Text mining real-world data to evaluate systemic anti-cancer therapy

Laar, S.A. van

Part III

Real-world treatment safety

Chapter 6

Application of electronic health record text mining: Real-world tolerability, safety, and efficacy of adjuvant melanoma treatments

Sylvia A. van Laar, Ellen Kapiteijn, Kim B. Gombert-Handoko, Henk-Jan Guchelaar, Juliëtte Zwaveling

Cancers. 2022; 14(21): 5426

Abstract

Introduction: Nivolumab (N), pembrolizumab (P), and dabrafenib plus trametinib (D+T) are registered as adjuvant treatments for resected stage III and IV melanoma since 2018. Electronic health records (EHR) are a real-world data source that can be used to review treatments in clinical practice. In this study, we applied EHR text-mining software to evaluate the real-world tolerability, safety, and efficacy of adjuvant melanoma treatments.

Methods: Adult melanoma patients receiving adjuvant treatment between January 2019 and October 2021 at the Leiden University Medical Center, The Netherlands, were included. CTcue text-mining software was used to con-struct rule-based queries and perform context analysis for patient inclusion and data collection from structured and unstructured EHR data.

Results: In total, 122 patients were included: 54 patients treated with nivolumab, 48 with pembrolizumab, and 20 with D+T. Significantly more patients discontinued treatment due to toxicity on D+T (N: 16%, P: 6%, D+T: 40%), X^2 (6, n=122) =14.6, p=0.024. Immune checkpoint inhibitors (ICI) mainly showed immune-related treatment-limiting adverse events (AEs), and chronic thyroid-related AE occurred frequent (hyperthyroid-ism: N: 15%, P: 13%, hypothyroidism: N: 20%, P: 19%). Treatment-limiting toxicity from D+T was primarily a combination of reversible AEs, including pyrexia and fatigue. The 1-year recurrence-free survival was 70.3% after nivolumab, 72.4% after pembrolizumab, and 83.0% after D+T.

Conclusions: Text mining EHR is a valuable method to collect real-world data to evaluate adjuvant melanoma treatments. ICI were better tolerated than D+T, in line with RCT-results. For BRAF+-patients, physicians must weigh the higher risk of reversible treatment-limiting AEs of D+T against the risk of long-term immune-related AEs.

1. Introduction

In 2020, approximately 300,000 patients worldwide were diagnosed with melanoma of the skin, accounting for 1.7% of all cancer diagnoses [1]. In the Netherlands, the incidence of melanoma has more than doubled in the last 20 years from 18/100,000 people in 2001 to 43/100,000 in 2021 with a mortality rate of 4–5/100,000 [2]. The introduction of immune checkpoint inhibitors (ICI) (e.g., nivolumab, pembrolizumab and ipilimumab) and inhibitors of the mitogen-activated protein kinase pathway (e.g. BRAF inhibitors and MEK inhibitors) have improved the treatment of metastatic melanoma in the past years [3]. In 2018, nivolumab (N), pembrolizumab (P), and the combination of dabrafenib plus trametinib (D+T) were registered by the European Medicines Agency as adjuvant treatment in resected stage III and IV of melanoma [4-7]. Patients receive adjuvant treatment after surgical resection, for a maximum of 12 months or until treatment-limiting toxicity or recurrence of the disease.

The results of the phase III trials that were the basis for the indication expansion are summarized in Table 6.1. Eligibility criteria differed between trials, e.g., the inclusion of resected stage IV in the CheckMate 238 trial, and inclusion only of patients with a BRAF V600E or V600K mutation in the COMBI-AD trial [8]. Furthermore, all treatments were superior to their comparator regarding recurrence-free survival but concluding overall survival results are yet unknown.

As these patients are, in principle, cured after surgery, the safety profile of adjuvant therapy may be even more relevant than in the setting of palliative treatment. Regarding safety, nivolumab and pembrolizumab are comparable, but differ from dabrafenib plus trametinib treatment. Grade 3 or 4 adverse events (AEs) occurred in 25.4% and 31.6% of the study populations of nivolumab and pembrolizumab versus 41% in dabrafenib plus trametinib treated patients, and 9.7% and 13.8% of the patients discontinued treatment due to toxicity, compared to 26% in the dabrafenib and trametinib treated. However, most reported AEs on ICI were skin reactions and fatigue. All immune-related (ir)AEs combined also have a high incidence, of which hypothyroidism and hyperthyroidism – both manifestations of thyroiditis – were most frequent, but also include, e.g., diabetes mellitus type I [9, 11]. Of these immune-related endocrine toxicities it is presumed they result in permanent and irreversible dysfunction, resulting in lifelong hormone supplementation [14]. This contrasts with the AEs of dabrafenib plus trametinib, of which pyrexia, fatigue and nausea are most common and easily reversible after treatment interruption [12, 15].

Table 6.1. Phase III trial results for adjuvant treatments of melanoma

	Nivolumab	Pembrolizumab	Dabrafenib plus trametinib
Phase III trial	Checkmate 238 [8, 9]	EORTC/KEYNOTE-054 [10, 11]	COMBI-AD [12, 13]
Comparator	Ipilimumab	Placebo	Placebo
Eligibility criteria	Resected stage IIIb, IIIc and IV melanoma, ECOG PS: 0 or 1	Resected stage IIIa, IIIb, and IIIc melanoma, ECOG PS: 0 or 1	Resected stage IIIa, IIIb, or IIIc melanoma with a BRAF V600E or V600K mutation, ECOG PS: 0 or 1
Recurrence-free survival	1-year NIV: 71% IPI: 61% 4-year NIV: 51.7% IPI: 41.2% HR: 0.71, 95% CI = 0.60–0.86	1-year PEM: 75% PLA: 61% 3.5-year PEM: 60% PLA: 41% HR: 0.59, 95% CI = 0.49–0.70	1-year D+T: 88% PLA: 56% 5-year D+T: 52% PLA: 36% HR: 0.51, 95% CI = 0.42–0.61
Overall survival	4-year NIV: 77.9% IPI: 76.6% HR: 0.87 95% CI = 0.66–1.14	-	3-year D+T: 86% PLA: 77% HR: 0.57 95% CI = 0.42–0.79*
≥ Grade 3 AE	NIV: 25.4% IPI: 55.2%	PEM: 31.6% PLA: 18.5%	D+T: 41% PLA: 14%
Most common AE	Skin reactions: 44.5% Fatigue: 34.5% Gastrointestinal: 25.2%	All immune-related AE: 37.3% Fatigue or asthenia: 37.1% Skin reactions: 28.3%	Pyrexia: 63% Fatigue: 47% Nausea: 40%
AE leading to discontinuation	NIV: 9.7% IPI: 42.6%	PEM: 13.8% PLA: 2.2%	D+T: 26% PLA: 3%

Abbreviations: AE: adverse event, D+T: dabrafenib plus trametinib, ECOG PS: Eastern Cooperative Oncology Group Performance Status, NIV: nivolumab, PEM: pembrolizumab: PLA: placebo, 95% CI: 95% confidence interval.
* did not meet the prespecified interim analysis boundary of p=0.000019.

Since RCT results may not represent the benefits and risks of treatments in clinical practice, real-world data can add insightful information and support decision making [16]. The electronic health record (EHR) is one of the sources that contains relevant real-world data for cancer treatment evaluation, since it includes, e.g., hospital visits, patient demographics, medication orders, laboratory data, vital signs, and imaging results [17]. However, as most data is captured in free-text notes, manual chart review is still the standard method for data extraction from EHR, which is very labor intensive and time-consuming. Previously we validated a text-mining tool to extract data

from EHR for the evaluation of metastatic renal cell carcinoma treatments (mRCC) and showed that this method is accurate and seven times faster than manual data extraction [18]. This tool has already been used in other real-world studies, e.g., to review mRCC treatment patterns and outcomes in two hospitals, to review the use of granulocyte-colony stimulating factor and incidence of febrile neutropenia in breast cancer patients, and the identification of treosulfan-induced myalgia in a pediatric hematopoietic stem cell transplantation patients [19-21].

