Patient-reported outcomes for monitoring symptomatic toxicities in cancer patients treated with immune-checkpoint inhibitors: A Delphi study

André Manuel Da Silva Lopes a,k, Sara Colomer-Lahiguera a,k, Nuria Mederos Alfonso a, Veronica Aedo-Lopez a, Gilliosa Spurrier-Bernard b, Lærke Kjær Tolstrup c, Helle Pappot d, Sandrine Aspeslagh e, Anne Rogiers f, Bart Neyns g, John B. Haanen h, Sandra A. Mitchell i, Alfredo Addeo j, Olivier Michielin a, Manuela Eicher a,k,*

a Department of Oncology, Lausanne University Hospital (CHUV), Lausanne, Switzerland
b MelanomeFrance, Teilhet, France
c Department of Oncology, Research Unit, Odense University Hospital, Odense, Denmark
d Department of Oncology, Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark
e Medical Oncology, University Hospital Brussels, Brussels, Belgium
f Department of Psychiatry, Brugmann University Hospital, Brussels, Belgium
g Department of Medical Oncology, Universitair Ziekenhuis Brussel Oncologisch Centrum, Brussels, Belgium
h Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, the Netherlands
i Outcomes Research Branch, Healthcare Delivery Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD, USA
j Department of Oncology, University Hospital of Geneva, Geneva, Switzerland
k Institute of Higher Education and Research in Healthcare, Faculty of Biology and Medicine, University of Lausanne and Lausanne University Hospital, Lausanne, Switzerland

Received 5 May 2021; received in revised form 12 August 2021; accepted 13 August 2021

Abstract  Background: Immune-related adverse events (IrAEs) associated with the use of immune checkpoint inhibitors (ICIs) may not be fully covered by existing measures like the PRO-CTCAE. Selecting PRO-CTCAE items for monitoring symptomatic adverse events is hindered by the heterogeneity and complexity of IrAEs, and no standardised selection process exists.

KEYWORDS
Patient-reported outcomes; Immune checkpoint inhibitors;
We aimed to reach expert consensus on the PRO-CTCAE™ symptom terms relevant for cancer patients receiving ICIs and to gather preliminary expert opinions about additional symptom terms reflecting ICI symptomatic toxicities. Additionally, we gathered expert consensus about a core set of priority symptom terms for prospective surveillance and monitoring.

**Design:** This Delphi study involved an international panel of experts (n = 6 physicians; n = 3 nurses, n = 1 psychiatrist and n = 1 patient advocates). Experts prioritised the relevance and importance of symptom terms to monitor in patients treated with ICIs.

**Results:** Experts reached a consensus on the relevance of all (n = 80) PRO-CTCAE™ Symptom Terms. Consensus on the importance of these symptom terms for prospective monitoring in patients receiving ICIs was reached for 81% (n = 65) of these terms. Additional symptoms terms (n = 56) were identified, with a consensus that 84% (47/56) of these additional symptom terms should also be considered when monitoring symptomatic IrAEs.

**Conclusion:** This study identified a prioritised list of symptom terms for prospective surveillance for symptomatic IrAEs in patients receiving ICI treatment. Our results indicate the need to strengthen the validity of PRO measures used to monitor patients receiving ICIs. While these results provided some support for the content validity of the PRO CTCAE™ and resulted in a preliminary set of salient symptomatic adverse events related to the use of ICIs, broader international agreement and patient involvement are needed to further validate our initial findings.

© 2021 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. **Introduction**

The growing complexity of cancer care motivates efforts to improve the safety, effectiveness and tolerability of cancer treatments. With the recent widespread adoption of immune checkpoint inhibitors (ICIs) for an expanding number of disease indications, a wide range of new immune-related adverse events (IrAEs) has been reported [1]. While detection and monitoring of treatment toxicity is a priority across cancer care, it is particularly important during immunotherapy treatment. IrAEs are thought to be effects of an over-activated immune system that can affect almost any organ (‘off-target’ effects), varying in frequency and severity, with the most severe leading to hospitalisation, treatment discontinuation, long-term or permanent conditions or even death [2–6]. Despite frequent patient follow-up visits while on treatment, IrAEs can rapidly progress in severity [2], underlining the need to empower patients with the means to self-monitor and self-report their symptoms [1].

The Common Terminology Criteria for Adverse Events (CTCAE) are standardised criteria used by clinicians to identify, grade and report adverse events (AEs) experienced by patients receiving cancer therapies, including ICIs [7–9]. However, accurately and reliably reporting AEs can be challenging, prompting the United States Food and Drug Administration (FDA) to call for the inclusion of the patient’s perspective when describing symptomatic AEs through the collection of patient-reported outcomes (PROs) [5]. PROs are defined as ‘any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else’ [11]. Their use in clinical trials to track symptomatic toxicities of cancer treatments can improve the management of those symptoms, thereby preserving the health-related quality of life, and allowing patients to remain in treatment for longer, and decreasing emergency department visits [12,13]. Moreover, using PROs can enhance patient-clinician communication, allowing for a complete discussion of therapy side effects during office visits [13,14].

The PRO version of the CTCAE (PRO-CTCAE™) was developed by the US National Cancer Institute to address the need to capture through self-reporting the symptomatic toxicities experienced by patients participating in cancer clinical trials [15]. The PRO-CTCAE™ Item Library is comprised of 124 items representing 78 symptomatic adverse events drawn from the CTCAE [16]. For each of these symptomatic AEs, PRO items were created to evaluate attributes of presence or absence, amount, frequency, severity and interference with usual activities. For a given AE, one to three attributes were selected depending on the content of the CTCAE criteria and the nature of the symptom. The PRO-CTCAE™ has demonstrated favourable validity, reliability and responsiveness in a large, heterogeneous sample of United States patients undergoing cancer treatment [15]. Researchers select the relevant symptom terms for prospective surveillance, considering the agent under study, trial goals and the patient population [15]. Regarding the use of the PRO-CTCAE™ items to declare symptomatic adverse events, FDA recommends...
selecting a set of the most important symptomatic AEs that are expected to occur [17]. However, research on methods to select appropriate symptom-related PROs is still limited [18,19].

