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BRAF inhibitor treatment is feasible in the oldest-old advanced melanoma patients

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Although new compounds have improved the treatment landscape of metastatic melanoma, very limited data exist on the efficacy and safety of treating older patients with novel agents. Here, we provide results of BRAF (BRAFi) ± MEK (MEKi) inhibitor treatment in patients over 75 years (oldest-old patients) with metastatic melanoma. Between 2011 and 2020, 34 consecutive patients with metastatic melanoma over 75 years of age (range 75–89) were treated with BRAFi ± MEKi at the Comprehensive Cancer Center of Helsinki University Hospital. Data on clinical and histopathological features, toxicity, response rate (RR), progression-free survival (PFS) and overall survival (OS) were collected. Patients were treated with BRAFi (*n*=22) or BRAFi in combination with MEK inhibitor (MEKi) (*n*=12). Grade 1–2 adverse events occurred in 68% of the patients, 32% had grade 3 adverse effects, dose reductions were made for 41% of patients and 29% terminated treatment due to toxicity. Overall, the RR was 62%. Complete responses were achieved in 27% of the patients, and 35% had partial responses. The median PFS was 8 months (range 0–57), and the median OS was 15 months (range 0–71). Tailored BRAFi ± MEKi treatment for older patients is feasible. Adverse effects occur frequently but are manageable by dose adjustment. The occurrence of toxicity of monotherapy was similar to that of combination therapy. The RR and median OS from our retrospective study are comparable with those reported in clinical trials and combination therapy produced somewhat more and longer-lasting responses. Hence, it seems that older patients may benefit from BRAFi treatment. *Melanoma Res* 31: 218–223

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Introduction

Modern treatment has significantly improved the prognosis of patients with metastatic melanoma. In developed countries, melanoma incidence continues to increase as the population ages. For reasons that are not entirely clear, old age is an independent poor prognostic factor in melanoma [1,2].

A mutated BRAF gene is an oncogenic driver that occurs in approximately half of the primary melanomas [3]. In patients older than 70 years, BRAF mutations occur in only approximately 30% of melanomas [3]. Nevertheless, BRAF mutation-positive advanced melanoma comprises a significant patient group among older patients with melanoma.

The three BRAF inhibitors (BRAFi) and the three MEK inhibitors (MEKi) that European Medicines Agency and U.S. Food and Drug Administration have approved for the treatment of BRAF-mutated metastatic melanoma are vemurafenib, dabrafenib and encorafenib combined with cobimetinib, trametinib and binimetinib, respectively [4–7]. Treatment with a single BRAFi leads to responses in 48–53% of patients with BRAF-mutant metastatic melanoma [5,8]. Treatment of BRAF-mutant melanoma with a single MEKi is ineffective compared to treatment with a single BRAFi. However, a dual blockade with both BRAFi and MEKi leads to slower development of drug resistance as well as higher response rates (RR) and thus to longer progression-free survival (PFS) compared to BRAFi monotherapy; therefore, the use of combination therapy is preferred [6,7,9]. The toxicity profile of single BRAFi therapy and combination therapy with MEKi differ. Single BRAFi therapy adverse effects depend on which BRAFi is used. Vemurafenib is associated with skin toxicity whereas dabrafenib causes pyrexia. The incidence of fever, diarrhea, fatigue and cardiotoxicity increase as a result of the addition of MEKi to BRAFi therapy [10].

Due to co-morbidities, multiple medications, changes in metabolism and frailty, older patients are more prone to medication-related toxicities than younger ones [11–13]. In clinical trials, patients with poor performance status or comorbidities are excluded and older patients with cancer are thus underrepresented [14,15]. Also, in the clinical trials leading to approval of BRAFi and MEKi, the oldest-old patients had limited inclusion. In trials reporting the efficacy of BRAFi or combination treatment, the median age of patients was 53–57 years [7]. A subgroup analysis consisting of 50 patients over 75 years old is only

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available from the BRIM-3 trial [5]. As a consequence, there is limited data on the outcome of targeted therapy in older patients with metastatic melanoma. This creates a challenge for treating physicians when considering whether the expected benefits of targeted treatment are superior to safety in a patient group with decreased life expectancy and decreased tolerance to adverse effects. The need for more data in this group of patients is imminent.

Older patients with cancer are both overtreated and undertreated, which leads to inappropriate use of resources, worse survival, functional decline and quality of life for these patients [16,17].

