feel by the cancer after immunotherapy?

not at all very much

(please mark on the left bar )

8. Did you experience side effects from the immunotherapy that have now completely subsided?

☐ Yes ☐ No

If yes, please answer the following questions:

8a. Please mark which side effects of the immunotherapy you had temporarily:

☐ Mouth dryness / Xerostomia
☐ Respiratory distress / Pneumonitis
☐ Diarrhea / Colitis
☐ Pancreas inflammation / Pancreatitis
☐ Liver inflammation / Hepatitis
☐ Kidney inflammation / Nephritis
☐ Thyroid function changes / Thyroiditis
☐ Hypophysitis / Inflammation of the pituitary gland
☐ Vitiligo
☐ Circumscribed white coloration of the hair / Leukotrichia
☐ Joint complaints / Arthralgia
☐ Muscle complaints / Myalgia
☐ Neurological complaints, please describe: _____
☐ other temporary side effects, please describe: _____

8b. Which drugs were used to treat these reversible side effects?
☐ No drug therapy was conducted
☐ I don't know
☐ Steroids (cortisone) for acute treatment: prednisolone, urbason, budesonide, or similar
☐ Steroids (hydrocortisone, fludrocortisone) as substitution therapy
☐ L-thyroxine
☐ Insulin
☐ TNF inhibitors: etanercept (Enbrel®), infliximab, or similar
☐ Rituximab (MabThera®)
☐ NSAIDs: ibuprofen, diclofenac, etoricoxib, or similar
☐ other medications: _____

9. Are you currently still suffering from persistent side effects from immunotherapy?
☐ Yes ☐ No

If yes, please answer the following questions:

9a. Please mark which side effects of the immunotherapy you currently still have:
☐ Mouth dryness / Xerostomia
☐ Respiratory distress / Pneumonitis
☐ Diarrhea / Colitis
☐ Diabetes mellitus
☐ Thyroid function changes / Thyroiditis
☐ Hypophysitis / Inflammation of the pituitary gland
☐ Vitiligo
☐ Circumscribed white coloration of the hair / Leukotrichia
☐ Joint complaints / Arthralgia
☐ Muscle complaints / Myalgia
☐ Neurological complaints, please describe: _____
☐ other persistent side effects, please describe: _____

9b. In the past week, including today, how burdened have you felt by the side effects you reported?

not at all — very much

(please mark on the left bar )

9c. Please mark the extent to which the following statement applies to you: The less I have to do with the cancer, the more I am burdened by the ongoing side effects:

I don't agree — I agree

(please mark on the left bar )

9d. Are the persistent side effects currently being treated with medication?
☐ Yes ☐ No

If yes, please answer the following questions:

9e. What medications are currently used to treat the side effects?
☐ I don't know
☐ Steroids (cortisone) for acute treatment: prednisolone, urbason, budesonide, or similar
☐ Steroids (hydrocortisone, fludrocortisone) as substitution therapy
☐ L-thyroxine
☐ Insulin
☐ TNF inhibitors: etanercept (Enbrel®), infliximab, or similar
☐ Rituximab (MabThera®)
☐ NSAIDs: ibuprofen, diclofenac, etoricoxib, or similar
☐ other medications: _____

9f. During the past week, including today, how burdened have you felt by taking the above-mentioned medications?

not at all — very much

(please mark on the left bar )

10. Under each heading, please tick the one box that best describes your health today:

MOBILITY	☐ I have no problems in walking about. ☐ I have slight problems in walking about. ☐ I have moderate problems in walking about. ☐ I have severe problems in walking about. ☐ I am unable to walk about.
SELF-CARE	☐ I have no problems washing or dressing myself. ☐ I have slight problems washing or dressing myself. ☐ I have moderate problems washing or dressing myself. ☐ I have severe problems washing or dressing myself. ☐ I am unable to wash or dress myself.
USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	☐ I have no problems doing my usual activities. ☐ I have slight problems doing my usual activities. ☐ I have moderate problems doing my usual activities. ☐ I have severe problems doing my usual activities. ☐ I am unable to do my usual activities.
PAIN / DISCOMFORT	☐ I have no pain or discomfort. ☐ I have slight pain or discomfort. ☐ I have moderate pain or discomfort. ☐ I have severe pain or discomfort. ☐ I have extreme pain or discomfort.
ANXIETY / DEPRESSION	☐ I am not anxious or depressed. ☐ I am slightly anxious or depressed. ☐ I am moderately anxious or depressed. ☐ I am severely anxious or depressed. ☐ I am extremely anxious or depressed.

