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Original Research

Pyrexia in patients treated with dabrafenib plus trametinib across clinical trials in *BRAF*-mutant cancers

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Abstract ***Background:*** Dabrafenib plus trametinib has demonstrated clinical benefit across multiple *BRAF*-mutant tumours, leading to approval for resected stage III and metastatic melanoma, non–small-cell lung cancer (NSCLC) and anaplastic thyroid cancer. Pyrexia is a common adverse event in patients treated with dabrafenib plus trametinib. Here, we characterise the incidence, patterns and management of pyrexia in patients receiving dabrafenib plus trametinib in clinical trials.

Methods: Patients (N = 1076) included in the analysis received dabrafenib plus trametinib in the following clinical trials: phase II registration trial in advanced NSCLC (N = 82), phase III COMBI-AD study in resectable stage III melanoma (N = 435) and phase III COMBI-d and COMBI-v studies in unresectable or metastatic melanoma (N = 209 and N = 350, respectively).

Results: Among the 1076 patients enrolled in the clinical trials, 61.3% developed pyrexia, 5.7% developed grade 3/4 pyrexia and 15.6% developed a protocol-defined serious pyrexia event. Among the 660 patients with pyrexia, 33.0% had 1 occurrence, 19.8% had 2

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occurrences and 47.1% had ≥3 occurrences. The incidence of pyrexia was highest early in treatment and decreased with time on treatment. Temporary dose interruption of dabrafenib or trametinib was the most common and effective management strategy.
Conclusions: Pyrexia is the most common adverse event associated with dabrafenib plus trametinib but is manageable with dose interruption.
Trial registration: ClinicalTrials.gov (Phase II NSCLC, NCT01336634; COMBI-AD, NCT01682083; COMBI-d, NCT01584648; COMBI-v, NCT01597908).

1. Introduction

Combination therapy with dabrafenib plus trametinib has been approved by the US Food and Drug Administration (FDA), European Commission and Australian Therapeutic Goods Administration (TGA) for the treatment of *BRAF* V600–mutant unresectable or metastatic melanoma, as adjuvant therapy for resected *BRAF* V600–mutant stage III melanoma, and the treatment of *BRAF* V600–mutant advanced non–small-cell lung cancer and has been approved by the FDA and TGA for the treatment of *BRAF* V600–mutant anaplastic thyroid cancer [1–6]. Pyrexia, defined as a body temperature ≥38.0 °C, is a common adverse event that occurs with varying frequency in patients treated with dabrafenib ± trametinib and other approved BRAF inhibitors [1,7–11].

In the COMBI-d and COMBI-v trials, pyrexia occurred in 58% of patients with advanced or metastatic disease treated with dabrafenib plus trametinib. The rate of treatment discontinuation due to adverse events was 18%, and 4% of patients discontinued treatment due to the incidence of pyrexia [1]. In the COMBI-AD trial, 63% of patients treated with adjuvant dabrafenib plus trametinib experienced pyrexia, and the reported rate of treatment discontinuations due to any adverse event was 26%. Pyrexia and chills led to the discontinuation of treatment with adjuvant dabrafenib plus trametinib in 9% and 4% of patients, respectively [7,12].

The most common adverse event associated with dabrafenib plus trametinib in both the adjuvant and metastatic setting is pyrexia, the majority of which are grade 1 (38.0 °C–39.0 °C) or 2 (>39.0 °C–40.0 °C) events. In addition, pyrexia is the most frequent adverse event leading to treatment discontinuation [1,7,13]. However, risk factors associated with pyrexia or the pathogenesis of fever are not well understood [13]. Here, we present a comprehensive analysis of pyrexia to better characterise the incidence, patterns and management of pyrexia in patients treated with dabrafenib plus trametinib in the controlled trial setting using data from phase II and phase III clinical studies.

2. Materials and methods

Clinical trial data were queried for reports of pyrexia in patients treated with dabrafenib plus trametinib using the following terms: *pyrexia*, *fever*, *hyperpyrexia*, *hyperthermia*, *sweating fever*, *body temperature increased*, *cytokine release syndrome*, *influenza-like illness*, *systemic inflammatory response syndrome* and *tumour-associated fever*. Trials included the phase II registration trial (NCT01336634; N = 82) in advanced non–small-cell lung cancer, the phase III COMBI-AD (NCT01682083; N = 435) study in resectable stage III melanoma and the phase III COMBI-d (NCT01584648; N = 209) and COMBI-v (NCT01597908; N = 350) studies in unresectable or advanced metastatic melanoma. Patients randomised to the active comparator or placebo arms in these trials were not included in this analysis.

