Bridging the gap between clinical trials and real-world for advanced melanoma: Results of the Dutch Melanoma Treatment Registry

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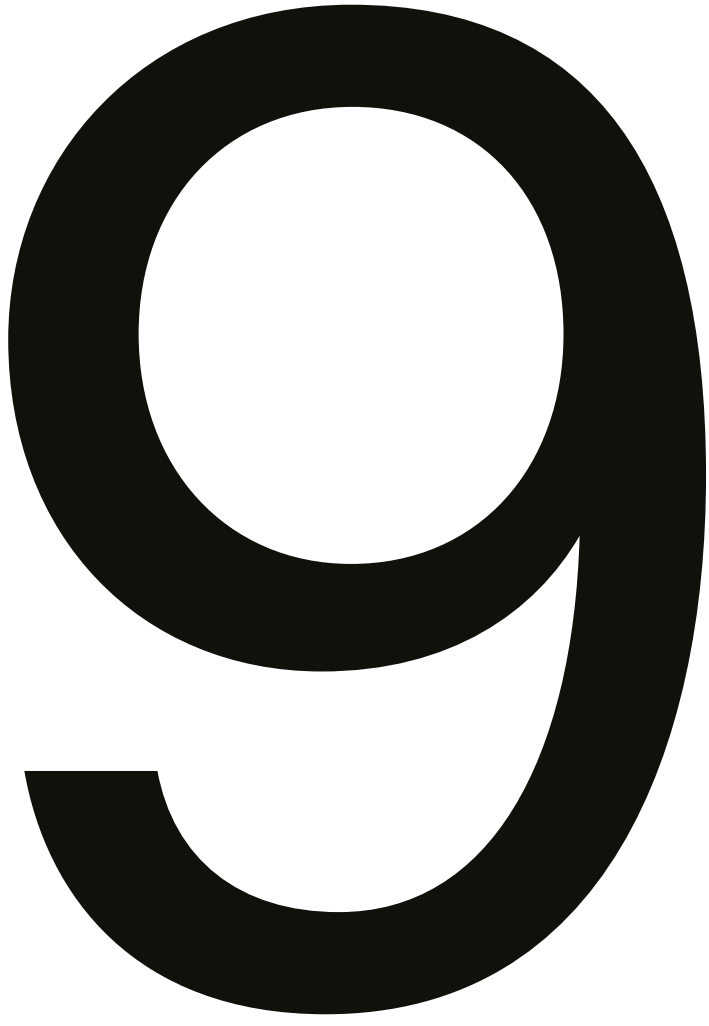

Discussion and future perspectives

Introduction

In the Netherlands, the incidence of (all stage) melanoma has continued to rise in recent decades.[1] Advanced melanoma was a difficult disease to treat and the prognosis was poor. Historically, the median overall survival (OS) for patients with newly diagnosed advanced melanoma has been 6-8 months.[2] Beginning in 2010, a new era of anti-cancer drugs for (advanced) melanoma began after remarkable results were observed in phase III trials. In the past decade, nearly a dozen immunotherapies and targeted therapies have been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA).[3–8]

The efficacy-effectiveness knowledge gap

Randomised controlled trials (RCTs) investigate the extent to which a new treatment is beneficial under 'ideal' circumstances (created in an RCT), also called the efficacy.[9] These 'ideal' circumstances are created by studying a selected patient population in a highly controlled setting in which patients are intensively monitored by specialized personnel.

New systemic therapies for advanced melanoma were licensed for a much less restricted patient population and used in less controlled settings than the RCTs. As new drugs or drug combinations became rapidly approved one after another, there was only limited experience with new systemic therapies for use in daily clinical practise.

This meant that when new systemic therapies for advanced melanoma were introduced in the Netherlands, it was not known to what extent these new treatments were beneficial under routine treatment conditions in daily clinical practise, also referred to effectiveness. This efficacy-effectiveness knowledge gap included safety, adverse events and the effectiveness of new systemic therapies in both patients who were 'trial-like' and those who were not represented (trial-ineligible) in RCTs. Also, the benefit of new treatments for rare types of advanced melanoma, such as mucosal melanoma, was not known.

Assigning the right treatment to the right patient at the right time by the right healthcare provider can help improve the quality of care. Bridging the knowledge gap between trials and real-world enables more effective use in daily clinical practice, benefiting both patients and society.[10]

Unique real-world data in the Netherlands

Since 2013, all patients with advanced melanoma who receive systemic treatment are registered in the Dutch Melanoma Treatment Registry (DMTR). When the era of new systemic treatments started in 2012, the Dutch Society of Medical Oncologists (NVMO) advocated fast accessibility to newly available anti-cancer drugs for Dutch patients with advanced melanoma. This was approved by the Dutch Minister of Health on two conditions: centralisation of melanoma care and registration of real-world data of all patients with advanced melanoma in the Netherlands.

The general objectives of the DMTR were to provide insight in real-world use, safety and effectiveness of new treatments, to improve the quality of melanoma care by clinical auditing and benchmarking between melanoma centres, to provide transparency of the quality of melanoma care and to perform outcome research. To fulfil all these purposes, a comprehensive dataset of more than 500 variables was agreed between the involved stakeholders. The nationwide and population-based character and the comprehensiveness of the DMTR data make it a unique real-world data source.

This thesis utilized the DMTR data to generate real-world evidence on new systemic therapies in advanced melanoma in daily clinical practise.

Bridging the efficacy-effectiveness gap

Safety and survival in the era of new treatment options

In the Netherlands, implementation of all immune- and targeted therapies was fast and safe [Chapter 2]. Parallel to newly approved more effective systemic therapies the use of new treatments shifted year after year. In 2013, 76% of patients registered in the DMTR received a systemic therapy and this increased to 89% in 2017. In 2017, anti-PD-1 monotherapies, BRAK plus MEK inhibitors and ipilimumab plus nivolumab were the dominant first-line systemic therapies [Chapter 2]. Percentages of grade 3-4 AEs of all new systemic therapies were comparable to those in the phase III trials and no new safety signals were observed [Chapter 2].

In 2013, the overall survival (OS) was already higher compared with historical survival of patients with advanced melanoma and this increased to a median of 18 months in 2017.[2] This corresponds to what other real-world studies found in Denmark, Canada and the Unites States.[11–14] Interestingly, data from the Dutch Cancer Registration (NKR) may indicate that, despite a sustained increase in incidence, mortality due to (all stage) melanoma in the Netherlands has stabilized in recent years.[1] This is an additional indication that patients with advanced melanoma in the Netherlands have benefitted from the fast availability of the entire package of immune- and/or targeted therapies [Chapter 2].

Patients not represented in phase III trials

The magnitude of the efficacy-effectiveness gap for new systemic therapies for advanced melanoma is illustrated by the fact that 40% of all patients in the Netherlands treated with (a) systemic therapy were not represented in the phase III trials (trial-ineligible patients) [Chapter 3]. The OS of trial-ineligible patients (8.8 months) lagged behind the OS of real-world patients resembling those in phase III trials (trial-like patients; 23 months). Trial-ineligibility was due to brain metastasis and/or Eastern Cooperative Oncology Group performance score (ECOG PS) of

≥2 in 86% of trial-ineligible patients [Chapter 3]. Nearly 70% of trial-ineligible patients had brain metastases.