11. Please mark an X on the scale to indicate how your health is today:

the worst health you can imagine — the best health you can imagine

(please mark on the left bar )

12. Please mark the extent to which the following statements apply to you:

12a. I was adequately informed about the side effects of immunotherapy:

I don't agree — I agree

(please mark on the left bar )

12b. I would have chosen a different treatment option, if the extent of the side effects had been clear to me in advance:

I don't agree — I agree

(please mark on the left bar )

12c. The side effects have shown me that the treatment works:

I don't agree — I agree

(please mark on the left bar )

12d. During therapy, I (would) have immediately reported possible side effects to my doctor:

I don't agree — I agree

(please mark on the left bar )

12e. I (would) have reported side effects late or not at all, as I was concerned about tumor progression during a break in therapy:

I don't agree — I agree

(please mark on the left bar )

12f. I (would) have reported side effects late or not at all, as I was not aware that they existed due to the therapy and could be dangerous:

I don't agree — I agree

(please mark on the left bar )

Please check if you have answered all the questions and submit the questionnaire.

Thank you very much for your participation!

- to be completed by the physician - [only for outpatient clinics]

1. Type of cancer:
   - ☐ Melanoma
   - ☐ Squamous cell carcinoma
   - ☐ Merkel cell carcinoma
   - ☐ Lung carcinoma (NSCLC)
   - ☐ Renal cell carcinoma
   - ☐ Urothelial carcinoma
   - ☐ Hodgkin lymphoma
   - ☐ Other entity: _____

2. Current stage of cancer:

   Stage _____ by classification _____

3. Previous drug-based anti-cancer treatment:
   - ☐ Ipilimumab + nivolumab
   - ☐ Atezolizumab
   - ☐ Avelumab
   - ☐ Cemiplimab
   - ☐ Durvalumab
   - ☐ Ipilimumab
   - ☐ Nivolumab
   - ☐ Pembrolizumab
   - ☐ Dabrafenib + trametinib
   - ☐ Vemurafenib + cobimetinib
   - ☐ Encorafenib + binimetinib
   - ☐ Talimogen laherparepvec (T-VEC®)
   - ☐ Chemotherapy
   - ☐ other antitumor agents: _____

4. Last administration of immune-checkpoint inhibitor:

   _____ (dd.mm.yyyy)

5. Current drug-based anti-cancer treatment:
   - ☐ There is currently no drug-based cancer treatment
   - ☐ Ipilimumab + nivolumab
   - ☐ Atezolizumab
   - ☐ Avelumab
   - ☐ Cemiplimab
   - ☐ Durvalumab
   - ☐ Ipilimumab
   - ☐ Nivolumab
   - ☐ Pembrolizumab
   - ☐ Dabrafenib + trametinib
   - ☐ Vemurafenib + cobimetinib
   - ☐ Encorafenib + binimetinib
   - ☐ Talimogen laherparepvec (T-VEC®)
   - ☐ Chemotherapy
   - ☐ other antitumor agents: _____

- additional questions for patients - [only online]

1. Please indicate the current stage of cancer:

   Stage _____

2. Do you currently receive other drug-based anti-cancer therapies, such as targeted therapy or chemotherapy?
   - ☐ Yes
   - ☐ No

LMU KLINIKUM
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Effects of Autoimmunity

Questionnaire for Patients with Autoimmune Diseases

Dear patient,

Autoimmune diseases can have a significant impact on quality of life. Immunotherapies with so-called immune-checkpoint inhibitors can also lead to autoimmune side effects, which can be distressing for patients. By means of the following questionnaire, we would like to find out more about how you feel and how you deal with possible impairments caused by your autoimmune disease. At the same time, we interview patients who suffer from autoimmune side effects as part of immunotherapy.

Please make sure you meet all of the following criteria:

- You are at least 18 years old.
- You have been diagnosed with an autoimmune disease.
- You have not received any immunotherapy for cancer (more precisely: no immune-checkpoint inhibitors such as atezolizumab, avelumab, cemiplimab, durvalumab, ipilimumab, nivolumab, pembrolizumab).

Please read the questions carefully and mark the answers as follows: [only for outpatient clinics]

- Boxes are marked by ticking: ☐☐☒
  If you wish to change an answer, please black out the incorrectly made cross and check another box:
  ☐☒■
- If there is an answer bar, please tick the expression that suits you:

The information is recorded and evaluated anonymously. Please make sure that you do not enter (e.g. in free text) any personal data such as name, address or date of birth. It is not possible to draw any conclusions about your person.

Thank you very much for your participation!

This survey is conducted by:

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University Hospital, LMU Munich
Department of Dermatology and Allergology
Dermatooncology
Frauenlobstr. 9-11
80337 Munich, Germany

A. Information about the survey

1. Please provide today's date:

_____ (dd.mm.yyyy)

2. Is this your first time taking part in this survey?
☐ Yes ☐ No

B. Personal Information

1. Your gender: ☐ female ☐ male ☐ diverse

2. Your Age: _____ (in years)

3. Your highest educational level:
☐ no degree (yet)
☐ lower secondary school certificate (or equivalent)
☐ secondary school certificate (or equivalent)
☐ general qualification for university entrance (or equivalent)
☐ university degree (or equivalent)
☐ postgraduate (or equivalent)

4. Your marital status:
☐ living alone
☐ living with partner
☐ married / in a civil partnership
☐ divorced / civil partnership annulled
☐ widowed / life partner deceased