The aim of this study was to apply a text-mining tool to retrospectively review the tolerability, safety, and efficacy of new adjuvant treatments for melanoma in a Dutch clinical hospital setting.

2. Methods

We performed a retrospective EHR review by collecting data from EHR through text mining. The study protocol was reviewed and approved by the Medical Ethics Review Committee of the Leiden University Medical Center (LUMC), Leiden, The Netherlands, which waived the need for informed consent.

2.1 Electronic health record text mining

We retrospectively identified patients and collected all data from the electronic health record with text-mining software (CTcue B.V., Amsterdam, The Netherlands). This software program enables rule-based text mining of the EHR, which can extract both data from structured data (e.g., medical prescriptions and laboratory values) and unstructured, free-text notes (e.g., medical notes and correspondence). Previously, we validated this tool and method to collected real-world data of renal cell carcinoma treatments in clinical practice [18].

Figure 6.1 shows the four steps taken within the program, per tab, from start until the export of the final dataset. First, rule-based queries were constructed in the criteria tab, to select the correct patient population. Secondly, the cohort tab gives a brief overview of the selected patients and the criteria on which they were included. The context of a datapoint can be further expanded by selecting the datapoint; in case of free-text notes, the system shows the complete form or report with the specified key word(combination)s. An overview of all cases that matched the search results, e.g., all

free-text forms with a hit, added to all structured data points, e.g., lab values between a specific period, is provided. The patient cohort is confirmed by reviewing all hits in unstructured text. In case of missing data necessary for patient inclusion, a patient is not included. Similarly, rule-based queries were constructed for the collection of data in the questions tab and all data from unstructured text was confirmed per patient by context analysis.

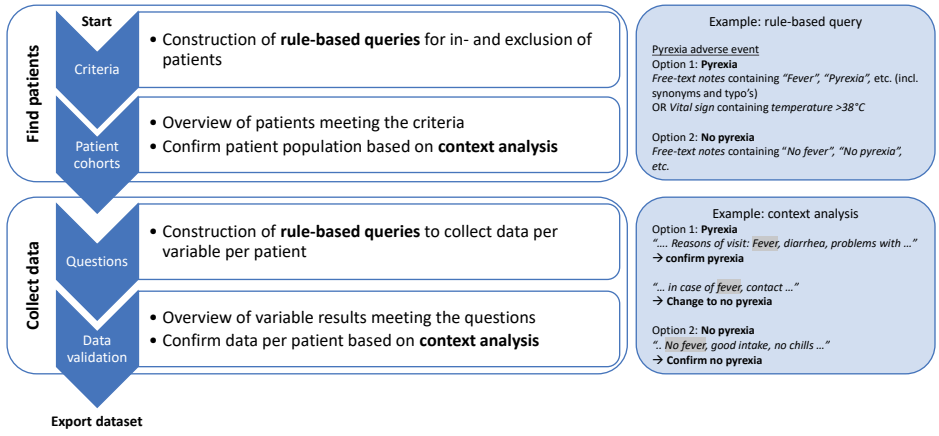

Figure 6.1. Steps taken to find patients and collect data with the text-mining tool, including the construction of rule-based queries and context analysis.

2.2 Patient population

Patients were included in a university medical center, the LUMC, Leiden, The Netherlands. We aimed to include all patients aged 18 years and older with melanoma if they started adjuvant treatment of nivolumab or pembrolizumab, and dabrafenib plus trametinib between January 2019 and October 2021. Therefore, the search criteria included: 1. Patients who received nivolumab, pembrolizumab or dabrafenib plus trametinib, 2. Patients with a reimbursement code (diagnosis treatment code) specific for melanoma, 3. A free-text note that confirmed use of the treatment (e.g., search for terms as "nivolumab", "nivo", "Opdivo®"), 4. A free-text note that confirmed the adjuvant aspect of the treatment (e.g., "stage III", "adjuvant"). The complete list of criteria is available in Supplementary File S6.1.

2.3 Data collection

The following patient characteristics were collected at start of treatment: age, sex, performance status, disease stage (according to the 7th edition of the American Joint Committee on Cancer [AJCC]), primary tumor location, subtype, brain metastases, lactate dehydrogenase (LDH), ulceration status, and BRAF-, NRAS- and KIT mutation status. Also, the following outcomes were collected: the time on treatment, the reason to end the treatment, most common AEs as reported in the RCTs (abdominal pain, arthralgia, asthenia, chills, cough, diarrhea, dyspnea, fatigue, headache, nausea, pruritus, pyrexia, and rash, with additionally irAEs (colitis, diabetes mellitus type 1, hepatitis, hyperthyroidism, hypothyroidism, pneumonitis)), all treatment-limiting AEs, and recurrence of melanoma. The common terminology criteria for adverse events (CTCAE) v5.0 were used to grade the severity of adverse events in the context analysis.

2.4 Statistical analysis

Data management and analysis were performed using R Statistical Software (v4.1.1; R CoreTeam 2021). We used descriptive statistics to describe the patient- and disease characteristics. The time on treatment and time until recurrence per patient were visualized in a swimmer plot and the median time on treatment per reason to end treatment was calculated. Chi-square test was performed to test for differences in tolerability (treatment-limiting toxicity) between treatments. Per treatment, the RFS was analyzed with the Kaplan-Meier method and visualized in a survival plot. All statistical analyses were exploratory.

3. Results

By text mining, 217 patients with melanoma were identified in the EHR. Patients who received their systemic treatment as palliative treatment (n=93) were excluded after context analysis (Figure 6.2).

In total, 122 melanoma patients were included in the study, 54 patients started with nivolumab, 48 with pembrolizumab and 20 patients with dabrafenib plus trametinib between January 2019 and October 2021. The median age of the patients was 59 years (range: 21–84), and more than half of the patients was male (61.5%). All baseline patient- and disease characteristics are shown in Table 6.2.

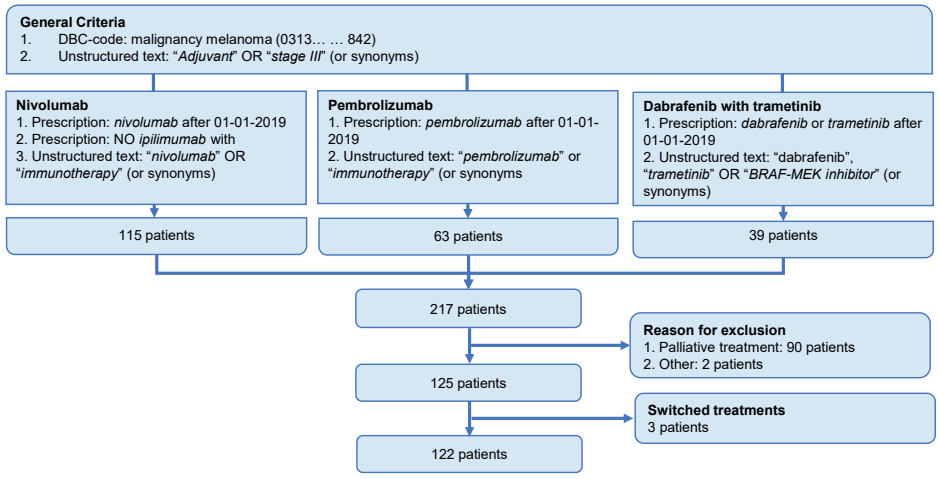

Figure 6.2. Patient flow chart. DBC-code: diagnosis-treatment combination code.