Prognostically the most important unfavourable factors in the trial-ineligible patient population were LDH level of >2x ULN, followed by ECOG PS of ≥1 and symptomatic brain metastasis [Chapter 3]. The prognostic subgroups created with these factors showed that the trial-ineligible population was prognostically heterogeneous, meaning that there was a wide spread of predicted survival within most subgroups and long-term survival could be achieved within most subgroups. Only the subgroups of patients with *LDH of >2x ULN plus ECOG PS of ≥2 plus (a)symptomatic brain metastasis* and *LDH of >1x ULN plus ECOG PS of ≥2 plus symptomatic brain metastasis* had uniformly poor predicted survival [Chapter 3].

This information can help set realistic treatment goals and expectations for patients who are not represented in RCTs and who (have to) decide to undergo systemic treatment. Given the high proportion of patients with brain metastases that comprised the trial-ineligible population, patients with brain metastasis should be included in RCTs to increase their generalizability.[15] This is challenging due to the multimodality of treating brain metastases, but clinical trials in this setting have been and are being performed.

Prognostic factors for survival

In the Dutch real-world advanced melanoma population, the prognostic factors associated with death were baseline LDH level ≥1x ULN, ECOG performance score of ≥1, distant metastases in ≥3 organ sites, brain- and liver metastasis [Chapter 2]. These prognostic factors are well-known in the international literature.[16–20] As stated in the previous paragraph, clinicians and patients can use the prognostic information of abovementioned patient- and disease characteristics to better manage expectations of the outcomes of systemic treatment.

An important additional finding was that before and beyond 6 months after diagnosis the hazard ratios for death were different. Elevated LDH levels and higher ECOG PS were significantly associated with death in both periods, but to a lesser extent in the period beyond 6 months. These factors may determine short-term mortality and/or the ability to reach and sustain a durable response. Patient with BRAF-mutant melanoma had favourable survival compared to BRAF wild-type melanoma in the first 6 months and this effect disappeared beyond 6 months [Chapter 2]. Shorter time to response and high response rates of targeted therapy could explain this finding.[3,4,21] Immune checkpoint inhibitors are known for delayed clinical effects and long-term survival which could enhance the non-proportionality of the hazard for death.[22]

For research it would be interesting to analyse the association with survival of the 6-month patient- and disease characteristics in addition to the baseline characteristics. Based on this thesis prognostic factors such as LDH level, ECOG performance score, distant metastases in

≥3 or <3 organ sites and brain- and liver metastases are factors of interest. This may help clinicians implement a 6-month evaluation moment to inform patients on their prognosis.

Immune checkpoint inhibitors in real-world

Anti-PD-1 monotherapy

The anti-PD-1 antibodies, nivolumab and pembrolizumab, were the second type of immunotherapy approved for advanced melanoma. With objective response rates of 33-40%, median OS of 20.3-37.5 months and only 10% to 12% grade 3-4 AEs, anti-PD-1 antibody results are superior to ipilimumab, which was the first immunotherapy approved for advanced melanoma.[5,23–26]

In real-world, anti-PD-1 antibodies were safe and used effectively as first-line treatment for advanced melanoma [Chapter 5]. The median OS of trial-like patients was comparable to those observed in the anti-PD-1 antibody phase III trials with a median OS of 31 months [Chapter 5]. Twenty-nine percent of patients treated with anti-PD-1 monotherapy in the first-line did not meet ≥1 trial eligibility criteria. Despite having a worse prognosis than trial-like patients, the median OS of trial-ineligible patients still was 17 months.[2] Fifteen percent of the real-world population experienced grade 3-4 AEs.

ECOG PS of ≥1, liver metastasis and symptomatic brain metastasis were negatively associated with OS. These factors plus elevated LDH have high impact as they were also associated with death in a competing risk analysis for second-line treatment [Chapter 5]. That anti-PD-1 monotherapy is less effective in patients with one or more of these prognostic factors should be considered when choosing the right first-line treatment.

Achieving a CR with anti-PD-1 monotherapy is an indicator of long-term survival. One-third of patients had a complete or partial response (CR or PR) two years after the start of anti-PD-1 monotherapy [Chapter 5]. In total, 20% of patients treated with first-line anti-PD-1 monotherapy reached a CR and these patients had a 2-year OS probability from the first reported CR of 92%. These results correspond to those observed by Robert et al. using data from a phase Ib trial.[27]

Given the AEs, necessity for hospital visits and (associated) health-care cost, patients would benefit from early anti-PD-1 discontinuation. However, criteria for optimal treatment duration are not available. Jansen et al. observed that patients in whom a CR is achieved a minimal treatment duration of 6 months was favourable.[28] We found that after anti-PD-1 discontinuation, the ongoing survival was high in patients who had a CR or PR at the moment of discontinuation [Chapter 6]. In patients who discontinued anti-PD-1 monotherapy, fast initial response (PR or CR) to anti-PD-1 monotherapy and anti-PD-1 discontinuation with a CR were positively associated with survival [Chapter 6].

In the RCTs, patients were treated up to 2 years (and even more) with anti-PD-1 monotherapy, but early anti-PD-1 discontinuation seems feasible. The median treatment duration in our real-world was less than 12 months and some patients responded to rechallenge with anti-PD-1 monotherapy [Chapter 6]. Response rates after rechallenge with anti-PD-1 monotherapy as high as 70% have been reported.[29] The Safe Stop trial currently enrolling in the Netherlands, investigates whether discontinuation upon first radiological PR or CR after minimal 6 months of anti-PD-1 monotherapy is a feasible treatment strategy.[30] Until these results are available, our findings may guide early anti-PD-1 discontinuation.

Ipilimumab plus nivolumab combination therapy

In the CheckMate-067 trial, combining the CTLA-4 and anti-PD-1 antibodies ipilimumab plus nivolumab led to a 5-year OS of 52% compared to 44% for nivolumab monotherapy.[31] However, a 55% of patients experienced severe treatment-related AEs and 36% discontinued treatment due to any grade AEs.[32] In trial setting, discontinuation because of an AE did not affect the OS.[33]

Compared to the CheckMate-067 trial, patients in real-world who received first-line ipilimumab plus nivolumab were younger and mainly had an ECOG PS of 0-1, but had a higher disease burden, reflected by higher percentages of patients with stage M1c disease, elevated LDH levels and brain metastases [Chapter 7]. Survival outcomes of trial-like patients were similar to those in the CheckMate-067 trial [Chapter 7].[31]

Interestingly, trial-ineligible patients could also reach long-term survival (4-year OS of 39%) [Chapter 7]. Brain metastases were the main reason of trial-ineligibility. Overall survival of patients who had none or asymptomatic brain metastases was comparable (4-year OS of 48% vs. 45%), but in the multivariable analysis asymptomatic brain metastases were associated with death. This is proof that having asymptomatic brain metastasis does not preclude long-term survival, provided that the patient has other favourable prognostic factors. Even patients with symptomatic brain metastasis had a 4-year OS probability of 36%. Given the historical median OS for patients with brain metastases of 3.5 months, our study illustrates the progress that has been made in the real-world setting.[34] It should be emphasized that these results are achieved through a combination of systemic with local treatments (surgery or radiotherapy).

