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Treatment patterns and outcomes of Stage IIIB/IIIC melanoma in France, Germany and the UK: A retrospective and prospective observational study (MELABIS)

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Summary

Aim: Real-world data on treatment patterns/outcomes in patients with advanced melanoma, while scarce, are useful for health technology assessments that govern patient access in many countries. We collected retrospective data on treatment patterns among patients in France, Germany and the UK with Stage IIIB/IIIC melanoma with macroscopic lymph node involvement, whose primary melanoma and regional lymph node metastases had been completely resected.

Methods: Patients ≥18 years were diagnosed between 1 January 2009 and 31 December 2011. Data were obtained from patients' medical records and a patient survey.

Results: Forty-nine centres provided data on 558 patients: 53.6% had Stage IIIB disease; 58.2% were of working age (<65 years), 22.5% reported a change in employment status due to melanoma, 8% were on long-term sick leave; and 35.1% were deceased over the study period. Overall median distant metastases-free survival was 23.4 months and median disease-free survival was 13.3 months. Hospitalisation frequency increased during distant metastatic/terminal disease phases. Adjuvant therapy was received by 7.0% (14/199) of patients in France, 2.6% (5/195) in the UK, and 33.5% (55/164) in Germany. Low-dose interferon was used more frequently than other regimens. High-dose interferon was associated with discontinuation in 28.6% and dose delay/reduction in 33.3% of patients.

Conclusions: Rapid disease progression combined with increased use of healthcare resources in later phases of disease result in a high burden-of-illness for patients and healthcare providers. The use of adjuvant interferon therapy varies considerably in this population in the countries studied, highlighting the need for improved treatments for melanoma.

1 | INTRODUCTION

The incidence of malignant melanoma is increasing. While surgical resection can be curative, particularly for early disease, Stage III disease with macroscopic (clinically detectable) lymph node involvement has a poor prognosis, with a 5-year overall survival (OS) rate of 29%-51%.[1,2] There are few adjuvant treatment options for resected Stage III melanoma; interferon alpha and pegylated interferon alpha modestly extend disease-free survival (DFS), but have limited effect on OS and may be associated with substantial toxicity.[3,4] Patient selection for interferon therapy requires careful consideration of the individual's likely benefit and risk, and may also be influenced by physician experience with the product and cost considerations. Therefore, its use may differ between centres or countries.

In many countries, access to new and potentially expensive treatments may be influenced by health technology assessment (HTA), which commonly evaluates whether the benefit offered by a medicine is worth its cost. Evidence of the treatment's effect on patient outcomes, including survival, usually comes from clinical trials. In addition to clinical trial data, high-quality, country-specific real-world data that describe current treatment patterns, outcomes, resource utilisation and costs in routine clinical practice, are valuable in the HTA and reimbursement decision-making process. For malignant melanoma, such data are scarce, especially for small subgroups of patients (ie, Stage IIIB/IIIC).[5-7] Therefore, we conducted an observational burden-of-illness study in France, Germany and UK. We collected real-world data on treatment patterns and healthcare resource use among patients with Stage IIIB/IIIC melanoma with macroscopic lymph node involvement, whose primary melanoma and regional lymph node metastases had been completely resected.

2 | METHODS

This retrospective study was conducted in 49 specialist cancer centres, tertiary referral centres (14 in France, 17 in Germany, 18 in the UK) selected to provide a range of geographic locations, sizes and institution types. Ethics committee approvals and study design details are provided in Data S1.

Medical records in each centre were screened for patients presenting with (or progressing to) stage IIIB/IIIC melanoma between 1 January 2009 and 31 December 2011. Patients (living or deceased) were eligible if they were ≥18 years of age and had macroscopic (clinically detectable) lymph node involvement at diagnosis of stage IIIB/IIIC disease, and if they had undergone complete surgical resection with therapeutic lymphadenectomy (Figure 1). Patients were excluded if they had received a blinded or unlicensed active adjuvant therapy in a clinical trial, in order to be consistent the observational nature of the study.

