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Original Research

The real-world impact of modern treatments on the survival of patients with metastatic melanoma

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Abstract Between 2010 and 2015, pivotal trials with strict enrolment criteria led to the approval of several new treatments for metastatic melanoma (MM). We sought to determine the impact of these treatments in the 'real world'. We took advantage of the Danish MM database (DAMMED), which contains data on the entire, unselected population diagnosed with MM within Denmark. All MM cases (excluding ocular MM, n = 837) diagnosed in three non-consecutive years marked by major changes in the first-line treatments (2012: interleukin-2 and BRAF inhibitors; 2014: anti–CTLA-4: Cytotoxic T-Lymphocyte Antigen 4 and 2016: anti–PD-1: programmed cell death protein 1 and MEK inhibitors) were retrieved. Patients were grouped into 'trial-like' and 'trial-excluded' based on the common trial eligibility criteria. In the 'trial-like' population (39% of all MM), the median overall survival (OS) was not reached in 2016 versus 18.8 months in 2014 (hazard ratio [HR] 0.52, 95% confidence interval [CI] 0.35–0.75; p = 0.0005) and 16.5 months in 2012 (HR 0.41, 95% CI 0.27–0.63; p < 0.0001). In the 'trial-excluded' population (61% of all MM), 75% had brain metastases and/or (performance status) PS ≥ 2. Here, the median OS improved to 6.9 months in 2016 versus 5.2 months in 2014 (HR 0.66, 95% CI 0.52–0.84; p = 0.0008) and 4.2 months in 2012 (HR 0.66, 95% CI 0.52–0.84; p = 0.0007). Subgroup analysis of the BRAF wild-type population showed an improved 1-year survival rate in 2016 versus 2014 (35.9% vs 18.8%,

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p = 0.0153). In conclusion, the introduction of modern treatments has led to an improved survival of real-world patients with MM, regardless of their eligibility to clinical trials and the BRAF status. These data support the application of modern treatments to patient populations which are not represented in pivotal trials.

1. Introduction

Over the past 7 years, the approval of multiple new drugs has led to a paradigm shift in the management of metastatic melanoma (MM). Based on the results of pivotal phase III clinical trials demonstrating the superiority of anti-PD-1–containing regimens [1–3] or BRAF inhibitors (BRAFi)–containing plus MEK inhibitors (MEKi)–containing regimens [4] over the previous standard of care, these treatments have become available in most developed countries. Today, it is standard practice to consider the administration of treatment regimens containing anti-PD-1 antibodies or BRAFi plus MEKi to every patient with newly diagnosed MM [5,6].

Despite most of our current knowledge being based on the results from pivotal phase III trials, these studies represent only a minority of the real-world MM patient population. Strict enrolment criteria [7], such as the absence of active central nervous system metastases or PS $\leq$ 1, have prevented the enrolment of a broader MM population. Thus, it is not uncommon for clinicians to treat patients with MM who do not precisely fit the criteria of pivotal clinical trial participation. It is a matter of debate whether the results from these trials can be applied to the entire population of patients with MM as strong evidence of efficacy in the 'trial-excluded' patient populations of MM is lacking.

In this retrospective, geographically defined population-based study, we provided real-world evidence that major changes in the management of MM have led to an improved survival of patients with MM, regardless of their eligibility ('trial-like' or 'trial-excluded') for pivotal clinical trials.

2. Materials and methods

2.1. Study design

We performed a descriptive population-based study analysing all registered cases of MM in Denmark that were referred for medical treatment and had an initial oncological evaluation between January 1st and December 31st of 2012, 2014 and 2016, respectively. All cases were retrieved from the Danish MM database (DAMMED), section MMM-DK, which has an estimated coverage of >95% of all MM cases occurring in Denmark. More details on the DAMMED are provided in a previous study [7]. In Denmark, all patients diagnosed with MM, not amenable to complete surgical resection or other forms of available local treatment options, are offered a first evaluation at one of the three MM reference centres within 14 days from referral; thus, MMM-DK does not contain data on patients with resectable MM for whom no systemic treatment options were available in Denmark in the study period. The DAMMED is approved by the Danish Data Protection Agency (approval number: 2011-41-6802), and the study was approved by the Danish Patient Safety Authority.