C. Information about your Disease and Therapy

1. Which autoimmune disease do you suffer from?
☐ Addison's disease / Primary adrenocortical insufficiency
☐ Ankylosing spondylitis
☐ Autoimmune hepatitis
☐ Autoimmune thyroiditis / Autoimmune hypothyroidism / Hashimoto's thyroiditis
☐ Autoimmune hyperthyroidism / Graves' disease
☐ Bullous pemphigoid
☐ Crohn's disease
☐ Dermatomyositis
☐ Diabetes mellitus type 1
☐ Giant cell arteritis
☐ Hypophysitis / Inflammation of the pituitary gland
☐ Idiopathic pulmonary fibrosis
☐ Lichen ruber
☐ Multiple sclerosis
☐ Myasthenia gravis
☐ Myositis / Muscular atrophy

☐ Neurodermatitis / Atopic dermatitis
☐ Pemphigus vulgaris
☐ Polymyalgia rheumatica
☐ Polymyositis
☐ Polyneuropathy: Chronic inflammatory demyelinating polyneuropathy
☐ Polyneuropathy: Guillain-Barré syndrome
☐ Primary biliary cholangitis / Primary sclerosing cholangitis
☐ Psoriasis vulgaris
☐ Psoriatic arthritis
☐ Rheumatoid arthritis / Chronic polyarthritis
☐ Sarcoidosis
☐ Sjogren's syndrome
☐ Systemic sclerosis / Systemic scleroderma
☐ Systemic lupus erythematosus
☐ Ulcerative colitis
☐ Vasculitis / Vascular inflammation
☐ Vitiligo
☐ other autoimmune disease: _____

2. How long have you had the autoimmune disease?

_____ (mm.yyyy)

3. Has there been an acute worsening / exacerbation of the autoimmune disease within the last week including today?
☐ Yes ☐ No

4. How burdened have you felt by the autoimmune disease in the last week, including today?
not at all very much
(please mark on the left bar)

5. Is the above-mentioned autoimmune disease currently being treated with medication?
☐ Yes ☐ No

If yes, please answer the following questions:

5a. Which drugs are currently used to treat the autoimmune disease??
☐ I don't know
☐ Steroids (cortisone) for acute treatment: prednisolone, urbason, budesonide, or similar
☐ Steroids (hydrocortisone, fludrocortisone) as substitution therapy
☐ L-thyroxine
☐ Insulin
☐ TNF inhibitors: etanercept (Enbrel®), infliximab, or similar
☐ Rituximab (MabThera®)
☐ NSAIDs: ibuprofen, diclofenac, etoricoxib, or similar
☐ other medications: _____

5b. During the past week, including today, how burdened have you felt by taking the above-mentioned medications?

not at all — very much

(please mark on the left bar )

6. Under each heading, please tick the one box that best describes your health today:

MOBILITY	☐ I have no problems in walking about. ☐ I have slight problems in walking about. ☐ I have moderate problems in walking about. ☐ I have severe problems in walking about. ☐ I am unable to walk about.
SELF-CARE	☐ I have no problems washing or dressing myself. ☐ I have slight problems washing or dressing myself. ☐ I have moderate problems washing or dressing myself. ☐ I have severe problems washing or dressing myself. ☐ I am unable to wash or dress myself.
USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	☐ I have no problems doing my usual activities. ☐ I have slight problems doing my usual activities. ☐ I have moderate problems doing my usual activities. ☐ I have severe problems doing my usual activities. ☐ I am unable to do my usual activities.
PAIN / DISCOMFORT	☐ I have no pain or discomfort. ☐ I have slight pain or discomfort. ☐ I have moderate pain or discomfort. ☐ I have severe pain or discomfort. ☐ I have extreme pain or discomfort.
ANXIETY / DEPRESSION	☐ I am not anxious or depressed. ☐ I am slightly anxious or depressed. ☐ I am moderately anxious or depressed. ☐ I am severely anxious or depressed. ☐ I am extremely anxious or depressed.

7. Please mark an X on the scale to indicate how your health is today:

the worst health you can imagine — the best health you can imagine

(please mark on the left bar )

Please check if you have answered all the questions and submit the questionnaire.

Thank you very much for your participation!

Supplementary Table 1: ICI-cohort (n = 200): patient demographics and clinical characteristics

Supplementary Table 1
ICI-cohort (n = 200): patient demographics and clinical characteristics.

