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Preferences of German melanoma patients for interferon (IFN) α-2b toxicities (the DeCOG "GERMELATOX survey") versus melanoma recurrence to quantify patients' relative values for adjuvant therapy

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Abstract

Currently interferon alfa-2b (IFNα-2b) is an approved adjuvant drug for high-risk melanoma patients that leads to an improvement in disease-free survival (DFS). However, it is unclear whether it also impacts overall survival. Widespread use of adjuvant high-dose IFNα has been tempered by its significant toxicity and its limited efficacy. Current therapeutic strategies like immune checkpoint blockade or targeted therapy may also be useful in the adjuvant setting. Therefore, it is important to weigh the trade-offs between possible side effects and therapeutic benefit.

We assessed patient utilities for health states associated with IFN therapy. Utilities are measures of preference for a specific health state on a scale of 0 (death) to 1 (perfect health).

Editor: Tobias Sinnberg.

Funding/support: The study was sponsored by Merck & Co. All patients have given written informed consent, and the trial was approved by the local ethics committee. An abstract containing parts of the submitted data has been accepted as an abstract for the ASCO Annual Meeting in 2015. KCM serves as consultant to Roche, BMS, MSD and received travel grants and speaker fees from Roche, BMS, MSD, GSK, Amgen. AH serves as consultant to Roche, Novartis, Amgen, Celgene, GSK, MedImmune, MelaSciences, Merck Serono, Oncosec, Eisai and received speaker fees, travel grants, and research funding from Roche, Novartis, Amgen, Celgene, GSK, MedImmune, MelaSciences, Merck Serono, Oncosec, and Eisai. CB has received speaker honoraria, research grants, awards, and/or travel grants from Janssen-Cilag, Kreussler, Lilly, and medi. AF serves as consultant to GSK, Novartis, Roche and received travel grants and speaker fees from BMS, Roche, MSD, GSK, Novartis. RG serves as consultant to Roche, BMS, MSD, Amgen, Almirall, Leo, Pfizer, Novartis, GSK and received travel grants and speaker fees from Roche, BMS, MSD, GSK, Novartis, Merck, Almirall, Amgen, Galderma, Janssen, Boehninger and received research funding from Roche, Novartis, Johnson and Johnson, Pfizer. CG serves as consultant to Amgen, BMS, MSD, Novartis, Roche, Leo, Philogen and received travel grants and speaker fees from Amgen, BMS, MSD, Novartis, Roche, Leo, Philogen and received research funding from BMS, Novartis, Roche. TH serves as consultant to BMS and received travel grants and speaker fees from BMS, MSD, Roche and received research funding from BMS. LH serves as consultant to BMS, Roche, Merck, GSK, MSD and received travel grants and speaker fees from Roche, MSD, BMS, Roche, GSK and received research funding from BMS, MSD, GSK, Roche. TK received travel grants from MSD. Dr Livingstone serves as consultant to BMS, Boehringer-Ingelheim, Amgen and received travel grants and speaker fees from Medac, Amgen, Roche. CL serves as consultant to BMS, Roche, MSD, Novartis and received travel grants, speaker fees and speakers' bureau fees from BMS, Roche, MSD, Novartis and received research funding from BMS, Roche, MSD, Novartis, Eisai, GSK, BioNTech. LVM received travel grants and speaker fees from BMS, MSD, IGEA, Amgen, Roche. BML received travel grants and speaker fees from Novartis and BMS. DS serves as consultant to Roche, BMS, GSK, Novartis, Amgen, Delcath, Boehringer Ingelheim, Merck, MSD, Pfizer, AstraZeneca and received travel grants, speaker fees and speakers' bureau fees from Roche, BMS, GSK, Novartis, Amgen, Delcath, Boehringer Ingelheim, Merck, MSD, Pfizer, AstraZeneca and received research funding from Merck, BMS. BS is employed by MSD Sharp and Dohme GmbH and owned stock or held an ownership interest in Merck. PT serves as consultant to Amgen, Roche, BMS, Novartis, GSK and received travel grants and speaker fees from BMS, Roche. JU serves as consultant to GSK, Novartis, MSD, Roche and received travel grants and speakers' bureau fees from Amgen, GSK, MSD, Novartis, and Roche. TW received travel grants from Roche Pharma AG and received research funding from B. Braun Surgical, MSD and owned stock or held an ownership interest in Bayer AG, Merck KG, Fresenius Medical Care. MA has received grants and/or honoraria as a consultant, speaker, and/or advisory board member from Almirall, GSK, and Leo.