Using the PRO-CTCAE™ to describe symptomatic toxicities of ICIs poses some challenges. PRO-CTCAE™ development, like that of other PRO measures (PROMs), has to date focused on the symptomatic toxicities of chemotherapy, radiotherapy and targeted therapy across multiple tumour types [15]. As such, the anticipated symptomatic toxicities associated with the use of ICIs, like vitiligo and xerophthalmia, may not be fully addressed by the current version of the PRO-CTCAE™ Item Library. The uniqueness of IrAEs associated with ICIs raises questions about the suitability of existing PROMs to capture ICI-related symptomatic toxicities, and a recent review has identified gaps in the content validity of existing PROMs, including the PRO-CTCAE™ [20,21,22]. Consequently, several clinical trials have reported the use of multiple PROMs, combining cancer-specific and disease-specific instruments, to address the large spectrum of IrAEs [20]. The highly variable and heterogeneous profile of symptomatic IrAEs experienced by patients receiving ICI treatment also presents a challenge in defining a parsimonious and acceptable PRO strategy that both limits patient burden and is sufficiently comprehensive [19]. This underscores the need to systematically appraise the content validity of the symptom terms included in the PRO-CTCAE™ Item Library with respect to the toxicities commonly associated with ICIs, identify candidate symptom terms for expansion of the library, and derive consensus among experts on core domains to be addressed when monitoring for symptomatic IrAEs.

The aim of this study was to reach a consensus on the PRO-CTCAE™ Symptom Terms relevant for cancer patients treated with ICIs and gather preliminary expert opinions on additional PRO symptom terms that could be related to symptomatic ICI toxicity. Additionally, we gathered expert consensus on the importance of each symptom term when monitoring patients receiving ICI therapy, thereby identifying a core set of symptoms to be evaluated in that population.

2. Material and methods

We applied a Delphi technique [23,24] as part of a larger study on the use of electronic patient-reported outcomes monitoring of melanoma and lung cancer patients treated with ICIs.

2.1. Expert recruitment

When recruiting an expert panel, we aimed to represent European physicians, nurses and patients, experienced in at least two of four fields of expertise: immunology, lung cancer, melanoma and PROs. For physicians and nurses, we reviewed relevant publications and presentations in the medical field across these domains and contacted the experts directly. In particular we aimed to recruit clinically active staff in university hospitals with at least two years of experience and renowned researchers in their field. We identified patient advocates serving in leadership roles of national and international patient advocacy groups related to the aforementioned fields of expertise and with experience in dealing with ICIs and their side effects.

A total of 15 experts (N = 8 physicians; N = 6 nurses; N = 2 patient advocates) were identified through convenience sampling and contacted by e-mail. Experts were sent a plan of the Delphi study that included its background and goals, the number of rounds planned, and how the data would be used.

2.2. Delphi planning

This Delphi included four rounds during which experts replied to an online questionnaire. They were e-mailed a secure link and required to log in to a personal account in order to view and reply to the questionnaires. Google Forms and LimeSurvey were used to develop the online questionnaires. STATA® 14 and Microsoft Excel 2016 were used to analyse the data. Through the duration of the Delphi, experts were able to contact the investigators for any questions regarding the online questionnaires, including technical support.

Four investigators collected, reviewed and anonymised expert’s answers before sharing them with the other experts that were blinded. Results from each round were presented in a word document and shared via e-mail with all experts. The four investigators were not blinded as they were required to contact the experts to follow up on replies needing further clarification. The overall process is illustrated in Fig. 1.

2.3. Delphi round 1

The first round of the Delphi aimed to identify relevant PRO-CTCAE™ Symptom Terms and collect experts’ suggestions on additional symptoms to monitor in the aforementioned population. The 80 symptom terms were grouped according to the categories defined in the PRO-CTCAE™ Item Library Quick Guide [25].

Experts were asked to classify each term as ‘Relevant’, ‘Not relevant’ or ‘Do not know’. A free-text option to add comments to their answers was provided. The consensus was set at 75% agreement, in accordance to the European Society of Medical Oncology’s consensus meeting the guidelines [26]. If a term was considered not relevant to monitor in patients receiving ICIs by 75% of all experts, it was excluded from the following round.
Round 1 - Relevance of PRO-CTCAE™ Symptom Terms and new PROs - Expert Panel (N=11)

- **PRO-CTCAE™ Symptom Terms (N=80)**
  - Not Relevant PRO-CTCAE™ Symptom Terms (N=0)

- **New PRO Symptom Terms suggested by experts (N=60)**
  - Rejected by the investigators (N=6):
    - Not PROs (N=5)
    - Redundant with existing PRO-CTCAE™ Symptom Terms (N=1)

  **Relevant PRO-CTCAE™ Symptom Terms (N=80)**

  **Validated by investigators (N=54)**

Round 2 – Importance of Symptom Terms and new PROs
Expert Panel (N=11)

- Added PRO-CTCAE™ Symptom Terms reaching consensus (N=20):
  - Level 1 Importance (N=17)
  - Level 2 Importance (N=3)
  - Level 3 Importance (N=0)

  **PRO-CTCAE™ Symptom Terms without a consensus (N=60)**

  **New PRO Symptom Terms (N=40)**

  **Added New PRO Symptom Terms reaching consensus (N=14):**
  - Level 1 Importance (N=11)
  - Level 2 Importance (N=3)
  - Level 3 Importance (N=0)

Round 3 – Importance of Symptom Terms and new PROs
Expert Panel (N=11)

- Added PRO-CTCAE™ Symptom Terms reaching consensus (N=15):
  - Level 1 Importance (N=8)
  - Level 2 Importance (N=7)
  - Level 3 Importance (N=0)

  **PRO-CTCAE™ Symptom Terms without a consensus (N=45)**

  **New PRO Symptom Terms (N=32)**

  **Added New PRO Symptom Terms with a consensus (N=10):**
  - Level 1 Importance (N=9)
  - Level 2 Importance (N=1)
  - Level 3 Importance (N=0)

Round 4 – Importance of Symptom Terms and new PROs
Expert Panel (N=9)

- Added PRO-CTCAE™ Symptom Terms reaching consensus (N=30):
  - Level 1 Importance (N=5)
  - Level 2 Importance (N=23)
  - Level 3 Importance (N=2)

  **PRO-CTCAE™ Symptom Terms without a consensus (N=15)**

  **New PRO Symptom Terms (N=9)**

  **Added New PRO Symptom Terms with a consensus (N=23):**
  - Level 1 Importance (N=9)
  - Level 2 Importance (N=13)
  - Level 3 Importance (N=1)

---

This flowchart depicts the number of Symptom Terms where a consensus was reached for each round. Only terms where a consensus was not reached were repeated in the following round.