2.2. Selection of common trial enrolment criteria

Seven predefined trial exclusion criteria were selected to define the 'trial-like' and 'trial-excluded' groups. The negative criteria were the following:

- Eastern Cooperative Oncology Group/World Health Organization PS $\geq$ 2
- Active brain metastases or leptomeningeal metastases
- Any serious or uncontrolled medical conditions
- Autoimmune diseases
- Previous malignancies in the last 3 years
- Immunosuppressive medications
- Unmeasurable disease according to Response Evaluation Criteria in Solid Tumours, 1.1 (implemented as patients with small lesions, deemed unmeasurable, were not enrolled in phase III trials)

For more details on these criteria, please refer to our previous work [7].

2.3. Selection of year of diagnosis

Owing to major changes in the availability of first-line standard treatments, 2012, 2014 and 2016 were chosen as 'model' years. Only intravenous interleukin-2 (i.v. IL-2), chemotherapy and monotherapy with BRAFi were available during the whole of 2012; anti–CTLA-4 antibodies were available during the whole of 2014 and anti–PD-1 antibodies (not in combination with anti–CTLA-4) and MEKi (in combination with BRAFi) were available during the whole of 2016. Data on patients diagnosed in 2014 were reported in a previous publication [7], but here, we present an updated analysis

with a larger number of patient cases which were not retrieved previously due to incomplete records.

2.4. Data retrieval and statistical analysis

The database was locked on November 1st 2018. Data were extracted from MMM-DK, and analyses were performed using Graphpad Prism 5.0. Patients with insufficient records, defined as missing data for two or more items including PS, immunosuppressive medications, autoimmune diseases, significant comorbidities or other malignancies were excluded from the analysis. Overall survival (OS) was analysed using a two-sided log-rank test. Contingency data (e.g. landmark survival) were compared with the Fisher's exact test. Hazard ratios (HR) for death (from any cause) and corresponding confidence intervals (CIs) were estimated using the Mantel–Haenszel approach. Survival curves for each treatment group were estimated with the use of the Kaplan–Meier method. All p-values are two sided.

3. Results

3.1. Patient population and eligibility criteria

A total of 842 patient cases, referred for systemic treatment of active cutaneous, mucosal or MM with unknown primary in 2012, 2014 or 2016, were retrieved from the Danish melanoma database, section MMM-DK. Of these, three patients were excluded because of insufficient records; thus, a total of 839 patient cases were available for analysis. Most patients were diagnosed with MM from primary cutaneous MM (81.5%, n = 684), whereas 14.2% (n = 119) had MM of an unknown primary origin, and 4.3% (n = 36) had metastatic mucosal melanoma. 39.7% (n = 333) were BRAF mutated, 48.3% (n = 405) were BRAF wild type and 12.0% (n = 101) were not tested for the BRAF mutation. Importantly, the population with an unknown BRAF status accounted for 33% of patients diagnosed in 2012. Therefore, we excluded the 2012 group from further subgroup analyses according to the BRAF status. A minority of patients (6.2%, n = 52) received a first-line treatment within a clinical trial, which may have improved survival compared with the standard treatments available in the year of diagnosis.

To understand what proportion of patients is represented in registration of clinical trials, we have applied the same criteria we have previously used [7] to define the percentage of patients which meet seven predefined criteria commonly used for enrolment in all pivotal phase III MM immunotherapy trials. Overall, 61% (n = 512) did not meet at least one enrolment criteria. We defined this group as 'trial-excluded'. In contrast, 39% (n = 327) met all enrolment criteria, and this group was defined as 'trial-like'.

Table 1
Baseline characteristics and first-line treatments of 'trial-like' patients.

