The impact of patient characteristics and disease-specific factors on first-line treatment decisions for BRAF-mutated melanoma: results from a European expert panel study

Paolo A. Ascierto[a], Lars Bastholt[c], Pier F. Ferrucci[b], Johan Hansson[d], Iván Márquez Rodas[e], Miranda Payne[f], Caroline Robert[h], Luc Thomas[i], Jochen S. Utikal[j], Pascal Wolter[k], Amber Kudlac[g], Harriet Tuson[g] and Jan McKendrick[g]

Treatment decisions for advanced melanoma are increasingly complex and guidelines provide limited advice on how to choose between immunotherapy and targeted therapy for first-line treatment. A Delphi study was carried out to understand which patient characteristics and disease-related factors inform clinicians' choices of first-line treatment for BRAF-mutated melanoma. Twelve European melanoma specialists experienced in using immunotherapies and targeted agents participated in a double-blind two-phase Delphi study. In phase 1, participants completed a questionnaire developed after reviewing patient characteristics and disease-related factors reported in trials, clinical guidelines, and health technology assessments. Phase 2 was an expert panel meeting to explore outstanding issues from phase 1 and seek consensus, defined as 80% agreement. Twenty patient-related and disease-related characteristics were considered. There was consensus that tumor burden (83% of clinicians) and disease tempo (83%) are very or extremely important factors when selecting first-line treatment. Several components were deemed important when assessing tumor burden: brain metastases (82% of clinicians) and location of metastases (89%). There was consensus that disease tempo can be quantified in clinical practice, but not on a formal classification applicable to all patients. Lactate dehydrogenase level is a component of both tumor burden and disease tempo; all clinicians considered lactate dehydrogenase important when choosing first-line treatment. The majority (92%) did not routinely test programmed death ligand-1 status in patients with melanoma. Clinicians agreed that choosing a first-line treatment for advanced melanoma is a complex, multifactorial process and that clinical judgment remains the most important element of decision-making until research can provide clinicians with better scientific parameters and tools for first-line decision-making. *Melanoma Res* **28:333–340 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.**

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[a]Istituto Nazionale Tumori Fondazione G. Pascale, Naples, [b]European Institute of Oncology, Milan, Italy, [c]Odense University Hospital, Odense, Denmark, [d]Karolinska Institutet, Stockholm, Sweden, [e]Hospital General Universitario Gregorio Marañon, Madrid, Spain, [f]Oxford University Hospitals NHS Foundation Trust, Oxford, [g]PRMA Consulting Ltd, Fleet, UK, [h]Gustave-Roussy and Paris-Sud University, Villejuif, [i]Lyon 1 University, Lyon Cancer Research Center, Centre Hospitalier Lyon-Sud, Pierre-Bénite, France, [j]German Cancer Research Center (DKFZ) and Heidelberg University, Mannheim, Germany and [k]CHR Verviers East Belgium, Verviers, Belgium

Correspondence to Jan McKendrick, PGDip, PRMA Consulting Ltd, Linea House, Harvest Crescent, Ancells Business Park, Fleet GU51 2UZ, UK
Tel: +44 1252 786284; fax: +44 1252 279297;
e-mail: jmckendrick@prmaconsulting.com

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Introduction

Melanoma is an aggressive cancer and the prognosis is poor for patients with advanced disease [1]. There were an estimated 22 000 deaths from melanoma across Europe in 2012 [2]. Systemic treatment for metastatic melanoma had little impact on survival before 2011 [3]. Patients were entered into clinical trials, in accordance with guideline recommendations at that time, as few effective treatments were available. Since then, a number of immunotherapies (immune checkpoint inhibitors) and targeted therapies (BRAF/MEK inhibitors for patients with a BRAF V600 genetic mutation) have been developed and approved for the treatment of melanoma [4–10]. Treatment decisions have become increasingly complex as new products and therapeutic combinations are approved and adopted into clinical practice [10,11].

Although a number of international and national guidelines on the management of advanced melanoma are

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available, these can be of limited value as it is difficult to update the information frequently enough to keep pace with the rapidly changing treatment landscape [3,12–21]. There is no consensus on the factors that should guide the choice of first-line treatment class (immunotherapy or targeted therapy) in the clinic or on whether a single treatment algorithm can or should be followed in all patients.