* New PRO Symptom Terms - two new symptom terms were developed by experts in Round 2 after revising the terms rejected by the investigators. These were added in Round 3 for importance assessment.

Fig. 1. Number of PRO symptom terms validated by Delphi round.
Experts were also asked to add any additional symptoms not covered by the PRO-CTCAE™ that they deemed relevant for monitoring adverse events in this patient population. Suggested additional symptom terms were assessed by the investigators according to predefined requirements (evidence that the symptom had been observed in the patient population and that it was likely related to ICIs; no redundancy with existing PRO-CTCAE™ terms; a clear description of the symptom; and amenable to self-reporting) and submitted to the following round. If a Symptom Term did not meet these criteria, the suggesting expert was approached by e-mail or phone to clarify what was intended to be addressed. Investigators would draft an assessment to be reviewed separately by the remaining experts in the following round.

2.4. Delphi round 2

In the second round, experts were asked to assess the importance of monitoring symptoms represented by the PRO-CTCAE™ items found relevant in the previous round and new suggested ones. For assessing their importance, experts were advised to consider: (i) the likelihood that the symptom can be meaningfully self-reported by the patient; (ii) the likelihood that the symptom is related to an IrAE and (iii) how consequential the resulting IrAE would be to the patient. Importance was rated on a 5-point Likert scale ranging from 1- ‘not important’ to 5 ‘very important’.

Three levels of importance were defined by grouping ratings together: level 1 included ratings 4 ‘rather important’ and 5 ‘very important’; level 2 included rating 2 ‘slightly important’ and 3 ‘moderately important’; and the remainder ‘not important’ were level 3. The consensus was defined as 75% agreement in one of the three levels of importance.

Furthermore, as part of this second round, experts were asked to review and validate the investigators’ decision of rejection or validation of each of the new symptoms proposed in the previous round. Experts could choose ‘Agree’, ‘Disagree’ or ‘Undecided’. If experts expressed disagreement or were undecided, they were encouraged to provide a rationale for their opinion using a free text field.

2.5. Delphi round 3

The third round of the Delphi shared the same goal and was structurally similar to the second round, featuring the same 5-point Likert scale with an added ability to comment on each of the answers. Experts were able to see the overall results of the previous round as they replied to each question and were encouraged to express their views on the previous results. The intent was to understand why there was no consensus in certain PRO terms.

2.6. Delphi round 4

The fourth round of the Delphi featured a questionnaire with the same structure as that of rounds 2 and 3. Experts were invited to a real-time online discussion after they consented to being unmasked to other experts. Experts who were unavailable for the online discussion were given the option to reply to the questionnaire, with the written comments of the live discussion, at a later date.

The live discussion was moderated by the investigators. Each of the participating experts was able to access the same questionnaire and reply to it at the same time. In addition to expressing their opinions verbally during the live discussion, experts were encouraged to write them down in the questionnaire.

2.7. Ethical considerations

Since no medical data were collected, this study is not covered by the Human Research Act and did not require ethical approval. All experts consented to participate in all expert rounds in written form.

3. Results

3.1. Expert panel

The Delphi process took place between July 2019 and May 2020. Eleven experts were available and consented to participate in the Delphi by e-mail. All experts participated in rounds one to three, and nine experts participated in the final round (n = 1 physician and n = 1 nurse were unavailable) due to decreased availability during the SARS-CoV-2 pandemic. All experts had training and experience relevant to at least two fields of expertise, as described in Table 1.

3.2. PRO-CTCAE™ symptom terms

In round one, all (n = 80) PRO-CTCAE™ Symptom Terms were considered relevant to the target population. With respect to the importance to monitor, a consensus was reached for 65/80 (81%) of the PRO-CTCAE™ Symptom Terms. Among the Symptom Terms considered rather or very important (n = 30), 23% belonged to the gastro-intestinal subgroup, followed by pain (13%), respiratory (10%), cutaneous terms (10%). In the slightly or moderately important category (n = 33), 24% of the terms were cutaneous symptoms, followed by gynecologic/urinary, sexual and miscellaneous terms at 15%
each. Two terms were considered ‘not important’. Overall results are portrayed in Fig. 1. The percentage of agreement by the level of importance for each symptom term is presented in Table 2. An infographic listing the terms ordered by level of importance is available for PRO-CTCAE™ Symptom Terms (Fig. 2) and the terms suggested by experts (Fig. 3).

Oral, cutaneous and gynecologic/urinary terms, each make up 20% of the 15 PRO-CTCAE™ Symptom Terms where no consensus on importance was achieved. For the gynecologic/urinary terms, in particular, experts expressed difficulty in relating the occurrence of these symptoms to the immune-checkpoint blockade. They also noted that several terms in this subgroup and the sexual terms subgroup were likely underreported in the literature, as they may not often be discussed with patients.

3.3. New PRO symptom terms

In round one, experts suggested 60 new symptom terms, of which six were rejected by the investigators for the following round, with unanimous agreement from the experts. These included five symptom terms that could not be meaningfully captured by patient self-report (‘Arrhythmia’, ‘Arthritis’, ‘Asthenia’, ‘Cellulitis’ and ‘Sudden increase in caries’) and one (‘Symptom-related Fatigue’) that was considered difficult to differentiate from the existing PRO-CTCAE™ Symptom Term ‘Fatigue’. To address ‘Arthritis’ and ‘Cellulitis’, experts suggested and validated two new terms: ‘Swelling of the joints’ and ‘Heat or burning sensation in an area of the body’, respectively. Thus, 56 new symptom terms were rated on the importance to monitor.

Expert consensus was reached in 47 of the 56 new symptom terms. Of these, 62% (n = 29) were considered ‘rather’ or ‘very important’, 36% (n = 17) were classed as ‘slightly’ or ‘moderately important’, and one term ‘not important’. The number of items per Delphi round is illustrated in Fig. 1. Expert consensus for each term is described in Table 3.

Consensus on importance was not achieved in nine (14%) of the new terms. These were among the most discussed. Abdominal cramps were among the terms where experts considered that complete contextual information was crucial to determine its importance. Specifically, it would be considered increasingly important as other symptoms were manifested, like diarrhoea or abdominal pain, or if confounding variables like menstrual pain were present.