	Outpatient ICI-cohort n = 147 (73.5%)	Support group ICI-cohort n = 53 (26.5%)	P-value	Total ICI-cohort n = 200 (100.0%)
Gender, n (%)				
Female	65 (44.2)	33 (62.3)	0.024[a]	98 (49.0)
Male	82 (55.8)	20 (37.7)		102 (51.0)
Age at time of survey, years				
Mean (SD)	64 (14.2)	51 (11.2)	< 0.001[b]	60 (14.6)
Median (range)	64 (23.0-91.0)	54 (24.0-72.0)		60 (23.0-91.0)
Marital status, n (%)				
Partnered	109 (74.1)	43 (81.1)	0.308[a]	152 (76.0)
Not partnered	38 (25.8)	10 (18.8)		48 (24.0)
Education, n (%)				
Low qualification	41 (27.9)	5 (9.4)	0.003[c]	46 (23.0)
Middle qualification	56 (38.1)	20 (37.7)		76 (38.0)
High qualification	50 (34.0)	28 (52.9)		78 (39.0)
Type of cancer, n (%)				
Melanoma	141 (95.9)	52 (98.1)	0.816[d]	193 (96.5)
Squamous cell carcinoma	3 (2.0)	0 (0.0)		3 (1.5)
Merkel cell carcinoma	3 (2.0)	1 (1.9)		4 (2.0)
Stage of cancer, n (%)				
IIA-IIC	2 (1.4)	2 (3.8)	0.592[c]	4 (2.0)
IIIA	12 (8.2)	3 (5.7)		15 (7.5)
IIIB	32 (21.8)	10 (18.9)		42 (21.0)
IIIC	24 (16.3)	7 (13.2)		31 (15.5)
IIID	1 (0.7)	1 (1.9)		2 (1.0)
IV	76 (51.7)	30 (56.6)		106 (53.0)
Metastatic status, n (%)				
Complete response	100 (68.0)	35 (66.0)	0.484[d]	135 (67.5)
Partial response	15 (10.2)	7 (13.2)		22 (11.0)
Stable disease	18 (12.2)	3 (5.7)		21 (10.5)
Progressive disease	11 (7.5)	6 (11.3)		17 (8.5)
Non-metastatic disease	3 (2.0)	2 (3.8)		5 (2.5)
ICIs received, n (%)[e]				
Pembrolizumab	63 (42.9)	19 (35.8)	0.374[a]	82 (41.0)
Nivolumab	55 (37.4)	24 (45.3)	0.315[a]	79 (39.5)
Ipilimumab plus nivolumab	36 (24.5)	23 (43.4)	0.010[a]	59 (29.5)
Ipilimumab	11 (7.5)	7 (13.2)	0.262[d]	18 (9.0)
Avelumab	2 (1.4)	1 (1.9)	1.000[d]	3 (1.5)
Cemiplimab	2 (1.4)	0 (0.0)	1.000[d]	2 (1.0)
Time since last ICI administration				
Mean (SD), months	24 (21.0)	21 (18.3)	0.398[c]	23 (20.4)
Median (range), months	17 (2.8-102.0)	16 (3.5-85.5)		16 (2.8-102.0)
12 weeks to < 6 months, n (%)	24 (16.3)	9 (17.0)	0.394[c]	33 (16.5)
6 months to < 12 months, n (%)	30 (20.4)	15 (28.3)		45 (22.5)
12 months to < 30 months, n (%)	54 (36.7)	17 (32.1)		71 (35.5)
≥ 30 months, n (%)	39 (26.5)	12 (22.6)		51 (25.5)
Prior non-ICI therapy, n (%)				
None	120 (81.6)	[f]	[f]	[f]
Yes	27 (18.4)	[f]	[f]	[f]
Prior non-ICI therapy, n (%)[e]				
Prior targeted therapy	22 (15.0)	[f]	[f]	[f]
Prior chemotherapy	2 (1.4)	[f]	[f]	[f]
Prior oncolytic virus therapy	2 (1.4)	[f]	[f]	[f]
Prior cytokine therapy	7 (4.8)	[f]	[f]	[f]
Current anti-cancer therapy, n (%)				
None	130 (88.4)	41 (77.4)	0.050[a]	171 (85.5)
Yes	17 (11.6)	12 (22.6)		29 (14.5)
Type of current anti-cancer therapy, n (%)				
Current targeted therapy	14 (9.5)	[f]	[f]	[f]
Current chemotherapy	3 (2.0)	[f]	[f]	[f]
Reversible irAEs, n (%)				
Patients without reversible irAEs	73 (49.7)	23 (43.4)	0.434[a]	96 (48.0)
Patients with reversible irAEs	74 (50.3)	30 (56.6)		104 (52.0)
Persistent irAEs, n (%)				
Patients without persistent irAEs	86 (58.5)	14 (26.4)	< 0.001[a]	100 (50.0)
Patients with persistent irAEs	61 (41.5)	39 (73.6)		100 (50.0)
Persistent irAEs per affected patient, n				
Mean (SD)	2.2 (1.5)	2.7 (1.9)	0.133[c]	2.4 (1.7)
Median (range)	2.0 (1.0-6.0)	2.0 (1.0-8.0)		2.0 (1.0-8.0)
Type of persistent irAE, n (%)[e]				
Arthralgia	24 (16.3)	17 (32.1)	0.015[a]	41 (20.5)