Each centre aimed to enrol between 5 and 30 patients. In sites with more than 30 potentially eligible patients, a systematic quasi-random

What's known

- Patients with Stage IIIB/IIIC melanoma with macroscopic lymph node involvement, whose primary melanoma and regional lymph node metastases had been completely resected, have a high risk of recurrence and are therefore considered candidates for adjuvant systemic therapy. Interferon (including various regimens) has been approved in European countries as an adjuvant therapy. However, little is known about the real-world treatment and clinical outcomes for these patients.

What's new

- Most patients with resected stage IIIB/IIIC melanoma with macroscopic lymph node involvement receive no adjuvant systemic therapy in France, the UK, and Germany. Low- or intermediate-dose was used more frequently than high-dose interferon, pegylated interferon was rarely used. Among patients receiving high-dose interferon, one-third had dose delays and/or reductions and more than a quarter discontinued therapy due to toxicity.
- The modest survival benefit and potential toxicity of interferon therapy may contribute to its apparently low level of use.
- Our findings indicate there is an important unmet need to develop more effective and broadly applicable treatments to prevent recurrence and improve survival in this group of patients.

sampling method was used for patient selection to avoid bias at the site-level and domination of one site over the others. Data were extracted from patients' medical records by their physicians or site staff using a custom electronic data collection form. Information was collected from the time of diagnosis of stage IIIB/IIIC with macroscopic lymph node involvement until death or until the last entry in the record. A patient survey was administered to patients still living at the time of the study to obtain information unavailable in the medical records.

2.1 | Study variables

Information extracted from medical records included patient demographic and disease characteristics, secondary and supportive care received, type of adjuvant treatments administered, resource utilisation data, and information about disease recurrence and progression. Information on direct and indirect costs was also collected and will be reported in another manuscript. Performance status (PS) was collected using the Eastern Co-operative Oncology Group (ECOG) or Karnofsky scales. The patient survey (provided in the Supplementary Material) collected information on medical care received outside of the main cancer treatment centre and

FIGURE 1 Study flow. *10 patients reported progression dates before the start of adjuvant treatment or during adjuvant treatment, which continued unchanged after progression was reported to have occurred, five had reported surgical resection dates during or after the end of adjuvant treatment, one reported first and second disease progression dates on the same day

employment status. Patients were asked to recall information over the previous 3 months, except for hospitalisations and changes in employment status, which could be reported regardless of when they occurred. Quality life was measured using the EQ-5D questionnaire (three-level version), and using the UK tariff (scoring algorithm) to calculate utility scores from health status data collected in all countries.

2.2 | Analysis and data quality checks

Results were generated by country as descriptive summaries and no statistical comparisons were performed. Where Karnofsky scores were reported, these were converted to ECOG-PS [8] (for 97 patients; 35 in France, 57 in Germany, and 4 in the UK). Survival outcomes were estimated by the Kaplan–Meier method; we report medians and 95% confidence intervals (95%CI) for each outcome, by country. Upper CIs estimates that could not be computed due to infrequent events were termed "non-estimable."

The electronic data capture system included range and logic checks. A study coordinator monitored the progress of the medical record abstraction form completion and data entry rates. Double data entry was used for patient survey responses to minimise errors. No formal external validation of the medical record abstraction or patient survey data was possible, as validation would have required contact with physicians and/or patients and access to patient identifying information.

3 | RESULTS

3.1 | Patient and disease characteristics

Of 917 patients screened for eligibility, 559 met inclusion/exclusion criteria and medical record abstraction was completed for 558 (Figure 1). Mean duration of follow-up in the medical record ranged from 22 months in the UK to 27 months in France (Table 1). There were 308 patients invited to complete the patient survey, of whom 173 (response rate 56%) participated.

Overall, 55.7% (311/558) of patients were male (Table 1). The most common primary tumour site in each country was the lower limb, followed by the upper trunk (Table 2). The percentage of patients with Stage IIIB disease was 46.2% (92/199) in France, 56.7% (93/164) in Germany, and 58.5% (114/195) in the UK.