Other terms like ‘Infusion-related reaction’ were considered either too broad to be meaningfully assessed by patient self-report or were more amenable to direct observation by clinicians during infusion. Experts also noted that some of the suggested PRO terms, like ‘overalertness’, were more likely related to the corticosteroid treatment for the IrAEs than a symptom of ICI toxicity. Additional comments from experts on symptom terms can be found in Appendix Table A1.

3.4. Discussion

Experts reached a consensus on the salience of all (n = 80) terms in the PRO-CTCAE™ Item Library for surveillance for symptomatic adverse events in cancer patients being treated with ICIs. A consensus was also reached on the importance of these terms, with 30 terms endorsed as very important by 75% or more of the Delphi panellists. Among the new terms suggested by experts, 56 new PRO terms were proposed as potentially salient in capturing side effects of ICIs, and a consensus was reached that 45 of these terms are candidates for item development to expand the PRO-CTCAE™ Item Library for patients treated with ICI therapy.

Several caveats should be considered in interpreting these study findings. While the international expert panel reflected a diversity of professional experiences and disciplinary perspectives, the panel was small and drawn predominantly from Switzerland (five out of 11 experts). Expert roles were not equally represented, with only one patient advocate participating. While differences in expertise may increase the challenge of reaching
Table 2
Expert agreement (%) on the importance level of PRO-CTCAE™ Symptom Terms (1/2).

| Symptom Term                        | Importance level<sup>a</sup> | Symptom Term                        | Importance level<sup>a</sup> | Symptom Term                        | Importance level<sup>a</sup> |
|-------------------------------------|------------------------------|-------------------------------------|------------------------------|-------------------------------------|------------------------------|
|                                     | 1   | 2   | 3   |                             | 1   | 2   | 3   |                             | 1   | 2   | 3   |
| **Oral Terms**                      |     |     |     | **Oral Terms**              |     |     |     | **Oral Terms**              |     |     |     |
| Dry mouth                           | 56  | 44  | 0   | Mouth/throat sores          | 44  | 56  | 0   | Voice quality changes       | 0   | 82  | 18  |
| Difficulty swallowing               | 91  | 0   | 9   | Cracking at the corners of the mouth (cheliosis/cheilitis) | 0   | 56  | 44  | Hoarseness                  | 0   | 100 | 0   |
| **Gastrointestinal Terms**          |     |     |     | **Gastrointestinal Terms**  |     |     |     | **Gastrointestinal Terms**  |     |     |     |
| Taste changes                       | 9   | 82  | 9   | Heartburn                   | 44  | 44  | 12  | Constipation                | 91  | 9   | 0   |
| Decreased appetite                  | 90  | 0   | 10  | Gas                         | 0   | 89  | 11  | Diarrhea                    | 100 | 0   | 0   |
| Nausea                              | 90  | 0   | 10  | Bloating                    | 0   | 89  | 11  | Abdominal Pain              | 100 | 0   | 0   |
| Vomiting                            | 91  | 0   | 9   | Hiccups                      | 0   | 78  | 22  | Fecal incontinence          | 82  | 9   | 9   |
| **Respiratory Terms**               |     |     |     | **Respiratory Terms**       |     |     |     | **Respiratory Terms**       |     |     |     |
| Shortness of Breath                | 100 | 0   | 0   | Cough                       | 82  | 18  | 0   | Wheezing                    | 100 | 0   | 0   |
| **Cardio-circulatory Terms**        |     |     |     | **Cardio-circulatory Terms**|     |     |     | **Cardio-circulatory Terms**|     |     |     |
| Swelling                            | 91  | 9   | 0   | Heart palpitations          | 91  | 9   | 0   |                             |     |     |     |
| **Cutaneous Terms**                 |     |     |     | **Cutaneous Terms**         |     |     |     | **Cutaneous Terms**         |     |     |     |
| Rash                                | 90  | 10  | 0   | Hand-foot syndrome          | 67  | 33  | 0   | Radiation skin reaction     | 0   | 100 | 0   |
| Skin dryness                        | 0   | 100 | 0   | Nail loss                   | 0   | 100 | 0   | Skin darkening              | 9   | 82  | 9   |
| Acne                                | 0   | 89  | 11  | Nail ridging                | 0   | 82  | 18  | Stretch marks               | 0   | 56  | 44  |
| Hair loss                           | 11  | 78  | 11  | Nail discoloration          | 0   | 56  | 44  |                             |     |     |     |
| Itching                             | 82  | 9   | 9   | Sensitivity to sunlight     | 0   | 100 | 0   | Hives                       | 82  | 18  | 0   |
| **Bed/pressure sores**              |     |     |     | **Bed/pressure sores**      |     |     |     | **Bed/pressure sores**      |     |     |     |
| Numbness & tingling                 | 91  | 9   | 0   | Dizziness                   | 91  | 10  | 0   |                             |     |     |     |
| **Neurological Terms**              |     |     |     | **Neurological Terms**      |     |     |     | **Neurological Terms**      |     |     |     |
| Blurred vision                      | 91  | 9   | 0   | Visual floaters             | 67  | 33  | 0   | Ringing in ears             | 44  | 56  | 0   |
| Flashing lights                     | 100 | 0   | 0   | Watery eyes                 | 22  | 78  | 0   |                             |     |     |     |
| **Attention/Memory Terms**          |     |     |     | **Attention/Memory Terms**  |     |     |     | **Attention/Memory Terms**  |     |     |     |
| Concentration                       | 91  | 9   | 0   | Memory                      | 82  | 18  | 0   |                             |     |     |     |
| **Pain Terms**                      |     |     |     | **Pain Terms**              |     |     |     | **Pain Terms**              |     |     |     |
| General Pain                        | 91  | 9   | 0   | Muscle pain                 | 91  | 9   | 0   | Headache                    | 91  | 9   | 0   |
| Joint pain                          | 100 | 0   | 0   |                             |     |     |     |                             |     |     |     |
| **Sleep/Wake Terms**                |     |     |     | **Sleep/Wake Terms**        |     |     |     | **Sleep/Wake Terms**        |     |     |     |
| Insomnia                            | 56  | 44  | 0   | Fatigue                     | 82  | 18  | 0   |                             |     |     |     |
| **Mood Terms**                      |     |     |     | **Mood Terms**              |     |     |     | **Mood Terms**              |     |     |     |
| Anxious                             | 0   | 89  | 11  | Discouraged                 | 0   | 100 | 0   | Sad                         | 0   | 100 | 0   |