Pyrexia events were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. In the clinical trials, an additional term, *serious pyrexia events*, was defined as episodes that resulted in death, were life-threatening, led to hospitalisation or prolongation of existing hospitalisation, resulted in disability or incapacity, constituted a congenital anomaly or birth defect and/or were accompanied by grade ≥3 hypotension that was clinically significant per investigator discretion, dehydration requiring intravenous fluids or rigors/chills.

The individual phase II [5] and phase III studies [7,14,15] were previously approved by the ethics review board for each institute where the study was carried out, and the procedures followed were in accordance with the precepts of Good Clinical Practice and the Declaration of Helsinki. Informed consent was not required for this pooled analysis due to the investigation being a retrospective study. All authors had full access to all the data in the study.

3. Results

3.1. Overview of pyrexia observed in clinical trials

A total of 1076 patients treated with dabrafenib plus trametinib in the phase II non–small-cell lung cancer, COMBI-AD, COMBI-d and COMBI-v clinical trials were included in this analysis; 61.3% (660 of 1076) of patients were reported to experience pyrexia (2253 total pyrexia events) (Table 1). Grade 1 or 2 pyrexia was observed in >55.4% (596 of 1076) of the total patient population, with 5.7% (61 of 1076) of patients experiencing grade 3 or 4 events. Among the 660 patients who developed pyrexia, >90% of pyrexia events were grade 1 or 2 and <10% of pyrexia events were grade 3 or 4. Across trials, approximately 90% (2020 of 2253) of pyrexia episodes were considered to be non-serious adverse events. The median age of patients treated with dabrafenib plus trametinib who experienced pyrexia was 53 years, and 55% of patients were male. Similar to previous reports [13], no correlation was observed between age and sex and the development of pyrexia. The median time to onset of pyrexia was 27 days (range, 1–716 days) among patients treated with dabrafenib plus trametinib.

Among all patients treated with dabrafenib plus trametinib included in this analysis, 32.4% (349 of 1076) experienced 1 or 2 occurrences of pyrexia. Analysis of recurrent pyrexia among patients who experienced at least a single event (n = 660) demonstrated that 218 patients (33.0%) had a single occurrence of pyrexia, 131 patients (19.8%) had 2 occurrences and 311 patients (47.1%) had ≥3 occurrences (Fig. 1).

In both the metastatic and adjuvant setting, the incidence of all-cause adverse events was reported to be highest during the first 3 months of treatment with dabrafenib plus trametinib and to decrease over time as duration of treatment increased. This trend was also observed for individual adverse events, including pyrexia. In this analysis, 67.0% (442 of 660) of patients experienced multiple (>1) episodes of pyrexia, with a median duration of 0.9 months (range, 0–21 months) between the first and second episodes. Similar to previous reports, 57.1% (377 of 660) of patients experienced a second episode of pyrexia within the first 3 months after the first episode of pyrexia, while 5.9% (39 of 660) of patients experienced a second episode of pyrexia between 3 and 6 months from the time of the first episode of pyrexia (Table 2). The majority of recurrent episodes were considered low grade, with 7.7% of patients with pyrexia (51 of 660) experiencing recurrent (>1) grade 3 or 4 pyrexia events. No pyrexia-related deaths were reported.