Trial-like patients	Year 2012 (n = 83)	Year 2014 (n = 129)	Year 2016 (n = 115)
Mean age (average)	61	64	65
Men no.(%)	42 (51)	79 (61)	51 (44)
PS = 0 no.(%)	56 (67)	92 (71)	78 (68)
LDH < ULN no.(%)	46 (58)[a]	81 (64)[b]	71 (62)[c]
M1c no.(%)	46 (55)	74 (57)	66 (57)
First-line treatments	**Year 2012 (n = 83)**	**Year 2014 (n = 129)**	**Year 2016 (n = 115)**
Anti–CTLA-4 no.(%)	21 (25)[d]	104 (81)	10 (9)[e]
Anti–PD-1 no.(%)	0 (0)	1 (1)[f]	89 (77)
IL-2 no. (%)	42 (51)	1 (1)	1 (1)
BRAFi no. (%)	7 (8)[g]	9 (7)	20 (17)[h]

LDH, lactate dehydrogenase; IL-2, interleukin-2; BRAFi, BRAF inhibitors.
Not reported for [a]n = 3; [b]n = 2 and [c]n = 1.
[d]All patients treated in ipilimumab 10 mg/kg versus 3 mg/kg, NCT01515189.
[e]All patients treated with anti–CTLA-4 in combination with anti–PD-1 in the trial Checkmate-511, NCT02714218.
[f]One patient treated in the trial Checkmate-067, NCT01844505.
[g]n = 2 patients treated in COMBI-v trial, NCT01597908.
[h]n = 12 patients were treated with BRAFi + MEKi with or without anti–PD-1 in the trial Keynote-022, NCT02130466.

3.2. Characteristics of patients diagnosed in 2012, 2014 and 2016

Of the total population of patients available for analysis, 28.7% (n = 241) were diagnosed in 2012, 33.8% (n = 284) in 2014 and 37.4% (n = 314) in 2016. This gradual increase in new MM diagnoses may reflect a general increase in melanoma incidence [8] rather than improved diagnostic methods. The proportion of 'trial-excluded' patients ranged from 54.6% (n = 155) in 2014 to 65.6% (n = 158; p = 0.0124 vs 2014) in 2012 and 63.1% (n = 198; p = 0.0371 vs 2014) in 2016. This may be due to the higher proportion of patients with the known baseline brain status (computed tomography or magnetic resonance scan) in 2012 (80.9%, n = 195) and 2016 (77.4%, n = 243) versus 2014 (57.0%, n = 162, p < 0.0001 vs either 2012 or 2016), and it is reflected by a slightly higher proportion of patients with known active brain metastases in 2012 (27.4%, n = 66) and 2016 (26.4%, n = 83) versus 2014 (23.2%, n = 66; p = not significant). The vast majority of the whole 'trial-excluded' patient population had known active brain metastases and/or PS ≥ 2 (75.0%, n = 384), and the relative proportion of these patients was consistent among the selected years (74.1% in 2012, 80.0% in 2014 and 71.9% in 2016). In the remaining 25% (n = 128) of the 'trial-excluded', 10.9% (n = 14) were treated with immunosuppressive medications; 31.3% (n = 40) had serious or uncontrolled medical conditions; 21.1%

(n = 27) had autoimmune diseases and 24.2% (n = 31) had previous malignancies; 34 additional patients, accounting for 26.6%, were excluded because of unmeasurable disease.

3.3. Baseline characteristics of patients diagnosed in 2012, 2014 and 2016 according to trial eligibility

We investigated whether the baseline characteristics of 'trial-like' or 'trial-excluded' patients, diagnosed in the 3 distinct years, were similar. As reported in Tables 1 and 2, the baseline characteristics, including patients with PS = 0, elevated lactate dehydrogenase (LDH) or M1c disease, were consistent throughout, whereas the sex distribution varied. As we have previously shown [7], the characteristics of 'trial-excluded' patients are very different from those of clinical trial and/or 'trial-like' patients, as a much higher proportion have a PS $\geq$ 1, elevated LDH and/or M1c disease.