Myalgia	20 (13.6)	18 (34.0)	0.001[a]	38 (19.0)
Hypothyroidism	16 (10.9)	20 (37.7)	< 0.001[a]	36 (18.0)
Hypophysitis	12 (8.2)	3 (5.7)	0.763[d]	15 (7.5)
Diabetes mellitus	2 (1.4)	2 (3.8)	0.286[d]	4 (2.0)
Adrenal insufficiency	2 (1.4)	2 (3.8)	0.286[d]	4 (2.0)
Xerostomia	12 (8.2)	6 (11.3)	0.576[d]	18 (9.0)
Polyneuropathy	3 (2.0)	7 (13.2)	0.004[d]	10 (5.0)
Neuropathy (CN VIII)	1 (0.7)	0 (0.0)	1.000[d]	1 (0.5)
Vitiligo	14 (9.5)	6 (11.3)	0.709[a]	20 (10.0)
Dermatitis/pruritus	4 (2.7)	4 (7.5)	0.212[d]	8 (4.0)
Leukotrichia	4 (2.7)	4 (7.5)	0.212[d]	8 (4.0)
Lichen ruber	4 (2.7)	0 (0.0)	0.575[d]	4 (2.0)
Pneumonitis/respiratory distress	7 (4.8)	9 (17.0)	0.014[d]	16 (8.0)
Colitis	5 (3.4)	6 (11.3)	0.071[d]	11 (5.5)
Pancreatitis	1 (0.7)	1 (1.9)	0.461[d]	2 (1.0)
Hepatitis	1 (0.7)	0 (0.0)	1.000[d]	1 (0.5)
Current persistent irAE therapy, n (%)[g]				
None	21 (34.4)	7 (17.9)	0.073[a]	28 (28.0)
Yes	40 (65.6)	32 (82.1)		72 (72.0)
Persistent irAE medications per treated patient, n				
Mean (SD)	1.6 (0.7)	1.7 (0.6)	0.530[c]	1.7 (0.7)
Median (range)	1.5 (1.0-3.0)	2.0 (1.0-3.0)		2.0 (1.0-3.0)

[a] Chi-square test was used. [b] Unpaired t-test was used. [c] Mann-Whitney test was used. [d] Fisher's exact test was used. [e] Multiple responses are possible. [f] No data available due to different survey settings. [g] Among patients with persistent irAEs. ICI, immune checkpoint inhibitor; SD, standard deviation; irAE, immune-related adverse event; CN, cranial nerve.

Supplementary Table 2: AI-cohort (n = 2705): patient demographics and clinical characteristics

Supplementary Table 2
AI-cohort (n = 2705): patient demographics and clinical characteristics.

	Non-exacerbated AI-cohort n = 1837 (67.9%)	Exacerbated AI-cohort n = 868 (32.1%)	P-value	Total AI-cohort n = 2705 (100.0%)
Gender, n (%)				
Female	1608 (87.5)	783 (90.2)	0.043[a]	2391 (88.4)
Male	229 (12.5)	85 (9.8)		314 (11.6)
Age at time of survey, years				
Mean (SD)	47 (11.7)	47 (11.3)	0.792[b]	47 (11.6)
Median (range)	48 (18.0-81.0)	48 (18.0-84.0)		48 (18.0-84.0)
Marital status, n (%)				
Partnered	1356 (73.8)	633 (72.9)	0.624[a]	1989 (73.6)
Not partnered	481 (26.2)	235 (27.1)		716 (26.5)
Education, n (%)				
Low qualification	182 (9.9)	121 (13.9)	< 0.001[c]	303 (11.2)
Middle qualification	731 (39.8)	403 (46.4)		1134 (41.9)
High qualification	924 (50.3)	344 (39.6)		1268 (46.9)
AIs per patient, n				
Mean (SD)	1.5 (0.8)	1.7 (1.0)	< 0.001[c]	1.6 (0.9)
Median (range)	1.0 (1.0-9.0)	1.0 (1.0-11.0)		1.0 (1.0-11.0)
Type of AI, n (%)[d]				
Addison's disease	141 (7.7)	36 (4.1)	< 0.001[a]	177 (6.5)
Ankylosing spondylitis	55 (3.0)	58 (6.7)	< 0.001[a]	113 (4.2)
Autoimmune gastritis	9 (0.5)	3 (0.3)	0.762[e]	12 (0.4)
Autoimmune hematological disorders	19 (1.0)	9 (1.0)	0.995[a]	28 (1.0)
Autoimmune hepatitis	69 (3.8)	23 (2.6)	0.138[a]	92 (3.4)
Autoimmune hyperthyroidism	132 (7.2)	41 (4.7)	0.015[a]	173 (6.4)
Autoimmune hypothyroidism	299 (16.3)	146 (16.8)	0.722[a]	445 (16.5)
Bullous pemphigoid	2 (0.1)	3 (0.3)	0.336[e]	5 (0.2)
Collagenosis (others)	6 (0.3)	9 (1.0)	0.027[e]	15 (0.6)
Crohn's disease	88 (4.8)	47 (5.4)	0.486[a]	135 (5.0)
Dermatomyositis	18 (1.0)	9 (1.0)	0.889[a]	27 (1.0)
Diabetes mellitus type 1	150 (8.2)	21 (2.4)	< 0.001[a]	171 (6.3)
Giant cell arteritis	5 (0.3)	2 (0.2)	1.000[e]	7 (0.3)
Hypophysitis	14 (0.8)	4 (0.5)	0.368[a]	18 (0.7)
Idiopathic pulmonary fibrosis	4 (0.2)	5 (0.6)	0.157[e]	9 (0.3)
Lichen ruber	40 (2.2)	31 (3.6)	0.034[a]	71 (2.6)
Lichen sclerosus	7 (0.4)	4 (0.5)	0.753[e]	11 (0.4)
Multiple sclerosis	49 (2.7)	17 (2.0)	0.265[a]	66 (2.4)
Myasthenia gravis	64 (3.5)	36 (4.1)	0.393[a]	100 (3.7)
Myositis	28 (1.5)	18 (2.1)	0.302[a]	46 (1.7)
Neurodermatitis	29 (1.6)	12 (1.4)	0.697[a]	41 (1.5)
Pemphigus vulgaris	17 (0.9)	6 (0.7)	0.536[a]	23 (0.9)

