

# Delphi panel for consensus on the optimal management of dabrafenib plus trametinib-related pyrexia in patients with melanoma

Ricky Frazer, Avinash Gupta, Christopher Herbert, Miranda Payne, Sergio Diaz-Mendoza, Sally-Anne Vincent and Elena Kovaleva

*Ther Adv Med Oncol*

2022, Vol. 14: 1–13

DOI: 10.1177/  
17588359221127681

© The Author(s), 2022.  
Article reuse guidelines:  
sagepub.com/journals-  
permissions

## Abstract

**Purpose:** Dabrafenib and trametinib combination therapy (dab + tram) is indicated to treat BRAF V600 mutation-positive unresectable/metastatic melanoma and as adjuvant treatment for resected stage III disease. Dab + tram-related pyrexia may require early therapy discontinuation. A modified Delphi panel was conducted to develop consensus on the optimal management of dab + tram-related pyrexia in patients with melanoma.

**Methods:** In all, 10 UK oncologists experienced in melanoma management participated in a three-round modified Delphi study (Round 1: one-to-one interview; Rounds 2 and 3: email survey). In each round, participants rated the extent of their agreement with statements about defining and managing dab + tram-related pyrexia. Consensus was defined as >80% agreement for critical management (CM) and >60% for non-critical management (NCM) statements.

**Results:** All 10 participants completed Round 1; 9 completed Rounds 2 and 3. Consensus was reached on 42/66 statements (20 CM and 22 NCM). Drug-related pyrexia was agreed as being strictly an elevation of body temperature, although other symptoms may be present (89% agreement). Panelists agreed on the need for simple and generic guidance on dab + tram-related pyrexia management that does not differentiate between patient groups (100%), and that management of first and second dab + tram-related pyrexia episodes should be the same regardless of treatment intent (100%). Regarding CM, participants agreed that both dab and tram should be interrupted for pyrexia (100%) without considering the use of steroids (89%); patients on dab + tram presenting to non-oncology services with pyrexia should be directed to an oncology-specific service as soon as possible and assessed for infection (100%). NCM statements on steroid use following dab + tram interruption and when to restart dab + tram did not reach consensus.

**Conclusions:** These consensus statements provide a framework on optimal management of dab + tram-related pyrexia in patients with melanoma which should inform future guidelines.

**Keywords:** consensus, dabrafenib, melanoma, pyrexia, trametinib

Received: 1 March 2022; revised manuscript accepted: 2 September 2022.

## Introduction

The development and use of immune and targeted therapies have changed the way melanomas are treated, with durable survival benefits in select groups of patients.<sup>1</sup> The goal of treatment is to

prolong survival with minimal impairment of quality of life. Therefore, drug-related adverse events require prompt and effective management to ensure that patients derive optimal benefit from therapy.<sup>2</sup>

Correspondence to:

**Ricky Frazer**  
Consultant Medical  
Oncologist, Velindre  
University NHS Trust,  
Velindre Cancer Centre,  
Velindre Road, Cardiff,  
Wales CF14 2TL, UK  
[ricky.frazer@wales.nhs.uk](mailto:ricky.frazer@wales.nhs.uk)

**Avinash Gupta**  
The Christie NHS  
Foundation Trust,  
Manchester, England

**Christopher Herbert**  
University Hospital Bristol,  
Bristol, England

**Miranda Payne**  
Oxford University Hospitals  
NHS Trust, Oxford,  
England

**Sergio Diaz-Mendoza**  
**Sally-Anne Vincent**  
OPEN Health, Marlow,  
England

**Elena Kovaleva**  
Novartis Pharmaceuticals  
UK LTD, England

N.B. Please note that one author, Sally-Anne Vincent, is managing the submission and reviewing proofs, but Dr. Frazer should be listed as the corresponding author if the manuscript is accepted.

Dabrafenib (TAFINLAR<sup>®</sup>, Novartis Pharmaceuticals Corporation) plus trametinib (MEKINIST<sup>®</sup>, Novartis Pharmaceuticals Corporation) combination therapy (dab + tram) is an anti-BRAF/MEK-targeted therapy indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation and for the adjuvant treatment of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection.<sup>3,4</sup> In patients with metastatic melanoma treated with dab + tram, durable and long-term survival was seen, with approximately one-third of clinical trial patients remaining alive at 5 years.<sup>5</sup> However, pyrexia symptoms commonly appear during treatment, with 51–59% of clinical trial patients experiencing pyrexia.<sup>5–7</sup> Patients receiving treatment with dab + tram who experience pyrexia may require treatment modification and permanent therapy discontinuation.<sup>6,7</sup>

Pyrexia resolves in most patients receiving dab + tram following treatment interruption and usually is not an indicator of possible neutropenic sepsis.<sup>6</sup> To optimize patient care and support healthcare providers (HCPs), consensus on the management of pyrexia is needed, particularly for HCPs outside an oncology-specific service. To develop consensus on the optimal management of dab + tram-related pyrexia in patients with melanoma, a modified Delphi panel was conducted. A Delphi panel allows for the systematic collection and aggregation of informed judgments from experts and is an iterative technique characterized by repeated rounds of controlled feedback to achieve consensus. In healthcare research, Delphi panels are widely used and are proven to be a rigorous and feasible way to obtain consensus.<sup>8</sup>