	France	Germany	UK	Overall
Patients, n	199	164	195	558
Centres, n	14	17	18	49
Mean duration of follow-up, months	27	26	22	-
Age at first diagnosis, n (%)				
18-39 years	26 (13.1)	16 (9.8)	15 (7.7)	57 (10.2)
40-44 years	18 (9.0)	10 (6.1)	14 (7.2)	42 (7.5)
45-49 years	8 (4.0)	15 (9.1)	18 (9.2)	41 (7.3)
50-54 years	15 (7.5)	10 (6.1)	20 (10.3)	45 (8.1)
55-59 years	26 (13.1)	20 (12.2)	23 (11.8)	69 (12.4)
60-64 years	25 (12.6)	26 (15.9)	20 (10.3)	71 (12.7)
≥65 years	81 (40.7)	67 (40.9)	85 (43.6)	233 (41.8)
Gender, n (%)				
Male	111 (55.8)	98 (59.8)	102 (52.3)	311 (55.7)
Female	88 (44.2)	66 (40.2)	93 (47.7)	247 (44.3)

Fine needle aspiration (FNA) cytology was performed in 22.1% (44/199) of patients in France, 5.5% (9/164) in Germany and 42.1% (82/195) in the UK. The proportion of patients who underwent sentinel lymph node biopsy (with/without FNA) was 21.1% (42/199) in France, 45.7% (75/164) in Germany, and 25.6% (50/195) in the UK. Imaging techniques (with or without palpation) were used to document lymph node status in 82.4% (164/199) of patients in France, 85.4% (140/164) in Germany and 67.2% (131/195) in the UK. The proportion of patients with documented extra-capsular lymph node extension was 10.4% (17/164) in Germany, 41.2% (82/199) in France, and 34.9% (68/195) in the UK.

3.2 | Adjuvant therapy

The percentage of patients who received adjuvant therapy was 7.0% (14/199) in France, 2.6% (5/195) in the UK and 33.5% (55/164) in Germany. Interferon was not used in the UK, was little-used in France 2.0% (4/199), but there was some use in Germany 32.9% (54/164). Overall, low-dose interferon was used more frequently (4.5%) than high-dose (3.8%), intermediate-dose (1.6%) or pegylated interferon (0.5%). The mean duration (SD; standard deviation) of adjuvant therapy across all countries was approximately 20 weeks (SD 16 weeks) for pegylated interferon, 36 weeks for high-dose interferon (SD 22 weeks), 57 weeks (SD 28 weeks) for intermediate-dose interferon and 47 weeks (SD 31 weeks) for low-dose interferon. Dose delays and/or dose reductions occurred in 33.3% (7/21) of patients receiving high-dose interferon and 8.0% (2/25) receiving low-dose interferon. Discontinuation of therapy due to toxicity occurred in 28.6% (6/21) of patients receiving high-dose interferon and 8.0% (2/25) receiving low-dose interferon.

3.3 | Survival outcomes

During the study period, 62.9% (351/558) of patients developed disease recurrence. In 59.0% (207/351) of these patients, the recurrence was distant metastatic disease (with or without locoregional recurrence) (Table 3). The remaining 144 patients developed recurrence with locoregional disease, of whom 52.4% (57.1%, 32/56 in France, 43.6%, 17/39 in Germany and 54.2%, 26/48 in the UK) later developed distant metastatic disease during the study period. Overall, 196 patients (35.1%) were deceased, with 90.8% (178/196) of deaths attributed to melanoma.

Median (95% CI) DFS ranged from 11.5 months (8.8-14.8) in France to 16.4 months (10.6-22.4) in Germany (Figure 2). Median distant metastasis-free survival (DMFS) ranged from 22.3 months (18.0-32.9) in the UK to 24.0 months (15.1-not estimable) in Germany. OS at 3 years was 65.2% (57.2-72.1) in France, 58.5% (49.0-66.8) in Germany, and 56.3% (46.9-64.6) in the UK. Median OS was reached only in the UK [42.0 months (29.0-not estimable)].