3.1 Time on treatment

The adjuvant treatment was ended for 97 (79%) of the patients, 25 patients were still on treatment at the time of data extraction (Figure 6.3). The mean time on treatment of patients, who ended treatments was 10.2 months for nivolumab (interquartile range [IQR]: 6.4–12.0), 11 months for pembrolizumab (IQR: 4.2–12.4), and 8.4 months for dabrafenib plus trametinib (IQR: 2.2–11.6).

3.2 Adverse events

The reported AEs are summarized in Table 6.3. Fatigue was the most reported AE in all groups (N: 77.8%, P: 75.0%, D+T: 80.0%), followed by diarrhea (44.5%) and headache (29.6%) for patients treated with nivolumab; diarrhea (23.0%), and nausea, pruritus, and hypothyroidism (all 18.8%) for patients treated with pembrolizumab, and pyrexia (65.0%) and nausea (55.0%) for dabrafenib plus trametinib treatment. The adverse events include the following severe AEs: hepatitis (3.7%), asthenia (1.9%) and diarrhea (1.9%) on nivolumab, diarrhea (4.2%) and colitis (2.1%) on pembrolizumab, and nausea, incl. vomiting (5.0%) on dabrafenib plus trametinib.

3.3 Treatment-limiting toxicity

In total, in twenty (16.4%) patients, treatment was ended early due to toxicity. The reason to end the adjuvant treatment due to toxicity was significantly different between the treatment groups, with more patients ending treatment in the dab-

rafenib plus trametinib group (8/15), than patients treated with nivolumab (9/46), and pembrolizumab (3/36), X^2 (6, n=122) =14.6, p=0.024. Eight patients stopped within the first three months (N: 2, P: 1, D+T: 5) (Figure 6.3), and in this group, in total, 28 treatment-limiting AEs were reported (Table 6.4). IrAEs were most reported as treatment-limiting in patients treated with nivolumab (8/9) and pembrolizumab (2/3), including hepatitis, colitis, pneumonitis, and thyroiditis. Pyrexia (5/8), skin disorders (4/8), chills and nausea (both 3/8) were most reported in patients treated with dabrafenib plus trametinib (n=8). An overview of treatment-limiting AEs per patient is available in Supplementary File S6.2.

	Nivolumab (n = 54)		Pembrolizumab (n = 48)		Dabrafenib plus trametinib (n = 20)	
Reason stop	**n (%)**	**Median time** months, (1st - 3rd quartile)	**n (%)**	**Median time** months, (1st - 3rd quartile)	**n (%)**	**Median time** months, (1st - 3rd quartile)
End of treatment	22 (41)	12.1 (12.0 - 12.2)	20 (42)	12.5 (12.4 - 12.5)	6 (30)	12.1 (11.9 - 12.3)
Recurrence	14 (26)	6.0 (4.1 - 8.2)	12 (25)	4.2 (4.2 - 5.3)	1 (5)	2.3 (-)
Toxicity	9 (17)	6.4 (4.0 - 7.4)	3 (6)	4.1 (3.4 - 7.6)	8 (40)	1.8 (1.4 - 3.3)
Other	1 (2)	9.2 (-)	1 (2)	1.4 (-)	-	-
On treatment	8 (15)	6.9 (5.4 - 8.1)	12 (25)	9.7 (9.0 - 10.2)	5 (25)	8.8 (8.7 - 9.7)
Recurrence						
○ No	39 (72)		36 (75)		17 (84)	
▲ Yes	15 (28)		12 (25)		3 (15)	

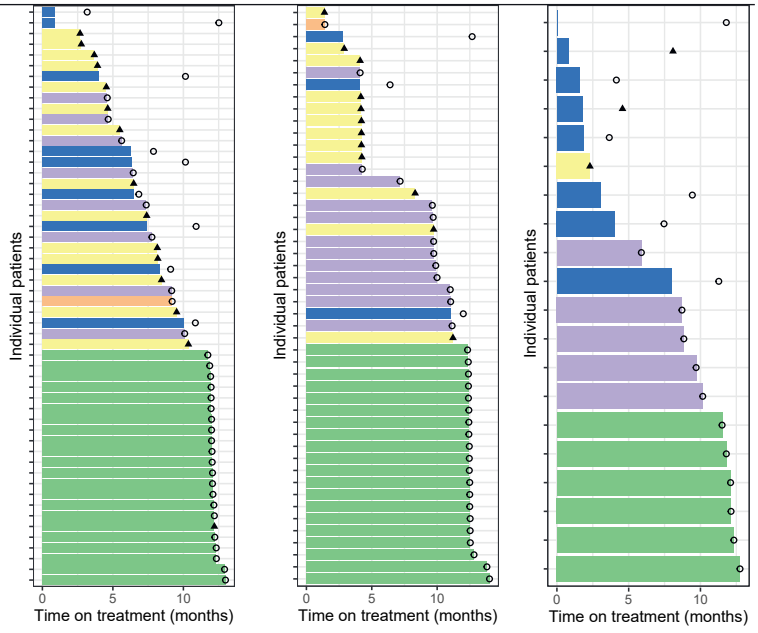

Figure 6.3. Patients' time on treatment, causes of treatment discontinuation, and recurrence per treatment.

Table 6.2. Patient characteristics

Characteristics	Nivolumab (n=54)	Pembrolizumab (n=48)	Dabrafenib plus trametinib (n=20)	All patients (n=122)
Median age (range) – year	61 (21–84)	57.5 (23–80)	57.5 (31–73)	59 (21–84)
Sex , no. (%)				
Male	35 (64.8)	31 (64.6)	9 (45.0)	75 (61.5)
Female	19 (35.2)	17 (35.4)	11 (55.0)	47 (38.5)
ECOG performance status, no. (%)				
0	32 (59.3)	24 (50.0)	9 (45.0)	65 (53.3)
1	7 (13.0)	5 (10.4)	1 (5.0)	13 (10.7)
Unknown	15 (27.8)	18 (37.5)	10 (50.0)	43 (35.2)
Disease stage, no. (%) AJCC 7				
III	34 (63.0)	48 (100)	20 (100)	102 (83.6)
Unspecified	3 (5.6)	1 (2.1)	1 (5.0)	5 (4.1)
IIIa	1 (1.9)	20 (41.7)	5 (25.0)	26 (21.3)
IIIb	10 (18.5)	19 (39.6)	9 (45.0)	38 (31.1)
IIIc	20 (37.0)	8 (16.7)	5 (25.0)	33 (27.0)
Resected IV	20 (37.0)	-	-	20 (16.4)
Primary tumor location, no. (%)				
Head or neck	6 (11.1)	6 (12.5)	2 (10.0)	14 (11.5)
Body	19 (35.2)	22 (45.8)	8 (40.0)	49 (40.2)
Extremities	17 (31.5)	13 (27.1)	6 (30.0)	36 (29.5)
Acral	1 (1.9)	3 (6.3)	1 (5.0)	5 (4.1)
Mucosal	1 (1.9)	-	-	1 (0.8)
Unknown primary	9 (16.7)	2 (4.2)	3 (15.0)	14 (11.5)
Unknown	1 (1.9)	2 (4.2)	-	3 (2.5)
Subtype, no. (%)				
Superficial spreading	16 (29.6)	25 (52.1)	11 (55.0)	52 (42.6)
Nodular	9 (16.7)	8 (16.7)	5 (25.0)	22 (18.0)
Acral lentiginous	-	2 (4.2)	1 (5.0)	3 (2.5)
Spindle cell	-	3 (6.3)	-	3 (2.5)
Unclear	29 (53.7)	10 (20.8)	3 (15.0)	42 (34.4)
LDH above ULN , no. (%)				
Yes	5 (9.3)	-	-	5 (4.1)
No	43 (79.6)	44 (91.7)	20 (100.0)	107 (87.7)
Unknown	6 (11.1)	4 (8.3)	-	10 (8.2)
Ulceration , no. (%)				
Yes	-	15 (31.3)	1 (5.0)	16 (13.1)
No	14 (25.0)	25 (52.1)	5 (25.0)	44 (36.1)
Unknown	40 (74.1)	8 (16.7)	14 (70.0)	62 (50.8)

Table 6.2 continues on next page.