## Methods

### *Study design*

The Delphi method allows for anonymous, expert input that aims to achieve consensus through three rounds of controlled feedback. The traditional Delphi method starts with an open-ended set of questions, allowing all panel members complete freedom in their responses. As a result, the number of items requiring consideration can be extremely high, leading to very lengthy second-round questionnaires, which can discourage panel members from participating and lead to difficulties in sustaining experts' interest in the study.<sup>8</sup> The modified Delphi technique substitutes the

initial open-ended round of statements of the classical Delphi method with input from a steering committee (SC) of therapy area experts to develop the first draft of consensus statements. These statements are further expanded and refined during three rounds of feedback with a panel of experts.<sup>8</sup>

In this modified Delphi panel, HCPs specializing in oncology in the National Health Service (NHS) from the United Kingdom (UK) were invited to provide input on consensus statements regarding the optimal management of dab + tram-associated pyrexia in patients with melanoma. This selection of panelists reflects individuals who provide daily management of melanoma patients in the UK. Four clinical experts were asked to form the Delphi panel SC. As members of the SC, these experts outlined the Delphi panel statement framework (including eligibility criteria for Delphi panelists and number of panelists), set the analysis rules for critical and non-critical management consensus statements (Table 1), and invited additional experts to participate as panelists. All panelists provided written consent to participate in the Delphi panel and complete the survey.

According to the governance arrangements for research ethics committees, studies conducted with NHS staff who are recruited by virtue of their professional role are exempt from research ethics committee review in the UK; therefore, no ethics committee reviewed this study.<sup>9</sup>

Critical management statements were classified as statements that are directly related to pyrexia management and considered critical in the management of patients with pyrexia; non-critical management statements were those that are not considered critical or essential for the management of patients with drug-related pyrexia. Consensus statements were developed and shared with the panelists in three rounds of review.

### *Survey development*

The surveys administered to the Delphi panelists aimed to develop consensus on four main topics: (1) to define the characteristics, signs and symptoms, and clinical features of drug-related pyrexia; (2) to define patient populations requiring different approaches to pyrexia management; (3) to define pyrexia management strategies, outcomes, and resolution; and (4) to define the continuation of treatment after successful management of

**Table 1.** Consensus statement analysis rules.

| Critical management   | Non-critical management   |
|---|---|
| Rule 1  |   |
| Questions that show variable response patterns (<40% spread across response options in a non-skewed way) will be removed  | Questions that show variable response patterns (<40% spread across response options in a non-skewed way) will be removed  |
| Rule 2  |   |
| Questions with responses between 40% and 80% will be re-asked with three response options: disagree, neutral, and agree   | Questions with responses between 40% and 60% will be re-asked with three response options: disagree, neutral, and agree   |
| Rule 3  |   |
| Questions that showed skewed response pattern with majority of responses (>80%) spread across three options will be summed and asked back with a binary response option: agree and disagree | Questions that showed skewed response pattern with majority of responses (>60%) spread across three options will be summed and asked back with a binary response option: agree and disagree |
| Rule 4  |   |
| Questions with >80% of agreement will be asked back with a binary response option: agree and disagree   | Questions with >60% of agreement will be asked back with a binary response option: agree and disagree   |
| Rule 5  |   |
| Binary questions with >80% of agreement will be considered as consensus   | Binary questions with >60% of agreement will be considered as consensus   |
| Rule 6  |   |
| 3-point Likert scale questions in the third round with >80% of agreement will be considered as consensus  | 3-point Likert scale questions in the third round with >60% of agreement will be considered as consensus  |

drug-related pyrexia. The surveys also aimed to obtain feedback on general questions related to treatment and/or management guidelines.

Within each of the four topics, questions addressed critical and non-critical management of drug-related pyrexia. During each survey round, panelists were asked to rate the extent to which they agreed with each question using Likert scales or binary (disagree/agree) responses (Table 2).

During the first round, panelists participated in one-to-one telephone interviews to complete a paper-based survey. Statements were both quantitative (Likert scales) and qualitative (open-ended/free response) to allow panelists to provide response rationales. The first-round answers were analyzed qualitatively (content analysis) and quantitatively (mean, mode, median, interquartile range, and frequency). For the second round, the qualitative results from the first round were

**Table 2.** Consensus statement response options.

| 5-point Likert scale | 3-point Likert scale | Binary option |
|----------------------|----------------------|---------------|
| 1. Strongly disagree | 1. Disagree          | Disagree      |
| 2. Disagree          | 2. Neutral           | Agree         |
| 3. Neutral           | 3. Agree             |               |
| 4. Agree             |                      |               |
| 5. Completely agree  |                      |               |

used to refine statements and to develop new ones to be asked during the second-round survey. The statements for the second round were reviewed and approved by the SC. Questions for the second and third rounds were quantitative, and the results were analyzed according to the analysis rules; binary responses or 3- or 5-point Likert scales were selected by the SC depending on the level of consensus achieved for the same statement in the prior survey round. The second

and third (final) rounds of the Delphi panel were conducted *via* PDF survey, which was sent by email to panelists. After each round, the SC shared the results with panelists, including the panelist's previous answer and the mean, median, mode, interquartile range, and frequency of answers for each consensus statement.