3.4. Treatments administered to patients diagnosed in 2012, 2014 and 2016

Given the increasing availability of treatments over the past decade and their potential impact on survival, we analysed which first-line treatments were administered to the study population.

In the 'trial-like' patient group, in 2012, most patients (51%, n = 42) were treated with first-line i.v. IL-2, whereas 28% (n = 23) participated in a clinical trial which may have improved their survival compared with the standard treatments available at the time (n = 21 were enrolled in the study CA184-169, ipilimumab 10 mg/kg vs 3 mg/kg trial NCT01515189). In 2014, 81% (n = 104) received first-line treatment with anti–CTLA-4 antibodies, whereas only one patient participated in a clinical trial which potentially improved survival compared with standard of care (Checkmate-067 NCT01844505 [9], where this subject was treated with nivolumab monotherapy). In 2016, at least 77% (n = 89) were treated first line with a regimen containing one anti–PD-1 drug. They received anti–PD-1 as a standard treatment, anti–PD-1 in Keynote-252 (NCT02130466, a combination trial stopped prematurely because of a lack of survival benefit from the combination regimen versus anti–PD-1 alone [10]) or in Checkmate-511 (see below). Nineteen percent participated in clinical trials potentially improving their survival over the standard of care available in 2016 (Checkmate-511 [n = 10, ipilimumab plus nivolumab given at two different doses, NCT02714218] and Keynote-022 [n = 12, dabrafenib plus trametinib plus pembrolizumab or placebo with an estimated 50% of patients receiving anti–PD-1, NCT02130466]). Thus, an estimated of more than 80% of patients in the 2016 group received first-line treatment with a regimen containing one anti–PD-1 drug. First-line treatments administered to 'trial-like' patients are summarised in Table 1.

In the 'trial-excluded' group, a sizable proportion of patients did not receive any systemic treatment (48% in 2012, 43% in 2014 and 34% in 2016; 2014 vs 2016: p = 0.098 and 2012 vs 2016: p = 0.009). The most common first-line treatments administered were temozolomide (34%) in 2012, BRAFi (23%) and anti–CTLA-4 (19%) in 2014 and anti–PD-1 (34%) and BRAFi with or without MEKi (27%) in 2016. First-line treatments administered to 'trial-like' patients are summarised in Table 2.

Overall, few confounding factors were identified. While in the 'trial-like' population, a minor impact of anti–CTLA-4 administered in clinical trials in 2012 cannot be excluded, it is unlikely that clinical trial participation had a major impact on the survival of the overall 'trial-like' population in 2014 and 2016. Therefore, any potential differences in survival in the trial-like populations of 2014 and 2016, or in the overall trial-excluded population, are presumed to be caused by the progressive introduction of novel standard treatment regimens.

Table 2
Baseline characteristics and first-line treatments of 'trial-excluded' patients.

Trial-excluded patients	Year 2012 (*n* = 158)	Year 2014 (*n* = 155)	Year 2016 (*n* = 199)
Mean age (average)	68	69	70
Men no.(%)	101 (64)	86 (55)	121 (61)
PS = 0 no.(%)	39 (25)[a]	31 (20)[c]	52 (27)[e]
LDH < ULN no.(%)	64 (51)[b]	60 (43)[d]	88 (49)[f]
M1c no.(%)	121 (77)	128 (83)	148 (74)
First-line treatments	**Year 2012 (*n* = 158)**	**Year 2014 (*n* = 155)**	**Year 2016 (*n* = 199)**
Anti–CTLA-4 no.(%)	5 (3)[g]	30 (19)	0 (0)
Anti–PD-1 no.(%)	0 (0)	0 (0)	69 (35)
BRAFi no. (%)	7 (4)	35 (23)	54 (27)
TMZ no. (%)	54 (34)	20 (13)	8 (4)
No treatment no. (%)	76 (48)	67 (43)	68 (34)

TMZ = temozolomide.
Not reported for [a]*n* = 3; [b]*n* = 32; [c]*n* = 1; [d]*n* = 5; [e]*n* = 6 and [f]*n* = 15 patients.
[g]All patients treated in ipilimumab 10 mg/kg versus 3 mg/kg, NCT01515189.