Polymyalgia rheumatica	42 (2.3)	16 (1.8)	0.458[a]	58 (2.1)
Polymyositis	26 (1.4)	16 (1.8)	0.401[a]	42 (1.6)
Polyneuropathy: CIDP	8 (0.4)	7 (0.8)	0.268[e]	15 (0.6)
Polyneuropathy: GBS	4 (0.2)	1 (0.1)	1.000[e]	5 (0.2)
Primary biliary/sclerosing cholangitis	47 (2.6)	22 (2.5)	0.971[a]	69 (2.6)
Psoriasis vulgaris	137 (7.5)	87 (10.0)	0.024[a]	224 (8.3)
Psoriatic arthritis	134 (7.3)	127 (14.6)	< 0.001[a]	261 (9.6)
Rheumatoid arthritis	107 (5.8)	94 (10.8)	< 0.001[a]	201 (7.4)
Sarcoidosis	185 (10.1)	85 (9.8)	0.822[a]	270 (10.0)
Sjogren's syndrome	215 (11.7)	154 (17.7)	< 0.001[a]	369 (13.6)
Systemic sclerosis	66 (3.6)	50 (5.8)	0.009[a]	116 (4.3)
Systemic lupus erythematosus	181 (9.9)	78 (9.0)	0.474[a]	259 (9.6)
Ulcerative colitis	79 (4.3)	48 (5.5)	0.158[a]	127 (4.7)
Vasculitis (others)	68 (3.7)	38 (4.4)	0.398[a]	106 (3.9)
Vitiligo	204 (11.1)	74 (8.5)	0.039[a]	278 (10.3)
Time since onset of AI, months				
Mean (SD)	148 (145.1)	132 (131.7)	0.019[c]	143 (141.1)
Median (range)	96 (0.5-745.6)	86 (0.2-678.7)		89 (0.2-745.6)
Current AI therapy, n (%)				
None	445 (24.2)	186 (21.4)	0.158[e]	631 (23.3)
Yes	1386 (75.4)	677 (78.0)		2063 (76.3)
Unknown	6 (0.4)	5 (0.6)		11 (0.4)
AI medications per treated patient, n				
Mean (SD)	1.9 (1.1)	2.1 (1.2)	< 0.001[c]	1.9 (1.1)
Median (range)	2.0 (1.0-9.0)	2.0 (1.0-8.0)		2.0 (1.0-9.0)

[a] Chi-square test was used. [b] Unpaired t-test was used. [c] Mann-Whitney test was used. [d] Multiple responses are possible. [e] Fisher's exact test was used. AI, non-ICI-induced autoimmune disease; SD, standard deviation; CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain-Barré syndrome.

Supplementary Table 3: ICI-cohort (n = 200): prevalence of persistent irAEs (by time since last ICI administration)

Supplementary Table 3
ICI-cohort (n = 200): prevalence of persistent irAEs (by time since last ICI administration).

	Outpatient ICI-cohort n = 147 (73.5%)	Support group ICI-cohort n = 53 (26.5%)	P-value	Total ICI-cohort n = 200 (100.0%)
Persistent irAEs, n (%)				
Patients without persistent irAEs	86 (58.5)	14 (26.4)	< 0.001[a]	100 (50.0)
Patients with persistent irAEs	61 (41.5)	39 (73.6)		100 (50.0)
Patients with persistent irAEs to all patients by time since last ICI administration, n of n (%)				
Patients with long-term irAEs	*28 of 54 (51.9)*	*20 of 24 (83.3)*	*0.008[a]*	*48 of 78 (61.5)*
12 weeks to < 6 months	13 of 24 (54.2)	8 of 9 (88.9)	0.107[b]	21 of 33 (63.6)
6 months to < 12 months	15 of 30 (50.0)	12 of 15 (80.0)	0.053[a]	27 of 45 (60.0)
Patients with chronic irAEs	*33 of 93 (35.5)*	*19 of 29 (65.5)*	*0.004[a]*	*52 of 122 (42.6)*
12 months to < 30 months	17 of 54 (31.5)	12 of 17 (70.6)	0.004[a]	29 of 71 (40.8)
≥ 30 months	16 of 39 (41.0)	7 of 12 (58.3)	0.292[a]	23 of 51 (45.1)

[a]Chi-square test was used. [b] Fisher's exact test was used. ICI, immune checkpoint inhibitor; irAE, immune-related adverse event.