3.4 | Quality of Life and employment status

The mean (95% CI) health utility weight estimates based on the EQ-5D index for the subset of patients providing a patient survey were 0.79 (0.74-0.84) for patients who were disease-free (n=95, ranging from 0.75 in the UK to 0.84 in France), 0.80 (0.71-0.88) for patients with locoregional recurrence (n=33, ranging from 0.73 in France to 0.85 in Germany) and 0.71 (0.62-0.80) for patients with distant metastasis and/or terminal disease (n=40 ranging from 0.67 in Germany to 0.75 in the UK).

More than half of patients (58.2%, 325/558) were of working age (aged <65 years) at diagnosis. Approximately 8% (14/173) of patients reported being on long-term sick leave, disability leave, or a leave of absence, and 22.5% (38/169, data were missing for four patients) stated that their employment status changed as a result of their melanoma. Employment status was affected in 21/56 patients (37.5%) in Germany, 6/58 (10.3%) in France and 11/55 (20.0%) in the UK.

TABLE 2 Clinical and disease characteristics

Number (%)	France (n=199)	Germany (n=164)	UK (n=195)	Overall (n=558)
Melanoma stage at time of diagnosis				
Stage IIIB	92 (46.2)	93 (56.7)	114 (58.5)	299 (53.6)
Stage IIIC	107 (53.8)	71 (43.3)	81 (41.5)	259 (46.4)
Site of skin melanoma related to stage IIIB/IIIC disease				
Head	19 (9.5)	17 (10.4)	10 (5.1)	46 (8.2)
Neck	10 (5.0)	9 (5.5)	9 (4.6)	28 (5.0)
Upper limb	21 (10.6)	28 (17.1)	26 (13.3)	75 (13.4)
Lower limb	78 (39.2)	48 (29.3)	57 (29.2)	183 (32.8)
Upper trunk	47 (23.6)	38 (23.2)	53 (27.2)	138 (24.7)
Lower trunk	19 (9.5)	24 (14.6)	27 (13.8)	70 (12.5)
Unknown	9 (4.5)	-	4 (2.1)	13 (2.3)
Other	2 (1.0)	3 (1.8)	9 (4.6)	14 (2.5)
Data not available	0	1 (0.6)	2 (1.0)	3 (0.5)
Ulceration of tumour				
Yes	85 (42.7)	68 (41.5)	63 (32.3)	216 (38.7)
No	78 (39.2)	66 (40.2)	81 (41.5)	225 (40.3)
Data not available	36 (18.1)	30 (18.3)	51 (26.2)	117 (21.0)
Primary method used to detect macroscopic LN lymph node status				
Palpation only	14 (7.0)	11 (6.7)	44 (22.6)	69 (12.4)
Imaging only	37 (18.6)	44 (26.8)	35 (17.9)	116 (20.8)
Palpation and imaging	127 (63.8)	96 (58.5)	96 (49.2)	319 (57.2)
Data not available	21 (10.6)	13 (7.9)	20 (10.3)	54 (9.7)
Number of lymph nodes invaded at the time of macroscopic lymph node metastasis				
1	97 (48.7)	84 (51.2)	86 (44.1)	267 (47.8)
2	33 (16.6)	31 (18.9)	38 (19.5)	102 (18.3)
3	12 (6.0)	15 (9.1)	18 (9.2)	45 (8.1)
4 or more	45 (22.6)	31 (18.9)	46 (23.6)	122 (21.9)
Matted nodes	6 (3.0)	1 (0.6)	4 (2.1)	11 (2.0)
Data not available	6 (3.0)	2 (1.2)	3 (1.5)	11 (2.0)
Extra-capsular extension	82 (41.2)	17 (10.2)	68 (34.9)	167 (29.9)
ECOG performance status				
0	112 (56.3)	74 (45.1)	88 (45.1)	274 (49.1)
1	38 (19.1)	14 (8.5)	22 (11.3)	74 (13.3)
2	6 (3.0)	0 (0)	4 (2.1)	10 (1.8)
3	1 (0.5)	0 (0)	2 (1.0)	3 (0.5)
Not reported	42 (21.1)	76 (46.3)	79 (40.5)	197 (35.3)

ECOG, Eastern Co-operative Oncology Group.