#### *Data analysis*

The SC agreed that critical management statements required consensus (i.e. panelists answered the same way) of  $\geq 80\%$  of panelists and that non-critical management statements required consensus of  $\geq 60\%$ . Survey responses were extracted for each question into a Microsoft Excel database, and responses were assigned a score (i.e. 1–5, 1–3, or 1–2) corresponding to each response scale.

Levels of dispersion (interquartile range), central tendencies (mean, median, and mode), and percentage frequencies of responses to each statement were calculated between each round for Likert scales. Frequencies were calculated for binary options. Qualitative data from the panelists' interviews were collated to analyze the content. The qualitative content analysis focused on similar opinions and terms of reference inductively identified. All comments and answers from the panelists were addressed either to refine existing statements or to create new statements for the subsequent rounds.

#### *Panelist selection*

Purposive sampling was used to recruit panelists who are especially knowledgeable about the subject of interest, as recommended for qualitative and mixed-methods methodologies.<sup>10</sup> The SC agreed to recruit 10 panelists; it was decided that this sample size would be sufficient for reasonable geographic consensus. During the first SC meeting, members compiled a list of potential clinicians to invite as panelists. Clinicians were selected to participate using the following pre-specified inclusion criteria: practicing oncologist in the UK, experience managing patients with melanoma, and an interest in research of drug-related pyrexia.

### **Results**

In all, 10 practicing oncologists in the UK participated as panelists in the three-round modified Delphi panel. In all, 66 statements were evaluated

by the panel over three rounds of surveys. All 10 panelists completed Round 1, and 9 panelists completed Rounds 2 and 3 of the study.

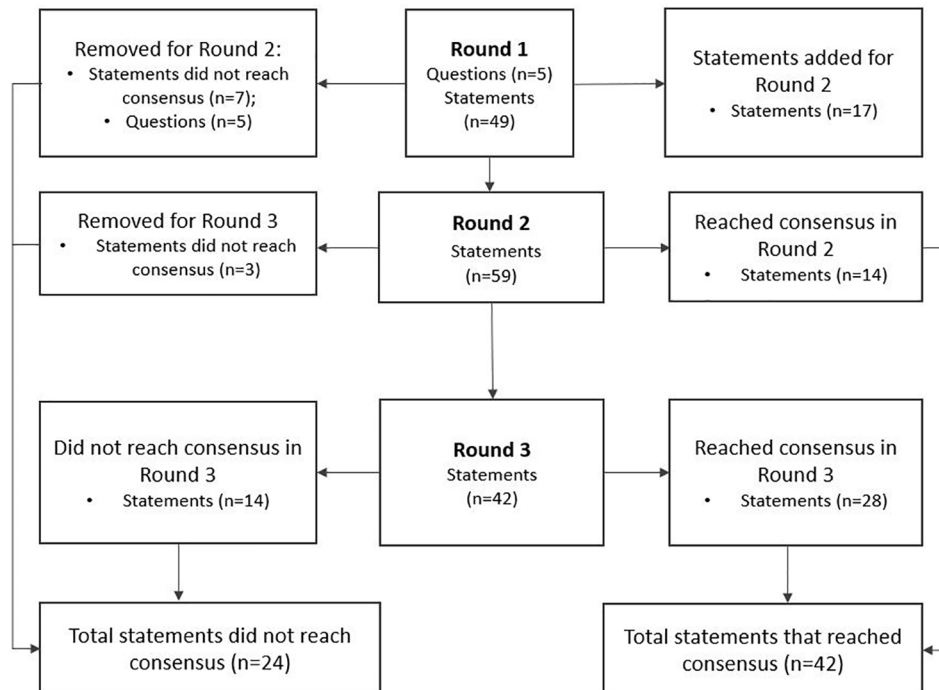
A total of 42 statements reached consensus (Figure 1), 36 of which reached positive consensus, meaning that panelists agreed on the statement in question. Negative consensus, where the panelists disagreed with the statement, was reached for six statements. Of the 42 statements that reached consensus, 20 concern critical management, and the remaining 22 regard non-critical pyrexia management issues. Critical management statements achieving consensus were related to two of the four main topics, with most statements related to pyrexia management strategies.

#### *Topic 1: Defining drug-related pyrexia*

Several critical management statements were identified for topics related to defining drug-related pyrexia (Table 3). The expert panel agreed on 'drug-related pyrexia' as a term that could be used to refer to the type of pyrexia associated as a side effect of medical treatment (100% agreement) and recommended that patients presenting with pyrexia be assessed for infection before receiving antibiotics (100% agreement). The panel also agreed (89% agreement) with a statement defining pyrexia as strictly an elevation of body temperature, and that other symptoms such as chills, rigors, night sweats, flu-like symptoms, and/or hypotension are not critical to the definition of drug-related pyrexia.

#### *Topic 2: Patient populations requiring different approaches to pyrexia management*

The Delphi panel did not define any patient populations that would require a different approach to pyrexia management. The panelists reached consensus on three non-critical management statements (Table 4). The panelists unanimously agreed that treatment of first and second dab + tram-related pyrexia episodes should be the same regardless of treatment intent. The panelists agreed that the common terminology criteria (CTC) grading of pyrexia is not particularly relevant to the overall management of dab + tram-related pyrexia (78% agreement) and that management of the first or second episode of dab + tram-related pyrexia in the adjuvant setting should consider the impact on the patient's quality of life and their willingness to accept side effects (89% agreement).