The authors report no conflicts of interest.

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Medicine (2016) 95:46(e5375)

Received: 9 June 2016 / Received in final form: 12 October 2016 / Accepted: 12 October 2016

http://dx.doi.org/10.1097/MD.0000000000005375

Utilities were determined for health states associated with adjuvant IFN among 130 German low-risk melanoma patients using the standard gamble technique. Four IFNα-2b toxicity scenarios and the following 3 posttreatment outcomes were assessed: disease-free health and melanoma recurrence (with or without previous use of IFNα-2b) resulting in cancer death. Patients were asked to trade-off the improvement in 5-year DFS and the IFN-related side effects.

Utilities for melanoma recurrence (mean 0.60) were significantly lower than for all IFNα-2b toxicity scenarios (mean 0.81–0.90). Patients were willing to tolerate mild-to-moderate and severe toxicity for a 50% and 75% chance of 5-year DFS, respectively. Both utilities and threshold benefits were mostly independent from patient characteristics like gender, income, and social situation. Significant impact was only observed by age and previous personal experience with cancer.

On average, German patients were willing to trade even severe IFNα-2b toxicity for reducing the rate of melanoma recurrence. This result points out the importance of a relapse-free survival for melanoma patients. The utilities measured in our study can be applied to decision-making processes in clinical trials of new adjuvant drugs.

Abbreviations: DFS = disease-free survival, IFN = interferon, OS = overall survival, QoL = quality of life.

Keywords: adjuvant IFNα, malignant melanoma, patient reported outcome

1. Introduction

Despite trends toward an earlier diagnosis, the prognosis of patients with high-risk primary melanoma (American Joint Committee of Cancer stage IIC) or with macroscopic nodal involvement remains poor. These patients have a relapse rate of 50% to 90% which usually results in death.[1]

Previous trials concerning adjuvant interferon alfa (IFNα) have shown conflicting results, but 1 recent meta-analysis supports the efficacy of IFNα for the adjuvant treatment of melanoma in terms of both disease-free survival (DFS) and to a lesser extent—overall survival (OS). In fact, the risk reduction associated with IFNα was statistically significant for both DFS (17%, 95% CI 13%–22%) and OS (9%, 95% CI 3%–15%).[2]

The enthusiasm for the widespread use of adjuvant IFN treatment has been tempered by concerns for the toxicity of the regimen as well as frequent occurrence of fatigue and depression in conjunction with the limited benefit.[3] In consequence, IFN is not a recognized and preferred treatment modality in all countries. Anyway, our approach serves as a model for general patient views and attitudes towards adjuvant treatment.

The toxicity is characterized by mainly constitutional symptoms, especially fever and a flu-like syndrome, as well as hematologic and neurologic side effects. These side effects markedly impair quality of life (QoL).[4–8]

The value of different health states, including morbidity, QoL, and side effects, can be described with so-called health utilities, or utilities for short. Utilities represent the strength of a person's preferences for different outcomes; they range from 0 (representing death) to 1 (representing perfect health). Utilities of specific outcomes are determined by surveying a sample of either healthy individuals or patients.[9]

The utility of melanoma recurrence was rated much lower than even severe IFNα-2b toxicity by US patients, as shown by Kilbridge et al.[10]

So far, the preferences of German melanoma patients have not been analyzed. In particular, it is unclear if the results of Kilbridge et al can be applied to this patient population.

2. Methods

2.1. Patient and study centers

Ten German skin cancer centers with high expertise in treating melanoma were involved in this observational trial. The recruitment was well balanced between northern and southern centers (Table 1).

