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The Danish metastatic melanoma database (DAMMED)

A nation-wide platform for quality assurance and research in real-world data on medical therapy in Danish melanoma patients

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1 **The Danish Metastatic Melanoma Database (DAMMED):**
2 **A nation-wide platform for quality assurance and**
3 **research in real-world data on medical therapy in**
4 **Danish melanoma patients**

5

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23 **Abstract**

24 Background: Clinical trials enroll patients with specific diseases based on certain pre-defined
25 eligibility criteria. Disease registries are crucial to evaluate the efficacy and safety of new
26 expensive oncology medicines in broad non-trial patient populations.

27 Methods: We provide detailed information on the structure, including variables, and the scientific
28 results from a nation-wide Danish database covering advanced melanoma, illustrating the
29 importance of continuous real-world data registration. Disease status and treatment-related
30 information on all patients with American Joint Committee on Cancer (AJCC) 8th edition stage III
31 or IV melanoma candidates to medical treatment in Denmark are prospectively registered in the
32 Danish Metastatic Melanoma Database (DAMMED).

33 Results: By January 1st, 2021, DAMMED includes 4156 patients and 7420 treatment regimens.
34 Response rates and survival data from published randomized clinical trial data are compared
35 with real-world efficacy data from DAMMED and presented. Overall, nine independent
36 manuscripts highlighting similarities and discrepancies between real-world and clinical trial
37 results are already reported to date.

38 Conclusion: Nation-wide disease registries take into consideration the complexity of daily
39 clinical practice. We show a concrete example of how disease registries can complement
40 clinical trials' information, improving clinical practice, and support health-related technology
41 assessment.

42

43 **Keywords: Real-world Evidence, metastatic melanoma, database structure,**
44 **immunotherapy, adjuvant therapy, targeted therapy**

45 **1.1 Introduction**

46 Melanoma is a disease of constantly increasing incidence. In Denmark, around 3000 patients
47 are diagnosed every year, with an increase of 2.7%/year over the last ten years[1, 2]. Close to
48 350 patients are diagnosed with inoperable metastatic melanoma each year in Denmark, and a
49 similar number of patients present with stage III/stage IV resectable disease[1]. When the
50 disease is metastatic, patients who are left untreated have a dismal survival of around six
51 months, and until 2011, none of the available treatments had shown to improve survival[3].
52 Since 2011, the medical therapy of metastatic melanoma has changed dramatically[4]. Immune
53 checkpoint inhibitors (ICI) and inhibitors of the mitogen-activated protein (MAP) kinase pathway
54 BRAF inhibitors and the MAP kinase (MEK) inhibitors have all been approved for the treatment
55 of metastatic melanoma based on positive results from clinical trials. Recently, both ICIs and
56 BRAF plus MEK inhibitors have also proven effective in the adjuvant treatment of high-risk
57 melanoma within clinical trials. With this, the medical costs for caring for these patients have
58 increased, and the implementation, effectiveness, and societal impact of these healthcare
59 innovations is emerging.

60 To measure the efficacy and safety of these therapies in the broad population of patients with
61 melanoma in an entire country, the nation-wide Danish Metastatic Melanoma Database
62 (DAMMED) was established in 2011. In contrast to standard electronic health records (HER),
63 this registry collects extensive information on disease status and medical therapy with a clear
64 research-oriented focus to generate real-world evidence on medical melanoma interventions.

65 Denmark has a strong tradition and proven ability to generate real-world evidence from nation-
66 wide registries with a near-universal coverage[5]. A similar national registry, The Danish
67 Melanoma Database (DMD), collecting detailed clinical, surgical, pathological, and follow-up
68 information on patients suffering from cutaneous melanoma, was established in 1985 by The
69 Danish Melanoma Group (DMG) [6]. This registry, however, does not collect information on
70 medical oncological treatments.

71 Here, we describe the design and the objectives of DAMMED alongside initial results from this
72 real-world registry.

73

74 **2.1 Material and methods**

75

76 **2.1.1 Objectives**

77 The overall aim of the registry is to generate real-world evidence to ensure evidence-based
78 treatment guidelines of the highest quality. Based on retrospective evaluation of hospital files,
79 we collect key clinical data on all patients with melanoma candidates for medical therapy in
80 Denmark. Thus, the database enables us to investigate how real-world treatment efficacy and
81 safety compare with available evidence from clinical trials, which have formed the basis of our
82 current treatment strategies. Furthermore, the database constitutes a significant platform for
83 clinical research on the medical treatment of melanoma patients.