Table 6.2. *Continued*

Characteristics	Nivolumab (n=54)	Pembrolizumab (n=48)	Dabrafenib plus trametinib (n=20)	All patients (n=122)
BRAF mutation , no. (%)				
Yes	28 (51.9)	17 (35.4)	20 (100.0)	65 (53.3)
No	21 (38.9)	20 (41.7)	-	41 (33.6)
Unknown	5 (9.3)	11 (22.9)	-	16 (13.1)
NRAS mutation , no. (%)				
Yes	18 (33.3)	12 (25.0)	1 (5.0)	31 (25.4)
No	28 (51.9)	13 (27.1)	15 (75.0)	56 (45.9)
Unknown	8 (14.8)	23 (47.9)	4 (20.0)	35 (28.7)
KIT mutation , no. (%)				
Yes	-	1 (2.1)	-	1 (0.8)
No	45 (83.3)	31 (64.6)	17 (85.0)	93 (76.2)
Unknown	9 (16.7)	16 (33.3)	3 (15.0)	28 (23.0)
Previous systemic therapy for melanoma , no. (%)				
Adjuvant	1 (1.9)	1 (2.1)	1 (5.0)	5 (4.1)
Neo-adjuvant	1 (1.9)	-	3 (15.0)	3 (2.5)

3.4 Recurrence

In total 28 patients (23.0%) ended treatment due to recurrence, 15 of the patients were treated with nivolumab, 12 with pembrolizumab and 1 with dabrafenib plus trametinib (Figure 6.3). The recurrence probability at 1 year was 70.3% (95% CI: 58.1–85.0) for nivolumab, 72.4% (95% CI: 60–87.3) for pembrolizumab, and 83.0% (95% CI: 67.1–1) for dabrafenib plus trametinib (Figure 6.4). The No median RFS was reached for any of these treatments within the maximum follow-up period of 13 months.

4. Discussion

In an effort to optimize data extraction from EHRs and to evaluate the tolerability, safety and efficacy of nivolumab, pembrolizumab and dabrafenib plus trametinib as adjuvant treatments for resected stage III and IV melanoma, we performed a retrospective study by text mining the EHR in a university hospital. This is the first real-world study on adjuvant treatment in resected stage III and IV melanoma with retrieval of clinical data by text mining. By collecting a sufficient amount of data, this study shows that text mining EHR is a valuable and effective new method. The majority of the 122 included patients received ICI (N: 45%, P: 39%), and 16% of our patients received dabrafenib

Table 6.3. Adverse events

	Nivolumab (n=54)		Pembrolizumab (n=48)		Dabrafenib plus trametinib (n=20)	
Adverse events, no. (%)	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Abdominal pain	2 (3.7)	-	4 (8.3)	-	1 (5.0)	-
Arthralgia	2 (3.7)	-	2 (4.2)	-	2 (10.0)	-
Chills	2 (3.7)	-	-	-	9 (45.0)	-
Cough	12 (22.2)	-	7 (14.6)	-	4 (20.0)	-
Diarrhea	22 (42.6)	1 (1.9)	9 (18.8)	2 (4.2)	1 (5.0)	-
Dyspnea	6 (11.1)	-	4 (8.3)	-	-	-
Fatigue or asthenia	43 (79.6)	-		-	16 (80.0)	-
Fatigue	42 (77.8)	-	36 (75.0)	-	16 (80.0)	-
Asthenia	1 (1.9)	1 (1.9)	1 (2.1)	-	1 (5.0)	-
Headache	16 (29.6)	-	8 (16.7)	-	10 (50.0)	-
Nausea, incl. vomiting	13 (24.1)	-	9 (18.8)	-	10 (50.0)	1 (5.0)
Pyrexia	15 (27.8)	-	4 (8.3)	-	13 (65.0)	-
Skin reaction	17 (31.5)	-	9 (18.8)	-	6 (30.0)	-
Pruritus	13 (24.1)	-	9 18.8)	-	3 (15.0)	-
Rash	9 (16.7)	-	2 (4.2)	-	5 (25.0)	-
Immune-related adverse events						
Colitis	3 (5.6)	-	1 (2.1)	1 (2.1)	-	-
Diabetes Mellitus type 1	-	-	-	-	-	-
Hepatitis	-	2 (3.7)	-	-	-	-
Hyperthyroidism	8 (14.8)	-	6 (12.5)	-	-	-
Hypothyroidism	11 (20.4)	-	9 (18.8)	-	-	-
Pneumonitis	-	-	2 (4.2)	-	-	-

plus trametinib, and we found that adjuvant ICI was better tolerated than dabrafenib plus trametinib, which had a higher risk of treatment-limiting AEs, although reversible.

Even though included patients were treated in the adjuvant setting for melanoma, patient populations slightly differ since the studied treatments are applied for specific indications within adjuvant treatment (e.g., D+T for BRAF positive patients only, and nivolumab also for resected stage IV). Furthermore, dabrafenib plus trametinib was only available through an expanded access program until November 2020, potentially influencing treatment choice. Therefore, our results should be interpreted with caution when comparing treatments head-to-head.

Table 6.4. Treatment-limiting adverse events in patients who ended treatment due to toxicity. Patients could have one, or combinations of adverse events.

Adverse events, no.	Nivolumab n=9	Pembrolizumab n=3	Dabrafenib plus trametinib n=8
Allergic reaction	-	-	1
Arthalgia	1	1	1
Chills	-	-	3
Decreased appetite	-	-	1
Fatigue	-	-	2
Fever	-	-	5
Headache	-	-	1
Liver function disorders	-	-	1
Malaise	-	-	2
Myalgia	-	1	2
Nausea	-	-	3
Skin disorder	-	-	4
Syncope	-	-	1
Tachycardia	-	-	1
Immune-related adverse events	8	2	-
Adrenalitis	1	-	-
Colitis	2	1	-
Hepatitis	2	-	-
Hypocortisolism	1	-	-
Meningitis	1	-	-
Myocarditis, no.	1	-	-
Myositis, no.	1	-	-
Polymyalgia rheumatica, no.	1	-	-
Pneumonitis, no.	2	1	-
Thyroiditis, no.	2	-	-

4.1 Tolerability

As the investigated treatments are administered adjuvant after surgery, the accepted toxicity, and therefore tolerability, might be valued differently than during palliative treatment. In this small study, significantly more patients treated with dabrafenib plus trametinib ended their treatment due to treatment-limiting toxicity (53%), than after treatment with ICI (N: 20%, P: 8%). This is not completely unexpected, as the rate for treatment-limiting toxicity in COMBI-AD trial of dabrafenib plus trametinib was also higher (26%), than in the CheckMate 238-trial for nivolumab (8%), and the EORTC