Patients with low-risk melanoma, defined as T1a, no sentinel node biopsy or significant comorbidities were eligible. This patient group was chosen because they have gained experience of a melanoma diagnosis but have not been confronted with the conflict of making the choice of IFNα-2b therapy in real life.

2.2. Utility assessment

Patients were surveyed by a standardized paper-based questionnaire. The patients' utilities were measured using the standard gamble method,[11] where participants are asked to make a hypothetical choice between a specific health state as described in a scenario and a certain probability of instant painless death. The higher the probability of death accepted by patients in order to avoid a health state, the lower its utility. In order to familiarize the patients with the standard gamble technique, 2 test scenarios were used in advance of the questionnaire. The following 4 scenarios as used by Kilbridge et al presented a range of possible side effects during IFNα-2b therapy: IFNα-2b treatment without side effects, IFN treatment with mild-to-moderate side effects. IFN treatment with laboratory abnormalities (hepatotoxicity and myelosuppression) requiring dose reduction and causing mild-to-moderate clinical side effects, IFN treatment with severe clinical side effects also requiring dose reduction. As posttreatment outcomes, scenario E described melanoma recurrence after IFNα-2b therapy with mild-to-moderate side effects and subsequent death from melanoma. Finally, scenario F described melanoma recurrence without adjuvant IFNα-2b therapy and melanoma death.

Table 1

Number of participants, divided by study center (full study cohort).

	Patients	
	n	%
Kiel	32	21.3
Lübeck	12	8.0
Hamburg	8	5.3
Buxtehude	1	0.7
Erlangen	13	8.7
Hannover	14	9.3
Essen	18	12.0
Mainz	22	14.7
Mannheim	10	6.7
Tübingen	20	13.3
Total	150	100.0

2.3. Threshold questions

In addition to standard gambles, we directly assessed the patients' preferences for IFNα-2b by threshold questions. Patients were asked to choose between skipping IFNα-2b treatment with a 25% chance of being melanoma-free after 5 years and IFNα-2b with mild-to-moderate side effects. We asked for their personal minimum acceptable chance to stay melanoma-free 5 years after treatment in the case of mild-to moderate or severe side effects.

2.4. Additional assessments

Furthermore, we evaluated specific psychological aspects in our patients. As a standardized measure of health outcome, the EQ-5D-3L[12] questionnaire was used. The EORTC-QLC-30 questionnaire version 3.0[13] was used to measure QoL.

2.5. Statistical approach

Utilities were calculated according to Kilbridge et al[10] by subtraction of the values indicated by the participants for the different scenarios and division by 100.

The association of utilities with sociodemographics and clinical parameters of patients, threshold questions, psychological aspects (EQ 5D-3L, EORTC QLC-30) were assessed using Spearman correlations or Mann–Whitney tests, depending on variable scaling.

3. Results

After informed consent, 174 patients (Table 2) agreed to participate; among them, 150 patients filled in the questionnaire. Plausibility checks testing for misorder of scenarios resulted in the exclusion of n=17 cases (11.6%) from analysis. Three patients needed to be excluded due to missing data. Thus, 130 patients were available for the analysis.

3.1. Patient characteristics

To characterize the study cohort, sociodemographics of the full analysis set of 147 patients are presented (Table 2).

The patient cohort nearly equally consisted of female and male subjects (49% female vs 51.0% male). Patients had a median age of 54.6 years; 95% were German. About 2/3 of patients were working. A total of 6% reported that they were currently affected by another cancer and further 17.0% named other antecedent malignancies. A total of 78% had closely related persons affected by cancer which were relatives in 61.9%, life partners in 8.8%, and friends in 20.4%.

Most frequent concurrent comorbidities reported by patients were arterial hypertension (36.1%), obesity (16.0%), chronic lower back pain, and thyroidal diseases (15.6% each).

3.2. Utilities

The scenarios A to D captured the range of possible outcomes during and after adjuvant IFNα-2b; Scenario E described recurrence after therapy and scenario F recurrence without foregoing IFNα-2b therapy (Table 3).