84

85 **2.1.2 Study population**

86 Since 2011, we have registered all melanoma cases considered for medical therapy in Denmark
87 in DAMMED. Patients with melanoma are now treated at four oncological centers in Denmark,
88 and all centers agree on standardized treatment protocols and national guidelines. Oncological
89 treatment outside of these four centers, i.e., private hospitals, is not possible in Denmark,
90 wherefore all patients considered for medical therapy will be captured in the database. Also,
91 patients not receiving antineoplastic therapy will be registered as long as they have been
92 referred for evaluation at the oncological melanoma center. Patients being diagnosed with
93 metastatic melanoma at other institutions and not referred for oncological evaluation due to,
94 e.g., poor performance status will not be captured and therefore not registered.

95 We include patients offered treatment for unresectable American Joint Committee on Cancer
96 (AJCC) 8th edition[7] stage III or IV melanoma, as well as patients, offered adjuvant medical
97 therapy after radical surgery for regional or distant metastatic disease. In the adjuvant group, we

98 aim to comprise all patients eligible for treatment enabling us to include evaluation also on
99 patients who, despite eligibility, will not receive adjuvant therapy.

100

101 **2.1.3 Structure and dataset**

102 The database structure was developed as a custom-made, web-based database, using
103 Structured Query Language (SQL) format.

104 Retrospective entering of data on toxicity might interfere with data quality since these data are
105 challenging to validate. To be useful for scientific purposes, we concluded that toxicity data
106 needed to be included prospectively in a separate database. Based on these considerations,
107 DAMMED has full focus on clinical and preclinical efficacy data without focusing on toxicity
108 data. We have recently initiated prospective entering of toxicity data on patients receiving
109 adjuvant therapy in a connected IMMUNOTOX database. As a beginning, only these patients
110 will be registered, but when this is established, also patients with metastatic disease receiving
111 immunotherapy will be registered in the IMMUNOTOX database.

112 The steering committee, consisting of the three founding members (IMS, HS, LB), is responsible
113 for daily operations and evaluation of scientific protocols applying for data extraction from the
114 registry. Two data managers assist in the continuous improvement of the registry and data
115 extraction for scientific purposes. Medical students are hired to extract data from patient files
116 and manually enter data into the registry. The medical students are educated to extract the
117 data, and responsible clinicians perform necessary quality control on selected key data.

118 A yearly data report containing all patients treated from the beginning of the registry to
119 December 31 in the previous year is produced and used as a catalog of inspiration for research.
120 The data report is presented and discussed at a yearly meeting in May. The meeting includes
121 all oncologists involved in treating the patients together with representatives from the funding
122 medical companies. The data report is not publicly available but can be obtained when relevant
123 upon request.

124 Baseline data (type of melanoma (skin, mucosal, ocular, or unknown primary), BRAF status,
125 and personal data which are constant over time form the registration basis. After that, data on
126 adjuvant therapy or treatment for metastatic disease are included. This means that all
127 subsequent data are directly related to a specific treatment regimen. With subsequent treatment
128 lines, updated data on tumor characteristics are added to the particular regimen (Figure 1). A
129 list of variables included in the registry is depicted in Table 1.

130

131 **2.1.4 Funding**

132 Oncologists involved in the registry work are contributing as part of their clinical employment.
133 However, funding is necessary for salaries to data managers and medical students. For this, we
134 have received funding from medical companies involved in the development of medical
135 products for the treatment of patients with melanoma. In 2020, the companies who have
136 accepted to fund the operation of the registry are BMS, Merck MSD, Novartis, Roche, and
137 Pierre Fabre.

138

139 **2.1.5 Approval**

140 The registry and the informed consent form have received legal approval by the Danish Data
141 Protection Agency and the Danish Patient Safety Authority. Also, approval was granted for
142 retrospective data use until September 2016, although no written informed consent was
143 obtained prior to that date.