A Delphi study with a panel of expert clinicians was carried out to identify the patient characteristics and disease-specific factors that influence choices of first-line treatment in advanced melanoma and how these factors and concepts are defined and used in clinical practice. This paper is focused on BRAF-mutated advanced melanoma.

Participants and methods

Study design

This was a two-phase double-blind Delphi panel study comprising a questionnaire, developed from a review of existing literature (phase 1), and a face-to-face expert panel meeting (phase 2). Panel members did not know the sponsor of the study during the course of the study and the panel members' identities were not disclosed to the study sponsor. Blinding was removed after completion of the study.

Setting and participants

Approximately 40 clinicians from Europe who were anticipated to fulfill the predefined screening criteria were selected and contacted by PRMA Consulting to gauge their interest and availability for participating in the study. From these, 12 were then recruited to participate in the study. All of the clinicians had had experience with using immunotherapy and BRAK/MEK-targeted therapies and substantial clinical experience defined as board certification or specialist accreditation, with at least 2 years as an attending physician or a consultant. Clinical research experience was also required, as evidenced by the publication in the 36 months preceding the study of at least two articles or conference abstracts on the treatment of melanoma.

Data collection

Phase 1 (questionnaire)

Questionnaire development was informed by a review of trials of BRAF/MEK-targeted therapies, clinical guidelines for melanoma, and technology appraisals by the UK National Institute for Health and Clinical Excellence (NICE), which identified patient characteristics and disease-related factors that may influence treatment decisions. This research is described in Supplementary Appendix (Supplemental digital content 1, *http://links.lww.com/MR/A41*).

The evidence review identified 20 factors of interest, although there was some overlap between concepts (Fig. 1). Two of these factors – tumor burden and disease tempo (the rate at which disease progresses) – were of particular interest because they were not well defined in treatment guidelines; a further two – serum lactate dehydrogenase (LDH) level, and programmed death ligand-1 (PD-L1) status – were included as their role in treatment decision-making was unclear.

The questionnaire was developed in collaboration with the sponsor of the study and two clinicians who were not part of the Delphi process. A series of categorical, numerical, and open-ended questions were incorporated to understand how tumor burden and disease tempo are assessed and measured in clinical practice, and the importance of these two factors plus PD-L1 status and LDH in first-line treatment decision-making for patients with BRAF-mutated and wild-type melanoma. Clinicians were also asked to report the relative importance of all 20 patient characteristics and disease-specific factors identified in the evidence review (Fig. 1), and their influence on first-line treatment decision-making (again by BRAF mutation status).

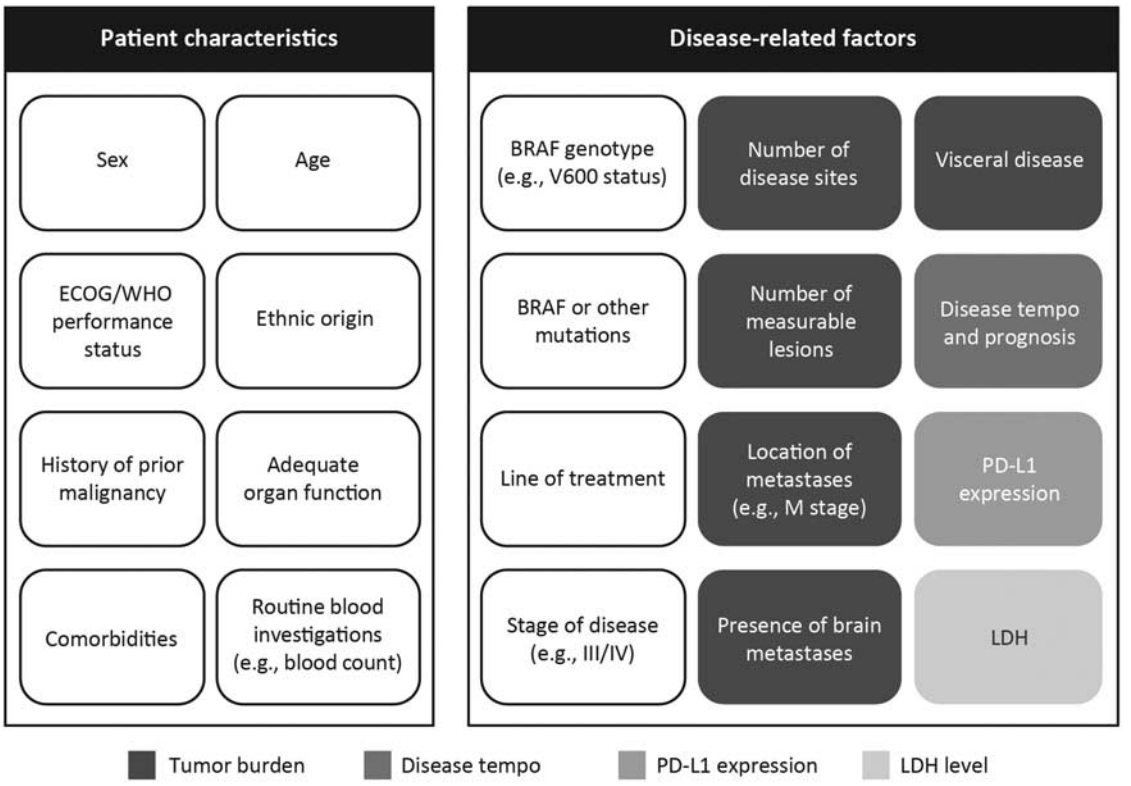
Participating clinicians completed the questionnaire by e-mail between December 2015 and January 2016. Responses for each question were summarized in an Excel database, maintaining the anonymity of each clinician to the sponsor and to the other participating clinicians. Consensus was defined as 80% of respondents in agreement and, where consensus was reached during phase 1, the question was not explored further. However, where consensus was not reached, the question was considered in phase 2 of the study.