A considerable number of 55 patients (42.3%, data not shown) would tolerate only a 0% risk of death in the standard gamble and thus have a treatment utility of 1.0 for scenario A (no side effects). This means that they would not accept any risk of dying in order to avoid adjuvant IFNα2b, even without any side effects.

Scenario B (mild-to-moderate side effects) showed a lower average utility of 0.9; 46 patients (35.4%) had a utility of 1.0.

In scenario C, patients showed a diminished mean utility compared to scenarios A and B. However, the median was stable at 0.99 and thus identical with the median found in scenarios A and B. A utility of 1.0 was observed in 35 patients (26.9%).

In scenario D, the patients' utilities dropped by 7.0% as compared to scenario C. The percentage of participants with a utility of 1.0 was 16.2% (n=21).

Scenario E showed the lowest utilities; however, some participants still had a utility of 1.0 (3.1% of patients, n=4). Scenario F was identical but without preceding IFNα-2b treatment, which resulted in similar utilities.

3.3. Threshold questions

Table 3 presents the threshold benefit for the chance of being melanoma-free at 5 years after adjuvant IFNα-2b treatment with mild-to-moderate side effects. Data were marked by high standard deviations and a threshold benefit for patients of 59.6% (±20.6 SD). Subsequently, we gave our subjects the same choice with an IFNα-2b therapy with severe clinical side effects. As expected, much higher chances of being melanoma-free at 5 years after adjuvant IFNα-2b treatment were required. Again, a considerable number of participants indicating percentages lower

Table 2

Sociodemographics facts of our patients.

Sociodemographic facts	Full analysis set n=147	(% or SD)
Gender (women)	71	(49)
Age	54.6	(SD 12.6)
Personal status (married/partnership)	119	(81)
Living situation (living alone)	20	(14)
Nationality (German)	139	(95)
Education level (intermediate secondary education or higher)	118	(80)
Professional training (polytechnic/university degree)	54	(37)
Professional situation (employed)	90	(61)
Self-experience with other malignancies	34	(23)
Experience with cancer: related persons	114	(78)
Any comorbidity	98	(67)
Daily medication	81	(55)

SD = standard deviation.

Table 3

Utilities for 7 health state scenarios measured using the standard gamble method. Participants are asked to make a hypothetical choice between a specific health state as described in a scenario and a certain probability of instant painless death. The higher the probability of death accepted by patients in order to avoid a health state, the lower its utility compared to perfect health (1.0).

Scenario	Mean	SD	Median
Scenario A: no side effects	0.94	0.14	0.99
Scenario B: mild-to-moderate side effects	0.90	0.18	0.99
Scenario C: laboratory side effects	0.88	0.20	0.99
Scenario D: severe side effects	0.81	0.25	0.90
Scenario E: IFN, recurrence, cancer death	0.60	0.32	0.50
Scenario F: recurrence, cancer death	0.60	0.31	0.50
Scenario G: disease-free	1.00	–	1.00

IFN = interferon, SD = standard deviation.

Table 4

Threshold benefit: minimal accepted chance of being melanoma-free at 5 years after adjuvant IFNα-2b treatment with mild-to-moderate or severe side effects.

	Mean	SD	Median	Min	Max	95% CI	Valid (n)
Mild-to moderate side effects	59.6	20.6	50	25.0	100.0	55.5–63.7	100
Severe side effects	69.8	22.5	75	25.0	100.0	65.5–74.2	105

SD = standard deviation.

than 25% were excluded from analysis. For our patients, the median threshold benefit was at 75% (Table 4).

3.4. EQ-5D

Mean EQ-5D-3L was 87.9 ± 12.3 SD, indicating a generally high level of health. Solely pain and discomfort were reported by an appreciable number of patients (n = 26), but answers fully stayed on level 2 (indicating some problems), and no subject marked level 3 (indicating extreme problems).