144

145 **2.1.6 Statistical analysis**

146 Recurrence-free survival (RFS) or progression-free survival (PFS) is defined as the time from
147 the start of medical treatment until relapse, progressive metastatic melanoma
148 appears/reappears, or death, whichever date comes first. Patients not in progression and alive
149 at the time of analysis are censored.

150 Overall survival (OS) is defined as the time from the date of the first treatment for metastatic
151 melanoma to death from any cause. Patients alive at the time of analysis are censored.

152

153 **3.1 Results**

154

155 **3.1.1 Patient and treatment characteristics**

156 The Registry was initiated in 2011 and includes all melanoma patients who are candidates for
157 medical oncological therapies, including patients with cutaneous, unknown primary, uveal, and
158 mucosal melanomas. Table 2 depicts patient characteristic for all metastatic melanoma patients
159 at the time of first line therapy included in the database. Patients from all regions of Denmark
160 are included. Also, data on patients treated for metastatic melanoma with high-dose Interleukin-
161 2 between 2007 and 2011 has been included. Since 2011, patients have received treatment
162 with drugs targeting BRAF and MEK as well as treatment with ICI, chemotherapy, and therapy
163 according to ongoing clinical trials. Clinical trials are registered with limited data and are
164 primarily included to illustrate the therapies given. From November 2018, details on adjuvant
165 treatment have also been included in the registry. By the end of 2020, the registry included data
166 on 4156 patients with metastatic melanoma of the skin, metastatic melanoma with unknown
167 primary, mucosal melanoma, or ocular melanoma. The subgroup of patients with either
168 metastatic cutaneous or unknown primary has received a total of 7420 treatment regimens
169 (Table 3).

170 When the first approvals for the use of targeted or ICI therapy appeared in 2011, the national
171 treatment policy in Denmark recommended using immunotherapy as first-line treatment if
172 possible. Patients with BRAF mutations were offered first-line targeted therapy in case a rapid
173 onset of response was needed, e.g., symptomatic brain metastases, or as a later therapy line
174 after immunotherapy. This policy is reflected in the data in Table 3.

175

176 **3.1.2 Outcome**

177 The first study we published based on DAMMED data[8], estimated that 55% of the patients
178 who receive treatment in the real world did not meet the main eligibility criteria of the registration
179 clinical trials of immunotherapy. Therefore, it was of utmost importance to estimate how real-
180 world efficacy matched data from the clinical trials. The new generation of active drugs in
181 metastatic melanoma treatment was almost unanimously tested in randomized trials against the
182 chemotherapy dacarbazine (DTIC).

183 Ipilimumab was the first ICI to be used in clinical practice. In Table 4, we have compared the
184 response rates and landmark survival data from published randomized clinical trial data on
185 ipilimumab single drug [9-12] (Table 4A), nivolumab or pembrolizumab single drug [10, 11, 13-
186 18] (Table 4B), ipilimumab plus nivolumab [11, 15, 16, 19] (Table 4C), and dabrafenib plus
187 trametinib [20-22] (Table 4D), with real-world efficacy data on the same drugs from DAMMED.

188

189 **3.1.3 Publications based on data from DAMMED**

190 Several manuscripts based on data from DAMMED have been published in international peer-
191 reviewed journals, illustrating the need for science based on real-world data.

192 Real-world data can be used to evaluate the implementation and effectiveness of new treatment
193 modalities in a broader patient group. The observation in our first paper[8] mentioned above
194 highlighted the need to study the safety and effectiveness of novel healthcare interventions in
195 this large group of patients who were not represented in pivotal clinical trials. In 2019, we
196 published a second manuscript investigating the impact of modern therapies on the real-world
197 survival of metastatic melanoma. We analyzed patients diagnosed with metastatic melanoma in
198 2012, 2014, and 2016 where new treatments in Denmark were introduced; BRAF inhibitors
199 (2012), anti-CTLA4 antibody ipilimumab (2014), and PD-1 inhibitors and BRAF/MEK inhibitors
200 (2016). Despite similar baseline characteristics, our results showed a statistically significant
201 improvement of OS from 2012 and 2014 to 2016 regardless of patients' eligibility for pivotal
202 clinical trials and BRAF mutational status [23]. Overall, we observed that even though patients

203 not eligible for clinical trials had a significantly worse outcome than the eligible group, they still
204 appeared to benefit from immunotherapy[8, 23]. These data were also used to show how real-
205 world evidence can guide healthcare policies in oncology [24]. In a recent manuscript
206 comparing the long-term survival of patients treated in the era before ICI therapies with patients
207 treated in the modern era [25], we showed that the number of long-term survivors significantly
208 increased and that patients more often were without progression in the ICI era. In 2019, we also
209 published a letter comparing the overall survival of patients with metastatic melanoma of
210 unknown primary and known cutaneous melanomas showing that OS rates were comparable
211 between the two groups [26].