The limited number of older patients in trials with metastatic melanoma leads to a dilemma resulting in treatment decisions lacking an evidence base. Are the results from younger patients applicable to older patients with metastatic melanoma? Here, we report real-life data on tolerability and efficacy of BRAFi treatment in 34 older patients with advanced melanoma. We focused on patients over 75 years of age.

Methods

Patients

We retrospectively analyzed data on all consecutive over 75-year-old patients with BRAF mutation-positive metastatic melanoma treated with targeted therapy between 2011 and 2020 at the Comprehensive Cancer Center (CCC) of Helsinki University Hospital. Approval from an institutional board was given for this study. Due to the retrospective nature of the study, no informed consent was required. Patients are characterized in Table 1. The criteria for starting BRAFi therapy were Eastern Cooperative Oncology Group (ECOG) performance status 0–2 and unresectable V600E or V600K BRAF mutation-positive stage III–IV melanoma. Patients were treated with either dabrafenib or vemurafenib as single agents or in combination with trametinib or cobimetinib, respectively. From 2019 onwards, the combination of encorafenib and binimetinib was also available. Computed tomography was used for the radiographic evaluation of response. Adverse effects were classified based on data from the electronic patient records according to CTCAE-criteria v4.0 [18]. We defined older patients as over 75 years old and the oldest-old patients as over 80 years old.

At Helsinki University Hospital's CCC, the oncogeriatric outpatient clinic team evaluates and treats patients over 80 years of age. This team comprises of an oncologist, a nurse with oncogeriatric training, and a geriatrician. Before their first visit, patients fill out a geriatric assessment questionnaire modified for Finnish circumstances from the Moffitt SAOP2 Screening Questionnaire [19]. During their treatment at the Helsinki University Hospital's CCC, the oncogeriatric nurse monitors these patients by phone and during visits according to individual needs. This allows the oncogeriatric team to detect adverse effects early and individually tailor treatment.

Table 1 Patient characteristics

	All patients		BRAF monotherapy		BRAF+MEK combination therapy	
Variable	Years	(range)	Years	(range)	Years	(range)
Age, median	79.5	(75–89)	81	(75–89)	76.5	(75–85)
	N	(%)	*N*	%	*N*	%
Gender						
Male	19	(56)	13	(59)	6	(50)
Female	15	(44)	9	(41)	6	(50)
ECOG						
0	8	(24)	5	(23)	3	(25)
1	22	(65)	15	(68)	7	(58)
2	4	(12)	2	(9)	2	(17)
Metastatic stage						
M1a	8	(24)	5	(23)	3	(25)
M1b	6	(18)	5	(23)	1	(8)
M1c	16	(47)	11	(50)	5	(42)
M1d	4	(12)	1	(5)	3	(25)
BRAF mutation						
V600E	27	(79)	17	(77)	10	(83)
V600K	6	(18)	4	(18)	2	(17)
Unknown	1	(3)	1	(5)	0	(0)
LDH						
≤ULN	22	(65)	15	(68)	7	(58)
≥ULN	12	(35)	7	(32)	5	(42)
Line of treatment						
1st	31	(91)	20	(91)	11	(92)
2nd	3	(9)	2	(9)	1	(8)
Charlson comorbidity index						
9–10	29	(85)	19	(87)	10	(83)
11–12	5	(15)	3	(14)	2	(17)
Previous treatments						
Chemotherapy	2	(6)	2	(9)	0	(0)
Immunotherapy	1	(3)	0	(0)	1	(8)
Following treatments						
Chemotherapy	4	(12)	3	(14)	1	(8)

ECOG, Eastern co-operative oncology group; LDH, lactate dehydrogenase

Statistical analyses

We collected data on patients' sex, age at treatment initiation, primary melanoma status (Breslow thickness, Clark, ulceration, mitoses, nodal status and stage), BRAF mutation status and assessment method (immunohistochemistry, PCR or NGS), stage of metastatic disease, performance status (ECOG), BRAFi used (dabrafenib, vemurafenib or encorafenib), the dosage of BRAFi, dose modifications/reductions, combination with MEKi (trametinib, cobimetinib or binimetinib), adverse effects and their grade using CTCAE-criteria v4.0 [18], comorbidities, number of medications, best overall response [20], duration of response, PFS and overall survival (OS). Comorbidities were graded using the Charlson comorbidity index [21]. Follow-up was defined as the time from initiation of BRAFi to the last follow-up or death. Time on treatment was defined as the time between the date of treatment initiation and the date of the last drug administration. PFS and OS were estimated using Kaplan–Meier. PFS after BRAFi therapy was calculated from treatment initiation to the date of progressive disease (PD), death, or last follow-up, whichever occurred

first. OS was calculated from treatment initiation to date of death or the latest follow-up. Statistical analyses utilized SPSS Statistics version 22. The date of data cutoff was 30 April 2020.