Overall survival of patients with BRAF-mutant melanoma was superior compared to BRAF wild-type melanoma, despite similar progression-free survival. Three quarters of the patients with BRAF-mutant melanoma received BRAF plus MEK inhibitors as second-line treatment [Chapter 7]. Part of the OS benefit of first-line ipilimumab plus nivolumab we observed probably was due to sequential treatment with BRAF plus MEK inhibitors. This underscores the results of the DREAMseq trial in which first-line ipilimumab plus nivolumab followed by dabrafenib plus trametinib (a BRAF plus MEK inhibitor combination) was superior to first-line dabrafenib plus

trametinib followed by ipilimumab plus nivolumab.[35] Van Breeschoten et al. showed in a DMTR-study that first-line anti-PD-1 monotherapy compared to first-line BRAF plus MEK inhibitor showed superior survival in patients with BRAF-mutant melanoma that had favourable patient- and tumour characteristics.[36] Patients with BRAF-mutant melanoma appear to benefit from sequential targeted therapy after anti-PD-1 monotherapy or ipilimumab plus nivolumab [Chapter 5 and 7].

Our results considering, ipilimumab plus nivolumab was safe and beneficial in daily clinical practice (i.e., under the 'unideal' circumstances of the real-world). Besides the efficacy proven in the CheckMate-067 trial, our study confirms the effectiveness of ipilimumab plus nivolumab in advanced melanoma. Even in patients with (a)symptomatic brain metastasis.

Mucosal melanoma - a rare type of melanoma

Mucosal melanoma, accounting for 1-2% of all melanomas, is a rare type of melanoma and this complicates research. Our research with the DMTR data showed that, in contrast to patients with advanced cutaneous melanoma, the OS of patients with advanced mucosal melanoma did not improve between 2013 and 2017, despite the introduction of novel systemic therapies [Chapter 4]. The median OS of patients with advanced mucosal melanoma of 11.8 months still was higher than the historical median OS of 6-8 months for advanced melanoma in general.[2] The fact that patient- and disease characteristics between patients with advanced mucosal and cutaneous melanoma were similar suggests that mucosal melanoma has an inherent worse prognosis. It is hypothesised this may be due to a different, more aggressive, biological behaviour.[37] Future research should focus on gaining more knowledge about the vulnerabilities of mucosal melanoma in order to increase the effectiveness of novel treatment strategies.

Advanced uveal melanoma and melanomas of unknown primary (other rare types of melanomas) could also be investigated with the real-world data of the DMTR. The prognosis of advanced uveal melanoma still is poor, despite the increased number of treatment options.[38] In contrast to uveal melanoma, the prognosis of advanced melanomas of unknown primary was better than cutaneous advanced melanomas with known primary, despite poorer baseline characteristics.[39] These real-world insights illustrate the importance of real-world evidence and the need for more research to better treat these rare types of melanomas. We emphasise the need for international collaboration allowing data exchange to increase sample size and research on rare types of melanomas.

(Neo)adjuvant treatment strategy

During this PhD, phase III trials were conducted on targeted- and immunotherapies as adjuvant treatment strategy in stage III melanomas [Chapter 8]. The efficacy as adjuvant therapy in stage III melanomas was proven for anti-PD-1 antibodies pembrolizumab and nivolumab and BRAF plus MEK inhibitor dabrafenib plus trametinib.[40,41] Patients with stage III melanomas are now

registered in the DMTR. First results of research with the DMTR data on high-risk melanoma are promising. Recurrence-free survival in real-world was comparable to trials even though more patients discontinued anti-PD-1 monotherapy earlier than by protocol.[42] A higher percentage of patients experienced toxicity of (neo)adjuvant anti-PD-1 monotherapy.[42]

In the future, the DMTR data will generate important real-world evidence on the effectiveness of (neo)adjuvant treatment strategies. Insights into rechallenge with the same treatment and previous other (neo)adjuvant treatments on effectiveness in recurrent disease will be of great value for daily clinical practice. And real-world evidence is needed on the effectiveness of immune- and targeted therapies for patients, who in the course of their melanoma, develop metastases early or late after these same systemic therapies were given in the (neo)adjuvant setting.

The Dutch Melanoma Treatment Registry as a blueprint

The potential of real-world data

Real-world data can be a powerful tool, without the expense of conducting a clinical trial, to create real-world evidence and insights of interest to patients, doctors, scientists, governing organisations, health-care insurers and medical product developers.[43] With real-world data post-market safety, adverse events (AEs) and accessibility across a country can be monitored. The extent of external validity of RCTs for real-world can be investigated by mirroring these clinical trials. In contrast to RCTs, in-depth analysis of risk factors, prognostic subgroups or rare manifestations of a disease can be performed, where analysis of heterogeneity of treatment effect is not possible due to the limited sample size that is only meant to test the primary hypothesis. The quality of care can be improved by learning from benchmarking data between hospitals. Furthermore, medical product developers can gain product-specific insights for post-market obligations and marketing purposes. Evaluation of medication and healthcare utilisation by health technology assessments can provide a basis for reimbursement schemes, support regulatory decisions and substantiate price negotiations, especially when patient-reported outcomes are added.[43]

Realizing the potential of the DMTR

The DMTR has fulfilled many of the above-mentioned purposes realizing the potential of real-world data. First, the purposes of the DMTR are elaborated, after which the lessons learned and future of the DMTR are discussed.

Output of outcome research with the Dutch Melanoma Treatment Registry

Outside this thesis the DMTR has also contributed to real-world evidence of advanced melanoma in a new era of systemic therapies. As the DMTR data has matured, more and more research could be conducted; until June 2022 a total of 30 articles have been published (figure 1). The research using the DMTR data can be roughly divided into four subgroups: real-world

outcomes (*n*=11), subgroup analysis (*n*=12) (in-depth research of clinical research questions (*n*=9), rare types of melanomas (*n*=3)), clinical audit and benchmarking (*n*=2), economic research (*n*=3) and miscellaneous (*n*=2; table 1).

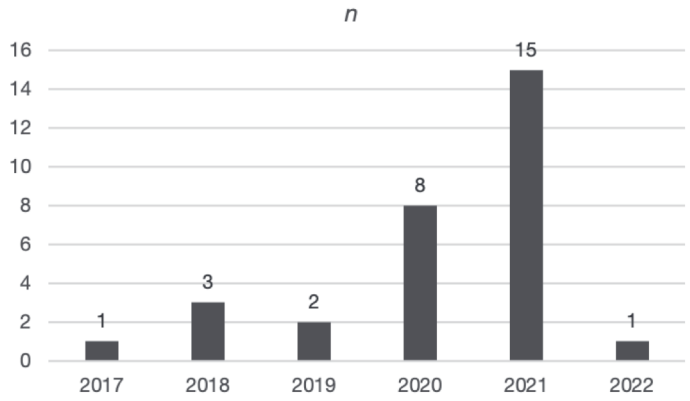

Figure 1 Number of articles published that use the data of the Dutch Melanoma Treatment Registry. Last updated in June 2022.