3.5. EORTC QLQ-C30

On average, patients showed high levels of physical functioning (94.1 ± 10.3), role functioning (90.2 ± 20.2), and social functioning (90.3 ± 20.2). Lower average levels were found for the emotional scale (76.7 ± 23.1) as well as for the cognitive scale (85.9 ± 21.0). Regarding the symptom scales, fatigue (16.1 ± 18.6), and insomnia (20.7 ± 27.7) were most prevalent. The mean global health state was good with a mean of 80.7 points (±17.0).

3.6. Association between utilities and threshold questions

We found a weak trend (Table 5) for negative correlations with threshold questions for the scenarios A to D and the same tendency for the scenarios E and F, but without significant differences between the scenarios. We also performed a correlation analysis with utilities for the preferences for avoiding the severe side effects and found no significant negative correlation coefficients.

3.7. Association between utilities and sociodemographics as well as clinical parameters

No impact of gender, social economic factors (living alone vs living with partner and/or children), income, nationality, or having a related person suffering from cancer on the utilities and threshold benefits was found (data not shown).

Patients with preexisting cancer did not have higher utilities but showed higher threshold benefits for the chance of being melanoma-free at 5 years after adjuvant IFNα-2b treatment with mild-to-moderate side effects (60.7% vs 50.7% on average, $P = 0.011$). The same phenomenon was observed for the scenario with severe side effects (68.5% vs 55.3% for the average threshold benefit, $P = 0.007$) and the minimum risk reduction for treatment with mild-to-moderate side effects (72.9% vs 60.3%, $P = 0.015$). Employed subjects showed significantly higher utilities for scenarios A to D as compared to nonemployed persons ($P = 0.001$–0.003).

Interestingly, older patients had lower utilities ($P = 0.001$–0.011) for the scenarios A to D and higher threshold benefits and a higher minimum risk reduction in the case of mild-to-moderate side effects. We found higher utilities in patients with higher education levels for scenarios C and D ($P = 0.043$ and 0.048).

3.8. Association between utilities and psychological aspects

In the EORTC questionnaire, the pain subscale revealed significant correlations with utilities for IFNα-2b treatment without side effects and mild-to-moderate side effects (Table 6). Negative correlation was observed with the threshold benefit of being 5 years melanoma-free after IFNα-2b treatment with mild-to-moderate side effects.

For the scales on physical functioning, emotional functioning, and social functioning, significant correlations with threshold benefit for IFNα-2b treatment with severe side effects were found (Table 7). Furthermore, the scales "nausea and vomiting" and the "fatigue" negatively correlated with threshold benefits for IFNα-2b treatment with severe side effects (Table 6).

Table 5

Spearman rank correlation between utilities and threshold questions: patients with low utilities for Scenarios D and E (severe side effects and relapse after IFN) needed higher chances being melanoma-free after 5 years.

		Utility A	Utility B	Utility C	Utility D	Utility E	Utility F
Threshold benefit: chance of being melanoma-free at 5 years after adjuvant IFNα-2b treatment with mild-to-moderate side effects	*r*	−0.14	−0.15	−0.12	−0.12	−0.05	−0.03
	P	0.169	0.154	0.242	0.236	0.606	0.805
	n	99	98	99	100	100	99
Minimum risk reduction in melanoma recurrence to accept mild-to-moderate side effects for adjuvant IFNα-2b treatment	*r*	−0.07	−0.02	−0.00	−0.01	0.03	0.07
	P	0.511	0.815	0.974	0.927	0.777	0.486
	n	95	94	95	96	96	95
Threshold benefit: chance of being melanoma-free at 5 years after adjuvant IFNα-2b treatment with severe side effects	*r*	0.04	−0.04	−0.17	**−0.20**	**−0.22**	−0.18
	P	0.666	0.712	0.088	**0.042**	**0.023**	0.067
	n	104	103	104	**105**	**105**	104

IFN = interferon.

Table 6

Spearman correlations between utilities and EORTC QLQ-C30 symptom scales: nausea and vomiting were negatively correlated with the threshold benefit in case of mild-to-moderate and severe side effects.