Results

Altogether, data on 34 consecutively treated patients (19 males, 15 females) were analyzed. The median follow-up time was 15 months (range 0–71). The median treatment duration was 7 months (range 0–54) for all patients; with BRAFi monotherapy, it was 6.5 months (range 0–54) and with combination treatment, it was 9 months (range 2–31). Fifteen patients received single dabrafenib and seven single vemurafenib. Ten patients were treated with the combination of dabrafenib and trametinib, one patient was treated with vemurafenib and cobimetinib, and one with the combination of encorafenib and binimetinib. Soon after treatment initiation, three patients switched from vemurafenib to dabrafenib and one patient from dabrafenib and trametinib to encorafenib and binimetinib due to toxicity.

Adverse events

Adverse effects are summarized in Table 2. All patients had at least one adverse effects. Fourteen patients treated with BRAFi monotherapy had grade 1–2 adverse effects and eight patients grade 3 adverse effects. Eight patients treated with BRAF1 and MEKi combination therapy had grade 1–2 adverse effects and four patients grade 3 adverse effects. No grade 4 adverse effects and no treatment-related deaths occurred. Ten (eight patients on BRAFi monotherapy and two patients on combination therapy) patients developed side effects that led to treatment termination. One of these patients experienced a rapid worsening of pulmonary fibrosis and could not be exposed to another BRAFi. Three patients who did not tolerate vemurafenib did well on dabrafenib. One patient, who changed from dabrafenib and trametinib to encorafenib and binimetinib, could continue therapy after the change of medicinal product. One patient was lost due to cerebral hemorrhage, which was thought to be unrelated to the BRAFi therapy based on the patient's previous history of cardiovascular disease and a cerebrovascular incident. Fifteen patients (44%) needed hospitalization (eight patients on BRAFi monotherapy and seven patients on combination therapy). The most common reasons for hospitalization were cardiac disorders ($n=3$), fever ($n=3$) and infections ($n=3$). Twelve of these patients (80%) returned home after the treatment of theadverse effect, and three patients (20%) needed further treatment in a primary healthcare unit after discharge from the hospital. Twelve patients (80%) could continue BRAFi ($n=6$) or BRAFi and MEKi combination therapy ($n=6$) after hospital discharge.

Despite adverse effects, the majority of patients could continue treatment with a tailored dosage or with the help of supportive medication. adverse effects were mainly reversible and reacted on dose adjustments.

Table 2 Toxicity according to CTCAE v4.0

	BRAFi monotherapy ($n=22$)				BRAFi+MEKi combination therapy ($n=12$)			
	Grade 1–2		Grade 3–4		Grade 1–2		Grade 3–4	
Adverse event	*N*	%	*N*	%	*N*	%	*N*	%
Fatigue	8	(36)	0	(0)	4	(33)	0	(0)
Verrucas	6	(27)	0	(0)	3	(25)	0	(0)
Rash	3	(14)	2	(9)	3	(25)	0	(0)
Cardiac arrhythmias	2	(9)	1	(5)	0	(0)	2	(17)
Pyrexia	1	(5)	0	(0)	2	(17)	1	(8)
Spinocellular carcinoma	0	(0)	3	(14)	0	(0)	0	(0)
Nausea	1	(5)	0	(0)	2	(17)	0	(0)
Hyperkeratosis	3	(14)	0	(0)	0	(0)	0	(0)
Diarrhea	2	(9)	0	(0)	0	(0)	0	(0)
Pruritus	2	(9)	0	(0)	0	(0)	0	(0)
Alopecia	2	(9)	0	(0)	0	(0)	0	(0)
Dry skin	2	(9)	0	(0)	1	(8)	0	(0)
Photosensitivity	1	(5)	0	(0)	0	(0)	0	(0)
Elevation of liver enzymes	0	(0)	0	(0)	1	(8)	0	(0)
Constipation	0	(0)	0	(0)	1	(8)	0	(0)
Erythema nodusum	0	(0)	0	(0)	1	(8)	0	(0)
Worsening of lung fibrosis	0	(0)	1	(5)	0	(0)	0	(0)
Allergic reaction	0	(0)	1	(5)	0	(0)	0	(0)
Basal cell carcinoma	0	(0)	1	(5)	0	(0)	0	(0)
Heart failure	0	(0)	1	(5)	0	(0)	0	(0)
Pulmonary embolism	0	(0)	0	(0)	0	(0)	1	(8)