Clinical audit and benchmarking

More than a century ago, surgeon Dr. Ernest Amory Codman stated that clinical outcomes of each treated patient should be monitored to improve the quality of care. He was despised by his colleagues for the idea of critically assessing one's own medical practise. Ten to fifteen years ago, the demand for transparent, hospital-specific outcomes came from society in the Netherlands. At the same time the medical professionals had the desire to gain more in-depth results to be able to improve their quality of care. In 2022, the Dutch Institute for Clinical Auditing facilitates systematic analysis of processes and outcomes of care of 23, mainly surgical, nationwide audits.[70]

Clinical auditing and benchmarking of surgical treatments is common, but to the field of medical oncology this was a new concept. The first quality indicators of the DMTR were mainly structure and process indicators. The only outcome indicators related to the primary purpose of the DMTR: the use and safety of new drugs. Safety was monitored by reporting adverse events and mortality due to an adverse event. New drugs were implemented fast across the Netherlands and the percentage of adverse events was comparable to trial data without differences between hospitals [Chapter 2]. These quality indicators were manageable due to the binary outcome measure and relatively short follow-up that was required, but did not reflect the quality of melanoma care. This raised the question what outcome indicators could be used to monitor and improve the quality of melanoma care.

The primary outcome measure in scientific research usually is overall survival, but there are obstacles to use this measure as an outcome indicator. To analyse survival, the data need a long

enough follow-up to be able to be assessed, but clinical auditing requires short feedback-loops for the plan-do-check-act cycle. Benchmarking melanoma centres is complicated by small size per melanoma centre per cohort year, which disallows casemix-adjustment. In oncology care, personal preferences and considerations of a patient play an important role in treatment choices. These limitations are an obstacle for clinical auditing and transparency purposes. However, discussing this outcome indicator may reduce discrepancies between melanoma centres and increase efficient use of systemic therapies to improve the melanoma care. There was significant variation in 2-year survival between melanoma centres in the Netherlands in 2014 and 2015, but this normalised in 2016 and 2017.[64]

The outcome indicator currently in development for the DMTR is focussing on end-of-life care. This indicator measures whether a patient received a systemic therapy in the 45 or 90 days before death. Reasons to investigate this topic is that there are concerns of safety, efficacy, cost-effectiveness and quality of life (or death) of systemic therapies in the end-of-life period.[71] Many factors influence the decision to start systemic therapy in an end-of-life situation. And sometimes it is not clear that the end of life is near. Still, this outcome indicator is an interesting starting point for in-depth analysis and discussion. In the Netherlands, there was significant variation between melanoma centres in the percentages of patients who received a new systemic therapy within 45 or 90 days before death.[52] Identifying this hospital variation is important as in-depth analysis and discussion of hospital variation can improve the quality of melanoma care.

An important value of the DMTR was that it allowed structured feedback of benchmarked outcomes between melanoma centres. This was a first for medical oncology in the Netherlands. Four times per year the scientific committee, consisting of medical oncologists from the melanoma centres, an oncologic surgeon, a pathologist and representatives of the institute of Medical Technology Assessment (iMTA), held a meeting in which the data supported a substantive discussion on what could improve the more effective treatment of advanced melanoma with new systemic therapies. Online benchmarked feedback was continuously available for medical oncologists. This synchronised and improved the quality of melanoma care across the Netherlands reflected by the normalisation of variation in OS between melanoma centres.[64]

Table 1 Articles published in which the data of the Dutch Melanoma Treatment Registry is use

Study	Year	Type	Subject
Jochems[44]	2018	Real-world outcomes	*Ipilimumab in real-world*
Schouwenburg[45]	2018	Real-world outcomes	*Vemurafenib in real-world*
van Zeijl[46]	2020	Real-world outcomes	*Anti-PD-1 monotherapy in real-world*

van Zeijl[47]	2020	Real-world outcomes	*Patients not represented in phase III trials*
van Zeijl[48]	2021	Real-world outcomes	*Survival outcomes from 2013 to 2017*
van Zeijl[49]	2021	Real-world outcomes	*Discontinuation of anti-PD-1 monotherapy*
Ismail[50]	2021	Real-world outcomes	*Brain metastasis in post-approval trials versus patient registries*
van Breeschoten[51]	2021	Real-world outcomes	*Outcomes according to BRAFV600 status*
van Breeschoten[36]	2021	Real-world outcomes	*BRAF/MEK inhibitors versus anti-PD-1 monotherapy (propensity-matched)*
van Breeschoten[52]	2022	Real-world outcomes	*End-of-Life use of systemic therapy in patients with advanced melanoma*
de Meza[42]	2021	Real-world outcomes	*Adjuvant treatment for melanoma in clinical practice*
Verheijden[53]	2020	Subgroup analysis	*Anti-TNF and survival in steroid refractory ipilimumab and anti-PD-1 treated patients*
van der Kooij[54]	2020	Subgroup analysis	*Adolescents and young adults versus older adults*
Verheijden[55]	2020	Subgroup analysis	*Risk of severe checkpoint inhibitor toxicity in more advanced disease*
Biewenga[56]	2021	Subgroup analysis	*Checkpoint inhibitor induced hepatitis, liver metastasis and outcomes*
van der Kooij[57]	2021	Subgroup analysis	*Checkpoint inhibition and pre-existing autoimmune disease*
de Glas[58]	2021	Subgroup analysis	*Older patients treated with checkpoint inhibitors*
Jochems[59]	2021	Subgroup analysis	*Systemic therapy in older patients*
van der Kooij[60]	2021	Subgroup analysis	*Sex-based differences in treatment with immune and targeted therapy*
van Zeijl[61]	2020	Subgroup analysis	*Outcomes of advanced mucosal melanoma*
Jochems§[38]	2019	Subgroup analysis	*Outcomes of advanced uveal melanoma*
Verver[39]	2021	Subgroup analysis	*Outcomes of advanced melanoma of unknown primary*
Schouwenburg[62]	2019	Subgroup analysis	*Treatment strategy for patients with highly elevated LDH*
Jochems[63]	2017	Clinical audit and benchmarking	*Quality assurance in the melanoma care*
van Breeschoten[64]	2021	Clinical audit and benchmarking	*Hospital variation in treatments and survival outcomes*
Franken[65]	2018	Economic research	*Real-world healthcare costs of ipilimumab*
Leeneman[66]	2020	Economic research	*Real-world healthcare costs of advanced cutaneous melanoma*
Franken[67]	2021	Economic research	*Trends in survival and costs in advanced melanoma*
Blankenstein[68]	2020	Miscellaneous	*Surgery for advanced melanoma in the era of new systemic therapy*
van Not[69]	2021	Miscellaneous	*The unfavourable effects of COVID-19 on Dutch advanced melanoma care*

Other purposes

The DMTR has been used for cost-effectiveness analysis by the iMTA. Their economic research showed that most healthcare costs of treatment of advanced melanoma are caused by the systemic therapy (>80%), followed by hospital admissions or visits, diagnostics and imaging.[66,67,72] Monthly costs were highest for ipilimumab plus nivolumab and ipilimumab monotherapy and "lowest" for nivolumab and pembrolizumab (chemotherapy not considered).[66] As the overall survival improved and more anti-cancer drugs became available, healthcare costs were stable over the years (€100 000 to €129 000 per year for one patient who receives a systemic therapy).[67] The total economic impact for all patients with advanced melanoma was approximately €450 million from July 2013 to December 2018.[67] It is important to realize is that the extent to which these newly introduced systemic therapies achieve off-treatment long-term survival will impact average costs made.