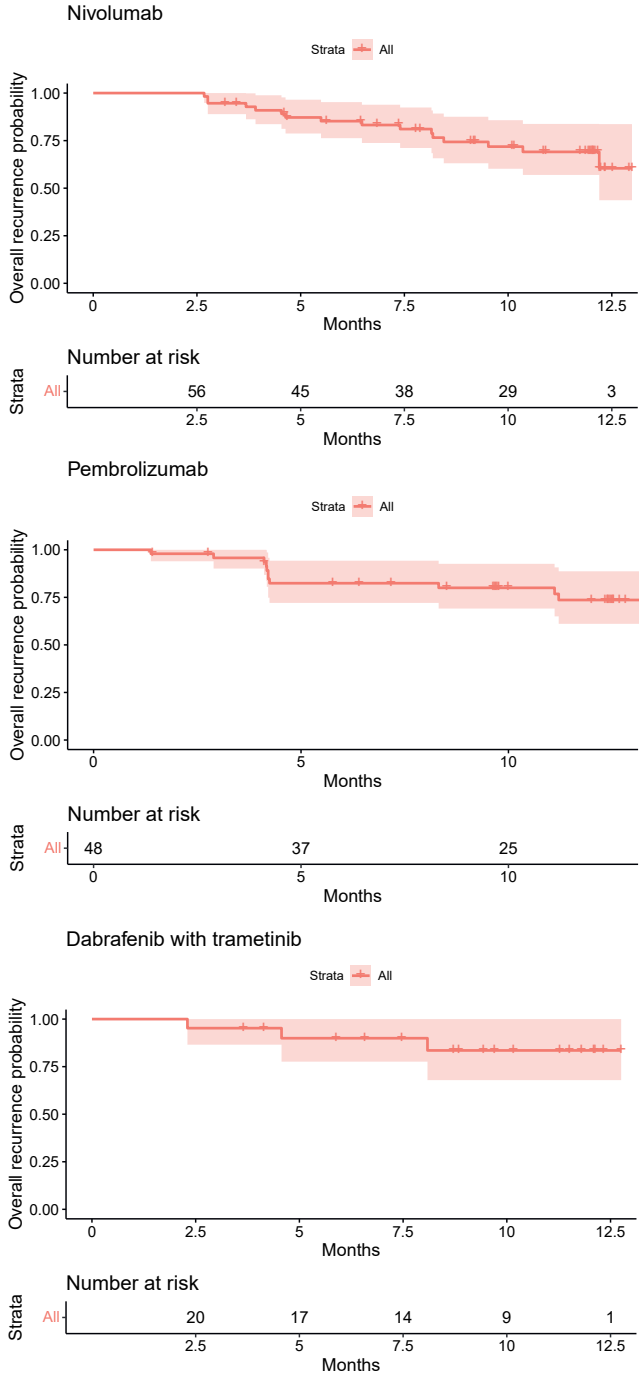

Figure 6.4. Kaplan–Meier curves representing the recurrence-free survival (RFS) of nivolumab, pembrolizumab, and dabrafenib plus trametinib 1-year RFS was 70.3% (95% confidence interval (CI): 58.1–85.0) for nivolumab, 72.4% (95% CI: 60–87.3) for pembrolizumab, and 83.0% (95% CI: 67.1–100) for dabrafenib plus trametinib.

1325/keynote-045 trial for pembrolizumab (14%) [9, 11, 12]. However, both for dabrafenib plus trametinib and nivolumab, the relative number of patients who ended treatment due to toxicity was higher than in the trials. This was also observed in the studies of de Meza et al. and Hoffmann et al., which showed higher treatment-limiting AEs on ICI in clinical practice [22, 23]. As far as we know, no other real-world data is yet published with treatment limiting toxicity rates for dabrafenib plus trametinib.

4.2 Safety

4.2.1 Immune checkpoint inhibitors

In this study, not all severe (≥ grade 3) AEs were treatment-limiting, and vice versa. However, the incidence of one or two concurring irAEs was mostly treatment-limiting. IrAEs are characterized by auto-reactive T-cells, and can affect many organs, as was demonstrated in this study by the variety of treatment-limiting AEs [24-26]. Furthermore, we reported severe hepatitis (n=2), asthenia (n=1), and diarrhea (n=1) during treatment with nivolumab, and diarrhea (n=2), and colitis (n=1) during pembrolizumab. De Meza et al. did report higher rates of severe AEs in clinical practice compared to the RCTs [22]. Due to the low incidence of the individual severe AEs, we could not determine if this was the case for our study population.

Besides, manifestations of thyroiditis, hyperthyroidism (N: 15%, P: 13%) and hypothyroidism (N: 20%, P: 19%) seemed to occur more often in this study than in the trials (hyperthyroidism, N: 8%, P: 10%; hypothyroidism: N: 10%, 14%) [9, 11]. Even though a thyroid-related AE not necessarily leads to treatment termination, patients often need lifelong hormone replacement [27], and therefore the occurrence of this type of AE might have a severe impact on an individual patient's quality of life.

The chronic aspect and the recurrence of irAEs can play a role in the treatment decision. In our study, we did not determine the duration of AEs, but Patrinely et al. also showed that in clinical practice irAEs appeared more often and were frequently persistent, than was shown in clinical trials [28]. Furthermore, restarting therapy after a significant irAE was shown to result in another irAE in 50% of the patients in both a population with renal cell carcinoma and lung cancer, even though mostly with a lower severity rate [29, 30].

4.2.2 Dabrafenib plus trametinib

For dabrafenib plus trametinib treatment, the only reported severe AE was nausea, even though a total of 28 AEs contributed to treatment discontinuation in eight patients. In contrast to ICI, it were always combinations of AEs (two up to six) that were treatment-limiting. Pyrexia (5/8), was the most frequent reported, which is not surprising, as pyrexia specifically is known to occur during treatment with dabrafenib plus trametinib [31]. In three occurrences, it was reported with, at least, chills and nausea. In total, pyrexia occurred in total in 13/20 patients, comparable to the RCT [12]. And, even though in the RCT pyrexia was also identified as the AE most often (9%) resulting in treatment discontinuation [32], the rate of five out of twenty patients in our population seemed higher.

In this study, five of the eight patients on dabrafenib plus trametinib with treatment-limiting toxicity ended treatment within three months. Early treatment-limiting toxicity (≤3 months) is especially undesirable since these patients might not benefit at all from adjuvant treatment. Remarkably, four out of the five patients were female. However, as these patient numbers are small, we were not able to substantiate this with statistical analysis. Atkinson et al. showed that the incidence of AEs on dabrafenib plus trametinib is the highest during the first three months [32], which is in accordance with the pattern we observed. To encourage patients to remain on treatment, patient education and empowerment could be useful. Mansfield et al. showed that the maximum acceptable risk for pyrexia in melanoma patients receiving dabrafenib plus trametinib was higher when the awareness of the benefits of the therapy is higher. Therefore longer follow-up results on efficacy of the COMBI-AD trial might be beneficial [33]. Furthermore, the COMBI-APlus trial showed that treatment interruption of both dabrafenib and trametinib in case of pyrexia at a temperature of ≥38°C, instead of discontinuation of only dabrafenib in case of pyrexia of ≥38.5°C, helped patients in the long term to remain on treatment [32].

4.3 Efficacy

The preliminary 1-year recurrence-free survival rates overlapped with the results of the RCTs [9, 11, 12]. Even though this is indicative for comparable efficacy, and RFS seems to be a valid surrogate endpoint for overall survival for adjuvant melanoma therapy, it is too soon for conclusions on real-world effectiveness [34]. De Meza et al. showed comparable 1-year survival rates of 87.0% for the stage IIIA, and 76.5% for

stage IIIB, and 60.3% for stage IIIC in a population treated with ICI in Dutch clinical practice [22]. Hoffmann et al. showed a RFS at 1-year of 77.1% after nivolumab and 63.5% after pembrolizumab in a Swiss population [23]. Furthermore, even though Koelblinger et al. showed a 1-year RFS rate of 64.8% in an Austrian population, they showed comparable distant metastasis free-survival compared to the Checkmate-238 trial (77.4% vs. 80%), and concluded treatment cost-effectiveness for the Austrian population [35]. All real-world studies showed comparable effectiveness to the RCTs, which is in line with our premature results. Hoffmann et al. is to our knowledge the only published study reviewing dabrafenib plus trametinib in clinical practice, however they only included three patients who finished their treatment [23].