Dose modifications

Table 3 summarizes dose modifications. In general, dose-limiting toxicity was common. Based on the clinician's judgment, 85% of patients started BRAFi therapy with a reduced dose; the most common initial dose was reduced 25–30%. This dose reduction scheme was based on recommended first dose reduction level in the prescribing information of the medicinal products. For the majority of patients, the BRAFi dosage had to be tailored during treatment. For 65% of patients, the dose was either reduced or escalated from the initial dosage, or the therapeutic compound was changed.

Comorbidities

Table 4 summarizes comorbidities. Charlson comorbidity index estimates comorbid conditions and survival [21].

Table 3 Targeted therapy dose modifications

	BRAFi monotherapy ($n=22$)		BRAFi+MEKi combination therapy ($n=12$)	
Category	*N*	%	*N*	%
Reduced initial dose	20	(91)	9	(75)
Dose modified after initiation	12	(55)	10	(83)
Reduced	4	(18)	1	(8)
Escalated	6	(27)	7	(58)
Switch to another compound	2	(9)	2	(17)
Treatment termination due to an adverse events	8	(36)	2	(17)

This index evaluates patients specifically in the operative setting and in the hospital and gives high scores for patients with metastatic solid tumors. The most common comorbid conditions were hypertension, hypercholesterolemia, hypothyroidism and diabetes.

Outcome

The overall RR to therapy was 62% (64% with BRAFi monotherapy and 58% with combination therapy). Seven patients treated with BRAFi monotherapy had a complete response (CR), seven had partial responses (PR), four had stable disease (SD) and one had PD. Two patients that were treated with a BRAFi and MEKi combination had CR, five had PR, three had SD and one had PD, respectively (Fig. 1). We were not able to evaluate the response of three patients because of the quick onset of adverse effects, rapid worsening of the performance status and short treatment duration. For a subset of responding patients, the palliative effect of BRAFi therapy was significant. After BRAFi therapy, four patients (12%) received second-line chemotherapy. The median PFS was 7 months (range 0–57; 95% CI, 2.8–11.2) in the BRAFi monotherapy group and 10 months (range 2–29; 95% CI, 7.1–12.9) in the combination therapy group (Fig. 2). The median OS was 15 months (range 0–71; 95% CI, 11.8–22.2) in the BRAFi monotherapy group and 14 months (range 2–33; 95% CI, 3.2–28.8) in the combination therapy group (Fig. 2). As of April 2020, five (15%) patients were still on treatment.