		Utility						Mild-to-moderate side effects		Severe side effects
		A	B	C	D	E	F	Threshold benefit	Min. risk reduction	Threshold benefit
Fatigue	*r*	0.05	0.09	0.05	0.04	0.07	0.10	−0.00	0.06	**−0.17**
	P	0.293	0.169	0.305	0.339	0.210	0.122	0.487	0.292	**0.043**
	n	127	127	128	129	127	126	99	95	**104**
Nausea and vomiting	*r*	−0.08	−0.06	−0.07	−0.02	0.09	0.08	**−0.20**	−0.04	**−0.17**
	P	0.179	0.247	0.200	0.429	0.166	0.192	**0.022**	0.349	**0.040**
	n	127	127	128	129	127	126	**99**	95	**104**
Pain	*r*	**0.15**	**0.16**	0.12	0.11	0.09	0.08	−0.11	−0.08	**−0.20**
	P	**0.043**	**0.036**	0.090	0.113	0.166	0.186	0.135	0.209	**0.022**
	n	**127**	**127**	128	129	127	126	99	95	**104**
Dyspnea	*r*	0.05	0.07	0.04	0.00	0.03	0.01	−0.00	0.14	0.04
	P	0.294	0.228	0.322	0.488	0.388	0.445	0.482	0.091	0.358
	n	127	127	128	129	127	126	99	95	104
Insomnia	*r*	−0.01	−0.01	−0.05	0.00	0.02	−0.01	−0.05	−0.10	−0.14
	P	0.442	0.448	0.307	0.488	0.418	0.453	0.307	0.179	0.082
	n	127	127	128	129	127	126	99	95	104
Appetite loss	*r*	0.01	0.06	0.08	0.10	−0.03	−0.03	−0.10	0.07	−0.09
	P	0.439	0.266	0.176	0.139	0.361	0.382	0.175	0.239	0.191
	n	127	127	128	129	127	126	99	95	104
Constipation	*r*	−0.07	−0.04	−0.02	0.04	0.02	0.06	0.00	−0.06	−0.10
	P	0.230	0.335	0.420	0.309	0.419	0.244	0.499	0.275	0.154
	n	126	126	127	128	126	125	98	94	103
Diarrhea	*r*	0.07	0.10	0.07	0.08	−0.05	0.10	−0.12	−0.04	0.06
	P	0.217	0.137	0.223	0.174	0.271	0.127	0.112	0.352	0.261
	n	127	127	128	129	127	126	99	95	104
Financial difficulties	*r*	0.07	0.13	0.08	0.09	0.01	−0.01	−0.13	0.03	−0.01
	P	0.206	0.077	0.188	0.164	0.463	0.459	0.102	0.378	0.456
	n	127	127	128	129	127	126	99	95	104

3.9. Perception of the survey procedure

A total of 101 patients (77.7%) stated that they were not negatively affected by participating in the survey. By contrast, 22.3% of patients (n = 29) stated that they agreed or strongly agreed with the statement that they were upset by answering the questions.

4. Discussion

This study intended to elicit preferences of German melanoma patients for IFNα-2b toxicity versus recurrence in order to quantify patients' relative values for adjuvant therapy of malignant melanoma. In our patient cohort, we found remarkably high

Table 7

Spearman correlation between utilities and EORTC QLQ-C30 functioning scales and QoL score: emotional and social functioning were positively correlated with the threshold benefit in the case of severe side effects.