4.4 Eligibility criteria

A Dutch nationwide registry showed that 40% of the patients who received treatment for advanced melanoma, were ineligible for phase III trials [36]. However, our study population with patients who received adjuvant treatment, in general, met the criteria from the trials. Key exclusion criteria in the phase III trials for adjuvant treatment were ECOG performance status ≥1, ocular (N, D+T), uveal (N) or mucosal (D+T) melanoma, previous systemic therapy for melanoma (all), auto-immune disease (N, P), uncontrolled infection (P) or use of systemic glucocorticoids (N, P) [9, 11, 12]. Even though the performance status is unknown for 35% of our patients – comparable to other real-world studies [37, 38] – there was no reason to believe this would be significantly different from phase III trials. Only seven (5.7%) patients that had previous systemic therapy for melanoma did not meet the eligibility criteria, including neo-adjuvant treatment in the PRADO trial and patients who switched adjuvant treatments after early AEs [39].

4.5 Need for real-world data

None of the treatments in this study, and in general, is clearly superior to the others regarding the tolerability, safety and efficacy combined, and proving superiority was not the aim of this study. However, for patients with a BRAF-mutation, a choice between adjuvant treatment with ICI or dabrafenib plus trametinib must be made. Overall, this study reflects the safety profiles shown in the RCTs, however incidence of thyroid-related irAEs during ICI, often chronic, and treatment-limiting AEs during both nivolumab and dabrafenib plus trametinib seemed higher. Furthermore, effectiveness, estimated by the 1-year RFS, was comparable with the trials. Weilandt et al. showed

that in a discrete choice experiment that overall response rate is the most important parameter for patients when choosing a treatment, followed by the 2-year survival rate, type of adverse events and the probability of treatment-limiting AEs. However, individual (e.g., age, sex, partnership) and disease-related (e.g., tumor burden, experience with ICI or BRAF-MEK inhibitors) resulted in variation of the preferences [40]. Livingstone et al. showed that these values overlap with factors Australian physicians and nurses consider in the recommendation of ICI to patients. [41].

To be able to inform melanoma patients on the risks and benefits related to their personal characteristics, more data is needed, which underlines the need for real-world data [42]. This study shows that these data can be collected with text mining from EHR. Even though this study represents only the population of a single university hospital, one of the fourteen melanoma centers in The Netherlands. Currently, data on this population are also collected from EHR by data managers for the Dutch Melanoma Treatment Registry since 2011. However, this is done manually by data managers, is updated once every year and does not include < grade 3 adverse events [22]. This study showed that data extraction using text mining is feasible, and in the future, can potentially be extended to other hospitals and registries, for efficient inclusion of larger populations.

4.6 Strengths and limitations

We used rule-based text mining to detect patients, and collect characteristics, outcomes, and adverse events from electronic health records. The advantage of this method is the faster and more standardized data extraction. Furthermore, the set of queries can repeatedly be reused to review the status of adjuvant melanoma treatments in this hospital in the future, for example on yearly basis, and has the potential to be implemented in other hospitals treating melanoma patients.

However, due to its retrospective design, the extracted data is both limited by the information stored in the EHR, which is prone to have missing data [43], and by the terms included in the queries [44]. In this study we aimed for a high sensitivity, by using extensive lists of keywords for the searches in unstructured text, and additionally performed visual context analysis to confirm outcomes, resulting in limited missing data. However, certain information can be underreported.

5. Conclusions

This was the first real-world study on adjuvant treatment in resected stage III and IV melanoma with retrieval of clinical data by text mining. In this study we showed that text mining EHR data valuable method to evaluate the tolerability, safety, and efficacy of adjuvant melanoma treatments. In this population we found a higher tolerability of ICI, as compared to dabrafenib plus trametinib, primarily due to pyrexia and fatigue. Regarding safety this study shows results comparable to the clinical trial data, except for a higher incidence of treatment-limiting AEs for both nivolumab and dabrafenib plus trametinib, thyroid-related irAEs for nivolumab and pembrolizumab, and some mild adverse events. Furthermore, all 1-year RFS rates were comparable. Implementation of text mining of EHR in multiple hospitals can further improve efficiency of capturing real-world data.

References

1. Sung, H., et al., *Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries.* CA: A Cancer Journal for Clinicians, 2021. **71**(3): p. 209-249.
2. Integraal Kankercentrum Nederland. *NKR-cijfers. Incidentie, Melanoom van de huid en externe geslachtsorganen, CR*. Available from: https://iknl.nl/nkr-cijfers?fs%7Cepidemiologie_id=526&fs%7Ctumor_id=243&fs%7Cregio_id=550&fs%7Cperiode_id=564%2C565%2C566%2C567%2C568%2C569%2C570%2C571%2C572%2C573%2C574%2C575%2C576%2C577%2C578%2C579%2C580%2C581%2C582%2C583%2C584%2C585%2C586%2C587%2C588%2C589%2C590%2C591%2C592%2C593%2C563%2C562%2C561&fs%7Cgeslacht_id=644&fs%7Cleeftijdsgroep_id=677&fs%7Cjaren_na_diagnose_id=687&fs%7Ceenheid_id=702&cs%7Ctype=line&cs%7CxAxis=periode_id&cs%7Cseries=epidemiologie_id&ts%7CrowDimensions=&ts%7CcolumnDimensions=periode_id&lang%7Clanguage=nl.
3. Curti, B.D. and M.B. Faries, *Recent Advances in the Treatment of Melanoma.* New England Journal of Medicine, 2021. **384**(23): p. 2229-2240.
4. European Medicines Agency. *CHMP post-authorisation summary of positive opinion for Keytruda*. 2018; Available from: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-keytruda-ii-47_en.pdf.
5. European Medicines Agency. *CHMP post-authorisation summary of positive opinion for Opdivo*. 2018; Available from: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-opdivo_en-1.pdf.
6. European Medicines Agency. *CHMP post-authorisation summary of positive opinion for Mekinist*. 2018; Available from: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-mekinist-ws/1274_en.pdf.
7. European Medicines Agency. *CHMP post-authorisation summary of positive opinion for Tafinlar*. 2018; Available from: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-tafinlar-ws-1274_en.pdf.
8. Ascierto, P.A., et al., *Adjuvant nivolumab versus ipilimumab in resected stage IIIB-C and stage IV melanoma (CheckMate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial.* Lancet Oncol, 2020. **21**(11): p. 1465-1477.
9. Weber, J., et al., *Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma.* New England Journal of Medicine, 2017. **377**(19): p. 1824-1835.
10. Eggermont, A.M.M., et al., *Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): distant metastasis-free survival results from a double-blind, randomised, controlled, phase 3 trial.* Lancet Oncol, 2021. **22**(5): p. 643-654.
11. Eggermont, A.M.M., et al., *Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma.* New England Journal of Medicine, 2018. **378**(19): p. 1789-1801.
12. Long, G.V., et al., *Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma.* New England Journal of Medicine, 2017. **377**(19): p. 1813-1823.
13. Dummer, R., et al., *Five-Year Analysis of Adjuvant Dabrafenib plus Trametinib in Stage III Melanoma.* New England Journal of Medicine, 2020. **383**(12): p. 1139-1148.
14. Wright, J.J., A.C. Powers, and D.B. Johnson, *Endocrine toxicities of immune checkpoint inhibitors.* Nature Reviews Endocrinology, 2021. **17**(7): p. 389-399.
15. Dimitriou, F., G.V. Long, and A.M. Menzies, *Novel adjuvant options for cutaneous melanoma.* Annals of Oncology, 2021. **32**(7): p. 854-865.