In the total patient population, the proportion of patients who experienced serious pyrexia events (see Materials and Methods) was 15.6% (168 of 1076). Similar to previous reports, the majority of events occurred within the first 3 months of treatment with dabrafenib plus trametinib. The median time to onset of

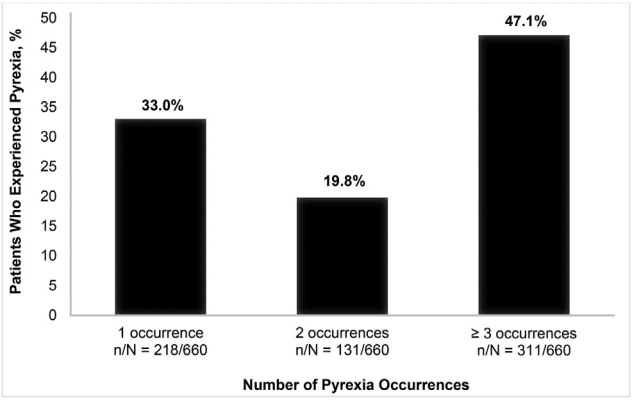

Fig. 1. Single versus multiple occurrences of pyrexia among patients who experienced pyrexia in clinical trials (N = 660).

Table 1
Summary of pyrexia events reported in patients treated with dabrafenib plus trametinib enrolled in clinical trials.[a]

Pyrexia events	Dabrafenib + Trametinib (N = 1076)	Patients With Pyrexia (n = 660)
Patients with pyrexia events, n (%)	660 (61.3)	–
Grade 1	301 (28.0)	301 (45.6)
Grade 2	295 (27.4)	295 (45.0)
Grade 3	60 (5.6)	60 (9.1)
Grade 4	1 (<1.0)	1 (<1.0)
Unknown	3 (<1.0)	3 (<1.0)
Total pyrexia events, n	2253	
Serious pyrexia event, n (%)[b]	233 (10.3)	

[a] Graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
[b] Serious pyrexia events were defined as episodes that resulted in death, were life-threatening, led to hospitalisation or prolongation of existing hospitalisation, resulted in disability or incapacity, constituted a congenital anomaly or birth defect, and/or were accompanied by grade ≥3 hypotension that was clinically significant per investigator discretion, dehydration requiring intravenous fluids, or rigors/chills.

Table 2
Time between first and second episodes of pyrexia in patients with recurrent events.

Patients, n (%)	Dabrafenib + Trametinib (n = 660)
Patients experiencing multiple pyrexia events	442 (67.01)
<3 months	377 (57.1)
3 to ≤6 months	39 (5.9)
>6 to ≤9 months	13 (2.0)
>9 to ≤12 months	4 (<1.0)
>12 to ≤ 24 months	9 (1.4)
>24 to ≤36 months	0
>36 months	0
Mean (SD), months	1.8 (2.83)
Median (range), months	0.9 (0–21)

serious pyrexia was 31 days. Recurrent episodes of serious pyrexia events were also rare and occurred in 3.9% (42 of 1076) of patients. Among the total patient population, 84.4% (908 of 1076) did not experience serious pyrexia and 11.7% (126 of 1076) experienced 1 occurrence of serious pyrexia, 2.5% (27 of 1076) experienced 2 occurrences and 1.4% (15 of 1076) experienced ≥3 occurrences (Fig. 2).

Across trials, the most common adverse events (>35%) observed among patients with pyrexia were fatigue (45.8%), chills (45.5%), nausea (45.0%), headache (39.2%) and diarrhoea (36.7%). Liver enzyme elevations were observed in 18.5% (122 of 660) of patients who had elevated alanine aminotransferase and 17.0% (112 of 660) who had elevated aspartate aminotransferase (Table 3). Complicated pyrexia, defined in this study as pyrexia accompanied by dehydration or renal failure, occurred in 3.3% of all patients (36 of 1076). Twenty-nine (2.7%) of these patients developed dehydration, and 7 (0.7%) of these patients developed renal failure.

Table 3
Adverse events most frequently reported with pyrexia regardless of causality in ≥10% of patients treated with dabrafenib plus trametinib.

Events, n (%)	Dabrafenib + Trametinib (n = 660)
Fatigue	302 (45.8)
Chills	300 (45.5)
Nausea	297 (45.0)
Headache	259 (39.2)
Diarrhoea	242 (36.7)
Vomiting	230 (34.8)
Arthralgia	205 (31.1)
Rash	194 (29.4)
Cough	149 (22.6)
Myalgia	136 (20.6)
Peripheral oedema	124 (18.8)
ALT increased	122 (18.5)
Influenza-like illness	118 (17.9)
Hypertension	115 (17.4)
AST increased	112 (17.0)
Decreased appetite	107 (16.2)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