		Utility						Mild-to-moderate side effects		Severe side effects
		A	B	C	D	E	F	Threshold benefit	Min. risk reduction	Threshold benefit
Physical functioning	*r*	−0.07	−0.08	−0.04	−0.01	−0.09	−0.03	0.07	0.07	**0.22**
	P	0.228	0.199	0.315	0.463	0.160	0.381	0.246	0.267	**0.013**
	n	127	127	128	129	127	126	99	95	**104**
Role functioning	*r*	0.01	−0.02	0.00	−0.09	−0.11	−0.11	−0.05	0.01	0.09
	P	0.434	0.420	0.483	0.143	0.118	0.116	0.315	0.475	0.185
	n	127	127	128	129	127	126	99	95	104
Emotional functioning	*r*	−0.06	−0.02	0.00	−0.02	−0.09	−0.06	0.15	0.06	**0.22**
	P	0.265	0.394	0.493	0.421	0.158	0.264	0.077	0.291	**0.012**
	n	127	127	128	129	127	126	99	95	**104**
Cognitive functioning	*r*	−0.07	−0.06	−0.03	−0.02	−0.08	−0.07	−0.05	−0.04	0.11
	P	0.232	0.243	0.378	0.391	0.179	0.202	0.319	0.343	0.127
	n	127	127	128	129	127	126	99	95	104
Social functioning	*r*	0.14	0.08	0.06	0.01	−0.07	−0.06	0.06	0.04	**0.28**
	P	0.056	0.182	0.242	0.465	0.229	0.251	0.269	0.347	**0.002**
	n	127	127	128	129	127	126	99	95	**104**
QoL score	*r*	**0.189**	0.13	0.10	0.09	−0.02	0.02	0.06	0.05	0.06
	P	**0.017**	0.067	0.127	0.142	0.419	0.433	0.267	0.322	0.285
	n	**128**	128	129	130	128	127	100	96	105

QoL = quality of life.

utilities for IFNα-2b treatment without side effects and mild-to-moderate side effects and abnormal blood test results. Even in the case of severe side effects, patients still showed noteworthy high utilities. The patients' utilities for melanoma recurrence were considerably lower. Here, a hypothetical preceded adjuvant IFNα-2b therapy did not influence the mean utility. High utilities even in the case of severe side effects and much lower utilities in the case of recurrence suggest that most of our patients were willing to accept severe side effects to avoid melanoma recurrence. This observation is congruent with the findings of Kilbridge[9] in US patients. In our study, only 7 patients (5.4%) had lower utilities for treatment with severe side effects than for melanoma recurrence, compared to 13.7% in the Kilbridge study ($\chi^2=4.7$, $P=0.031$).

The large standard deviations of the utilities of all scenarios hallmark distinctive interindividual differences in the values of and feelings about different health conditions, a finding which was also published by Jewell et al.[14] Remarkably, both utilities and threshold benefits were mostly independent of patient characteristics like gender, income, and social situation. Significant impact was only observed by age and previous personal experience with cancer. The latter might be explained by the experience with side effects during previous cancer therapies.

The association with age and employment status may indicate that younger patients at working age prefer to accept more pronounced side effects for the state of workability and life expectancy.

In comparison to the Kilbridge study,[10] similar utilities for the scenarios E and F and the increase of standard deviations from scenario A to scenario E and F were found. Kilbridge et al interpreted this finding as an unwillingness of subjects to risk death in a standard gamble for relatively benign health states. In contrast, we received differing results for the mean chance of being melanoma-free at 5 years after adjuvant IFNα-2b treatment with mild-to-moderate side effects or severe side effects and the minimum reduction in melanoma recurrence to accept mild-to-moderate side effects of adjuvant IFNα-2b. Here, German patients had considerably higher threshold benefits and required a higher risk reduction. A markedly lower percentage of German patients indicated that their answers show how they feel about different health conditions, that the questions made them think hard about personal values, and that the study could help doctors better understand how patients feel about their health. One could speculate that differences might be due to a social-desirability-response-bias that is more pronounced in an interview situation like in the Kilbridge study compared to a paper survey in our study.

The study shows some limitations. We did an investigation on a patient population experienced with low-risk melanoma. The patient selection was performed for ethical reasons and in accordance with Kilbridge who also emphasized the advantages and disadvantages of this selection. Thus, the patients' opinions are used as surrogates for patients in later disease stages. Furthermore, utilities of melanoma patients may change in the course of therapy, so our results do not evaluate this change over time.

In conclusion, we determined distinct patterns of utilities in German patients with low risk melanoma, which indicate the need for thorough patient information.

German patients rated the utility for melanoma recurrence much lower than the utility of IFNα-2b treatment even if associated with severe side effects. The results show an impressive concordance with the study performed by Kilbridge and demonstrate that it is helpful for our clinical routine to have more detailed information on the individual preferences of our patients available to improve shared decision making.

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