**Figure 1.** Delphi consensus statements by review round.

### *Topic 3: Pyrexia management strategies, outcomes, and resolution*

In all, 12 statements regarding definitions of pyrexia management strategies, outcomes, and management resolution achieved positive consensus; three statements reached negative consensus (Table 5). The panel reached 100% agreement on multiple statements regarding critical management. First, they agreed that for patients receiving dab + tram in the adjuvant or metastatic setting, it is preferable to interrupt both drugs rather than just one of the therapies. Second, patients receiving dab + tram who present to a non-oncology service should be put in contact with oncology staff as soon as possible, along with assessing for infection. Third, if patients receiving dab + tram present to a non-oncology service with pyrexia and the oncology-specific service is not available, the course of action is to interrupt dab + tram, assess for infection, and communicate with oncology service as soon as possible. Fourth, if patients are feeling worse after 24 h of having to interrupt dab + tram following an episode of drug-related pyrexia, the patients should be advised to contact their oncology triage service or clinical nurse specialist as soon as possible. Fifth, if patients receiving dab + tram experience a second episode of drug-related pyrexia, they should be advised to

interrupt dab + tram, take regular paracetamol and/or ibuprofen, and expect the symptoms to resolve within 24–72 h. Finally, the panel unanimously agreed that for patients receiving dab + tram who experience pyrexia, management with antibiotics before an infection has been confirmed could be an option if neutropenic sepsis is suspected. In addition, 89% of the panelists agreed with the following statements: For patients receiving dab + tram in the adjuvant setting who experience severe drug-related pyrexia, it is preferable to interrupt dab + tram without considering the use of steroids. The role of steroids in the management of drug-related pyrexia remains controversial, and among the expert group there was some difference of opinion. Furthermore, a review of the literature reveals that other consensus documents have included the use of steroids as a management strategy.<sup>11</sup> For patients receiving dab + tram in the metastatic setting who are not tolerating their current dose, it is advisable to consider switching to an alternative regimen after two or more treatment interruptions. Finally, for patients receiving dab + tram in the adjuvant setting who are not tolerating their current dose, it is advisable to consider suspending the treatment after two treatment interruptions with dose reductions.



**Table 3.** Statements reaching consensus on topic 1: Defining drug-related pyrexia.

| Statement  | Management classification | Response option      | % of participants |         |       |
|--|---------------------------|----------------------|-------------------|---------|-------|
|  |                           |                      | Disagree          | Neutral | Agree |
| A patient on dabrafenib and trametinib presenting with pyrexia who is neutropenic should have a history taken to assess for localizing symptoms (e.g. urinary tract symptoms, earache, abdominal pain, sore throat, diarrhea, cough, nausea)   | Critical                  | Binary               | 11                |         | 89    |
| Pyrexia is strictly an elevation of body temperature. When pyrexia presents as a side effect of a medical treatment, it could also be associated with other symptoms such as chills, rigors, night sweats, flu-like symptoms, and/or hypotension but these are not critical to the definition of pyrexia | Critical                  | Binary               | 11                |         | 89    |
| The term 'drug-related pyrexia' could be used to refer to the type of pyrexia associated with a side effect of a medical treatment   | Critical                  | Binary               | 0                 |         | 100   |
| A patient on dabrafenib and trametinib presenting with pyrexia should be assessed for infection before receiving antibiotics   | Critical                  | Binary               | 0                 |         | 100   |
| A patient on dabrafenib and trametinib presenting with pyrexia who is neutropenic should be investigated for sepsis  | Critical                  | Binary               | 0                 |         | 100   |
| If a patient on dabrafenib and trametinib who presents with pyrexia is not neutropenic, the drug treatment should be interrupted, and the symptoms of pyrexia treated  | Critical                  | 3-point Likert scale | 0                 | 11      | 89    |
| A patient with drug-related pyrexia could, but does not always, look sweaty and tired/fatigued in their presentation   | Non-critical              | Binary               | 0                 |         | 100   |

Three critical management statements achieved negative consensus (89% disagreement for all statements). The panelists disagreed with statements that dab + tram should not be suspended until drug-related pyrexia has been confirmed, or that it is preferable to interrupt only dabrafenib in patients experiencing dab + tram-related pyrexia in either the adjuvant or metastatic setting.

Regarding non-critical management statements, there was 100% agreement among panel members that if patients receiving dab + tram experience other side effects in addition to drug-related pyrexia, the duration of interruption of dab + tram should be affected. It was also agreed that treatment guidance for drug-related pyrexia

management in patients receiving dab + tram should be simple and generic.