3.2. Outcomes observed in patients with pyrexia across clinical trials

Outcomes of pyrexia were reported for 2252 of 2253 total pyrexia events, and >98% (2217 of 2253) of these cases had resolved or were improving at the time of this analysis. Temporary dose interruption of either dabrafenib or trametinib was the most frequently used strategy for management of pyrexia in patients treated in either the metastatic or adjuvant setting (Table 4). Among the patients who underwent dose interruptions, >99% (935 of 939) of pyrexia events were resolved, 3 patients had recovered with sequelae and 1 patient had not recovered at the time of the analysis. Treatment was discontinued in 62 of 660 patients (9.4%) with pyrexia, of whom 61 patients were reported to completely recover at the time of the data analysis. Management of pyrexia using dose reductions of either dabrafenib or trametinib was also reported in 225 of 2253 (10%) of pyrexia events. Of patients who experienced ≥1 pyrexia event, 15.5% (102 of 660) had an episode requiring corticosteroids for management. The median duration of treatment with any corticosteroid was 27.5 days (range, 1–885 days).

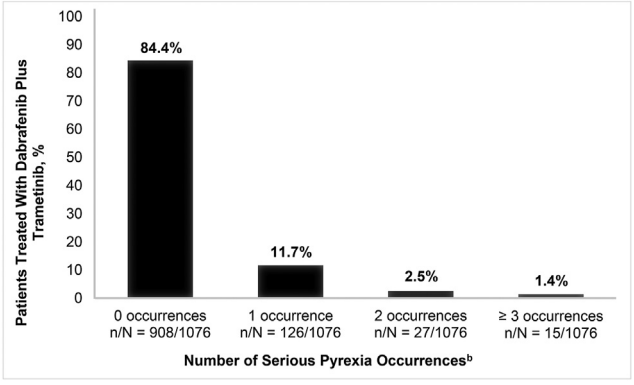

Fig. 2. Occurrences of serious pyrexia[a] events among all patients enrolled in the clinical trials (N = 1076). [a] Serious pyrexia events were defined as episodes that resulted in death, were life-threatening, led to hospitalisation or prolongation of existing hospitalisation, resulted in disability or incapacity, constituted a congenital anomaly or birth defect, and/or were accompanied by grade ≥3 hypotension that was clinically significant per investigator discretion, dehydration requiring intravenous fluids, or rigors/chills. [b] The median time to onset of serious pyrexia was 31 days.

4. Discussion

These data build on previously reported analyses [13] and represent the largest analysis of BRAF inhibitor plus MEK inhibitor–induced pyrexia to date, using clinical trial data across multiple indications and providing accurate incidence data and effective management strategies. Importantly, although pyrexia was common, 39% of patients across clinical trials did not experience any pyrexia events. Of those who had a pyrexia event, only 9.2% had a grade 3 or 4 event, and there were no deaths related to pyrexia. An important feature of pyrexia was that it was often associated with other symptoms, including fatigue, chills and nausea, which can also be a signal for the patient to temporarily cease both dabrafenib and trametinib until the pyrexia episode resolves. Indeed, the most common and effective management strategy was interruption of both dabrafenib and trametinib; the majority of patients resumed therapy, and only a small minority of patients went on to have recurrent pyrexia (≥2 episodes). Similar to previous reports, the majority of pyrexia episodes

Table 4
Outcomes of pyrexia management by episode (N = 2253) in all patients (N = 1076) enrolled in the clinical trials.

Action Taken[a]	Total, n	Outcomes, n (%)[b]			
		Complete Recovery	Condition Improving	Recovery With Sequelae	No Recovery
No change	1008	983 (43.6)	4 (<1.0)	6 (<1.0)	15 (<1.0)
Dose reduced	225	222 (9.9)	1 (<1.0)	2 (<1.0)	0
Dose interrupted	939	935 (41.5)	0	3 (<1.0)	1 (<1.0)
Administration of corticosteroids[c]	102	NR	NR	NR	NR
Treatment discontinued	62	61 (2.7)	0	0	1 (<1.0)
Not applicable	19	16 (<1.0)	0	0	2
Total	2253	2217 (98.4)	5 (<1.0)	11 (<1.0)	19 (<1.0)

NR, not reported.
[a] Includes either the reduction, interruption or discontinuation of either dabrafenib or trametinib.
[b] Percentages are based on the number of events for which the outcome was reported (N = 2253); outcomes were not reported for 1 event.
[c] Not included in the 2253 total; a patient would have received corticosteroids in addition to one of the other actions, such as treatment reduction or interruption.

occurred within the first 3 months of treatment, and if recurrent, events decreased over time [16,17].