To establish whether the introduction of novel treatments for MM had any impact on the survival of real-world patients with the baseline characteristics comparable to registration clinical trials, we analysed the outcome of 'trial-like' patients diagnosed in 2012, 2014 and 2016. At the time of database lock, the median OS was not reached for patients diagnosed in 2016, whereas it was 18.8 months in 2014 and 16.5 months in

2012. The HR for death in 2016 versus 2014 was 0.59 (95% CI, 0.42–0.85; p = 0.0041) and in 2016 versus 2012 was 0.45 (95% CI 0.30–0.648 p < 0.0001). The survival of patients diagnosed in 2014 versus 2012 was not significantly different, with an HR of 0.77 (95% CI 0.55–1.08; p = 0.13). The 1-year survival rates were 80% for 2016, 62% for 2014 and 60% for 2012 (Fig. 1A).

To exclude the impact of MEKi (introduced in Denmark in 2015) on survival, we performed a subgroup analysis of patients with BRAF wild-type MM (n = 67 in 2014 and n = 62 in 2016). Here, the median OS was not reached for patients diagnosed in 2016, whereas it was 13.3 months for 2014, with an HR for death of 0.39 (95% CI 0.24–0.64; p < 0.0001). The 1-year survival rates were 81% in 2016 versus 55% in 2014 (p = 0.0022) (Fig. 1B).

In line with results from pivotal trials, 'trial-like' patients diagnosed with MM in Denmark in 2016 had a clear survival advantage compared with those diagnosed in 2014 and 2012, regardless of the BRAF status.

3.6. Survival of 'trial-excluded' patients

We have previously shown that pivotal clinical trials of immunotherapy represent a minority of patients with MM [7]. To generate real-world evidence of the impact of modern treatments on this difficult patient population (74% with active brain metastases and/or PS ≥ 2), we analysed the survival of trial-excluded patients diagnosed in 2012, 2014 and 2016.

The median OS in 2016 was 6.9 months, whereas it was 5.2 months in 2014 and 4.2 months in 2012. The HR for death in 2016 versus 2014 was 0.66 (95% CI 0.52–0.84; p = 0.0008) and in 2016 versus 2012 was also 0.66 (95% CI 0.52–0.84; p = 0.0008). The survival of patients diagnosed in 2014 versus 2012 was not significantly different (HR 1.04; p = 0.41). The 1-year survival rates were 36% in 2016, 19% in 2014 and 22% in 2012 (Fig. 2A).

As in the 'trial-like' population, we excluded the impact of MEKi on survival by performing the same