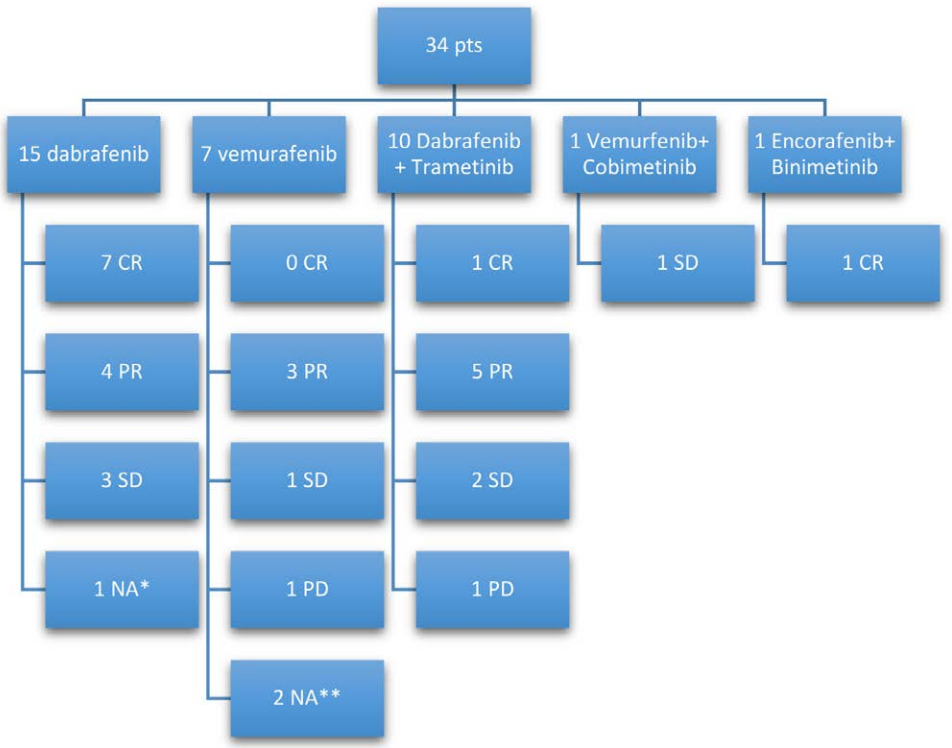
Table 4 Incidence of comorbidities

Disease	*N* (%)
Hypertension	18 (53)
Hypercholesterolemia	10 (29)
Hypothyroidism	4 (12)
Diabetes	4 (12)
Osteoporosis	3 (9)
Chronic obstructive pulmonary disease	2 (6)
Glaucoma	2 (6)
Rheumatoid arthritis	2 (6)
Coronary artery disease	1 (3)
Atrial fibrillation	1 (3)
Gout	1 (3)
Asthma	1 (3)

Discussion

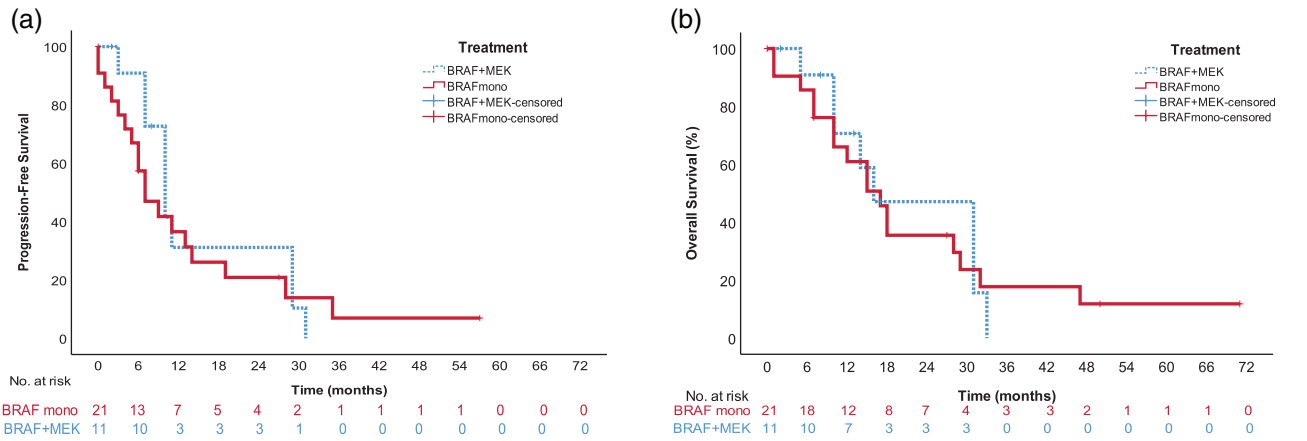
To the best of our knowledge, this is the first report of real-life data focusing on targeted therapy of older patients with metastatic melanoma. Our results show that

Fig. 1



Responses of patients. *Short treatment duration, data on response not available. **Two patients whose response could not be evaluated because of a death or an adverse event soon after treatment initiation; one death as a result of intracranial hemorrhage and one acute worsening of pulmonary fibrosis. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Fig. 2



Kaplan–Meier survival curves for progression-free survival (a) and overall survival (b) for 34 patients.

even in the oldest-old patient group, targeted therapy with BRAFi as a single agent or combined with MEKi is feasible. Our patients were selected seniors who received personally tailored targeted therapy.