The Dutch government organisation Zorginstituut Nederland (ZiNL) can use this information and the additional reports on the total costs and survival outcomes of the entire package of immune- and/or targeted therapies that were generated, to assess the therapeutic value and cost-effectiveness of new treatments and advice the government on reimbursement. Pharmaceutical parties received monthly reports on safety of their product and patient- and disease characteristics of patients treated with their product(s).

Lessons that can be learned from the DMTR

Data collection and data quality

The DMTR was specifically created and designed to fulfil all of its objectives. Consensus among stakeholders resulted in a 'minimal' dataset of more than 500 variables, of which sections of variables had to be registered for each systemic therapy a patient received. Data was collected manually from electronic healthcare records (EHRs) by trained 'data-employees' and all registered data had to be checked and approved by medical oncologists. This was the most labour-intensive process requiring most of the financial resources.

Despite efforts to ensure data quality, studies in this thesis had +/- 15% of cases with missing data in ≥1 variables necessary for multivariable analysis (non-complete cases) [Chapter 2].[48] There is methodology for dealing with missing data, such as multiple imputation which we used, but this is an area of research that is under development (especially for use with multivariable Cox models).[73] For imputation, assumptions about the missing data that cannot be verified are made. One should therefore first strive for more complete registration of data.

To meet the increased demand for phase IV research, given the accumulation of innovative new drugs, the efficiency of data registration needs to improve. Using existing data sources and structuring EHRs for automatic data extraction can help reduce registration burden and cost. Financial data can be used to pre-fill data in the registry and for cost-effectiveness research.

However, a truly sustainable solution to the hassle of data collection is one-time (structured) registration medical data as linked data and multipurpose availability (e.g., EHRs, clinical auditing, benchmarking and outcome research).[74]

Patient reported outcome measures

DMTR had the ambition to combine clinical outcomes with patient-reported outcome measures (PROMS) for cost-effectiveness research, clinical auditing of melanoma care through quality indicators, and use as decision support for doctors and patients in individual cases. However, the percentage of respondents to the PROMS questionnaires was low. Hypothesised reasons for the low response were that the scientific PROMS questionnaires were too long, many patients lacked digital skills and the PROMS were not used in the doctor's office to discuss patients' needs. At the DMTR scientific meetings medical oncologists reported that they felt hesitant to ask some of their patients to participate after communicating the diagnosis, especially if a patient had a poor prognosis. The General Data Protection Regulation (GDPR) complicated merging of the DMTR data with the PROMS data which was registered in a separate dataset using patient friendly software. In addition, relating PROMS to a specific systemic therapy was extremely complicated, because of the intervals between PROMS questionnaires and high variability in treatment duration and strategies.

There is some evidence that PROMS can improve patient-caregiver communication and increase patient satisfaction.[75] However, prerequisites for success of PROMS are sufficient intensity of feedback, targeting patients, nurses and doctors with easy-to-interpret meaningful results and training of patients and health professionals.[75] In other words, PROMS implementation affects the entire clinical work process and requires support and adaptation to a new way of working. An important lesson to be learned from the DMTR is that the PROMS implementation must be preceded by a realistic analysis of the objectives of PROMS and statistical, clinical and digital feasibility. It may be easier to implement PROMS in a disease-specific registry when PROMS are already an integral part of the clinical process, rather than implementing PROMS in the clinical process through a disease-specific registry.

Although implementation was unsuccessful for advanced melanoma, PROMS are relevant for the (neo)adjuvant use of systemic therapies. The potential reduction in quality of life must outweigh the chance for life prolongation. Patient reported experience measures (PREMS) could help improve how hospitals deliver quality of care. This information could allow hospitals to improve the quality of care and patients to informedly choose a hospital.

Limitations and considerations for the DMTR and real-world data in general

To realize its potential, real-world data must be of high quality, the data and daily clinical practice in the period studied must be well understood, and researchers must be aware of the limitations of statistical analysis. Here we describe some important considerations for the Dutch

Melanoma Treatment Registry (and for real-world data in general), including possible ways to handle some of the limitations.

Implications of daily clinical practise on the data

Daily clinical practise and its implications on the (analysis of the) data should be well understood by researchers. During this PhD-period, the available package of new drugs was rapidly changing for patients with advanced melanoma. The availability of new drugs depended upon the year a patient was diagnosed. In the Netherlands, there were no guidelines for the use of new drugs and all newly available drugs could be administered sequentially. The use of new drugs also changed as more experience was gained by the medical oncologists. This caused variability in treatment strategies that patients with advanced melanoma received, complicating statistical analysis.

For example, interpreting a supposedly straightforward analysis of first-line therapy with the DMTR data is challenging. Overall survival reflects the effectiveness of an entire sequential treatment strategy until the end of follow-up or when a patient dies. In multi-year analysis, one should be aware (and report) the influence of rapidly changing treatment landscape as was the case for advanced melanoma in the Netherlands [Chapter 2].

A more specific evaluation of the benefit of first-line treatment can be achieved by analysing progression-free survival or with the competing risks method.[76] The competing risk method analyses treatment failure (in this thesis defined as start of second-line treatment) and its competing risk death before treatment failure. Future analyses should also consider the treatment strategy of switching to another type of systemic therapy before progression in patients with stable disease or partial response.

Analysis of second- or third-line treatment is more complicated, as a patient can transit from first-, to second- to third-line treatment after (or without) progression, with the risk of dying at any time. In multi-state models, the sequences of states (that one patient can experience sequentially) and the competing risks (that are mutually exclusive) are modelled to evaluate the effect on the long-term outcomes.[67,77] Now that the treatment landscape for advanced melanoma has stabilized with anti-PD-1 monotherapy, BRAF plus MEK inhibitors and ipilimumab plus nivolumab as dominant treatments [Chapter 2], these analyses can help optimize treatment sequencing.

Statistical errors

Confounding by indication is a type of confounding bias that can lead to false inferences about the observed outcomes. There is confounding by indication when patient and/or disease characteristics are associated with the treatment choice and the outcome of interest. For advanced melanoma in the Netherlands, there are no guidelines for treatment choice and treatment choice depends on a patient's suitability to undergo treatment, as assessed by the

treating medical oncologist. For targeted- or immunotherapy in advanced melanoma, experience had to be gained in daily clinical practice with newly available drugs. This also changed how targeted- or immunotherapies were used by medical oncologists in different melanoma centres over the years.

Confounding by indication can be illustrated by patients with advanced melanoma who received targeted therapy. These patients had worse prognostic characteristics than patients who received immunotherapy.[36] This is probably because medical oncologists wanted to use the high response rate and shorter time to response of targeted therapy.[3,21,78] Immunotherapy with ipilimumab plus nivolumab is usually preferred in patients with a higher burden of disease, no BRAF V600 mutation, asymptomatic brain metastases, liver metastases, who are younger and have a low ECOG performance score, because this treatment is more burdensome.[31] As a consequence, a survival benefit of a therapy is not only due to treatment effect, but to the prognostic characteristics of the patient.