212 Elderly and fragile patients also are not included in clinical trials, as are patients with a rare
213 disease subtype. Real-world data is useful to broaden the understanding of treatment effects on
214 these subgroups of patients. Discussions on the impact of age on ICI's efficacy led to a
215 manuscript describing OS and PFS in elderly patients compared with younger patients. We
216 found that the effectiveness of ICI using ipilimumab (anti-CTLA-4) was comparable in younger
217 patients below the age of 70 and elderly patients above the age of 70. On the other hand, for
218 drugs targeting PD-1, the elderly patients had better survival than the younger patients [27]. In
219 a retrospective setting, we used real-world data from DAMMED to evaluate clinical factors and
220 outcome on all patients with metastatic uveal melanoma treated in Denmark before and after
221 introducing ICIs [28]. Response rates on chemotherapy, anti-PD-1, and combination
222 immunotherapy with ipilimumab and nivolumab were reported in a total of 126 uveal melanoma
223 patients showing increased response rates for combination therapy. Also, after introducing ICI,
224 an increase in OS was shown, underlining that patients with metastatic uveal melanoma benefit
225 from ICI therapy, despite relatively low response rates.

226 Therapies approved many years ago may not have been through the same approval process as
227 today's therapies are. Real-world data may help gain visibility on the efficacy and long-term
228 outcome for patients being treated with these drugs. Data on patients treated with high-dose
229 interleukin-2 and interferon as first-line therapy from 2007-2011 were collected. These data
230 show that treatment with high-dose Interleukin-2 can lead to long-term survival in a subset of
231 treated patients[29].

232 Also, the interest in investigating when to stop treatment is low for medical companies
233 wherefore data from registries may support guidelines on this subject. Contribution from
234 DAMMED to an international collaboration with several European countries and Australia led to
235 a publication on clinical outcomes on patients discontinuing anti-PD-1 therapy in the absence of
236 disease progression or toxicity [30]. It was shown that patients with a complete response after
237 more than six months of treatment had a low risk of relapse compared to patients with a partial
238 response or stable disease or patients discontinuing therapy before six months of treatment.

239 When investigating the safety of the new therapies on real-world patients it enables clinicians
240 and patients to understand the full measure of the treatments' potential harms. Recently, we
241 reported potential risk factors and efficacy of clinical management on patients developing
242 immune-related hepatitis after treatment with ICI [31]. We found that infection or antibiotic
243 therapy could be a possible risk factor for developing immune-related hepatitis. Also, we
244 observed a high risk of relapse of hepatitis during steroid tapering and a potential negative
245 impact of cumulative steroid dose on response to ICIs, which has led to a prospective clinical
246 trial investigating the optimal use of second-line immunosuppressants.

247

248

249 **4.1 Discussion**

250 DAMMED is a nation-wide registry including all metastatic melanoma patients offered medical
251 antineoplastic therapy in Denmark since 2010. Since medical treatment for melanoma is
252 centralized at only four institutions, with shared guidelines and a highly collaborative
253 environment, this process was implemented quickly. Antineoplastic therapy for melanoma is not
254 possible outside of these four centers, wherefore all given therapies will be captured in the
255 database. Patients not referred for oncological evaluation are hard to identify and will, in most
256 cases, not be registered in DAMMED. We estimate a coverage of around 95% of all patients
257 with metastatic melanoma diagnosed in Denmark.