3.5 | Resource utilisation

In France and Germany, most patients had specialist visits with dermatologists or dermato-oncologists/surgeons, whereas most patients in the UK had specialist visits with oncologists. Resource utilisation (including hospitalisation) was higher for patients in the distant metastatic and terminal disease phase than for those with locoregional disease progression only (Figure 3).

4 | DISCUSSION

We used a combination of medical record data abstraction and a patient survey to describe the burden-of-illness, current treatment patterns and clinical outcomes in patients with Stage IIIB/IIIC melanoma. Our analysis provides a unique picture of disease management practices and outcomes in routine clinical practice specific to France, Germany and the UK.

TABLE 3 Adjuvant therapy and disease progression

Adjuvant systemic therapy received, n (%)	France (n=199)	Germany (n=164)	UK (n=195)	Overall (n=558)
None	185 (93.0)	109 (66.5)	190 (97.4)	484 (86.7)
Interferon				
High dose	3 (1.5)	18 (11.0)	0 (0)	21 (3.8)
Intermediate dose	1 (0.5)	8 (4.9)	0 (0)	9 (1.6)
Low dose	0 (0)	25 (15.2)	0 (0)	25 (4.5)
Pegylated	0 (0)	3 (1.8)	0 (0)	3 (0.5)
Unknown[a]	1 (0.5)	0 (0)	0 (0)	1 (0.2)
Other[b]	9 (4.5)	1 (0.6)	5 (2.6)	15 (2.7)
Disease progression n (%)				
Deceased	66 (33.2)	59 (36.0)	71 (36.4)	196 (35.1)
Any recurrence	131 (65.8)	100 (61.0)	120 (61.5)	351 (62.9)
Type of first recurrence				
Locoregional	57 (43.5)	39 (39.0)	48 (40.0)	144 (41.0)
Further progression to distant metastases	32 (57.1)[c]	17 (43.6)	26 (54.2)	75 (52.4)
Distant metastasis	74 (56.5)	61 (61.0)	72 (60.0)	207 (59.0)

[a]Unknown therapy given in a blinded clinical trial investigating therapies licensed for stage IIIA/B melanoma.

[b]Includes: carboplatin/paclitaxel; bacillus Calmette-Guerin; radiotherapy; radio-chemotherapy. In France, 'other' also included 5 patients treated with interferon regimens at unspecified doses.

[c]Data missing for one patient. % equals number of patients with further progression of locoregional recurrence divided by all patients with locoregional recurrence.

The baseline characteristics of patients in our study were consistent with populations of patients with Stage III melanoma in the USA and Europe[2,9]; however, with patients more frequently being younger than 65 years of age and male.

There appeared to be regional differences in tumour staging methods, with imaging (with/without palpation) to determine lymph node status; FNA cytology was conducted more frequently in the UK, whereas sentinel node biopsy was more common in Germany. Somewhat fewer patients were diagnosed with extra-capsular node extension in Germany than the other countries, although the use of lymph node imaging methods was similar in France and Germany. There were also suggestions of regional differences in the use of adjuvant therapy, with a greater proportion of patients in Germany receiving adjuvant therapy, than in France, or the UK. Low- or intermediate-dose interferon was used more widely than the high-dose regimen; and dose reduction, delay and discontinuation due to toxicity were common, reflecting the toxicity of interferon therapy. The observation that dosing regimens for interferon varies widely is consistent with the lack of convincing evidence favouring one or another regimen.[3]

The proportions of patients with disease progression (locoregional or distant metastatic) were similar across countries, although in this sample, somewhat fewer patients with locoregional recurrence progressed to distant metastatic disease in Germany. Median DFS ranged from 11.5 to 13.6 months, which is similar to median DFS of approximately 1 year reported in placebo recipients with macroscopic lymph node involvement in clinical trials,[4,9] but somewhat lower than that reported in our study in Germany (16.4 months). Median DMFS of 22.3 to 24.0 months across all three countries was similar to median DMFS of 2 years reported in another study conducted in Europe.[4]