**Expert agreement (%) on the importance level of PRO-CTCAE™ Symptom Term (2/2)**

| Symptom Term                                      | Importance level<sup>a</sup> | Symptom Term                                      | Importance level<sup>a</sup> | Symptom Term                                      | Importance level<sup>a</sup> |
|--------------------------------------------------|------------------------------|--------------------------------------------------|------------------------------|--------------------------------------------------|------------------------------|
| **Gynecologic/Urinary Terms**                    |     | **Gynecologic/Urinary Terms**                   |     | **Gynecologic/Urinary Terms**                   |     | **Gynecologic/Urinary Terms**                   |
| Irregular periods/ vaginal bleeding               | 9   | 82  | 9   | Vaginal dryness                           | 0   | 100 | 0   | Urinary frequency                      | 78  | 22  | 0   |
| Missed expected menstrual period                  | 11  | 89  | 0   | Painful urination                        | 22  | 78  | 0   | Change in usual urine colour         | 0   | 33  | 67  |
| Vaginal discharge                                 | 10  | 80  | 10  | Urinary urgency                          | 56  | 44  | 0   | Urinary incontinence                 | 11  | 33  | 56  |
| **Sexual Terms**                                  |     |     |     | **Sexual Terms**                         |     |     |     | **Sexual Terms**                      |     |     |     |
| Achieve and maintain erection                    | 11  | 78  | 11  | Decreased libido                         | 0   | 89  | 11  | Unable to have orgasm                | 0   | 82  | 18  |
| Ejaculation                                       | 0   | 89  | 11  | Delayed orgasm                           | 0   | 80  | 20  | Pain with sexual intercourse        | 22  | 11  | 67  |
| **Miscellaneous Terms**                           |     |     |     | **Miscellaneous Terms**                  |     |     |     | **Miscellaneous Terms**              |     |     |     |
| Breast swelling and tenderness                    | 0   | 100 | 0   | Increased sweating                      | 18  | 82  | 0   | Nosebleed                           | 67  | 33  | 0   |
| Bruising                                          | 0   | 100 | 0   | Decreased sweating                      | 9   | 82  | 9   | Pain and swelling at injection site | 0   | 78  | 22  |
| Chills                                            | 89  | 11  | 0   | Hot flashes                              | 89  | 0   | 11  | Body odor                           | 0   | 11  | 89  |

- Level 1 – includes Symptom Terms considered ‘rather important’ or ‘very important’.
- Level 2 – includes Symptom Terms considered ‘slightly important’ or ‘moderately important’.
- Level 3 – includes Symptom Terms considered ‘not important’.

<sup>a</sup> Importance Level.
Fig. 2. Priority PRO-CTCAE™ symptom terms to monitor in cancer patients treated with immune checkpoint inhibitors.
| LEVEL 1                  | LEVEL 2                  | LEVEL 3                  |
|-------------------------|-------------------------|-------------------------|
| **Gastro-intestinal**   | **Oral**                | **Mood**                |
| Blood in stool          | Oral itchiness          | **Worries**             |
| Rectal bleeding         | Respiratory             |                         |
|                         | Congestion              |                         |
| **Respiratory**         | **Cutaneous**           |                         |
| Haemoptysis             | White spots/patches / Vitiligo |                  |
| Syncope                 | Neurological            |                         |
| Swelling of the joints | Clumsiness              |                         |
| **Neurological**        | **Visual/ Perceptual**  |                         |
| Confusion               | Impaired distance assessment |                |
| Coordination problems   | Pain                    |                         |
| Difficulty with eye and/or facial movements | Back pain              |                         |
| Loss of sensitivity     | Mood                    |                         |
| Muscle weakness         | Depressive mood         |                         |
| Slow reflexes           | Hopelessness             |                         |
| Speaking problems       | Irritability            |                         |
| Walking difficulties    | Lack of motivation       |                         |
|                         | Loss of interest         |                         |
|                         | Nervousness              |                         |
| **Visual/ Perceptual**  | **Gynecologic/ Urinary**|                         |
| Diplopia                | Change in urine smell   |                         |
| Dry eyes                |                         |                         |
| Epilepsy                |                         |                         |
| Hearing loss            |                         |                         |
| Photophobia             |                         |                         |
| Visual loss             |                         |                         |
| **Pain**                |                         |                         |
| Chest pain              |                         |                         |
| Eye pain                |                         |                         |
| Pain in extremities     |                         |                         |
| **Gynecologic/ Urinary**|                         |                         |
| Urinary retention       |                         |                         |
| **Miscellaneous**       |                         |                         |
| Blisters                | [Ocular] Cold/heat sensitivity |                |
| Fever                   | Infusion-related reaction |                |
| Flu-like symptoms       | Muscle cramps           |                         |
| General Malaise         | Neck stiffness           |                         |
| Joint stiffness          |                         |                         |
| Thirst                  |                         |                         |

The Symptom Terms listed above were suggested by the group of experts and require further development before being formulated as items in patient-reported outcomes measures, and used in clinical research and clinical practice. Importance of monitoring each symptom term was assessed considering:

1. The likelihood that the symptom can be detected by the patient;
2. The likelihood that the symptom is connected to an immune-related adverse event (IrAE);
3. How consequential the resulting IrAE would be to the patient.

Importance to monitor was rated as follows:

- **Level 1** (highest importance) - Terms that should be monitored in all patients treated with ICIs.
- **Level 2** (moderate importance) - Additional terms that should be considered to be monitored in patients treated with ICIs, according to specific needs of the population or clinical trial.
- **Level 3** (not important) - Terms that are unlikely to be related to IrAEs.

Experts could not reach consensus for some symptom terms. These should nevertheless be considered to be measured, according to specific needs of the population or clinical trial. New data on potential IrAEs related to the use of immune checkpoint inhibitors is ever-evolving, and should be considered when using this selection of symptom terms.