258 The retrospective character of the registry includes the risk of flaws and misinterpretation when
259 data are entered. To minimize such errors, every reported case is approved by the registry
260 responsible oncologist from each site to validate data. Toxicity data from the pivotal clinical trials
261 have a very high quality, mainly due to the monitoring process included in trial data capturing.
262 Registration of real-world toxicity carries an in-born risk of a much lower quality. Based on these
263 considerations, we decided from the beginning not to include data on toxicity in the DAMMED..
264 We have recently established a new database, IMMUNOTOX, connected to DAMMED, where
265 data on immune-related toxicities are entered prospectively. To secure a proper implementation
266 of this web-based registration of toxicities, we decided to include only patients treated with
267 immunotherapy on adjuvant indication. Therefore, no data on toxicity from metastatic melanoma
268 patients treated with immunotherapy are available at present.

269 Only a few other nation-wide registries covering melanoma exist. In Holland, a registry was
270 established together with the approval of the new treatment modalities in 2013. Therapies are
271 only reimbursed if the patients are entered in the Dutch Melanoma Treatment Registry (DMTR),
272 wherefore it is an actual nation-wide registry including all patients treated for melanoma in
273 Holland [32]. Other countries, such as Germany, also have large registries on patients with
274 melanoma. Still, since the treatment of melanoma patients is localized in many different centers
275 around the country, registration of all patients is challenging and will be biased by patients
276 treated at larger centers more often represented in the registry [33].

277 Even though DAMMED is a nation-wide registry with high patient coverage and clear
278 geographical definition, the population size of Denmark makes it challenging to draw firm
279 conclusions on small subgroups of patients or characterize rare events such as fatal toxicities
280 from immunotherapies[34]. In 2017, a collaboration between the German, the Dutch, and the
281 Danish Melanoma Registries was founded. This European Melanoma Registry (EUMelaReg,
282 <https://www.eumelareg.org>) has since evolved to include several other European countries with
283 existing melanoma registries or European countries that have been interested in establishing a
284 platform for a melanoma registry. The EUMelaReg is now taking form, and the first scientific
285 projects are in process. Likely, this extensive collaboration and gathering of smaller registries

286 will make it possible to draw more robust conclusions on real-world patients and explore the
287 outcome of also smaller subsets of patients.

288 Registries covering similar patient populations in other countries have recently confirmed our
289 significant findings, showing that pivotal clinical trials represent only a fraction of the broad real-
290 world patient population with metastatic melanoma [35-37]. Modern treatment interventions
291 appeared to impact patient survival, regardless of eligibility to trials, positively. Overall, clinical
292 trial representativeness of the real-world appeared low across a broad range of cancers.
293 Indeed, the same issue has been observed in other cancers such as lung cancer [38], colorectal
294 cancer[39], and renal cell carcinoma[40], highlighting how significant it is to evaluate the safety
295 and effectiveness of treatment interventions in the real world of oncology.

296

297

298 **5.1 Conclusion**

299 In conclusion, the Danish Melanoma Database for medical therapy, DAMMED, is a nation-wide
300 registry with high patient coverage. The variables included in the registry include details on
301 medical therapy and, together with the Danish melanoma registry, which covers baseline
302 surgical and pathological information, it creates a full picture of the treatment of Danish
303 melanoma patients. DAMMED forms the platform on which to build solid clinical research and to
304 evaluate real-world data for socioeconomic decisions.

305

306

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310

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320 conflicts of interest.

321

322 **CRedit author statement**

323 **EE:** Conceptualization, Methodology, Investigation, Writing - Original Draft. **IMS, HS, CAH, MD:**
324 Conceptualization, Methodology, Investigation, Writing - Review & Editing, Supervision. **LH, CR,**
325 **LMG:** Investigation, Writing - Review & Editing. **UHK:** Software, Formal Analyses. **LB:**
326 Conceptualization, Methodology, Investigation, Writing - Original Draft, Supervision