Phase 2 (panel meeting)

Questionnaire responses were used to develop a discussion guide for a panel meeting that took place on 12 February 2016. Generated questions explored further how tumor burden and disease tempo are assessed in clinical practice. Further consideration was also given to the importance of factors in first-line treatment decision-making, although the focus was on the choice between treatment classes (i.e. immunotherapy or BRAF/MEK-targeted therapy) for BRAF-mutated advanced melanoma.

At the start of the meeting, participating clinicians were provided with an overview of the results from phase 1 of the study. Where consensus had not been reached, clinicians' original responses were explored through facilitated discussion and they were asked to provide responses again, which were displayed anonymously using IML PowerPoint software (Lumi, Liphook, UK). As in phase 1, consensus was defined as at least 80% of respondents in agreement. If consensus was not achieved after two rounds of discussion and it was clear that consensus would not be reached, this was accepted as the final outcome. New questions were also developed for areas of particular interest.

Fig. 1



Patient characteristics and disease-specific factors that may influence first-line treatment decisions for BRAF-mutated melanoma. ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD-L1, programmed death ligand-1.

Results

The focus of this paper is on the assessment and measurement of tumor burden and disease tempo in first-line advanced melanoma and the importance of these factors plus PD-L1, LDH, and a range of other factors in treatment decision-making for BRAF-mutated advanced melanoma.

Participants

Twelve experienced, accredited clinical specialists from Europe participated in the study.

Use of clinical guidelines

Treatment guidelines were considered to play a role in directing clinical decision-making, although there was consensus (100% of clinicians agreed) that current guidelines did not provide sufficiently detailed information about how to choose between immunotherapy and BRAF/MEK-targeted therapy for the first-line treatment of BRAF-mutated melanoma. The majority of clinicians (75%) reported that the main reason for this was a lack of clinical evidence to inform such decision-making. The remaining clinicians stated that treatment guidelines become outdated quickly because of the rapidly changing landscape and could be difficult to interpret and implement in clinical practice because some terms used (e.g. tumor burden) are not clearly or consistently defined in practice. Some clinicians also commented that their national guidelines had limited relevance when selecting a class of treatment because they only include drugs that are funded or reimbursed in that country.

