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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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Abstract

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

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

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

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

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

1.1 Introduction

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

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

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

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

2.1 Material and methods

2.1.1 Objectives

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

2.1.2 Study population

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

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

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

2.1.3 Structure and dataset

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

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

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

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

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

2.1.4 Funding

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

2.1.5 Approval

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

2.1.6 Statistical analysis

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

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

3.1 Results

3.1.1 Patient and treatment characteristics

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

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

3.1.2 Outcome

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

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

3.1.3 Publications based on data from DAMMED

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

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

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

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

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

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

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

4.1 Discussion

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

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

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

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

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

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

5.1 Conclusion

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

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Disclosure

EE received honoraria for lectures and travel expenses from Bristol-Myers Squibb, MSD, Roche, Kyowa Kirin, and Pierre Fabre. IMS received honoraria for consultancies and lectures from Novartis, Roche, MSD, Bristol-Myers Squibb, and Pierre Fabre and restricted research grants from Novartis and BMS. HS received honoraria for lectures from Novartis, Roche, MSD, BMS, and Pierre Fabre and an unrestricted research grant from MSD. CAH received honoraria for lectures from MSD. MD received honoraria for lectures from Roche and Novartis and expenses to access to Online Educational Material from MSD. LB received honoraria for lectures from Novartis, Roche, MSD, BMS, and Pierre Fabre.The other authors reported no conflicts of interest.

CRediT author statement

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

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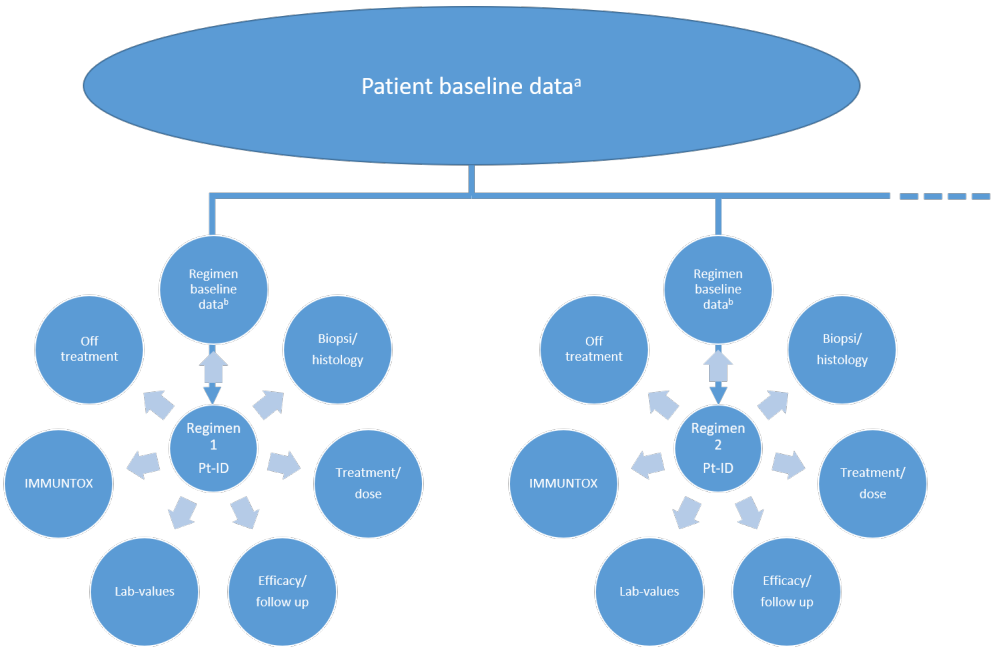
Fig. 1: Structure of the Danish Metastatic Melanoma Database (DAMMED).

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

Abbreviations: Pt-ID, patient identification



529 **Table 1: Variables in DAMMED**

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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/metastastic 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
		Concommitant 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

Notes: Variables may differ between treatment regimens. [a]according to figure 1, [b]only for metastatic regimens, [c]only for adjuvant regimens

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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	

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

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

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

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

Table 3: Distribution of patients with cutaneous melanoma or unknown primary in 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

Notes: Number of patients per December 31, 2020

Abbreviations: NA, not applicable

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

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

Notes: [a]Data from DAMMED for patients receiving any line of treatment for metastatic melanoma as of December 31, 2020.

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

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	41
		>1. line	*NA*	16	*NA*	*NA*	*NA*	38	34
DAMMED[a]			46	21	70	54	46	41	39

Notes: [a]Data from DAMMED for patients receiving any line of treatment for metastatic melanoma as of December 31, 2020

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

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*

Notes: [a]Data from DAMMED for patients receiving any line of treatment for metastatic melanoma as of December 31, 2020

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

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*

Notes: [a]Data from DAMMED for patients receiving any line of treatment for metastatic melanoma as of December 31, 2020

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