Fortunately, there are methods that adjust a large part of confounding by indication, such as multivariable models and propensity score matching. These methods correct for known and measured confounders. Prognostic factors for advanced melanoma were extensively registered in the DMTR. Using the DMTR data, first-line anti-PD-1 antibodies showed a survival benefit over first-line BRAF plus MEK inhibitors in a propensity score matched cohort.[36] Another method, which we will not further describe, is the instrumental variable analysis in which a factor that influences treatment choice independently of patient characteristics (an instrumental variable) is used as means of randomisation.[79]

Another statistical error to avoid is immortal time bias. This occurs when groups are analysed whose patients do not acquire membership until some time after the start of follow-up. Patients who fail before the future event cannot belong to a group. This is in fact a selection bias based on a future event. In our study of ipilimumab plus nivolumab, there would be immortal time bias if survival of patients who discontinued treatment due to grade 3 or 4 AEs were compared to the remaining patients. Patients who die before they can develop an AE cannot acquire membership of the groups that discontinued treatment due to grade 3 or 4 AEs. This statistical error can be avoided with models that take time-dependent information into account (e.g., time-dependent covariates in Cox models). A limitation of the DMTR data was that information on when a grade 3-4 AE occurred was missing.

Lead time bias occurs when there is an artificial survival advantage, because a disease stage can be identified earlier by, for example, improved imaging techniques.[80] Given that there were new treatment options for advanced melanoma, it paid off to search more intensively for metastasis at an earlier stage. For advanced melanoma in the Netherlands this phenomenon could not be investigated with the DMTR data. For advanced melanoma no guideline changes

for staging occurred in the Netherlands and we assume that lead time bias only had a small effect.

Future of the Dutch Melanoma Treatment Registry

Post-marketing requirements

Although DMTR data have already been used for many purposes, one could go one step further. A disease-specific registry can also serve the post-marketing study commitment that is required by of the regulatory authorities (e.g., EMA and FDA). Currently, post-approval clinical trials are conducted by the pharmaceutical companies, but real-world patients are still underrepresented and these trials often lack a comparator. By replacing the post-approval trials with disease-specific registries unnecessary duplication of effort and data can be avoided and a more inclusive population can be investigated. Ismail et al. have already shown that disease-specific registries have the potential to serve as post-approval trials.[50] Pharmacovigilance can also be conducted with the DMTR data as toxicity data is registered. In the field of haematology an initiative called the GoCART coalition was started for this purpose among others.[81]

Serving a multitude of purposes increases the relevance, cost-effectiveness and complexity of a registry, as participating stakeholders may have conflicting interests. Aligning the aims of a registry and the interests of stakeholders is a delicate and time-consuming process.[82] However, given the financial burden that new innovative drugs pose to society, it could be argued that surveillance of new drugs in real-world setting should be a requirement.

Utilizing all data sources

Data sources that already exist can, in theory, enhance real-world data. As stated before, financial data can increase efficiency of data collection. Utilising data on whole genome sequencing from the tumour and the host, molecular and pathology data could mean an exciting step forward to achieving real-world evidence and personalising medicine for (advanced) melanoma. International collaboration between melanoma registries around the world can boost melanoma research and quality of melanoma care; rare melanomas can be investigated and comparison of outcomes between countries becomes possible. Besides research, the international community can learn with and from each other on how data can be shared under the GDPR legislation, how registries should be designed and how data should be registered.

Trials within cohorts

Disease-specific registries could even be used to execute randomised controlled trials with the Trials within Cohorts (TwiCs) approach.[83] The principle of this method is that all eligible patients are identified within a registry. Some of these eligible patients are randomly selected to be part of the intervention group. The outcomes of the intervention group are compared to the remaining eligible patients. Especially in a versatile treatment environment, as was the case for advanced melanoma, the

control group more naturally receives the optimal care in daily clinical practice in that time frame (rather than a static control-group like standard care). Informed-consent replicates the normal process in daily clinical practise. Innovative treatments can reach patients even faster with this real-world approach of phase III trials.

To conclude: from trials to real-world to the individual patient

This thesis provides real-world evidence for new systemic therapies for advanced melanoma that bridges part of the knowledge gap between clinical trials and real-world. Disease-specific registries such as the DMTR can play an important role in generating real-world evidence that can benefit patients, doctors and other healthcare stakeholders. By using all available real-world data, research can be stimulated and the quality of melanoma care can be improved. The next step is to use real-world evidence to personalize melanoma care to support informed decision-making. Because, in the end, all that matters is the individual patient.

References

1. NKR Cijfers. Accessed December 20, 2021. https://iknl.nl/nkr-cijfers
2. Korn EL, Liu PY, Lee SJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. *J Clin Oncol*. 2008;26(4):527-534.
3. Long G V., Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: A multicentre, double-blind, phase 3 randomised controlled trial. *Lancet*. 2015;386(9992):444-451.
4. Ascierto PA, McArthur GA, Dréno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2016;17(9):1248-1260.
5. Hodi FS, Kluger H, Sznol M, et al. Abstract CT001: Durable, long-term survival in previously treated patients with advanced melanoma (MEL) who received nivolumab (NIVO) monotherapy in a phase I trial. In: American Association for Cancer Research (AACR); 2016:CT001-CT001.
6. Robert C, Long G V., Schachter J, et al. Long-term outcomes in patients (pts) with ipilimumab (ipi)-naive advanced melanoma in the phase 3 KEYNOTE-006 study who completed pembrolizumab (pembro) treatment. *J Clin Oncol*. 2017;35(15_suppl):9504-9504.
7. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2017;377(14):1345-1356.
8. Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: A randomised dose-comparison cohort of a phase 1 trial. *Lancet*. 2014;384(9948):1109-1117.
9. Kendall JM. Designing a research project: randomised controlled trials and their principles. *Emerg Med J*. 2003;20(2):164-168.
10. Eichler HG, Abadie E, Breckenridge A, et al. Bridging the efficacy–effectiveness gap: a regulator's perspective on addressing variability of drug response. *Nat Rev Drug Discov 2011 107*. 2011;10(7):495-506.
11. Rigo R, Doherty J, Koczka K, et al. Real-world Outcomes in Patients with Advanced Melanoma Treated in Alberta, Canada: A Time-Era Based Analysis. *Curr Oncol*. 2021;28(5):3978.

12. Cowey CL, Liu FX, Boyd M, Aguilar KM, Krepler C. Real-world treatment patterns and clinical outcomes among patients with advanced melanoma: A retrospective, community oncology-based cohort study (A STROBE-compliant article). *Medicine (Baltimore)*. 2019;98(28).

13. Yu SY, Mckavanagh D, McPherson I, Walpole E, Atkinson V, Hollingworth S. Survival of advanced melanoma patients treated with immunotherapy and targeted therapy: A real-world study. *Pharmacoepidemiol Drug Saf*. 2021;30(10):1371-1379.

14. Whitman ED, Liu FX, Cao X, Diede SJ, Haiderali A, Abernethy AP. Treatment patterns and outcomes for patients with advanced melanoma in US oncology clinical practices. *Futur Oncol*. 2019;15(5):459-471.

15. Kim ES, Bruinooge SS, Roberts S, et al. Broadening eligibility criteria to make clinical trials more representative: American society of clinical oncology and friends of cancer research joint research statement. *J Clin Oncol*. 2017;35(33):3737-3744.