*Topic 4: Continuation of treatment after successful management of drug-related pyrexia*

The panelists unanimously disagreed (100% disagreement) with the statement that restarting dab + tram at full dose after a first interruption for drug-related pyrexia requires the patient to be an inpatient (Table 6). Among other statements, Delphi panelists did not reach consensus on statements on steroid use following dab + tram interruption and the continuation of dab + tram treatment after discontinuation for pyrexia (Supplemental Table 1). As described earlier,

**Table 4.** Statements reaching consensus on topic 2: Patient population group(s) requiring different approaches to pyrexia management.

| Statement   | Management classification | Response option | % of participants |         |       |
|---|---------------------------|-----------------|-------------------|---------|-------|
|   |                           |                 | Disagree          | Neutral | Agree |
| In a patient receiving dabrafenib and trametinib presenting with drug-related pyrexia, the CTC grading of pyrexia is not particularly relevant to the overall management  | Non-critical              | Binary          | 33                |         | 67    |
| Treatment of the first or second episode of pyrexia in a patient on dabrafenib and trametinib is the same regardless of whether the patient is receiving treatment with adjuvant or palliative intent   | Non-critical              | Binary          | 0                 |         | 100   |
| Management of the first or second episode of pyrexia in a patient on dabrafenib and trametinib in the adjuvant setting would have to take in consideration the impact on the patient's quality of life and their willingness to accept side effects | Non-critical              | Binary          | 11                |         | 89    |

there remains debate and a degree of equipoise among the clinical community on the role steroids may play in the management of drug-related pyrexia.

No statements reached a positive consensus related to the continuation of treatment after successful management of drug-related pyrexia.

#### General questions on guidelines

Most non-critical management statements that achieved consensus were related to treatment guidelines (Table 7). The panel agreed (89% agreement) that patients would be able to self-manage drug-related pyrexia episodes if provided with appropriate guidance and information. The panel unanimously agreed that if oncology services are not available, the following statement should be included as patient-held information for HCPs about the appropriate management of dab + tram-related pyrexia: 'I am on targeted treatment for my melanoma. This is not a chemotherapy. Two out of 3 patients receiving this treatment will develop a non-infective (drug-related) fever. My risk of neutropenia is very low (X %); please ensure I have interrupted my dabrafenib and trametinib and then assess me for any evidence of infection as any other patient presenting with a fever'. Finally, the panel of experts agreed that an alert card (100% agreement), a phone app (100% agreement), or a keyring (100% agreement) would be appropriate for displaying patient-held information for HCPs about the

management of pyrexia associated with dab + tram treatment.

#### Discussion

Results from several studies show that dab + tram offers the possibility of durable and long-term efficacy in patients with advanced, BRAF v600-mutant metastatic melanoma.<sup>5,12,13</sup> However, drug-related pyrexia can occur during dab + tram treatment. Results from a combined analysis of adverse event data from the COMBI-d and COMBI-v studies show that 6% of patients treated with dab + tram experienced grade  $\geq 3$  pyrexia and 4% permanently discontinued therapy.<sup>5</sup> These results highlight the need for the prompt and effective management of pyrexia in patients treated with dab + tram.

As described above, we convened a modified Delphi panel to gain consensus on the optimal management of dab + tram-related pyrexia in patients with melanoma.

In terms of translation to real-life clinical practice, the expert panel agreed that the term 'drug-related pyrexia' could be used to refer to the type of pyrexia that is a side effect of medical treatment. Although 'pyrexia' is strictly an elevation of body temperature, patients who are receiving dab + tram presenting with this side effect may exhibit a pyrexia prodrome that includes symptoms not critical to the strict definition of pyrexia, including chills, rigors, night sweats, and flu-like

**Table 5.** Statements reaching consensus on topic 3: Pyrexia management strategies, outcomes, and defining resolution.

| Statement  | Management classification | Response option      | % of participants |         |       |
|--|---------------------------|----------------------|-------------------|---------|-------|
|  |                           |                      | Disagree          | Neutral | Agree |
| If a patient on dabrafenib and trametinib presents to a non-oncology service (e.g. their GP surgery or general medics) with pyrexia, the patient should be put in contact with the oncology-specific service as soon as possible, alongside assessing for infection  | Critical                  | Binary               | 0                 |         | 100   |
| If a patient on dabrafenib and trametinib presents to a non-oncology service (e.g. their GP surgery or general medics) with pyrexia, and the oncology-specific service is not available, interrupt the dabrafenib and trametinib, assess for infection and communicate with oncology service as soon as possible | Critical                  | Binary               | 0                 |         | 100   |
| If a patient interrupted dabrafenib and trametinib 24 h ago following an episode of drug-related pyrexia, and is now feeling worse, they should be advised to contact their Oncology Triage Service or Clinical Nurse Specialist as soon as possible   | Critical                  | Binary               | 0                 |         | 100   |
| If a patient on dabrafenib and trametinib presents with pyrexia, management with antibiotics before an infection is confirmed could be an option if it is suspected that the patient may have neutropenic sepsis   | Critical                  | 3-point Likert scale | 0                 | 0       | 100   |
| If a patient on dabrafenib and trametinib experiences a second episode of drug-related pyrexia, they should be advised to interrupt dabrafenib and trametinib, take regular paracetamol and/or ibuprofen, and expect the symptoms to resolve within 24–72 h  | Critical                  | Binary               | 0                 |         | 100   |
| If a patient receiving dabrafenib and trametinib in the metastatic setting is not tolerating their current dose, it is advisable to consider interrupting the treatment and switching to an alternative regimen after two or more treatment interruptions  | Critical                  | 3-point Likert scale | 0                 | 11      | 89    |
| If a patient receiving dabrafenib and trametinib in the adjuvant setting is not tolerating their current dose, it is advisable to consider suspending the treatment after two treatment interruptions with dose reductions   | Critical                  | 3-point Likert scale | 0                 | 11      | 89    |
| For a patient receiving dabrafenib and trametinib in the adjuvant setting who experiences drug-related pyrexia, it is preferable to interrupt both dabrafenib and trametinib rather than just one  | Critical                  | Binary               | 0                 |         | 100   |
| For a patient receiving dabrafenib and trametinib in the metastatic setting who experiences drug-related pyrexia, it is preferable to interrupt both dabrafenib and trametinib rather than just one  | Critical                  | Binary               | 0                 |         | 100   |
| If a patient receiving dabrafenib and trametinib in the adjuvant setting experiences severe drug-related pyrexia, it is preferable to interrupt the treatment without considering the use of steroids  | Critical                  | 3-point Likert scale | 0                 | 11      | 89    |