The combination of dabrafenib plus trametinib has been approved by regulatory agencies for several indications, including the treatment of *BRAF* V600–mutant unresectable or metastatic melanoma and as adjuvant therapy for *BRAF* V600–mutant stage III melanoma following resection [1,2,4]. With an overall survival rate of 34% and approximately 20% of patients progression free after 5 years, targeted therapy with dabrafenib plus trametinib has shown durable long-term disease control in an otherwise challenging treatment landscape for metastatic melanoma [1]. In COMBI-d/v and COMBI-AD, pyrexia was the most common adverse event [1,7]; kinetic safety analyses showed the frequency of pyrexia to be highest during the initial months of treatment and to decline rapidly with extended time on therapy [16,17]. However, pyrexia led to early treatment cessation in 4%–9% of patients, suggesting that optimising management of pyrexia may improve outcomes in some patients [1,12].

With widespread use of dabrafenib plus trametinib, an evidence-based pyrexia management algorithm has been developed (Fig. 3) [18]. In the clinical trials included in this analysis, temporary treatment interruption was the most frequently used strategy for managing pyrexia symptoms and resulted in >95% of patients having symptoms resolved or recovering at the time of this analysis. Previous reports have also confirmed that prompt dose interruption of both dabrafenib and trametinib at the very first signs of pyrexia or its prodrome is an effective management strategy [13,18]. Therefore, the new modified pyrexia syndrome management protocol calls for interrupting both dabrafenib and trametinib if patients develop ≥1 symptom of possible treatment-related pyrexia syndrome and restarting both drugs at the full dose when the patient has been symptom free for ≥24 h (Fig. 3) [18]. Alternatively, in patients with severe recurrent pyrexia, administration of corticosteroids can be considered as a prophylactic strategy instead of frequent therapy interruptions [18]. Generally, corticosteroids are initiated at a starting dose (e.g. for prednisone, the median effective starting dose is 25 mg [range, 10–50 mg]) and titrated down or up depending on the resolution of the pyrexia [13,19].

Across the clinical trials, pyrexia consistently occurred early and, even in patients with recurrent pyrexia, became less frequent with time. Cases suggestive of complicated pyrexia, in which adverse events such as chills, dehydration, renal insufficiency, or hypotension were observed concomitantly, occurred infrequently. The rate of treatment discontinuation due to pyrexia was <10% among all patients who discontinued treatment due to an adverse event across all included clinical trials. These data indicate that pyrexia can be effectively managed; thus, it is important to educate healthcare providers on management strategies to reduce the rate of treatment discontinuation in real-world practice.

The aetiology of dabrafenib plus trametinib–induced pyrexia is not well understood; however, it is hypothesised that the development of pyrexia may be linked to treatment with dabrafenib and the secretion of the proinflammatory cytokines interleukin (IL)-1β and IL-6 [13,20]. In biomarker analyses of patients treated with neoadjuvant dabrafenib and trametinib, IL-1β and IL-6 levels were observed to be elevated early during treatment. Interestingly, after treatment interruption of dabrafenib plus trametinib, levels of circulating IL-1β and IL-6 decreased to levels similar to those in patients who did not develop pyrexia [20]. Both IL-1β and IL-6 are proinflammatory cytokines considered to be endogenous pyrogens that lead to an increase in the thermoregulatory set point in the hypothalamus. In addition, such proinflammatory cytokines have been associated with symptoms such as chills and malaise, which often accompany pyrexia [21].