Choice of first-line treatment for BRAF-mutated melanoma

All clinicians except one confirmed using both immunotherapies and BRAF/MEK-targeted therapies for the first-line treatment of BRAF-mutated advanced melanoma. Seven of the clinicians used BRAF/MEK-targeted therapies in the majority of patients (range: 70–100%), whereas the remaining five either used immunotherapy in the majority of patients (range: 60–70%) or BRAF/MEK-targeted therapy and immunotherapy in an equal number of patients. Combinations of BRAF/MEK-targeted agents were preferred to BRAF or MEK monotherapy unless they were contraindicated because of their increased toxicity. For example, some patients have experienced ophthalmologic reactions, including uveitis, iridocyclitis, and iritis, with these combinations; a monotherapy is therefore the preferred option in patients with ocular problems. For immunotherapy, anti-PD-1

agents were generally preferred to ipilimumab. Although not the focus on this paper, this preference was also observed for BRAF wild-type advanced melanoma. The combination of ipilimumab and nivolumab was not available at the time of the study, but the clinicians considered that its introduction would further change the treatment landscape.

Most of the clinicians in the panel selected the class of first-line treatment primarily on the basis of their clinical experience. Almost half (five of 12) stated that the reimbursement status of different therapies influenced their choice of treatment in BRAF-mutated advanced melanoma; three of these five clinicians stated that they would increase their use of immunotherapies if restrictions were not in place. The most appropriate treatment choice for some patients was still considered to be enrollment in a clinical trial as this allows access to treatments that are not reimbursed or subject to restrictions in some countries.

Influence of tumor burden, disease tempo, PD-L1, and LDH on first-line treatment decisions

Tumor burden

Assessing and measuring tumor burden: In the phase 1 questionnaire, clinicians reported using several individual disease-specific components to assess tumor burden in first-line advanced melanoma. When considered in isolation, there was consensus that the location of metastases and presence of brain metastases were important factors to assess tumor burden (Table 1).

It was noted that many of the factors rated as important in assessing tumor burden related to the location, rather than the size, of the lesion, but phase 2 discussions confirmed that the size and location of lesions were not considered to be distinct factors, and both were considered important. The term 'key lesions' was used in clinical trials, but not clinical practice; the preferred terminology when referring to lesions of particular concern to the clinician was 'high-risk lesions'.

Clinicians confirmed that although clearly very relevant in defining tumor burden, the presence of brain metastases alone was not considered sufficient to determine the presence of a high tumor burden in the patient. Clinicians emphasized that their experience in assessing tumor burden is key as this concept is difficult to describe using fixed criteria as a number of interrelated components are important, and it is highly patient specific.

A number of methods are used to measure tumor burden in clinical practice. All the clinicians reported using computed tomography scanning to evaluate disease status and to define target lesions according to Response Evaluation Criteria In Solid Tumors (RECIST). The majority also reported physically examining visible/palpable lesions, using MRI, or using PET-CT in their assessments. The clinicians also considered a patient's general health status (performance status) according to the WHO criteria.

Components of tumor burden that influence first-line treatment decisions: The clinicians agreed that tumor burden is an important consideration when choosing a first-line treatment, and the majority (83%) considered it very or extremely important. However, all clinicians emphasized that it was difficult to identify which individual components are most important. A number of the components of tumor burden were considered either essential or useful (but not essential) in selecting between immunotherapy and BRAF/MEK-targeted therapy for first-line treatment (Fig. 2). The presence of nonresectable, symptomatic brain metastases alone was sufficient to determine the choice of first-line treatment for BRAF-mutated advanced melanoma when local treatment was not an option.

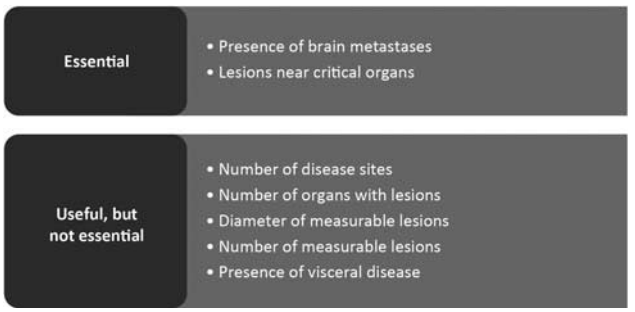
For a patient with BRAF-mutated melanoma who was considered to have a high tumor burden, there was consensus that BRAF/MEK-targeted therapy was preferred to immunotherapy (80%; two clinicians did not respond). However, it was suggested that this may change when the combination of ipilimumab plus nivolumab becomes available.