16. Manola J, Atkins M, Ibrahim J, Kirkwood J. Prognostic factors in metastatic melanoma: A pooled analysis of Eastern Cooperative Oncology Group trials. *J Clin Oncol*. 2000;18(22):3782-3793.

17. Gaudy-Marqueste C, Dussouil AS, Carron R, et al. Survival of melanoma patients treated with targeted therapy and immunotherapy after systematic upfront control of brain metastases by radiosurgery. *Eur J Cancer*. 2017;84:44-54.

18. Kelderman S, Heemskerk B, Van Tinteren H, et al. Lactate dehydrogenase as a selection criterion for ipilimumab treatment in metastatic melanoma. *Cancer Immunol Immunother*. 2014;63(5):449-458.

19. Joseph RW, Elassaiss-Schaap J, Kefford R, et al. Baseline tumor size is an independent prognostic factor for overall survival in patients with melanoma treated with pembrolizumab. *Clin Cancer Res*. 2018;24(20):4960-4967.

20. Diem S, Kasenda B, Spain L, et al. Serum lactate dehydrogenase as an early marker for outcome in patients treated with anti-PD-1 therapy in metastatic melanoma. *Br J Cancer*. 2016;114(3):256-261.

21. Ascierto PA, Long G V. Progression-free survival landmark analysis: a critical endpoint in melanoma clinical trials. *Lancet Oncol*. 2016;17(8):1037-1039.

22. Castañon E, Sanchez-Arraez A, Alvarez-Manceñido F, Jimenez-Fonseca P, Carmona-Bayonas A. Critical reappraisal of phase III trials with immune checkpoint inhibitors in non-proportional hazards settings. *Eur J Cancer*. 2020;136:159-168.

23. Robert C, Long G V., Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015;372(4):320-330.

24. Robert C, Schachter J, Long G V., et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372(26):2521-2532.

25. Schachter J, Ribas A, Long G V., et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). *Lancet*. 2017;390(10105):1853-1862.

26. Ascierto PA, Long G V., Robert C, et al. Survival Outcomes in Patients with Previously Untreated BRAF Wild-Type Advanced Melanoma Treated with Nivolumab Therapy: Three-Year Follow-up of a Randomized Phase 3 Trial. *JAMA Oncol*. 2019;5(2):187-194.

27. Robert C, Ribas A, Hamid O, et al. Durable complete response after discontinuation of pembrolizumab in patients with metastatic melanoma. *J Clin Oncol*. 2018;36(17):1668-1674.

28. Jansen YJL, Rozeman EA, Mason R, et al. Discontinuation of anti-PD-1 antibody therapy in the absence of disease progression or treatment limiting toxicity: clinical outcomes in advanced melanoma. *Ann Oncol*. 2019;30(7):1154-1161.

29. Reschke R, Ziemer M. Rechallenge with checkpoint inhibitors in metastatic melanoma. *JDDG J der Dtsch Dermatologischen Gesellschaft*. 2020;18(5):429-436.

30. Mulder EEAP, de Joode K, Litière S, et al. Early discontinuation of PD-1 blockade upon achieving a complete or partial response in patients with advanced melanoma: the multicentre prospective Safe Stop trial. *BMC Cancer*. 2021;21(1):323.

31. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med*. Published online September 28, 2019.

32. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(1):23-34.

33. Schadendorf D, Wolchok JD, Stephen Hodi F, et al. Efficacy and safety outcomes in patients with advanced melanoma who discontinued treatment with nivolumab and ipilimumab because of adverse events: A pooled analysis of randomized phase II and III trials. *J Clin Oncol*. 2017;35(34):3807-3814.

34. Agarwala SS, Kirkwood JM, Gore M, et al. Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. *J Clin Oncol*. 2004;22(11):2101-2107.

35. Atkins MB, Lee SJ, Chmielowski B, et al. DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing): A phase III trial—ECOG-ACRIN EA6134. *J Clin Oncol.* 2021;39:36_suppl, 356154-356154

36. van Breeschoten J, Wouters MWJM, Hilarius DL, et al. First-line BRAF/MEK inhibitors versus anti-PD-1 monotherapy in BRAF(V600)-mutant advanced melanoma patients: a propensity-matched survival analysis. *Br J Cancer*. 2021;124(7):1222-1230.

37. Kuk D, Shoushtari AN, Barker CA, et al. Prognosis of Mucosal, Uveal, Acral, Nonacral Cutaneous, and Unknown Primary Melanoma From the Time of First Metastasis. *Oncologist*. 2016;21(7):848-854.

38. Jochems A, van der Kooij MK, Fiocco M, et al. Metastatic uveal melanoma: Treatment strategies and survival - results from the Dutch Melanoma Treatment Registry. *Cancers (Basel)*. 2019;11(7).

39. Verver D, Grünhagen DJ, van Akkooi ACJ, et al. Clinical outcome of patients with metastatic melanoma of unknown primary in the era of novel therapy. *Cancer Immunol Immunother*. 2021;70(11):3123-3135.

40. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. *N Engl J Med*. 2017;377(19):1824-1835.

41. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. *N Engl J Med*. 2018;378(19):1789-1801.

42. de Meza MM, Ismail RK, Rauwerdink D, et al. Adjuvant treatment for melanoma in clinical practice - Trial versus reality. *Eur J Cancer*. 2021;158:234-245.

43. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence - What is it and what can it tell us? *N Engl J Med*. 2016;375(23):2293-2297.

44. Jochems A, Leeneman B, Franken MG, et al. Real-world use, safety, and survival of ipilimumab in metastatic cutaneous melanoma in The Netherlands. *Anticancer Drugs*. 2018;29(6):572-578.

45. Schouwenburg MG, Jochems A, Leeneman B, et al. Vemurafenib in BRAF-mutant metastatic melanoma patients in real-world clinical practice: Prognostic factors associated with clinical outcomes. *Melanoma Res*. 2018;28(4):326-332.

46. van Zeijl MCT, Haanen JBAG, Wouters MWJM, et al. Real-world Outcomes of First-line Anti-PD-1 Therapy for Advanced Melanoma: A Nationwide Population-based Study. *J Immunother*. 2020;43(8):256-264.

47. van Zeijl MCT, Ismail RK, de Wreede LC, et al. Real-world outcomes of advanced melanoma patients not represented in phase III trials. *Int J cancer*. 2020;147(12):3461-3470.

48. van Zeijl MCT, de Wreede LC, van den Eertwegh AJM, et al. Survival outcomes of patients with advanced melanoma from 2013 to 2017: Results of a nationwide population-based registry. *Eur J Cancer*. 2021;144:242-251.

49. van Zeijl MCT, van den Eertwegh AJM, Wouters MWJM, et al. Discontinuation of anti-PD-1 monotherapy in advanced melanoma—Outcomes of daily clinical practice. *Int J Cancer*. 2022;150(2):317-326.

50. Ismail RK, Sikkes NO, Wouters MWJMJM, et al. Postapproval trials versus patient registries: comparability of advanced melanoma patients with brain metastases. *Melanoma Res*. 2021;31(1):58-66.