Fig. 3. Additional symptom terms to monitor in cancer patients treated with immune checkpoint inhibitors.
consensus, there were no clear associations between expert background and deviation from consensus, although this can be due to the small sample size. Our findings should be replicated and extended with a larger, more balanced and more geographically diverse panel, including patients that are receiving or have received immune checkpoint inhibitors. We nevertheless maintain that diversity in expertise enriched the discussion, bringing together multiple perspectives and decreasing the likelihood of an authority bias.

The number of additional symptom terms experts identified for inclusion extends results of a prior systematic review [20] and provides preliminary evidence that the current PRO-CTCAE/C228 version was conceived with symptoms related to chemotherapy, radiotherapy and targeted therapies in mind, which may explain how more complex IrAEs elude existing symptom terms [15]. It is important to consider how the PRO-CTCAE/C228 is derived from the constantly evolving CTCAE, which has been updated to reflect some IrAEs. Some of the newly suggested PRO items do, in fact, reflect CTCAE terms included in version 5.0, such as photophobia. While updates to the current PRO-CTCAE/C228 item library are inbound, the use of some of the existing symptom terms will remain challenging in the context of ICIs. This is illustrated by some unexpected results on specific symptoms, such as the unanimous assessment of ‘radiation skin reaction’ as level 2 importance. Experts argued such a symptom could signal a broader autoimmune reaction. While there have been reports of ICI-induced radiation recall dermatitis [27–29], it can be questioned if this item would retain its original meaning to patients who were not treated with radiotherapy.

### Table 3

Agreement (%) on the importance level of PRO symptom terms suggest by experts.

| Symptom Term                        | Importance level | Symptom Term                        | Importance level |
|-------------------------------------|------------------|-------------------------------------|------------------|
|                                     | 1    | 2    | 3    | 1    | 2    | 3    |
| Abdominal cramps                    | 67   | 33   | 0    | Irritability | 0    | 89   | 11  |
| Back pain                           | 0    | 100  | 0    | Joint stiffness | 82   | 18   | 0   |
| Blisters                            | 78   | 22   | 0    | Lack of motivation | 0    | 89   | 11  |
| Blood in stool                      | 82   | 18   | 0    | Photophobia    | 100  | 0    | 0   |
| Change in urine smell               | 0    | 80   | 20   | Loss of interest | 10   | 80   | 10  |
| Chest pain                          | 82   | 18   | 0    | Loss of sensitivity | 80   | 20   | 0   |
| Clumsiness                          | 0    | 100  | 0    | Muscle weakness | 91   | 9    | 0   |
| [Ocular] Cold/heat sensitivity      | 11   | 78   | 11   | Neck stiffness  | 18   | 82   | 0   |
| Confusion                           | 90   | 10   | 0    | Nervousness    | 0    | 100  | 0   |
| Congestion                          | 0    | 89   | 11   | Oral itchiness | 0    | 100  | 0   |
| Coordination problems               | 91   | 9    | 0    | Over-alertness | 44   | 22   | 33  |
| Muscle cramps                       | 0    | 89   | 11   | Pain in extremities | 78   | 22   | 0   |
| Depressive mood                     | 11   | 89   | 0    | Paralysis      | 50   | 50   | 0   |
| Difficulty with eye                 | 80   | 10   | 10   | Rectal bleeding | 80   | 10   | 10  |
| and/or facial movements             |      |      |      |                |      |      |      |
| Diplopia                            | 80   | 10   | 10   | Sleepiness     | 44   | 56   | 0   |
| Dry eyes                            | 89   | 11   | 0    | Slow reflexes  | 82   | 18   | 0   |
| Epilepsy                            | 82   | 0    | 18   | Sore eyes      | 56   | 44   | 0   |
| Eye pain                            | 82   | 18   | 0    | Speaking problems | 91   | 9    | 0   |
| Eye redness                         | 33   | 67   | 0    | Syncope        | 100  | 0    | 0   |
| Fever                               | 90   | 9    | 0    | Thirst         | 100  | 0    | 0   |
| Flu-like symptoms                   | 78   | 22   | 0    | Muscle Twitching | 44   | 33   | 22  |
| General Malaise                     | 91   | 9    | 0    | Walking difficulties | 80   | 10   | 10  |
| Hearing loss                        | 82   | 18   | 0    | Urinary retention | 100  | 0    | 0   |
| Hemoptysis                          | 91   | 9    | 0    | Visual loss    | 80   | 20   | 0   |
| Hopelessness                        | 11   | 89   | 0    | Worries        | 0    | 22   | 78  |
| Impaired distance assessment        | 11   | 89   | 0    | Swelling of the joints | 100  | 0    | 0   |
| Increased appetite                  | 20   | 80   | 0    | Heat or burning sensation | 67   | 22   | 11  |
| and/or facial movements             |      |      |      |                |      |      |      |
| Infusion-related reaction           | 0    | 67   | 33   | White spots/patches/Vitiligo | 11   | 89   | 0   |

- Level 1 = includes Symptom Terms considered ‘rather important’ or ‘very important’.
- Level 2 = includes Symptom Terms considered ‘slightly important’ or ‘moderately important’.
- Level 3 = includes Symptom Terms considered ‘not important’.

Experts’ comments on these symptom terms can be found in Supplementary Table A1.

* Importance Level.
Experts mentioned that this effect could be potentially captured by other existing PRO-CTCAE™ cutaneous symptom terms. This argues for the need for further qualitative research on PRO-CTCAE™ Symptom Terms in patients treated with ICIs, not only to further characterise them in different contexts but also to guide item selection. Another issue evoked by experts is the development of symptom clusters that can alter the significance of individual symptoms, such as hoarseness within the context of ICI-triggered myasthenia gravis. Understanding of symptom clusters in ICI therapy is still developing, rendering the individual interpretation of some items ambiguous. This may have contributed to the unanimous agreement on level 2 importance to monitor hoarseness, as experts require more data to form a more complete opinion. Selection processes of PRO-CTCAE™ items should consider symptom clusters as more data on this phenomenon becomes available.

A large item library can pose important feasibility challenges as the patient burden is increased. The defined levels of importance may inform new ways to present patients with a large library of symptom terms, particularly when paired with computer-adaptive questionnaires and artificial intelligence. Level 1 terms could be used as a standard starting point, and terms from other levels could be called upon according to potential symptom associations or clusters. As item libraries are expanded to account for the diversity of ICI-related symptomatic IrAEs, these tools will become essential to balance the patient burden and the exhaustiveness of symptom-related PROMs.