327

328

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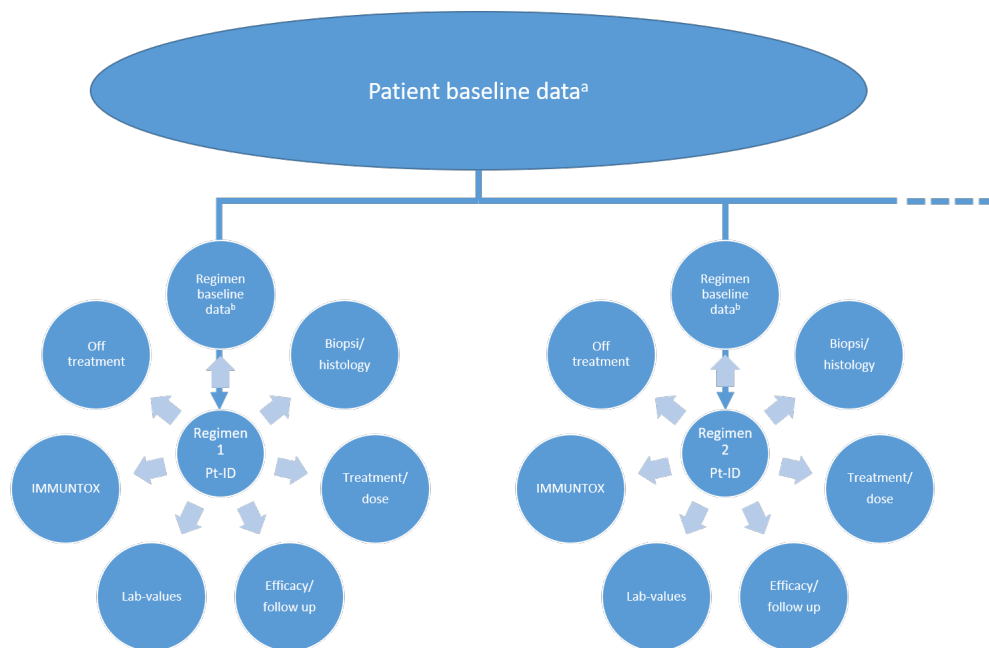
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515 **Fig. 1: Structure of the Danish Metastatic Melanoma Database (DAMMED).**

516 **Notes:** ^aPatient baseline data includes: demographic data, melanoma type (ie cutaneous,
517 unknown primary, ocular or mucosal), date of first melanoma diagnosis, BRAF mutation status,
518 including method of analysis, confirmation of informed consent, data on last seen alive/date of
519 death and cause of death. ^bRegimen baseline data is different between adjuvant and metastatic
520 regimens. For metastatic regimens, it includes line of therapy, organs involved, significant
521 comorbidities, other cancers, concomitant immunosuppressive medicine, and PD-L1 status with
522 the date of analysis. For adjuvant regimens, it includes: TNM classification at first melanoma
523 diagnosis and staging for patients with resected metastatic disease, date of definitive surgical
524 procedure, the radicality of surgical procedure (ie, R0/R1 resection), significant comorbidities,
525 other cancers, concomitant immunosuppressive medicine. We register all patients eligible for
526 adjuvant therapy. For patients not receiving adjuvant treatment, the reason why is documented.

527 **Abbreviations:** Pt-ID, patient identification



528

529 **Table 1: Variables in DAMMED**

530

| DAMMED registry^a | Category | Variable |
|------------------------------------|----------------------------|---|
| Patient baseline data | Demographic data | Date of birth |
| | | Gender |
| | Pathology | Type of melanoma |
| | | Date of first melanoma diagnosis |
| | | BRAF mutation status |
| | | NRAS mutation status |
| | Survival data | Last seen alive |
| | | Date of death |
| | | Cause of death |
| | | |
| Regime baseline data | | Patient-ID |
| | | Line of therapy for adjuvant/metastatic disease |
| | Dissemination ^b | Organs involved |
| | Stage ^c | TNM at initial diagnosis and at relapse if relevant |
| | | Date and radicality of surgery |
| | Decision ^c | Decision on adjuvant therapy and reason if no |
| | | |
| | Comorbidity | Significant comorbidities/autoimmune diseases |
| | | Concomitant immunosuppressive medicine |
| | PD-L1 status | PD-L1 status with date of analysis |
| | | |
| Biopsy/histology | Verification of diagnosis | Type and date of biopsy |
| | | |
| Treatment/dose | Details on therapy | Date of therapy |
| | | Dose and potential dose delay/reduction |
| | | |
| Efficacy/follow up | Response data | Date and method of scan |
| | | Response |

| | | |
|----------------------|-----------------------|--|
| | | |
| Lab-values | Baseline evaluation | Performance Status |
| | | Laboratory results |
| | | |
| IMMUNTOX | Toxicity ^c | Currently only registered for adjuvant therapy |
| | | |
| Off treatment | Progression data | Date last seen without progression |
| | | Date of progression |
| | | Reason for stopping treatment |