Supplementary Table 4: ICI-patients with ≥ 12 months since ICI discontinuation (n = 122): binomial logistic regression analysis of predictor variables for the occurrence of chronic irAEs

Supplementary Table 4
ICI-patients with ≥ 12 months since ICI discontinuation (n = 122): binomial logistic regression analysis of predictor variables for the occurrence of chronic irAEs.

Predictor variables[a]					95% CI for OR	
	B	OR (= e^B)	SEM	P-value	Lower	Upper
Gender (0 = female, 1 = male)	0.516	1.675	0.454	0.256	0.688	4.077
Age (years)	-0.016	0.984	0.016	0.322	0.953	1.016
Time since last ICI administration (months)	0.000	1.000	0.012	0.992	0.977	1.024
ICIs received (number)	-0.089	0.915	0.518	0.863	0.331	2.527
Administration of ipilimumab (0 = no, 1 = yes)	1.534	4.634	0.548	0.005	1.584	13.560
Reversible irAEs (0 = none, 1 = at least one)	-0.803	0.448	0.419	0.055	0.197	1.018
Recruitment cohort (0 = outpatient clinics, 1 = support groups)	1.119	3.062	0.523	0.032	1.099	8.534

[a] Binomial logistic regression analysis was conducted with Chi-square test (7) = 25.177, p < 0.001, n = 122. Correlations between predictor variables were low (r < 0.50), indicating that multicollinearity was not a confounding factor in the analysis. Based on the Nagelkerke's R^2 of 0.250 a Cohen's f^2 of 0.33 was calculated, which indicated a medium effect size. CI, confidence interval; OR, odds ratio; B, regression coefficient; e, Euler's number; SEM, standard error of the mean; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event.

Supplementary Table 5: ICI-cohort (n = 200): HRQoL (EQ-Index score, EQ-VAS score) in patients with persistent irAEs versus without persistent irAEs

Supplemental Table 5
ICI-cohort (n = 200): HRQoL (EQ-Index score, EQ-VAS score) in patients with persistent irAEs versus without persistent irAEs.

EQ-5D-5L scores[a] mean (SD)	EQ-Index score			EQ-VAS score		
	Outpatient ICI-cohort	Support group ICI-cohort	Total ICI-cohort	Outpatient ICI-cohort	Support group ICI-cohort	Total ICI-cohort
All patients (n = 200)	0.870 (0.179)	0.758 (0.247)	0.841 (0.205)	64.3 (22.8)	54.7 (25.1)	61.7 (23.8)
Patients without persistent irAEs (n = 100)	0.925 (0.120)	0.904 (0.113)	0.922 (0.119)	71.2 (20.4)	72.6 (24.3)	71.4 (20.9)
Patients with persistent irAEs (n = 100)	0.793 (0.217)	0.706 (0.262)	0.759 (0.238)	54.6 (22.6)	48.3 (22.3)	52.1 (22.6)
P-value	< 0.001[b]	0.005[b]	< 0.001[b]	< 0.001[c]	0.001[c]	< 0.001[c]
Patients without long-term irAEs (n = 30)	0.910 (0.132)	0.985 (0.017)	0.920 (0.125)	60.5 (24.0)	84.0 (11.6)	63.6 (24.0)
Patients with long-term irAEs (n = 48)	0.794 (0.210)	0.728 (0.252)	0.767 (0.228)	56.7 (22.6)	45.8 (23.2)	52.2 (23.2)
P-value	0.003[b]	0.005[b]	< 0.001[b]	0.557[c]	0.040[c]	0.040[c]
Patients without chronic irAEs (n = 70)	0.932 (0.115)	0.872 (0.119)	0.923 (0.117)	75.8 (16.9)	68.0 (27.0)	74.7 (18.6)
Patients with chronic irAEs (n = 52)	0.792 (0.226)	0.682 (0.276)	0.752 (0.249)	52.7 (22.8)	50.8 (21.7)	52.0 (22.2)
P-value	< 0.001[b]	0.089	< 0.001[b]	< 0.001[c]	0.073[c]	< 0.001[c]

[a] Higher EQ-5D-5L scores correspond to higher HRQoL, and vice versa. [b] Mann-Whitney test was used. [c] Unpaired t-test was used. EQ-5D-5L, EuroQol 5D-5L; SD, standard deviation; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event.

Supplementary Table 6: ICI-patients with ≥ 12 months since ICI discontinuation (n = 122): multiple linear regression analysis of predictor variables for the EQ-Index score

Supplementary Table 6
ICI-patients with ≥ 12 months since ICI discontinuation (n = 122): multiple linear regression analysis of predictor variables for the EQ-Index score.