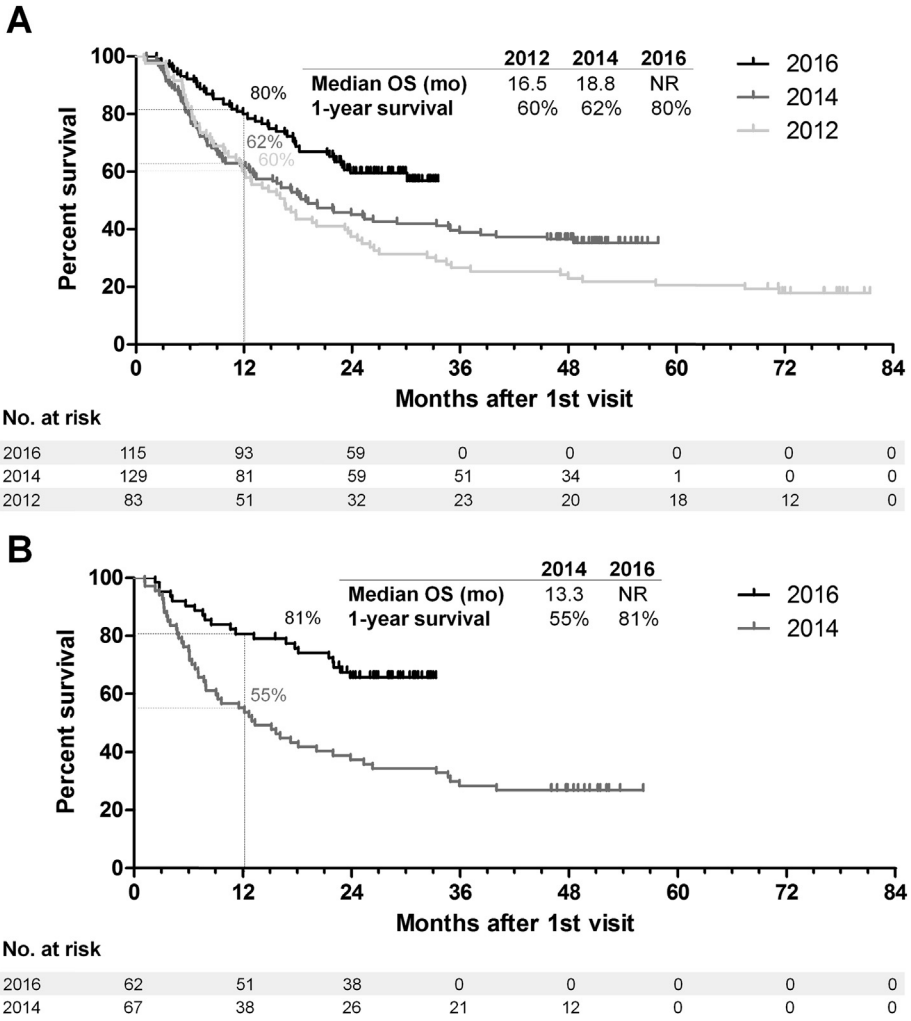

Fig. 1. Survival of 'trial-like' patients diagnosed with MM in 2012, 2014 or 2016 in Denmark. Kaplan–Meier plots showing the survival of (A) the overall population or (B) the BRAF wild-type subpopulation. mo, months; NR, not reached; MM, metastatic melanoma; OS, overall survival.