The aforementioned heterogeneity of the adverse effects that may be experienced by patients receiving ICI therapy makes self-reporting of symptomatic IrAEs complex, as illustrated by new terms such as ‘depressive mood’, ‘impaired distance assessment’ and ‘walking difficulties’. Experts’ comments on these and other terms can be found in Supplementary Table A1. While these examples require further refinement to better clarify what they intend to assess, they raise questions perpetrating the use of highly specific symptom terms as the most comprehensive approach to best reflect the patient experience regarding IrAEs. Experts were challenged to identify symptomatic components of clinical syndromes (e.g. pneumonitis, myasthenia gravis, iritis) that may have aspects that can be captured through a PRO (e.g. cough, changes in voice quality, visual disturbance) but which can only be identified precisely by the inclusion of clinician adverse event reports or information derived from diagnostic or laboratory testing.

Some new suggested PRO terms could be interpreted as redundant when considering existing PRO-CTCAE™ Symptom Terms, as is the case between ‘Sad’ (PRO-CTCAE™) and the expert suggestion ‘Depressive mood’, or ‘anxious’ (PRO-CTCAE™) and ‘worries’ (expert suggestion). This further illustrates the aforementioned complexity of symptoms, as experts appeared to have different representations of the same term. While these results provided some support for the content validity of the PRO CTCAE™ and resulted in a preliminary set of salient symptomatic adverse events related to the use of ICIs, broader international agreement and further validation, including patient involvement, is needed to continue to validate our initial findings. Further mixed methods studies examining the experiences of adverse effects of ICI are needed to develop and test additional PRO-CTCAE™ items and to identify efficient, interpretable and meaningful approaches to profile symptomatic adverse effects of ICI therapies.

Funding

This project was supported by the Swiss Institute for Experimental Cancer Research (ISREC) Foundation.

Author contributions

André Manuel Da Silva Lopes: Conceptualisation, Methodology, Formal analysis, Writing - Original Draft, Visualisation. Sara Colomer-Lahiguera: Methodology, Formal analysis, Writing - Original Draft, Visualisation. Nuria Mederos Alfonso: Writing - Review and Editing. Veronica Aedo-Lopez: Writing - Review and Editing. Gilliosa Spurrier-Bernard: Writing - Review and Editing. Lærke Kjer Tolstrup: Writing - Review and Editing. Helle Pappot: Writing - Review and Editing. Sandrine Aspeslagh: Writing - Review and Editing. Anne Rogiers: Writing - Review and Editing. Bart Neyns: Writing - Review and Editing. John B. Haanen: Writing - Review and Editing. Sandra A. Mitchell: Writing - Original Draft, Writing - Review and Editing. Alfredo Addeo: Conceptualisation, Methodology, Writing - Review and Editing. Olivier Michielin: Conceptualisation, Methodology, Supervision, Project administration, Writing - Review and Editing, Funding acquisition. Manuela Eicher: Conceptualisation, Methodology, Supervision, Project administration, Writing - Review and Editing, Funding acquisition.

Conflict of interest statement

The authors declare the following financial interests/personal relationships, which may be considered as potential competing interests: Da Silva Lopes reports grants from Fondation Recherche Cancer (ISREC) Foundation, during the conduct of the study; Dr. Colomer-Lahiguera reports grants from Fondation Recherche Cancer (ISREC) Foundation, during the conduct of the study; Dr. Mederos has nothing to disclose; Dr. Aedo-Lopez has nothing to disclose; Dr. Spurrier-Bernard reports grants from MSD France, grants from Novartis, personal fees from Bayer, other
from MPNE, WECAN, outside the submitted work; Dr. Tolstrup has nothing to disclose; Dr. Pappot has nothing to disclose; Dr. Aspeleagh reports and has received speaker fees from Roche, BMS, Novartis, Merck and Pfizer in the last 36 months; Dr. Rogiers has nothing to disclose; Dr. Neyns reports grants and personal fees from Novartis, grants and personal fees from Pfizer, personal fees from BMS, personal fees from MSD, outside the submitted work; Dr. Haanen reports grants and other from BMS, grants and other from MSD, grants and other from Novartis, grants and other from BioNTech, other from Achilles Tx, grants and other from Amgen, other from GSK, other from Immunocore, other from Ipsen, other from Merck Serono, other from Molecular Partners, personal fees from Neogene Tx, other from Pfizer, other from Roche/Genentech, other from Sanofi, other from Seattle Genetics, other from Third Rock Ventures, other from Vaximm, outside the submitted work; Dr. Mitchell has nothing to disclose; Dr. Addeo reports personal fees from BMS, personal fees from MSD, personal fees from AstraZeneca, personal fees from Pfizer, personal fees from Roche, personal fees from Boehringer, personal fees from Ely-Lilly, outside the submitted work; Dr. Michielen reports grants and personal fees from BMS, grants and personal fees from MSD, personal fees from Roche, personal fees from Novartis, grants and personal fees from Pierre-Fabre, grants and personal fees from Amgen, personal fees from GSL, grants from Merck, outside the submitted work; Dr. Eicher reports grants from Fondation Recherche Cancer ISREC, during the conduct of the study; grants and personal fees from Roche, grants and personal fees from BMS, grants from Kaiku Health, personal fees from VIFOR, outside the submitted work.

Acknowledgements

The authors would like to thank and acknowledge Prof. Bernard Burnand for his guidance in the planning of the Delphi study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.08.026.