(Continued)



**Table 5.** (Continued)

| Statement   | Management classification | Response option      | % of participants |         |       |
|---|---------------------------|----------------------|-------------------|---------|-------|
|   |                           |                      | Disagree          | Neutral | Agree |
| If a patient on dabrafenib and trametinib presents with pyrexia, dabrafenib and trametinib should not be suspended until drug-related pyrexia has been confirmed  | Critical                  | Binary               | 89                |         | 11    |
| For a patient receiving dabrafenib and trametinib in the adjuvant setting who experiences drug-related pyrexia, it is preferable to interrupt only the dabrafenib   | Critical                  | 3-point Likert scale | 89                | 11      | 0     |
| For a patient receiving dabrafenib and trametinib with metastatic setting who experiences drug-related pyrexia, it is preferable to interrupt only the dabrafenib   | Critical                  | 3-point Likert scale | 89                | 11      | 0     |
| If a patient on dabrafenib and trametinib is experiencing other side effects in addition to drug-related pyrexia, this should affect the duration of interruption of the dabrafenib and trametinib treatment  | Non-critical              | Binary               | 0                 |         | 100   |
| Guidance for drug-related pyrexia management in patients receiving dabrafenib and trametinib should be simple and generic; it does not need to be different for different patient groups (e.g. for patients receiving dabrafenib and trametinib in the adjuvant or metastatic settings) | Non-critical              | Binary               | 0                 |         | 100   |

GP, general practitioner.

**Table 6.** Statements reaching consensus on topic 4: Continuation of treatment after successful management.

| Statement   | Management classification | Response option | % of participants |         |       |
|---|---------------------------|-----------------|-------------------|---------|-------|
|   |                           |                 | Disagree          | Neutral | Agree |
| Restarting dabrafenib and trametinib at full dose after a first interruption for drug-related pyrexia requires the patient to be an inpatient | Non-critical              | Binary          | 100               |         | 0     |

symptoms. Patients presenting with drug-related pyrexia could, but may not always, look sweaty and tired/fatigued in their presentation. The panel noted that it was important for all HCPs who are involved in managing toxicities in melanoma patients to understand that pyrexia in patients treated with dab + tram may be related to the treatment itself and usually resolves upon interruption of drug treatment and is not usually an indicator of possible neutropenic sepsis.

Consensus on the management of pyrexia in patients on dab + tram was reached, including on the use of antibiotic therapy, treatment of multiple drug-related pyrexia episodes, and the role of treatment interruption and use of alternative

treatment regimens. In particular, it was agreed that both dab and tram should be interrupted rather than one of the drugs alone. This is important, as there appears to be a difference of practice among oncology professionals.

The Delphi panel did not define any patient populations that would require a different approach to pyrexia management. The panel noted that patients receiving dab + tram who present to a non-oncology service should be discussed with the oncology service as soon as possible and be assessed for infection.

Recommendations for patients experiencing a second episode of drug-related pyrexia include

**Table 7.** Statements reaching consensus for general questions on guidelines.

| Statement   | Management classification | Response option      | % of participants |         |       |
|---|---------------------------|----------------------|-------------------|---------|-------|
|   |                           |                      | Disagree          | Neutral | Agree |
| Patient and patient-carer education around drug-related pyrexia symptoms, what to look for and what to do, is important for the management of drug-related pyrexia  | Non-critical              | 3-point Likert scale | 0                 | 0       | 100   |
| All oncologists would benefit from guidelines for the management of drug-related pyrexia in patients receiving dabrafenib and trametinib  | Non-critical              | Binary               | 0                 |         | 100   |
| Oncologists specializing in melanoma would benefit from guidelines for the management of drug-related pyrexia in patients receiving dabrafenib and trametinib   | Non-critical              | Binary               | 0                 |         | 100   |
| Oncology triage services would benefit from guidelines for the management of drug-related pyrexia in patients receiving dabrafenib and trametinib   | Non-critical              | Binary               | 0                 |         | 100   |
| Acute physicians/general medics/AE services would benefit from guidelines for the management of drug-related pyrexia in patients receiving dabrafenib and trametinib  | Non-critical              | Binary               | 11                |         | 89    |
| Oncologist registrars would benefit from guidelines for the management of drug-related pyrexia in patients receiving dabrafenib and trametinib  | Non-critical              | Binary               | 0                 |         | 100   |
| Patients would be able to self-manage drug-related pyrexia episodes by providing them with appropriate guidance and information   | Non-critical              | Binary               | 11                |         | 89    |
| A traffic light system would be helpful for identifying patients with drug-related pyrexia at low and high risk   | Non-critical              | Binary               | 0                 |         | 100   |
| Guidelines for the management of drug-related pyrexia in patients receiving dabrafenib and trametinib should be the same regardless of the time/place the patient presents  | Non-critical              | Binary               | 11                |         | 89    |
| Guidelines for the management of drug-related pyrexia in patients receiving dabrafenib and trametinib should emphasize the importance of contact with an oncology-specific service, rather than management solely by a GP or general medic  | Non-critical              | Binary               | 0                 |         | 100   |
| Guidelines for the management of drug-related pyrexia in patients receiving dabrafenib and trametinib should include advice on what to do if a member of the oncology team is not immediately available   | Non-critical              | Binary               | 0                 |         | 100   |
| In case oncology services are not available, do you agree with the following statement to be included as patient-held information for healthcare professionals about the appropriate management of pyrexia associated with dabrafenib and trametinib treatment: 'I am on targeted treatment for my melanoma. This is not a chemotherapy. Two out of three patients receiving this treatment will develop a non-infective [drug-related] fever. My risk of neutropenia is very low (X %); please ensure I have interrupted my dabrafenib and trametinib and then assess me for any evidence of infection as any other patient presenting with a fever' | Non-critical              | 3-point Likert scale | 0                 | 0       | 100   |