531

532 **Notes:** Variables may differ between treatment regimens. ^aaccording to figure 1, ^bonly for

533 metastatic regimens, ^conly for adjuvant regimens

534

535

536

537 **Table 2: Patient characteristics of all metastatic melanoma patients at time of first line**
 538 **therapy for metastatic disease.**

| | No | % |
|---|-------------|----------|
| Total no of patients receiving first line therapy for metastatic melanoma# | 3051 | |
| Melanoma diagnosis | | |
| Cutaneous Melanoma | 2300 | 75.4 |
| Mucosal Melanoma | 109 | 3.6 |
| Ocular Melanoma | 210 | 6.9 |
| Melanoma - unknown primary | 432 | 14.2 |
| Total no of patients with cutaneous and unknown primary melanoma* | 2732 | |
| Gender | | |
| Female | 1096 | 40.1 |
| Male | 1636 | 59.9 |
| Age - median (range) | 66 | 15 - 120 |
| ECOG Performance Status | | |
| 0 | 1302 | 56.4 |
| 1 | 678 | 29.4 |
| 2 | 256 | 11.1 |
| 3 | 69 | 3.0 |
| 4 | 2 | 0.1 |
| Unknown | 425 | |
| M-stage (8th edition) | | |
| M1a | 480 | 17.6 |
| M1b | 389 | 14.2 |
| M1c | 1249 | 45.7 |
| M1d | 571 | 20.9 |

| | | |
|--------------------|------|------|
| BRAF-status | | |
| Wildtype | 1039 | 46.4 |
| BRAF mutation | 1199 | 53.6 |
| Not tested | 494 | |
| LDH | | |
| < ULN | 1109 | 49.6 |
| 1-2 x ULN | 847 | 37.9 |
| >2 x ULN | 278 | 12.4 |
| ND | 498 | |

539 #Patients who did not receive 1st line therapy for metastatic melanoma, including the 548
540 patients receiving adjuvant nivolumab and patients not receiving antineoplastic therapy, have
541 not been included in this table.

542 *Details below only includes patients with cutaneous and unknown primary metastatic
543 melanoma.

544 **Notes:** Number of patients per December 31st, 2020. Patients included in clinical trials,
545 receiving chemotherapy, or Interleukin 2 have not been registered with all details wherefore
546 missing data on, e.g., performance status and LDH will be present.

547 No: number; ULN: Upper limit of normal; LDH: Lactate dehydrogenase

548

549

550

551 **Table 3: Distribution of patients with cutaneous melanoma or unknown primary in**
 552 **different treatment regimens according to line of therapy**

| Treatment regimen | Line of therapy | Number of patients |
|---|-----------------|--------------------|
| Interleukin-2 (2007-2011) | 1st Line | 463 |
| | > 1st line | 28 |
| Ipilimumab (2011-2020) | 1st Line | 243 |
| | > 1st line | 425 |
| Pembrolizumab (2014-2020) | 1st Line | 724 |
| | > 1st line | 292 |
| Ipilimumab/nivolumab (2016-2020) | 1st Line | 283 |
| | > 1st line | 74 |
| Dabrafenib/trametinib (2014-2019) | 1st Line | 270 |
| | > 1st line | 302 |
| Encorafenib/binimetinib (2019-2020) | 1st Line | 69 |
| | > 1st line | 133 |
| Adjuvant nivolumab (November 2018-2020) | NA | 548 |

553

554 **Notes:** Number of patients per December 31, 2020

555 **Abbreviations:** NA, not applicable

556

557 **Table 4: Landmark efficacy data on efficacy from the pivotal clinical trials evaluating A)**
 558 **ipilimumab single drug, B) nivolumab or pembrolizumab single drug, C) ipilimumab and**
 559 **nivolumab in combination or D) dabrafenib and trametinib in combination in the**
 560 **treatment of metastatic melanoma. Data from DAMMED as of December 31, 2020 are**
 561 **added for each table**