16. Wang, S.V., et al., *Using Real-World Data to Extrapolate Evidence From Randomized Controlled Trials.* Clinical Pharmacology & Therapeutics, 2019. **105**(5): p. 1156-1163.
17. Casey, J.A., et al., *Using Electronic Health Records for Population Health Research: A Review of Methods and Applications.* Annu Rev Public Health, 2016. **37**: p. 61-81.
18. van Laar, S.A., et al., *An Electronic Health Record Text Mining Tool to Collect Real-World Drug Treatment Outcomes: A Validation Study in Patients With Metastatic Renal Cell Carcinoma.* Clinical Pharmacology & Therapeutics, 2020. **108**(3): p. 644-652.
19. van Laar, S.A., et al., *Real-world evaluation of supportive care using an electronic health record text-mining tool: G-CSF use in breast cancer patients.* Supportive Care in Cancer, 2022.
20. van Laar, S.A., et al., *Real-World Metastatic Renal Cell Carcinoma Treatment Patterns and Clinical Outcomes in The Netherlands.* Frontiers in Pharmacology, 2022. **13**.
21. van der Stoep, M.Y.E.C., et al., *Treosulfan-induced myalgia in pediatric hematopoietic stem cell transplantation identified by an electronic health record text mining tool.* Scientific Reports, 2021. **11**(1): p. 19084.
22. de Meza, M.M., et al., *Adjuvant treatment for melanoma in clinical practice – Trial versus reality.* European Journal of Cancer, 2021. **158**: p. 234-245.
23. Hoffmann, M., S. Hayoz, and B.C. Özdemir, *Prescription Patterns, Recurrence, and Toxicity Rates of Adjuvant Treatment for Stage III/IV Melanoma-A Real World Single-Center Analysis.* Biology (Basel), 2022. **11**(3).
24. Postow, M.A., R. Sidlow, and M.D. Hellmann, *Immune-Related Adverse Events Associated with Immune Checkpoint Blockade.* N Engl J Med, 2018. **378**(2): p. 158-168.
25. Khan, S. and D.E. Gerber, *Autoimmunity, checkpoint inhibitor therapy and immune-related adverse events: A review.* Seminars in cancer biology, 2020. **64**: p. 93-101.
26. Mor, A. and M. Strazza, *Bridging the Gap: Connecting the Mechanisms of Immune-Related Adverse Events and Autoimmunity Through PD-1.* Frontiers in cell and developmental biology, 2022. **9**: p. 790386-790386.
27. Darnell, E.P., et al., *Immune-Related Adverse Events (irAEs): Diagnosis, Management, and Clinical Pearls.* Current Oncology Reports, 2020. **22**(4): p. 39.
28. Patrinely, J.R., Jr, et al., *Chronic Immune-Related Adverse Events Following Adjuvant Anti–PD-1 Therapy for High-risk Resected Melanoma.* JAMA Oncology, 2021. **7**(5): p. 744-748.
29. Santini, F.C., et al., *Safety of retreatment with immunotherapy after immune-related toxicity in patients with lung cancers treated with anti-PD(L)-1 therapy.* Journal of Clinical Oncology, 2017. **35**(15_suppl): p. 9012-9012.
30. Abou Alaiwi, S., et al., *Safety and efficacy of restarting immune checkpoint inhibitors after clinically significant immune-related adverse events in metastatic renal cell carcinoma.* Journal for immunotherapy of cancer, 2020. **8**(1): p. e000144.
31. Heinzerling, L., et al., *Tolerability of BRAF/MEK inhibitor combinations: adverse event evaluation and management.* ESMO Open, 2019. **4**(3): p. e000491.
32. Atkinson, V., et al., *Improved pyrexia-related outcomes associated with an adapted pyrexia adverse event management algorithm in patients treated with adjuvant dabrafenib plus trametinib: Primary results of COMBI-APlus.* European Journal of Cancer, 2022. **163**: p. 79-87.
33. Mansfield, C., et al., *Risk tolerance in adjuvant and metastatic melanoma settings: a patient perspective study using the threshold technique.* Future Oncology, 2021. **17**(17): p. 2151-2167.
34. Suciu, S., et al., *Relapse-Free Survival as a Surrogate for Overall Survival in the Evaluation of Stage II-III Melanoma Adjuvant Therapy.* J Natl Cancer Inst, 2018. **110**(1).

35. Koelblinger, P., et al., *Adjuvant anti-PD-1 antibody treatment in stage III/IV melanoma: real-world experience and health economic considerations.* JDDG: Journal der Deutschen Dermatologischen Gesellschaft, 2021. **19**(8): p. 1186-1198.
36. van Zeijl, M.C.T., et al., *Real-world outcomes of advanced melanoma patients not represented in phase III trials.* Int J Cancer, 2020. **147**(12): p. 3461-3470.
37. Board, R., et al., *Metastatic melanoma patient outcomes since introduction of immune checkpoint inhibitors in England between 2014 and 2018.* Int J Cancer, 2021. **148**(4): p. 868-875.
38. Moser, J.C., et al., *Real-world survival of patients with advanced BRAF V600 mutated melanoma treated with front-line BRAF/MEK inhibitors, anti-PD-1 antibodies, or nivolumab/ipilimumab.* Cancer Med, 2019. **8**(18): p. 7637-7643.
39. Reijers, I.L.M., et al., *Personalized response-directed surgery and adjuvant therapy after neoadjuvant ipilimumab and nivolumab in high-risk stage III melanoma: the PRADO trial.* Nat Med, 2022.
40. Weilandt, J., et al., *Patient Preferences in Adjuvant and Palliative Treatment of Advanced Melanoma: A Discrete Choice Experiment.* Acta Derm Venereol, 2020. **100**(6): p. adv00083.
41. Livingstone, A., et al., *Adjuvant immunotherapy recommendations for stage III melanoma: physician and nurse interviews.* BMC Cancer, 2021. **21**(1): p. 1014.
42. Bica, I., et al., *From Real-World Patient Data to Individualized Treatment Effects Using Machine Learning: Current and Future Methods to Address Underlying Challenges.* Clinical Pharmacology & Therapeutics, 2021. **109**(1): p. 87-100.
43. Haneuse, S., et al., *Learning About Missing Data Mechanisms in Electronic Health Records-based Research: A Survey-based Approach.* Epidemiology, 2016. **27**(1).
44. Percha, B., *Modern Clinical Text Mining: A Guide and Review.* Annual Review of Biomedical Data Science, 2021. **4**(1): p. 165-187.

Supplementary data

Supplementary File S6.1A. Patient inclusion

A patient is included if it meets criteria 1, 2 and at least one of 3.							
	Inclusion criterium	Description	Type of data	Searched terms	Used for inclusion or exclusion	Time window	Comments
1.	DBC-code*	DBC	DBC	Specialism: 0313 (internal medicine) with diagnosis: 842 (melanoma/malignancy skin)	Inclusion		Diagnose behandel combinatie = diagnosis treatment combination, a code used for reembursements in the Netherlands
2.	Mention of adjuvant treatment or stage III	Verification adjuvant treatment or stage III	Text search	Stadium III OR stadium 3 OR stadium IIIa OR stadium IIIb OR stadium IIIc OR stage III OR stage 3 OR stage IIIa OR stage IIIb OR stage IIIc OR stage 3a OR stage 3b OR stage 3c OR st III OR st IIIa OR st IIIb OR st IIIc OR st3 OR st 3a OR st 3b OR st 3c OR Adjuvant Or adjuvante OR adjuvante behandeling	Inclusion		

Supplementary Table S6.1A continues on next page.