To ensure the quality in the treatment of older patients with cancer, the collaboration of oncologists and geriatricians is essential. Geriatric assessment, which is recommended by the International Society of Geriatric Oncology, gives insight into the patient's demographic data, social status, comorbidities, functional status, cognition, depression, nutrition, fatigue, polypharmacy and geriatric syndromes [22]. This valuable information addresses the potential harms and benefits of cancer treatments as age itself unsatisfactorily describes a patient's vulnerability. Geriatric assessment is part of a systemized, multimodal approach in the treatment planning of an older patient with cancer.

In our study, the oldest-old patients over 80 years completed a geriatric assessment form and were treated under the supervision of an oncogeriatric outpatient clinic that has the resources to conduct monitoring of these fragile patients and implement their therapy safely. In spite of a patient population with comorbid conditions, tailored dosage, and limited use of second-line therapy after targeted therapy failure, our PFS and OS values are similar to those from published previously trials [7,23]. Despite the relatively high frequency of adverse effects, functional status was mainly preserved during treatment due to dose adjustments and tailored therapy. Although 44% were hospitalized, the hospitalization was short and the majority could continue treatment afterward.

There were multiple reasons for selecting targeted therapy instead of immunotherapy as first-line therapy. When BRAFi therapy was introduced, the availability of immunotherapy options in Finland was limited. Some of our patients started their anticancer treatment before anti-PD-1 therapies became available for public use in Finland. Our patients were mostly not fit enough to enter clinical trials or did not want to receive therapy in a trial due to excess appointments and laboratory assessments. Targeted therapies deliver rapid ease of disease symptoms, and the adverse effects are manageable by adjusting the dosage, therapy discontinuation and interruption, and using supportive medications. In contrast, immune-related adverse effects are unpredictable and may be irreversible or appear late, despite treatment discontinuation. Due to frailty and comorbidities, the high-dose corticosteroid therapy needed to alleviate immune-related adverse effects would probably not have been feasible for these older patients. After targeted therapy discontinuation, only four patients received second-line therapy, and none of them received immunotherapy because of frailty.

In addition to prolonged survival, the benefits of cancer treatment include maintenance of the quality of life and functional status as well as palliation of cancer symptoms. Many older patients prefer oral medications such as BRAFis and MEKis, which are easy to take at home compared to intravenous treatment that requires regular visits to the treating unit. However, the adherence to oral therapy must be assessed carefully prior to treatment initiation [24]. Most older patients also favor rapid ease of symptoms despite the risk of not achieving a long response. Thus, the treating physicians must be able to evaluate what outcomes are of the greatest importance to the patient.

In conclusion, personally tailored treatment with targeted agents in older patients with melanoma leads to outcomes comparable with those reported in clinical trials with younger patients. The limitations of this study are the retrospective approach, the small number of patients, lack of quality of life data and the lack of an age-adjusted control

group. Although our number of patients is small, so is the number of older patients in trials leading to drug approvals. However, patients in our study were treated according to routine clinical practice, and as a consequence, the results may be relevant to similar patient populations.

We emphasize the importance of geriatric assessment when selecting patients as well as dose adjustments in the management of adverse effects When treating patients with older age, the goal should be the avoidance of functional decline, maintenance of independence as well as the quality of life.

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S.M., M.H. and L.M.K. involved in study design, data analysis and interpretation, manuscript editing, and manuscript preparation. S.M., M.H., L.M.K. and M.J. involved in data acquisition, quality control of data and algorithms, and manuscript review. L.M.K. involved in statistical analysis.

Conflicts of interest

L.M.K.: consulting or advisory role – Roche and Amgen; Speakers' Bureau – BMS and Roche; travel, accommodations, expenses – Merck; research funding – Finnish Melanoma Group Grant, Kurt och Doris Palanders Stiftelse Grant and HUH Comprehensive Cancer Center Grant. M.H.: consulting or advisory role – Merck, Bristol-Myers Squibb, Incyte, Novartis and Roche; Speakers' Bureau – Merck, Novartis and Bristol-Myers Squibb. S.M.: consulting or advisory role – Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Merck Group, Novartis, Roche and Sanofi; honoraria: Speakers' Bureau Bristol – Myers Squibb, Merck Sharp & Dohme and Sanofi; travel, accommodations, expenses – Amgen, Celgene, Merck Sharp & Dohme, Novartis and Roche; research funding – HUH Comprehensive Cancer Center Grant. For the remaining authors, there are no conflicts of interest.

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