References

[1] Champiat S, Lambotte O, Barreau E, et al. Management of immune checkpoint blockade dyssimmune toxicities: a collaborative position paper. Ann Oncol 2016;27(4):559–74. https://doi.org/10.1093/annonc/mdv623.
[2] Martins F, Sofiya L, Sykiotis GP, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol 2019. https://doi.org/10.1038/s41571-019-0218-0. Published online May 15.
[3] Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Canc 2016;54:139–48. https://doi.org/10.1016/j.ejca.2015.11.016.
[4] Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. Ann Oncol 2017;28(10):2377–85. https://doi.org/10.1093/annonc/mdx286.
[5] Balaji A, Zhang J, Wills B, et al. Immune-related adverse events requiring hospitalization: spectrum of toxicity, treatment, and outcomes. J Oncol Pract 2019;15(9):e825–34. https://doi.org/10.1200/JOP.18.00703.
[6] Pollack MH, Betof A, Dearden H, et al. Safety of resuming anti-PD-1 in patients with immune-related adverse events (irAEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma. Ann Oncol 2018;29(1):250–5. https://doi.org/10.1093/annonc/mdx642.
[7] National Institutes of Health. In: Common Terminology criteria for adverse events (CTCAE) version 5.0; 2017. Published online November 27, https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.
[8] Kluetz PG, Chingos DT, Basch EM, Mitchell SA. Patient-reported outcomes in cancer clinical trials: measuring symptomatic adverse events with the national cancer institute’s patient-reported outcomes version of the Common Terminology criteria for adverse events (PRO-CTCAE). Am Soc Clin Oncol Educ Book 2016;35:67–73. https://doi.org/10.14694/EDBK_159514.
[9] Di Maio M, Gallo C, Leigh NB, et al. Symptomatic toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials. J Clin Oncol 2015;33(8):910–5. https://doi.org/10.1200/JCO.2014.57.9334.
[10] Atkinson TM, Rogak LJ, Heon N, et al. Exploring differences in adverse symptom event grading thresholds between clinicians and patients in the clinical trial setting. J Cancer Res Clin Oncol 2017;143(4):735–43. https://doi.org/10.1007/s00432-016-2335-9.
[11] U.S. Department of Health and Human Services Food and Drug Administration F.D.A.. In: Guidance for industry. Patient-reported outcome measures: use in medical product development to support labeling claims; 2009 (FDA-2006-D-0362):43.
[12] Basch E, Deal AM, Kris MG, et al. Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. J Clin Oncol 2016;34(6):557–65. https://doi.org/10.1200/JCO.2015.63.0830.
[13] Howell D, Molloy S, Wilkinson K, et al. Patient-reported outcomes in routine cancer clinical practice: a scoping review of use, impact on health outcomes, and implementation factors. Ann Oncol 2015;26(9):1846–58. https://doi.org/10.1093/annonc/mdv181.
[14] Kotronoulas G, Kearney N, Maguire R, et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. J Clin Oncol 2014;32(14):1480–501. https://doi.org/10.1200/JCO.2013.53.5948.
[15] Basch E, Reeve BB, Mitchell SA, et al. Development of the national cancer institute’s patient-reported outcomes version of the Common Terminology criteria for adverse events (PRO-CTCAE). JNCT J Natl Cancer Inst 2014;106(9). https://doi.org/10.1093/jnci/dju244. dju244-dju244.
[16] National Cancer Institute. Patient-reported outcomes version of the Common Terminology criteria for adverse events (PRO-CTCAE). Published February 5. https://healthcaredelivery.cancer.gov/pro-ctcae/. [Accessed 5 February 2021].
[17] U.S. Department of Health and Human Services, Food and Drug Administration, Oncology Center of Excellence, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. In: Core patient-reported outcomes in cancer clinical trials guidance for industry; 2021. Published online June, https://www.fda.gov/media/149994/download. [Accessed 14 July 2021].

[18] Nissen A, Bager L, Pappot H. The use of PRO in adverse event identification during cancer therapy — choosing the right questions to ask. Acta Oncol 2019;58(5):596–602. https://doi.org/10.1080/0284186X.2018.1560496.

[19] Tolstrup LK, Bastholt L, Zwisler A-D, Dieperink KB, Pappot H. Selection of patient reported outcomes questions reflecting symptoms for patients with metastatic melanoma receiving immunotherapy. J Patient-Rep Outcomes 2019;3(1). https://doi.org/10.1186/s41687-019-0111-8.

[20] Colomer-Lahiguera S, Bryant-Lukosius D, Rietkoetter S, et al. Patient-reported outcome instruments used in immune-checkpoint inhibitor clinical trials in oncology: a systematic review. J Patient-Rep Outcomes 2020;4(1). https://doi.org/10.1186/s41687-020-00210-z.

[21] Hall ET, Singhal S, Dickerson J, et al. Patient-reported outcomes for cancer patients receiving checkpoint inhibitors: opportunities for palliative care—a systematic review. J Pain Symptom Manag 2019;58(1):137–156.e1. https://doi.org/10.1016/j.jpainsymman.2019.03.013.

[22] Faury S, Foucaud J. Health-related quality of life in cancer patients treated with immune checkpoint inhibitors: a systematic review on reporting of methods in randomized controlled trials. In: Montazeri A, editor. Plos one, vol. 15; 2020, e0227344. https://doi.org/10.1371/journal.pone.0227344. 1.

[23] Keeney S, Hasson F, McKenna H. The Delphi technique in nursing and health research: keeney/the Delphi technique in nursing and health research. Wiley-Blackwell; 2011. https://doi.org/10.1002/9781444392029.

[24] Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol 2014;67(4):401–9. https://doi.org/10.1016/j.jclinepi.2013.12.002.

[25] National Institutes of Health - National Cancer Institute. In: Patient-reported outcomes version of the Common Terminology criteria for adverse events (PRO-CTCAE) - Quick guide to the item library; 2020. Published online November 3.

[26] European Society of Medical Oncology Guidelines Committee. Consensus conference standard operating procedures. 2020. Published online January, https://www.esmo.org/content/download/77792/1426729/1/ESMO-Consensus-Conferences-Standard-Operating-Procedures-January-2020.pdf.

[27] Bilena C, Padia S, O’Brien B, Knoble J, Gokhale A, Rajagopalan M. Radiation recall dermatitis after treatment of stage IV breast cancer with nivolumab: a case report. Immunotherapy 2020;12(2):123–30. https://doi.org/10.2217/imt-2019-0020.

[28] Ellis SR, Vierra AT, Millsop JW, Lacouture ME, Kiuru M. Dermatologic toxicities to immune checkpoint inhibitor therapy: a review of histopathologic features. J Am Acad Dermatol 2020;83(4):1130–43. https://doi.org/10.1016/j.jaad.2020.04.105.

[29] Wang Y-Y, Tian X-C, Zhu L, Bai X-H, Zhao R. Concomitant radiation recall dermatitis and radiation recall pneumonitis induced by pembrolizumab. J Thorac Oncol 2020;15(10):e160–2. https://doi.org/10.1016/j.jtho.2020.05.014.