Table 1 **Importance of factors used to assess tumor burden**

Factors	Used to assess tumor burden [*n* (%)]	Rated as very (4) or extremely (5) important[b] (%)
Presence of brain metastases	**12 (100)**	**82**
Number of disease sites	**11 (92)**	60
Location of metastases (e.g. M stage)[a]	**11 (92)**	**89**
Key lesion location	**10 (83)**	78
Number of organs with lesions[a]	**10 (83)**	56
Lesions near critical organs	**10 (83)**	67
Presence of visceral disease	**10 (83)**	67
Diameter of measurable lesions	9 (75)	50
Number of measurable lesions	9 (75)	14
Key lesion size	8 (67)	43

Bold text is used to indicate consensus (≥80% agreement).
[a]One clinician did not respond to the question on location of metastases and another did not respond to the question on the number of organs with lesions.
[b]Only clinicians who reported using a factor in clinical practice and who rated the factor were included in the analysis.

Fig. 2



Components of tumor burden rated as essential or useful when selecting a first-line treatment class.

Disease tempo

Assessing and measuring disease tempo: There was consensus that disease tempo was quantifiable in clinical practice, but not on a formal classification that could be implemented routinely across all patients. Clinicians stated that they typically assessed disease tempo through discussion with the patient to identify symptoms and signs that the disease was progressing quickly, such as pain, change in performance status, rapid weight loss, presence of multiple symptoms, abnormal liver function (e.g. elevated transaminases or LDH), deteriorating neurological symptoms, deteriorating hematological signs, size of visible metastases, increased skin pigmentation (melanoderma), and fatigue. The clinicians used serial assessment of a patient's condition to measure the rate of disease progression. Although there was no consensus on the methods used, serial imaging (67%), physical examinations (50%), and assessment of the rate of deterioration in performance status (67%) were used by the majority of the participating clinicians.

Disease tempo was considered particularly difficult to assess in patients with newly diagnosed melanoma. However, clinicians considered that patients with metastatic disease at diagnosis often have a fast disease tempo.

Influence of disease tempo on first-line treatment choice: All the clinicians agreed that disease tempo is important when making first-line treatment decisions and the majority (83%) considered it very or extremely important. There was consensus that BRAF/MEK combination therapy is preferred for patients with BRAF-mutated melanoma and a fast disease tempo.

Impact of PD-L1 status

When the Delphi study was carried out, the majority of panel members (92%) did not routinely test PD-L1 status in patients with melanoma. Just over half of the respondents (58%) reported that PD-L1 was not at all or not very important in first-line treatment decisions. It was agreed that a negative PD-L1 status alone should not exclude a patient from treatment with anti-PD-1 immunotherapy.

Although PD-L1 testing was not considered important by the majority of the participating clinicians, nine of 11 clinicians (82%; one clinician did not respond) predicted that PD-L1 testing would become routine practice with the availability of ipilimumab in combination with nivolumab. However, two clinicians believed that PD-L1 would not be an appropriate predictive marker, even with the availability of ipilimumab plus nivolumab.

Importance of LDH levels

The participating clinicians considered the LDH level to be a component of both tumor burden and disease tempo. All clinicians confirmed that LDH is measured as part of routine blood tests, and the majority (75%) reported that the key threshold level is less than or equal to 2 versus more than two times the upper limit of normal. Consensus was reached that LDH is an important component of tumor burden (92%) and that a single measure of LDH, rather than serial measurements, is informative in an assessment of disease tempo (92%).

All the clinicians considered assessment of LDH to be important in first-line treatment decisions; three-quarters considered it very important and one-quarter considered it moderately important. Opinion was divided about the best treatment approach for patients with BRAF-mutated disease and high baseline LDH: half of clinicians reported that they would use targeted agents as a first-line treatment for these patients.

Influence of patient characteristics and disease-specific factors in first-line treatment decisions

The panel members believed that all first-line treatment decisions in advanced melanoma are complex and multidimensional, and agreed that it is difficult to apply a formulaic approach that would be relevant to all patients. Multiple interrelated factors must be considered and treatment must be personalized to the patient (Fig. 1).