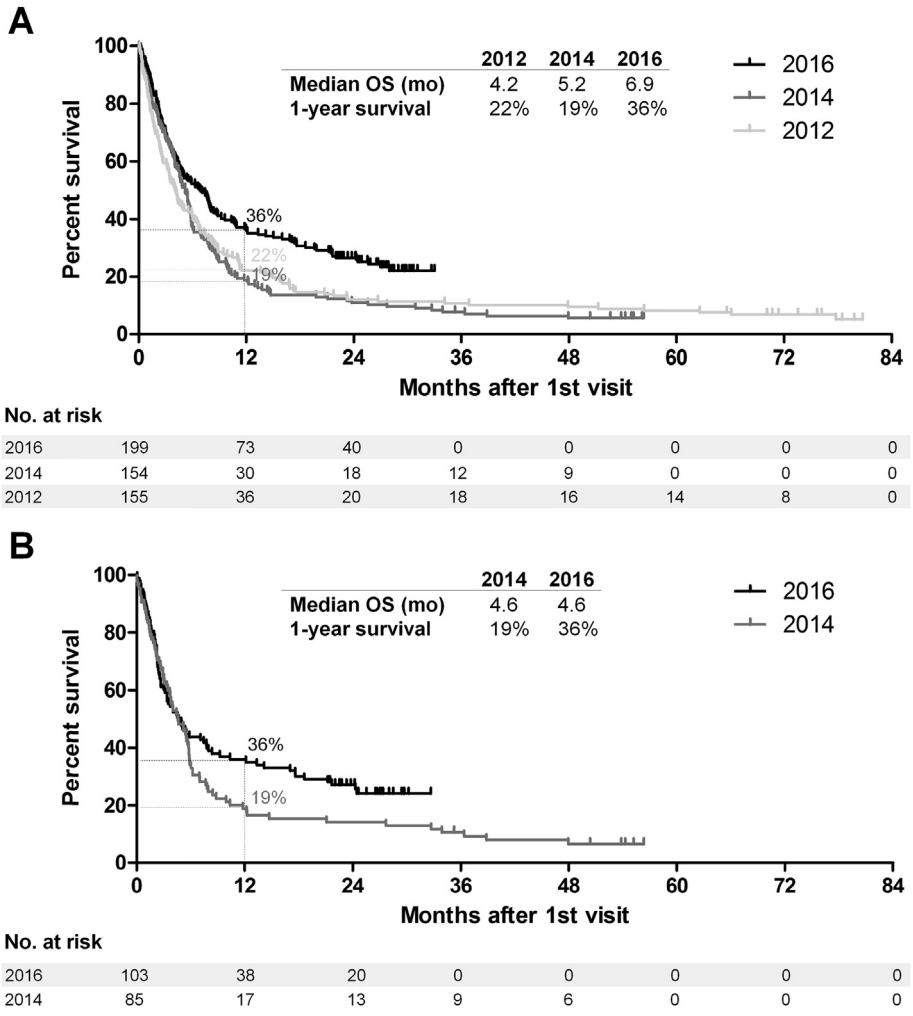

Fig. 2. Survival of 'trial-excluded' patients diagnosed with MM in 2012, 2014 or 2016 in Denmark. Kaplan–Meier plots showing the survival of (A) the overall population or (B) the BRAF wild-type subpopulation. mo, months; NR, not reached; MM, metastatic melanoma; OS, overall survival.

subgroup analysis of patients with BRAF wild-type MM (n = 103 in 2016 and n = 85 in 2014). Here, the median OS was 4.6 months both in 2016 and in 2014, with an HR of 0.76 (95% CI 0.55–1.05; p = 0.0925). Importantly, even though the median survival was identical, the 1-year survival rates were different being 36% in 2016 versus 19% in 2014 (p = 0.0153) (Fig. 2B).

Despite similar baseline characteristics, 'trial-excluded' patients diagnosed with MM in Denmark in 2016 demonstrated a survival advantage (reduced risk for death for the global trial excluded, improved 1-year survival rate only for the BRAF wild type) compared with those diagnosed in 2014 and 2012.

4. Discussion

As pivotal trials of metastatic cancer continue to be conducted in unrepresentative patient populations, there is currently high interest in studying the outcome of real-world patient populations treated with these drugs. Compared with clinical trial populations, real-world patients generally have inferior baseline characteristics and a worse prognosis. With this, previous studies have shown that the real-world use of anticancer drugs may fail to reproduce the clinical benefits observed in clinical trials [11]; thus, it is intensely debated whether the overall survival advantages observed in cancer drug trials can be automatically transferred to the real-world setting [12]. Except for notable tissue biomarkers, e.g. oncogenic drivers and targeted therapies [13], or more recently, PD-L1 expression in first-line treatment of lung cancer [14], regulatory approvals in solid tumour oncology do not limit the use of a certain drug to a specific subpopulation of patients with similar characteristics to the registration trial. Without proper evidence, clinicians managing patients who do not resemble the trial population may rely solely on their clinical judgement to make treatment decisions.

In this study, we took advantage of the DAMMED to generate real-world evidence. This is a very powerful

and innovative tool as it contains clinical data on the entire, unselected population within a nationwide geographical area that has been diagnosed with a specific metastatic cancer disease—it is namely a population-based registry for MM. Denmark is a geographically compact, homogeneous, high-income North European country with a modern healthcare system and universal health coverage. During the study period, evaluation and treatment of MM was centralised in only three academic centres; therefore, guidelines and database registration were homogeneous. The clinical outcomes of the entire patient population of Denmark can be used as a study case that can be applied to most other Western countries.