While we selected centres to achieve variation in geographic location, size, and type, the resulting sample may not be representative of all centres and physicians that treat patients with stage IIIB/IIIC melanoma in the study countries. We are unable to rule out variability in the quality and completeness of the existing medical records as a result of differences in recording practices. In addition, we were unable to conduct external validation of abstracted data. Finally, the study was designed to focus on the primary location of care (ie, the specialist's practice), which means that data from other healthcare settings, such as local hospital care or emergency department visits to other centres, were self-reported based on patient recall and collected, in most cases, for a limited period of the past 3 months.

Our study is one of several to provide real-world data describing country-specific treatment patterns and clinical outcome in patients with advanced melanoma.[5,6] The findings highlight that patients with Stage III melanoma are at high risk of disease recurrence, progression and death. Therefore, there is a clear need for more effective treatments for advanced melanoma. In a meta-analysis of clinical trials of patients with Stage II and III melanoma, interferon was associated with a 17% relative risk reduction in DFS and a 9% reduction in OS.[3] In our study, no patients in the UK, and very few in France received adjuvant treatment. The modest survival benefit and potential toxicity of interferon therapy may contribute to its apparently low level of use and may indicate boundaries of acceptance for future adjuvant therapies by the medical community. Our findings can aid decision-makers to
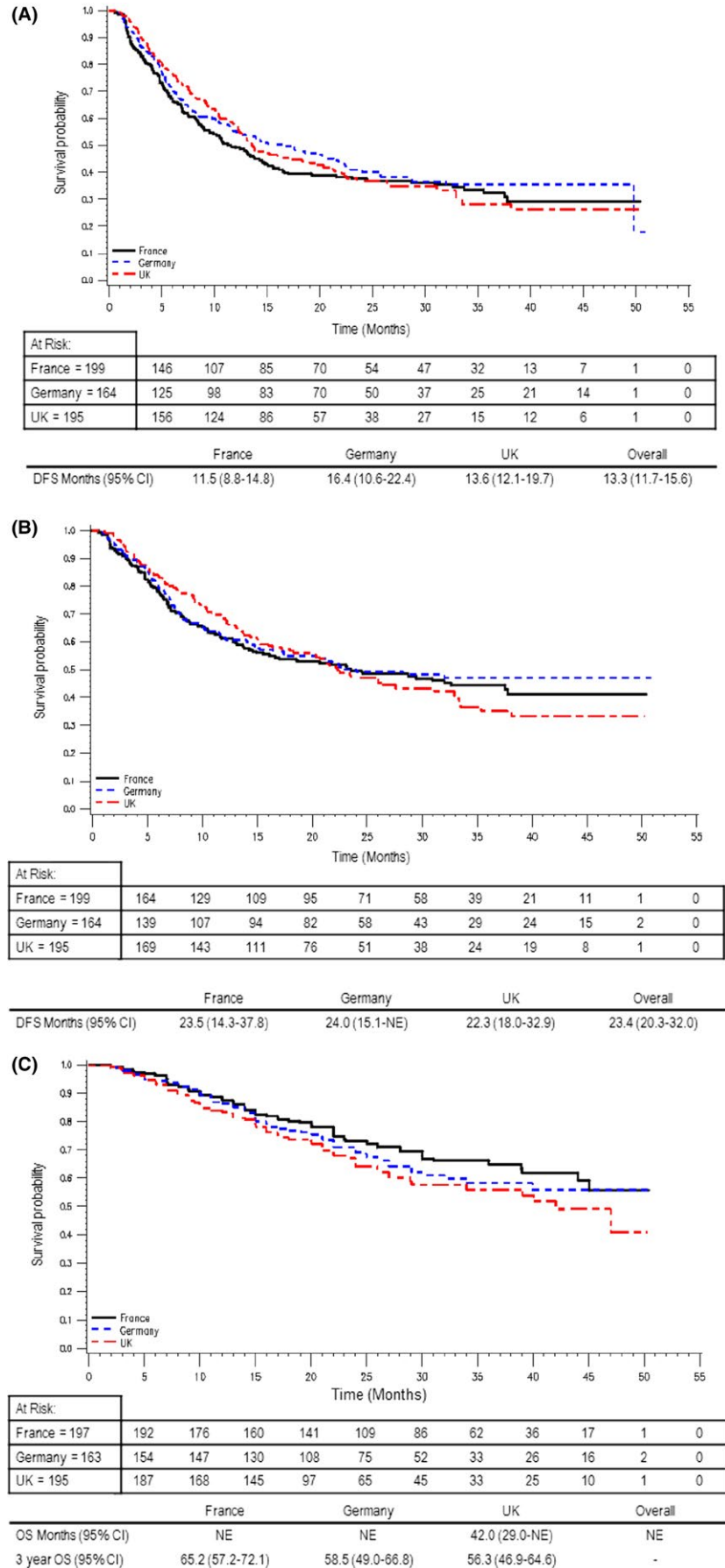
FIGURE 2 Kaplan–Meier survival curves for (A) disease-free survival (DFS), (B) distant metastasis-free survival (DMFS) and (C) overall survival (OS). NE, not estimable, At Risk: refers to the number of patients who have not yet experienced an event at each indicated time point
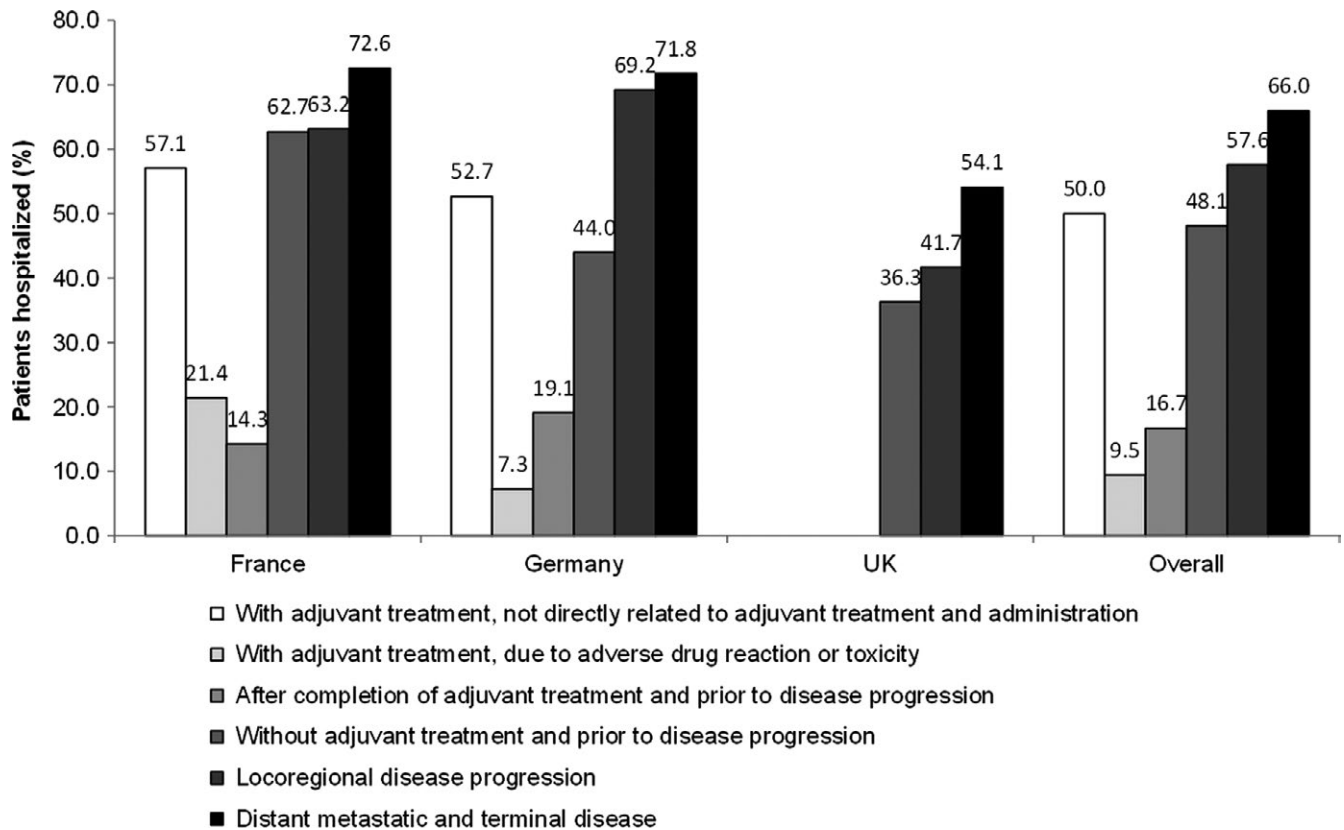
FIGURE 3 Percentage of patients hospitalised by disease phase (from medical record abstraction)