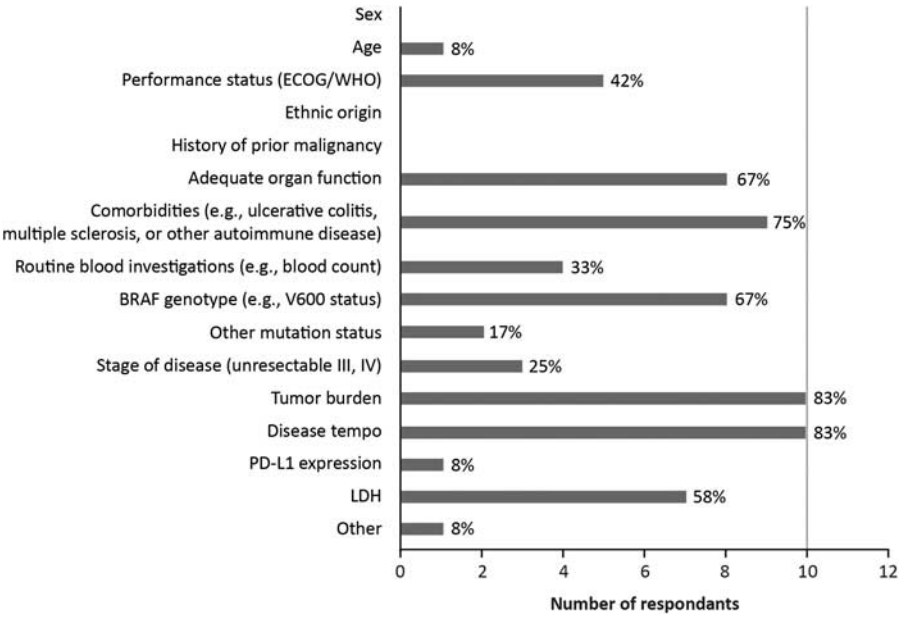
In phase 1, there was consensus that tumor burden (83%) and disease tempo (83%) are important factors in the choice of first-line treatment class for BRAF-mutated disease (Fig. 3).

In phase 2, clinicians were asked which factors other than tumor burden and disease tempo they would consider essential when advising a less experienced clinician about the choice of first-line treatment class for BRAF-mutated disease. Consensus was reached (92%) that it was also essential to consider comorbidities (e.g. history of autoimmune disease, ulcerative colitis, rheumatoid arthritis, or multiple sclerosis), organ function (92%), and performance status (83%).

Discussion

This study confirms that clinicians do not currently follow a single algorithm when selecting a first-line treatment for BRAF-mutated advanced melanoma. The clinicians

Fig. 3



Number of respondents who rated factors as either very or extremely important for selecting first-line treatment class in patients with BRAF-mutated melanoma.

described a personalized approach to the selection of treatment on the basis of extensive clinical experiences and subjective judgment or 'getting a sense of the patient'. This approach is consistent with National Comprehensive Cancer Network (NCCN) guidelines, which recognize that decisions on the treatment of individual patients rely on clinical judgment [17]. Clinicians noted that treatment guidelines cannot keep pace with the rapidly changing treatment landscape, and so provide limited information to guide first-line treatment decisions.

Although consensus was reached that some factors, including tumor burden and disease tempo, appear to strongly influence the selection of first-line treatment, the panel discussion highlighted that the choice between targeted therapy and immunotherapy relies more on clinical experience; socioeconomic factors, including the reimbursement status of different therapies, also influence the choice of treatment in some cases. Although the study explored the clinical decision-making process, the scientific rationale for those choices was not fully investigated (e.g. why clinicians would not use immunotherapy in patients with fast disease tempo).

Clinicians noted that the concepts of tumor burden and disease tempo are difficult to define and measure because they involve multiple interrelated components. The NCCN, European Society of Medical Oncology, and German S3 treatment guidelines recommend that a clinician take individual components of tumor burden and disease tempo into consideration when choosing treatment for advanced melanoma [13,17,19]. NCCN guidelines state rather simplistically that tumor burden can be defined by the size and number of tumor deposits, but the thresholds for defining high or low tumor burden are not clear. This study highlights the complexity of these concepts.

Clinicians reported that LDH is an important factor that relates to both tumor burden and disease tempo. NCCN guidelines refer to the role of LDH as a surrogate for tumor burden and as a prognostic indicator [17], recommending that LDH is measured in patients diagnosed with stage IV melanoma. Measurement of LDH is also an integral part of the American Joint Committee on Cancer melanoma staging system [22]. At the time of the Delphi study, the participating clinicians did not generally measure PD-L1 status, although some clinicians considered that it was likely to become a routine part of clinical assessment in the future, particularly with the availability of the combination of ipilimumab plus nivolumab. Other clinicians believed that PD-L1 status would not determine the choice of first-line treatment for BRAF-mutated melanoma even when this combination is available.