While the mechanisms driving induction of pyrexia have not been elucidated and factors identifying patients

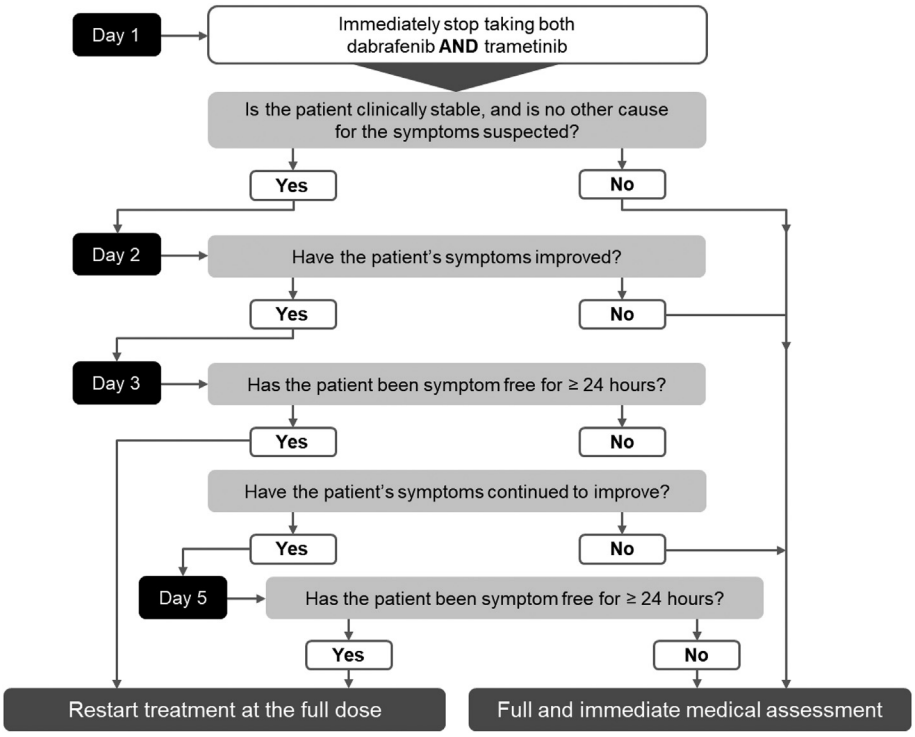

Fig. 3. Modified pyrexia syndrome management algorithm [18]. Reproduced from Atkinson *et al. Asia Pac J Clin Oncol.* 2016; 12 Suppl 7:5–12, with permission by Wiley and Sons. ©2016 John Wiley & Sons Australia, Ltd.

at higher risk of developing pyrexia remain unknown, optimising the management of pyrexia may lead to a longer duration of treatment and improved outcomes in some patients. A phase III clinical trial (NCT03551626; COMBI-APlus) is currently underway to evaluate the impact of an adaptable adverse event management algorithm on pyrexia-related outcomes, efficacy, and other health-related quality-of-life outcomes. In conclusion, while further optimisation of pyrexia management is warranted, this analysis demonstrates that pyrexia is common early during treatment, decreases in incidence with time, and can be effectively managed with dose interruption both in clinical trials and clinical practice.

Author contributions

All the authors developed the initial draft of the manuscript and made the decision to submit it for publication; all the authors contributed to subsequent drafts. The authors affirm the accuracy and completeness of the data and adherence of the trial to the protocol. Conception or design of the work, acquisition, analysis or interpretation of data, and drafting or revision of the work were done by D. Schadendorf, C. Robert, R. Dummer and G.V. Long. Acquisition, analysis, or interpretation of data and drafting or revising of the work were done by K.T. Flaherty, H.A. Tawbi and A.M. Menzies.

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Conflict of interest statement

DS has received research grants from Novartis, Bristol Myers Squibb, and Amgen; received consulting fees from, travel support from, and had advisory relationships with Novartis, Bristol Myers Squibb, MSD, Roche, Incyte, Array, Pierre Fabre, Pfizer, Sanofi-Genzyme, Regeneron, 4SC, InFlarX, Neracare, Ultimovacs, Sun Pharma, Philogen, Amgen, Merck-Serono, Immunocore, Sandoz-Hexal; received honoraria from Novartis, Bristol Myers Squibb, Pierre Fabre, Sanofi-Genzyme and Merck-Serono; and held leadership or fiduciary roles with Dermatologic Cooperative Oncology Group (DeCOG), German Cancer Society, Hilfe-Stiftung, Deutsche Hautkrebsstiftung, NVKH eV and EuMelaReg. CR has received consulting fees from and had advisory relationships with Bristol Myers

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