Predictor variables[a]				95% CI for B	
	B	SEM	P-value	Lower	Upper
Gender (0 = female, 1 = male)	0.057	0.035	0.109	-0.013	0.127
Age (years)	-0.002	0.001	0.108	-0.005	0.000
Time since last ICI administration (months)	-0.001	0.001	0.417	-0.003	0.001
ICIs received (number)	-0.011	0.044	0.800	-0.098	0.076
Administration of ipilimumab (0 = no, 1 = yes)	0.048	0.047	0.306	-0.045	0.141
Reversible irAEs (0 = none, 1 = at least one)	0.025	0.034	0.459	-0.042	0.092
Chronic irAEs (0 = none, 1 = at least one)	-0.163	0.037	< 0.001	-0.237	-0.090
Current drug-based anti-cancer therapy (0 = no, 1 = yes)	-0.055	0.050	0.273	-0.154	0.044
Recruitment cohort (0 = outpatient clinics, 1 = support groups)	-0.099	0.043	0.023	-0.184	-0.014

[a] Multiple linear regression analysis was conducted with F test $F(9, 112) = 4.373$, $p < 0.001$, n = 122. Variance inflation factor values were < 10, indicating that multicollinearity was not a confounding factor in the analysis. Durban Watson statistic value was 1.991, indicating that there is no autocorrelation in the residuals. Based on the R^2 of 0.260 a Cohen's f^2 of 0.351 was calculated, which indicated a large effect size. CI, confidence interval; B, regression coefficient; SEM, standard error of the mean; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event.

Supplementary Table 7: ICI-patients with ≥ 12 months since ICI discontinuation (n = 122): multiple linear regression analysis of predictor variables for the EQ-VAS score

Supplementary Table 7
ICI-patients with ≥ 12 months since ICI discontinuation (n = 122): multiple linear regression analysis of predictor variables for the EQ-VAS score.

Predictor variables[a]				95% CI for B	
	B	SEM	P-value	Lower	Upper
Gender (0 = female, 1 = male)	0.027	3.881	0.994	-7.663	7.717
Age (years)	-0.162	0.141	0.252	-0.442	0.117
Time since last ICI administration (months)	0.083	0.107	0.437	-0.129	0.296
ICIs received (number)	-6.488	4.802	0.179	-16.003	3.026
Administration of ipilimumab (0 = no, 1 = yes)	5.719	5.12	0.266	-4.425	15.863
Reversible irAEs (0 = none, 1 = at least one)	3.751	3.692	0.312	-3.564	11.066
Chronic irAEs (0 = none, 1 = at least one)	-23.413	4.061	< 0.001	-31.459	-15.366
Current drug based anti-cancer therapy (0 = no, 1 = yes)	-13.426	5.467	0.016	-24.259	-2.593
Recruitment cohort (0 = outpatient clinics, 1 = support groups)	-5.033	4.702	0.287	-14.349	4.283

[a] Multiple linear regression analysis was conducted with F test $F(9, 112) = 5.712$, $p < 0.001$, n = 122. Variance inflation factor values were < 10, indicating that multicollinearity was not a confounding factor in the analysis. Durban Watson statistic value was 1.783, indicating that there is no autocorrelation in the residuals. Based on the R^2 of 0.315 a Cohen's f^2 of 0.460 was calculated, which indicated a large effect size. CI, confidence interval; B, regression coefficient; SEM, standard error of the mean; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event.

Supplementary Table 8: ICI-patients with ≥ 12 months since ICI discontinuation (n = 122): evaluation of ICI therapy and patient education

Supplementary Table 8
ICI-patients with ≥ 12 months since ICI discontinuation (n = 122): evaluation of ICI therapy and patient education.

Consent to the statements mean (SD)	ICI-patients with chronic irAEs n = 52 (42.6%)	ICI-patients without chronic irAEs n = 70 (57.4%)	P-value[a]	Total ICI-cohort n = 200 (100%)
I was adequately informed about the side effects of immunotherapy.	73.9 (28.7)	89.3 (21.5)	< 0.001	82.8 (25.9)
I would have chosen a different treatment option, if the extent of the side effects had been clear to me in advance.	19.9 (29.4)	15.2 (28.3)	0.351	17.2 (28.8)
The side effects have shown me that the treatment works.	59.2 (36.2)	53.2 (36.6)	0.228	55.7 (36.4)
During therapy, I (would) have immediately reported possible side effects to my doctor.	90.3 (18.6)	86.2 (26.3)	0.618	88.0 (23.3)
I (would) have reported side effects late or not at all, as I was concerned about tumor progression during a break in therapy.	9.2 (19.7)	9.3 (18.9)	0.977	9.3 (19.2)
I (would) have reported side effects late or not at all, as I was not aware that they existed due to the therapy and could be dangerous.	7.7 (15.5)	10.7 (21.5)	0.626	9.4 (19.2)

[a] Mann-Whitney test was used. ICI, immune checkpoint inhibitor; SD, standard deviation; irAE, immune-related adverse event.

Supplementary Material 3: STROBE Statement for cross-sectional studies

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	4
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	Suppl. file
Outcome data	15*	Report numbers of outcome events or summary measures	7-15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Suppl. file
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	15-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.