(Continued)

**Table 7.** (Continued)

| Statement   | Management classification | Response option | % of participants |         |       |
|---|---------------------------|-----------------|-------------------|---------|-------|
|   |                           |                 | Disagree          | Neutral | Agree |
| An alert card would be appropriate for displaying patient-held information for healthcare professionals about the management of pyrexia associated with dabrafenib and trametinib treatment | Non-critical              | Binary          | 0                 |         | 100   |
| A phone app would be appropriate for displaying patient-held information for healthcare professionals about the management of pyrexia associated with dabrafenib and trametinib treatment   | Non-critical              | Binary          | 0                 |         | 100   |
| A keyring would be appropriate for displaying patient-held information for healthcare professionals about the management of pyrexia associated with dabrafenib and trametinib treatment     | Non-critical              | Binary          | 0                 |         | 100   |

AE, adverse event; GP, general practitioner.

treatment interruption and use of paracetamol and/or ibuprofen. Upon restarting dab + tram therapy at full dose following treatment interruption, the panel did not recommend hospital admission.

The panel did not reach consensus on statements regarding specific dosages and use of steroids for the management of drug-related pyrexia.

Lastly, the panel agreed that guidelines for the management of drug-related pyrexia could be beneficial for several healthcare services including oncologists, oncology triage services, acute physicians/general medics/adverse event services, and oncologist registrars.

Results from this modified Delphi panel align with the adapted pyrexia adverse event management algorithm used in the COMBI-i and COMBI-APlus studies. In both the COMBI-i study, which enrolled patients with metastatic melanoma receiving dab + tram *versus* dab + tram + immunotherapy, and the COMBI-APlus study, which enrolled patients receiving dab + tram in the adjuvant setting, an adapted pyrexia adverse event management algorithm was utilized which promptly interrupted dab + tram treatment at the onset of pyrexia (temperature  $\geq 38^{\circ}\text{C}$ ) or the associated prodrome (COMBI-i only; chills, rigors, night sweats, or influenza-like symptoms). In these studies, patients who remained symptom free for 24 or more hours could restart dab + tram at the same dose level. Overall, 52.7% and 67.8% of patients

receiving dab + tram experienced pyrexia in COMBI-i and COMBI-APlus, respectively, with the rate of grade  $\geq 3$  pyrexia 3.0% in COMBI-i and the rate of grade 3/4 pyrexia 3.8% in COMBI-APlus. Hospitalizations and treatment discontinuations due to pyrexia were 5.3% and 1.5% in COMBI-i and 4.3% and 2.4% in COMBI-APlus, suggesting that implementation of an adapted pyrexia treatment algorithm is effective in reducing severe pyrexia outcomes, such as high-grade pyrexia, hospitalization due to pyrexia, and discontinuation of treatment early due to pyrexia, while the overall safety profile and early efficacy data in COMBI-APlus appear consistent with those previously observed.<sup>12,14</sup>

As the number of treatments available to physicians increases for patients with melanoma, a clear understanding of the risks and benefits of therapy should be discussed with patients as the goal of therapy is to prolong survival without negatively affecting quality of life. Through the use of a modified Delphi panel, consensus was obtained on methods of managing drug-related pyrexia in patients with melanoma. In addition, this panel endorsed the use of simple treatment recommendations that were similar across adjuvant and metastatic patient populations. Outcomes from this Delphi panel should be used as a framework to aid in the development of guidelines that maximize the clinical benefits of dab + tram treatment and minimize the effects of drug-related pyrexia by providing clear strategies for its prompt identification and management.

## Declarations

### *Ethics approval and consent to participate*

According to the governance arrangements for research ethics committees, studies conducted with NHS staff who are recruited by virtue of their professional role are exempt from research ethics committee review in the UK; therefore, no ethics committee reviewed this study. All panelists provided written consent to participate in the Delphi panel and complete the survey.

### *Consent for publication*

Not applicable.