The Delphi approach uses iterative questioning on an issue to seek consensus [23]. It is a well-accepted methodology in healthcare research and is increasingly being adapted to include a face-to-face meeting, which allows facilitated discussion on selected topics [23–25]. This study is limited in that it represents the informed

clinical opinion of a small number of specialists, albeit with substantial experience in this area. In addition, several treatments that are now licensed in Europe for advanced melanoma were not available when the questionnaire was developed, notably the combination of ipilimumab plus nivolumab, which may change the treatment landscape considerably. Finally, this study focused on disease characteristics and patient-related factors that influence treatment decision-making, but in some countries and clinical centers, other factors relating to healthcare delivery or accessibility of testing may also be important.

This study could be repeated to understand how ongoing clinical developments and changes to the current treatment pathway (which may have occurred since the study was carried out) affect treatment decisions. Furthermore, as the panel represented clinicians from across Europe with varying clinical opinions and who have access to different treatments (influenced by local reimbursement and funding decisions), the study could be targeted to assess the views of clinicians from a specific country in more detail.

Further clinical research on advanced melanoma is required to inform treatment decisions and to personalize treatment on the basis of patient characteristics and disease-specific factors. The results of trials comparing BRAF/MEK-targeted therapies directly with anti-PD-1 immunotherapies will be important in this respect.

Trials that include patients with negative prognostic indicators, such as bulky disease, visceral metastases, or elevated LDH, and patients who generally do not qualify for inclusion in trials, such as those with poor performance status (ECOG status ≥ 2), will also be important for understanding appropriate treatment decision-making in a more clinically relevant patient population. However, until further clinical evidence is available, clinical judgment will remain the most important element of first-line decision-making.

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Conflicts of interest

Paolo A. Ascierto has had a consultant/advisory role for Bristol-Myers Squibb, Roche-Genentech, Merck Sharp & Dohme, Novartis, Array, Amgen, Merck-Serono, Pierre Fabre, Incyte, Genmab, NewLinks Genetics, Medimmune, Syndax, and AstraZeneca. Lars Bastholt has participated in advisory boards for Bristol-Myers Squibb, Roche, Novartis, Merck Sharp & Dohme, Eisai, and Bayer. Travel accommodation has been funded by Bristol-Myers Squibb, Novartis, Roche, Merck, and Merck Sharp & Dohme. Pier F. Ferrucci has had a consultant/advisory role for Bristol-Myers Squibb, Roche, Merck Sharp & Dohme, Novartis, Amgen. He has received travel accommodation by Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Novartis, GlaxoSmithKline. Johan Hansson has had a consultant/advisory role for Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Novartis, and Amgen, and has been principal investigator in trials sponsored by Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, and Novartis. Iván Márquez Rodas has had an advisory role for Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Novartis, GSK, Amgen, Pierre Fabre, and Bioncotech; travel accommodation has been funded by Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Novartis, GlaxoSmithKline, and Amgen. Miranda Payne has received fees and support to attend conferences from Bristol-Myers Squibb, GlaxoSmithKline, Novartis, and Merck Sharp & Dohme. Caroline Robert has had a consultant/advisory role for Bristol-Myers Squibb, Roche-Genentech, Merck Sharp & Dohme, Novartis, Amgen, Array, and Merck. Luc Thomas has been principal investigator in several trials in melanoma (without personal honoraria) sponsored by Roche, Genentech, Bristol-Myers Squibb, Intuiskin, GlaxoSmithKline, Immunid, Merck-Serono, Novartis, Galderma, and Pixience. Jochen S. Utikal is on the advisory board or has received honoraria from Roche, Novartis, Amgen, GlaxoSmithKline, Bristol-Myers Squibb, and Merck Sharp & Dohme. Pascal Wolter has been principal investigator in several trials in melanoma (without personal honoraria) sponsored by Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Novartis, GlaxoSmithKline, and Takeda, he has had a consultant/advisory role for Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Novartis, and Takeda without personal remuneration. For the remaining authors, there are no conflicts of interest.

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