As in a previous study, we showed that most patients with MM are not represented in pivotal phase III registration trials. This finding alone pointed to the urgent need to generate data on the outcome of modern treatments on real-world MM. In this study, we have addressed these issues by analysing the baseline characteristics and survival outcomes of all patients diagnosed with MM in Denmark during 3 model years, 2012, 2014 and 2016. These years were chosen because of the major changes in medical management of MM that occurred over the course of these years, as well as the expected similarities in the baseline characteristics of patients diagnosed with MM. Similar surgical and follow-up procedures after excision of a primary melanoma ± positive node were applied during the whole study period, with the exception of a new national follow-up programme implemented in late 2015/early 2016 [15]. However, the subgroups studied had similar baseline characteristics; thus, it does not appear that this issue impaired the validity of our results. In 2012, only i.v. IL-2, temozolomide and BRAFi were available for first-line treatment of MM. From January 2014, anti−CTLA-4 antibodies were available as a first-line treatment, whereas during 2015, both MEKi and anti−PD-1 became available for front-line treatment.

The data we obtained by studying the 'trial-like' patient population, which is similar to those enrolled in pivotal clinical trials, largely reproduce the results of such trials where treatment with anti−PD-1 antibodies (2016 group) resulted in an improved survival over previous regimens. In contrast, the introduction of anti−CTLA-4 antibodies (2014 group) did not have a major impact on the survival of the overall population, although here the data are potentially confounded by the ~25% of trial-like patients in 2012 who were treated with anti−CTLA-4 antibodies (ipilimumab 3 mg/kg or 10 mg/kg, the latter which is known to improve the outcomes versus 3 mg/kg)[16] on first line in a clinical trial, as opposed to the ~75% in 2014 treated with ipilimumab 3 mg/kg [16]. In contrast, data on the 'trial-excluded' patients provide an unprecedented opportunity to study the outcomes of an unselected MM population, which was not represented in randomised clinical trials. Here, we have shown that the introduction of anti−PD-1 and MEKi (added to BRAFi) improved the survival outcomes in the global non-trial patient population. Moreover, we reported that in BRAF wild-type patients (thus, excluding the effect of MEKi), a survival advantage at a landmark 1-year end-point was obtained after the introduction of anti−PD-1. Of note, in this trial-excluded patient population, a sizable proportion of patients (34%–48%) did not receive any systemic treatment. Nevertheless, the availability of novel treatments in the real world dictated the treating physician's decision to treat a certain proportion of patients (i.e. in 2016, the availability of treatments with a better toxicity/benefit profile resulted in a higher proportion of patients being treated). Thus, the survival advantage obtained in 2016 can be largely considered as the result of the introduction of anti−PD-1 and reinforce the importance of an experienced clinician's evaluation to initiate immunotherapy.

In conclusion, with all the limitations of a retrospective population-based registry study, we generated evidence that even patient populations which are not represented in clinical trials—mostly those with active brain metastases and/or PS ≥ 2—may benefit from modern treatments. Previous large randomised clinical trials did not answer this important clinical question. Prospective testing of cancer immunotherapies in 'trial-excluded' populations is warranted. Prospective clinical trials investigating this issue are already underway, and the initial results from CheckMate 172 [16], CheckMate 204 [17], COMBI-MB [18] and the ABC trial [19] support our findings.

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Conflicts of interest statements

M.D. received honoraries for lectures from Bristol-Myers Squibb, MSD, Sanofi Genzyme and AstraZeneca. I.M.S. received honoraries for consultancies and lectures from Novartis, Roche, Merck, Bristol-Myers Squibb and Incyte and restricted research grants from Novartis and BMS. L.B. served on the advisory board of Bristol-Myers Squibb, Roche, Novartis, Merck, EISAI and Bayer Healthcare. H.S. received honoraries for consultancies and lectures from Novartis, Merck, Bristol-Myers Squibb and Incyte and restricted research grants from MSD. All remaining authors have declared no conflicts of interest.

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