### *Author contribution(s)*

**Ricky Frazer:** Methodology; Project administration; Writing – original draft; Writing – review & editing.

**Avinash Gupta:** Methodology; Project administration; Writing – review & editing.

**Christopher Herbert:** Methodology; Writing – review & editing.

**Miranda Payne:** Methodology; Writing – review & editing.

**Sergio Diaz-Mendoza:** Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Writing – review & editing.

**Sally-Anne Vincent:** Formal analysis; Investigation; Project administration; Writing – review & editing.

**Elena Kovaleva:** Conceptualization; Methodology; Resources; Supervision; Writing – review & editing.

### *Acknowledgements*

The authors would like to thank the Delphi panelists for their contribution to this work, including Dr Pippa Corrie, Dr Helen Winter, Dr Guy Faust, Dr Toby Talbot, Dr Nicholas Coupe, Dr Patricio Serra-Bellver, Dr Sarah Westwell, Dr Shobha Silva, Dr Satish Kumar, and Dr Heather Shaw. Medical writing and editorial support were provided by Beth Leshner, PharmD, BCPS, and Catherine Mirvis, BA, of OPEN Health (Bethesda, MD) and funded by the study sponsor. Analysis and review support were provided by Laura Baldock and Navdeep Sahota of OPEN Health (Marlow, UK).

## Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by Novartis.

### *Competing interests*

Ricky Frazer: speaking and/or advisory fees from Bristol Myers Squibb (BMS), Eisai, Ipsen, Novartis, Pfizer, Pierre Fabre, Sanofi, Merck, and MSD. Christopher Herbert: speaker/advisory fees for BMS, Novartis, Pierre Fabre, and MSD. Elena Kovaleva: full-time employment by Novartis. Avinash Gupta: speaker and/or advisory fees from Amgen, BMS, and Novartis. Miranda Payne: speaker and advisory fees from BMS, LaRoche Posay, Pierre Fabre, Amgen, and Novartis. Sally-Anne Vincent: employee of OPEN Health, which received funding from Novartis for this study, during the conduct of the study and the composition of the manuscript. Sergio Diaz-Mendoza: an employee of OPEN Health during the conduct of the study and the composition of the manuscript.

### *Availability of data and materials*

Not applicable.

## Supplemental material

Supplemental material for this article is available online.

## References

1. Patel H, Yacoub N, Mishra R, *et al.* Current advances in the treatment of BRAF-mutant melanoma. *Cancers (Basel)* 2020; 12: 482.
2. Daud A and Tsai K. Management of treatment-related adverse events with agents targeting the MAPK pathway in patients with metastatic melanoma. *Oncologist* 2017; 22: 823–833.
3. Tafenlar (prescribing information). Novartis Pharmaceuticals Corporation; East Hanover, New Jersey. 2021.
4. Mekinist®. Prescribing information: Mekinist. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation, 2021.
5. Robert C, Grob JJ, Stroyakovskiy D, *et al.* Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *N Engl J Med* 2019; 381: 626–636.

6. Long GV, Stroyakovskiy D, Gogas H, *et al.* Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med* 2014; 371: 1877–1888.
7. Robert C, Karaszewska B, Schachter J, *et al.* Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med* 2015; 372: 30–39.
8. Keeney S, Hassson F and McKenna H. *The Delphi Technique in Nursing and Health Research*. England: Wiley-Blackwell, 2010.
9. Governance arrangements for research ethics committees: 2020 edition. [https://s3.eu-west-2.amazonaws.com/www.hra.nhs.uk/media/documents/GAfREC\\_Final\\_v2.1\\_July\\_2021\\_Final.pdf](https://s3.eu-west-2.amazonaws.com/www.hra.nhs.uk/media/documents/GAfREC_Final_v2.1_July_2021_Final.pdf) (accessed 1 March 2022).
10. Palinkas LA, Horwitz SM, Green CA, *et al.* Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. *Adm Policy Ment Health* 2015; 42: 533–544. DOI: 10.1007/s10488-013-0528-y
11. Thawer A, Miller WH Jr, Gregorio N, *et al.* Management of pyrexia-associated with the combination of dabrafenib and trametinib: Canadian consensus statements. *Curr Oncol* 2021; 28: 3537–3553.
12. Atkinson V, Robert C, Grob J-J, *et al.* Improved pyrexia-related outcomes associated with an adapted pyrexia adverse event (AE) management algorithm in patients (pts) treated with adjuvant dabrafenib + trametinib (dab + tram): primary results of COMBI-APlus. *J Clin Oncol* 2021; 39: 9525–9525.
13. Nathan P, Dummer R, Long GV, *et al.* LBA43 Spartalizumab plus dabrafenib and trametinib (Sparta-DabTram) in patients (pts) with previously untreated BRAF V600-mutant unresectable or metastatic melanoma: results from the randomized part 3 of the phase III COMBI-i trial. *Ann Oncol* 2020; 31: S1172.
14. Ascierto PA, Robert C, Nathan PD, *et al.* Pyrexia-related outcomes upon application of an adapted pyrexia management algorithm in patients (pts) with BRAF V600: mutant unresectable or metastatic melanoma treated with dabrafenib plus trametinib (DabTram) in the COMBI-i trial. *J Clin Oncol* 2021; 39: 9560–9560.

Visit SAGE journals online  
[journals.sagepub.com/  
home/tam](https://journals.sagepub.com/home/tam)

 SAGE journals