understand current treatment patterns, and can be used for further HTA of the benefits and costs of potential new treatments for malignant melanoma.

DISCLOSURES

OS and LB are employees of the GSK group of companies. OS and LB hold stock options or restricted shares from the GSK group of companies. RE, JB, CS, IK and SP were employees of the GSK group of companies at the time of the study. RE and CS hold stock options or restricted shares from the GSK group of companies. MH received honoraria from the GSK group of companies for advisory boards. PM received consulting fees and honoraria fees from the GSK group of companies, Roche, Merck, SciBase, Bristol-Myers Squibb, Novartis, and Leo. He also received research funding from Merck. FG acted as an investigator in the GSK group of companies' studies and as a scientific advisor for the same company. LDM, JK, and SW report funding from the GSK group of companies to their employer, RTI Health Solutions, during the conduct of the study. Kantar Health received fees from the GSK group of companies for the submission of the study protocol to ethics committees in France.

AUTHOR CONTRIBUTIONS

MH participated to the questionnaire/survey development, to the method selection and development, to the acquisition of data, the statistical data analysis, the assessment of robustness of results (sensitivity analysis), and critically reviewed the study report. PM provided substantial scientific input, participating to the questionnaire/survey development, determination of settings, the acquisition of data, and critically reviewed the study report. FG participated to the questionnaire/survey development, to the method selection and development, to the acquisition of data, and critically reviewed the study report. RE provided substantial scientific input participating to the questionnaire/survey development, and critically reviewed the study report. LB participated to the protocol/questionnaire/survey development, to the method selection and development, to the acquisition of data, and critically reviewed the study report. OS participated to the questionnaire/survey development, to the method selection and development, to the acquisition of data, and critically reviewed the study report. JB participated to the questionnaire/survey development and

critically reviewed the study report. CS participated to the questionnaire/survey development, to the method selection and development, to the acquisition of data, provided statistical support for analysis and reporting of data, and made substantial scientific input/contribution to the study report. SP had made substantial contribution to study concept and design and data acquisition, had revised critically the article and approved the final version. LM participated to the questionnaire/survey development, to the method selection and development, to the acquisition of data, provided statistical support for analysis and reporting of data, made substantial scientific input/contribution to the study report, and critically reviewed the study report. SW provided substantial scientific input participating to the questionnaire/survey development, to the method selection and development, to the development of the economic burden estimates (manuscript in development), and provided health economic support for analysis and reporting of data. JK provided substantial scientific input participating to the questionnaire/survey development, to the method selection and development, to the acquisition of data, and made substantial scientific input/contribution to the study report, and critically reviewed the study report. IK led the protocol/questionnaire/survey development, to the method selection and development and critically review the study report. All authors provided intellectual contributions to this manuscript, critically reviewed the manuscript and have approved the final version.

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SUPPORTING INFORMATION

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