562

563 **A)**

| Drug | Study | Response (%) | | OS (%) | | | | |
|---------------------|-------------------------|--------------|-----|--------|--------|--------|--------|--------|
| | | ORR | CRR | 1 year | 2 year | 3 year | 4 year | 5 year |
| Ipilimumab | CM-002 ⁹ | 11 | 2 | 46 | 24 | NA | NA | NA |
| | KN-006 ¹⁰ | 13 | 5 | 59 | 42 | 38 | 34 | 31 |
| | CM-067 ¹¹ | 19 | 6 | 67 | 45 | 34 | 30 | 26 |
| | CA184-169 ¹² | 12/15 | 2/2 | 48/54 | 31/38 | 23/31 | 20/27 | 19/25 |
| DAMMED ^a | | 20 | 8 | 54 | 36 | 30 | 26 | 22 |

564

565 Notes: ^aData from DAMMED for patients receiving any line of treatment for metastatic
 566 melanoma as of December 31, 2020.

567 Abbreviations: ORR, objective rate; CRR, complete response rate; OS, overall survival; CM,
 568 CheckMate; KN, KEYNOTE; NA, not applicable

569

570

571 **B)**

| Drug | Study | Response (%) | | OS (%) | | | | |
|-------------------------------|----------------------------|--------------|-----|--------|--------|--------|--------|--------|
| | | ORR | CRR | 1 year | 2 year | 3 year | 4 year | 5 year |
| Pembrolizumab or nivolumab | CM-066 ^{13,18} | 43 | 11 | 71 | 58 | NA | NA | NA |
| | KN-006 ^{10,14} | 37 | 12 | 74/68 | 55 | 48 | 42 | 39 |
| | CM-067 ^{11,15,16} | 45 | 19 | 74 | 59 | 52 | 46 | 44 |
| | KN-001 ¹⁷ | naïve | 41 | 25 | NA | NA | NA | 48 |
| >1. line | | NA | 16 | NA | NA | NA | 38 | 34 |
| DAMMED ^a | | 46 | 21 | 70 | 54 | 46 | 41 | 39 |

572

573 Notes: ^aData from DAMMED for patients receiving any line of treatment for metastatic
574 melanoma as of December 31, 2020

575 Abbreviations: ORR, objective rate; CRR, complete response rate; OS, overall survival; CM,
576 CheckMate; KN, KEYNOTE; NA, not applicable

577

578 **C)**

| Drug | Study | Response (%) | | OS (%) | | | | |
|------------------------------|----------------------------|--------------|-----|--------|--------|--------|--------|--------|
| | | ORR | CRR | 1 year | 2 year | 3 year | 4 year | 5 year |
| Ipilimumab + nivolumab | CM-067 ^{11,15,16} | 58 | 22 | 73 | 64 | 58 | 53 | 52 |
| | CM-004 ¹⁹ | 42 | 19 | 81 | 72 | 63 | NA | NA |
| DAMMED ^a | | 51 | 21 | 68 | 55 | 47 | NA | NA |

579

580 Notes: ^aData from DAMMED for patients receiving any line of treatment for metastatic
581 melanoma as of December 31, 2020

582 Abbreviations: ORR, objective response rate; CRR, complete response rate; OS, overall
583 survival; CM, CheckMate; KN, KEYNOTE; NA, not applicable

584

585 D)

| Drug | Study | Response (%) | | OS (%) | | | | |
|-------------------------|-------------------------|--------------|-----|--------|--------|--------|--------|--------|
| | | ORR | CRR | 1 year | 2 year | 3 year | 4 year | 5 year |
| Dabrafenib + trametinib | Combi-D ²¹ | NA | NA | NA | 52 | 43 | 35 | 32 |
| | Combi-V ²⁰ | NA | NA | NA | 53 | 44 | 39 | 36 |
| | Combi-D/V ²² | 68 | 19 | NA | 52 | 44 | 37 | 34 |
| DAMMED ^a | | 57 | 8 | 39 | 21 | 16 | NA | NA |

586

587 Notes: ^aData from DAMMED for patients receiving any line of treatment for metastatic
 588 melanoma as of December 31, 2020

589 Abbreviations: ORR, objective rate; CRR, complete response rate; OS, overall survival; CM,
 590 CheckMate; KN, KEYNOTE; NA, not applicable

591

592