51. van Breeschoten J, Wouters MWJM, de Wreede LC, et al. Nationwide Outcomes of Advanced Melanoma According to BRAFV600 Status. *Am J Clin Oncol*. 2021;44(2):82-89.

52. van Breeschoten J, Ismail RK, Wouters MWJM, et al. End-of-Life Use of Systemic Therapy in Patients With Advanced Melanoma: A Nationwide Cohort Study. *JCO Oncol Pract*. Published online August 9, 2022.

53. Verheijden RJ, May AM, Blank CU, et al. Association of Anti-TNF with Decreased Survival in Steroid Refractory Ipilimumab and Anti-PD1–Treated Patients in the Dutch Melanoma Treatment Registry. *Clin Cancer Res*. 2020;26(9):2268-2274.

54. van der Kooij MK, Wetzels MJAL, Aarts MJB, et al. Age Does Matter in Adolescents and Young Adults versus Older Adults with Advanced Melanoma; A National Cohort Study Comparing Tumor Characteristics, Treatment Pattern, Toxicity and Response. *Cancers (Basel)*. 2020;12(8).

55. Verheijden RJ, May AM, Blank CU, et al. Lower risk of severe checkpoint inhibitor toxicity in more advanced disease. *ESMO open*. 2020;5(6):e000945.

56. Biewenga M, van der Kooij MK, Wouters MWJM, et al. Checkpoint inhibitor induced hepatitis and the relation with liver metastasis and outcome in advanced melanoma patients. *Hepatol Int*. 2021;15(2):510-519.

57. van der Kooij MK, Suijkerbuijk KPM, Aarts MJB, et al. Safety and Efficacy of Checkpoint Inhibition in Patients With Melanoma and Preexisting Autoimmune Disease : A Cohort Study. *Ann Intern Med*. 2021;174(5):641-648.

58. de Glas NA, Bastiaannet E, van den Bos F, et al. Toxicity, Response and Survival in Older Patients with Metastatic Melanoma Treated with Checkpoint Inhibitors. *Cancers (Basel)*. 2021;13(11).

59. Jochems A, Bastiaannet E, Aarts MJB, et al. Outcomes for systemic therapy in older patients with metastatic melanoma: Results from the Dutch Melanoma Treatment Registry. *J Geriatr Oncol*. 2021;12(7):1031-1038.

60. van der Kooij M, Dekkers O, Aarts M, et al. Sex-Based Differences in Treatment with Immune Checkpoint Inhibition and Targeted Therapy for Advanced Melanoma: A Nationwide Cohort Study. *Cancers (Basel)*. 2021;13(18):4639.

61. van Zeijl MCT, Boer FL, van Poelgeest MIE, et al. Survival outcomes of patients with advanced mucosal melanoma diagnosed from 2013 to 2017 in the Netherlands - A nationwide population-based study. *Eur J Cancer*. 2020;137:127-135.

62. Schouwenburg MG, Suijkerbuijk KPM, Koornstra RHT, et al. Switching to Immune Checkpoint Inhibitors upon Response to Targeted Therapy; The Road to Long-Term Survival in Advanced Melanoma Patients with Highly Elevated Serum LDH? *Cancers (Basel)*. 2019;11(12):1940.

63. Jochems A, Schouwenburg MG, Leeneman B, et al. Dutch Melanoma Treatment Registry: Quality assurance in the care of patients with metastatic melanoma in the Netherlands. *Eur J Cancer*. 2017;72:156-165.

64. van Breeschoten J, van den Eertwegh AJM, de Wreede LC, et al. Hospital Variation in Cancer Treatments and Survival OutComes of Advanced Melanoma Patients: Nationwide Quality Assurance in The Netherlands. *Cancers (Basel)*. 2021;13(20).

65. Franken MG, Leeneman B, Jochems A, et al. Real-world healthcare costs of ipilimumab in patients with advanced cutaneous melanoma in the Netherlands. *Anticancer Drugs*. 2018;29(6):579-588.

66. Leeneman B, Uyl-de Groot CA, Aarts MJB, et al. Healthcare Costs of Metastatic Cutaneous Melanoma in the Era of Immunotherapeutic and Targeted Drugs. *Cancers (Basel)*. 2020;12(4).

67. Franken MG, Leeneman B, Aarts MJB, et al. Trends in survival and costs in metastatic melanoma in the era of novel targeted and immunotherapeutic drugs. *ESMO open*. 2021;6(6):100320.

68. Blankenstein SA, Aarts MJB, van den Berkmortel FWPJ, et al. Surgery for Unresectable Stage IIIC and IV Melanoma in the Era of New Systemic Therapy. *Cancers (Basel)*. 2020;12(5).

69. van Not OJ, van Breeschoten J, van den Eertwegh AJM, et al. The unfavorable effects of COVID-19 on Dutch advanced melanoma care. *Int J cancer*. Published online October 2021.

70. Beck N, Van Bommel AC, Eddes EH, Van Leersum NJ, Tollenaar RA, Wouters MW. The Dutch Institute for Clinical Auditing: Achieving Codman's Dream on a Nationwide Basis. *Ann Surg*. 2020;271(4):627-631.

71. Wiersma M, Ghinea N, Kerridge I, Lipworth W. "Treat them into the grave": cancer physicians' attitudes towards the use of high-cost cancer medicines at the end of life. *Sociol Health Illn*. 2019;41(2):343-359.

72. Franken MG, Leeneman B, Jochems A, et al. Real-world healthcare costs of ipilimumab in patients with advanced cutaneous melanoma in the Netherlands. *Anticancer Drugs*. 2018;29(6):579-588.

73. White IR, Royston P. Imputing missing covariate values for the Cox model. *Stat Med*. 2009;28(15):1982-1998.

74. Odgers DJ, Dumontier M. Mining Electronic Health Records using Linked Data. *AMIA Summits Transl Sci Proc*. 2015;2015:217. Accessed January 3, 2022.

75. Chen J, Ou L, Hollis SJ. A systematic review of the impact of routine collection of patient reported outcome measures on patients, providers and health organisations in an oncologic setting. *BMC Health Serv Res*. 2013;13(1):1-24.

76. Putter H, Fiocco M, Gekus RB. Tutorial in biostatistics: Competing risk and multi-state models. *Stat Med*. 2007;26(11):2389-2430.

77. Bakunina K, Hein Putter |, Versluis | Jurjen, et al. The added value of multi-state modelling in a randomized controlled trial: The HOVON 102 study re-analyzed. *Cancer Med*. 2021;00:1-11.

78. Larkin J, Ascierto PA, Dréno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med*. 2014;371(20):1867-1876.

79. Boef AC., le Cessie S, Dekkers OM. Instrumentele-variabele-analyse. *Ned Tijdschr Geneeskd*. Published online January 21, 2013:157:A5481.

80. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon: Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med*. 1985;312(25):1604-1608.

81. GoCART coalition – trusted partner and a leading force in the field of cellular therapies. Accessed May 20, 2022.

82. de Groot S, van der Linden N, Franken MG, et al. Balancing the Optimal and the Feasible: A Practical Guide for Setting Up Patient Registries for the Collection of Real-World Data for Health Care Decision Making Based on Dutch Experiences. *Value Heal*. 2017;20(4):627-636.

83. Relton C, Torgerson D, O'Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. *BMJ*. 2010;340(7753):963-967.