Supplementary File S6.1A. *Continued*

	Inclusion criterium	Description	Type of data	Searched terms	Used for inclusion or exclusion	Time window	Comments
3a.	Nivolumab use	Nivolumab prescription	Medication request	Nivolumab	Inclusion	>1 january 2019	
		Verification nivolumab use	Text search	Nivolumab OR nivo OR opdivo	Inclusion		
		Not together with ipilimumab (=palliative indication)	Medication request	Ipilimumab	Exclusion	Start is between start date nivolumab AND start date nivolumab + 3 weeks	
3b.	Pembrolizumab use	Pembrolizumab prescription	Medication request	Pembrolizumab	Inclusion	>1 january 2019	
		Verification pembrolizumab use	Text search	Pembrolizumab OR pembro OR keytruda	Inclusion		
3c.	Dabrafenib plus trametinib use	Dabrafenib	Medication request	Dabrafenib	Inclusion	>1 january 2019	
		Trametinib	Medication request	Trametinib	Inclusion	Start is between 1 week before start dabrafenib AND 1 week after dabrafenib	
		Verification dabrafenib plus trametinib use	Text search	Dabrafenib OR dab OR tafinlar OR trametinib OR tram OR mekinist	Inclusion		

Supplementary File S6.1B. Data collection

	Name data point	Type of data	Multiple choice labels	Collected answer	Searched terms/keywords	Keyword search restricted to	Time window	Comments
For treatment with dabrafenib and trametinib	Start date	Medication request		Start date	Oldest prescription date of dabrafenib OR trametinib			
	Stop	Medication request		Start date of the oldest prescription	Newest prescription date of dabrafenib OR trametinib			
	Stop date	Text search		Date of selected text source	Dabrafenib OR dab OR dabra OR tafinlar OR trametinib OR tram OR tramet OR mekinist OR tyrosine kinase inhibitor OR TKI OR braf met remmer OR braf met remmers OR braf mek inhibitor OR braf mek inhibitors OR behandeling staken OR stoppen OR staken OR discontinueren OR niet continueren OR gestaakt OR gestopt OR staak OR stop OR adjuvante behandeling OR adjuvant OR adjuvante OR neo-adjuvante	Consult, consulten, reports	Answer section "0-1 month after stop": between start date dab tram AND stop date dab tram+ 1 month Answer section "1-2 month after stop": between stop date dab tram+ 1 month AND stop date dab tram + 2 months Answer section "2-3 month after stop": between stop date dab tram+ 2 month AND stop date dab tram + 3 months Answer section "3-6 month after stop": between stop date dab tram+ 3 month AND stop date dab tram + 6 months Answer section "6-9 month after stop": between stop date dab tram+ 6 month AND stop date dab tram + 9 months Answer section "9-12 month after stop": between stop date dab tram+ 9 month AND stop date dab tram + 12 months	

Supplementary Table S6.1B continues on next page.

Supplementary File S6.1B. *Continued*

	Name data point	Type of data	Multiple choice labels	Collected answer	Searched terms/keywords	Keyword search restricted to	Time window	Comments
For treatment with nivolumab	Start date	Medication request		Start date	Oldest prescription date of nivolumab			
	Stop	Medication request		Start date of the oldest prescription	Newest prescription date of nivolumab			
	Stop date	Text search		Date of selected text source	Nivolumab OR nivo OR opdivo OR immunotherapy OR immunotherapie OR immuno therapie OR behandeling staken OR stoppen OR staken OR discontinueren OR niet continueren OR gestaakt OR gestopt OR staak OR stop OR adjuvante behandeling OR adjuvant OR adjuvante OR neo-adjuvante	Consult, consulten, reports	Answer section "0-1 month after stop": between start date nivolumab AND stop date nivolumab+ 1 month Answer section "1-2 month after stop": between stop date nivolumab+ 1 month AND stop date nivolumab + 2 months Answer section "2-3 month after stop": between stop date nivolumab+ 2 month AND stop date nivolumab + 3 months Answer section "3-6 month after stop": between stop date nivolumab+ 3 month AND stop date nivolumab + 6 months Answer section "6-9 month after stop": between stop date nivolumab+ 6 month AND stop date nivolumab + 9 months Answer section "9-12 month after stop": between stop date nivolumab+ 9 month AND stop date nivolumab + 12 months	

For treatment with pembolizumab`	Start date	Medication request	Start date	Oldest prescription date of pembrolizumab		
	Stop	Medication request	Start date of the oldest prescription	Newest prescription date of pembrolizumab		
	Stop date	Text search	Date of selected text source	Pembrolizumab OR pembro OR keytruda OR pem OR immunotherapy OR immunotherapie OR immuno therapie OR behandeling staken OR stoppen OR staken OR discontinueren OR niet continueren OR gestaakt OR gestopt OR staak OR stop OR adjuvante behandeling OR adjuvant OR adjuvante OR neo-adjuvante	Consult, consulten, reports	Answer section "0-1 month after stop": between start date pembrolizumab AND stop date pembrolizumab+ 1 month Answer section "1-2 month after stop": between stop date pembrolizumab+ 1 month AND stop date pembrolizumab + 2 months Answer section "2-3 month after stop": between stop date pembrolizumab+ 2 month AND stop date pembrolizumab + 3 months Answer section "3-6 month after stop": between stop date pembrolizumab+ 3 month AND stop date pembrolizumab + 6 months Answer section "6-9 month after stop": between stop date pembrolizumab+ 6 month AND stop date pembrolizumab + 9 months Answer section "9-12 month after stop": between stop date pembrolizumab+ 9 month AND stop date pembrolizumab + 12 months

Supplementary Table S6.1B continues on next page.

Supplementary File S6.1B. *Continued*

Name data point	Type of data	Multiple choice labels	Collected answer	Searched terms/keywords	Keyword search restricted to	Time window	Comments
Treatment outcomes							
Reason stop	Text search	Multiple choice options* - Toxicity - Recurrence - End or treatment - Did not end treatment - Other - Unclear	Multiple choice option + All treatment-limiting adverse events date of recurrence NA NA NA NA	Adverse event OR bijwerking OR bijwerkingen OR tox OR toxiciteit OR graad 3 OR graad 4 OR ernstig OR klachten OR last Terug OR recurrence OR metastasis OR metastasize OR gemetastaseerd OR uitgezaaid OR gemetestaseerd OR metastases OR uitgezaaide OR gemetast OR uitzaaiingen OR gemet OR meta's OR gemetastasseerd OR tumormetastase OR metastase OR metastasen OR metastasen lever OR tumor metastase	Consult, consulten, reports consul, consulten ALL radiology reports	Between start date treatment AND stop date treatment+ 1 month	*Reason of stop is based on the query stop date. In case of toxicity, all dose-limiting adverse events are extracted from text. In case of recurrence, the date of recurrence is selected by identifying the moment in constultation reports or radiology report.

	Recurrence after tox	Text search	Multiple choice options* - recurrence - no recurrence within 12 months	Multiple choice option + date of selected text source	Terug OR recurrence OR metastasis OR metastasize OR gemetastaseerd OR uitgezaaid OR gemetestaseerd OR metastases OR uitgezaaide OR gemetast OR uitzaaiingen OR gemet OR meta's OR gemetastasseerd OR tumormetastase OR metastase OR metastasen OR metastasen lever OR tumor metastase	Consult, consulten ALL radiology reports	Between Start date treatment AND start date treatment + 13 months	*Both multple choice answers have the same search criteria, chosen answer is based on content

Supplementary Table S6.1B continues on next page.

Supplementary File S6.1B. *Continued*

Name data point	Type of data	Multiple choice labels	Collected answer	Searched terms/keywords	Keyword search restricted to	Time window	Comments
Patient and disease characteristics							
Performance score	Measurement		Most recent value between 0 and 5 OR Most recent value between 0 and n	WHO performance OR WHO graad OR WHO klasse OR Definitieve WHO classificatie OR performance WHO OR inspanningstolerantie WHO-klasse OR WHO performance score OR WHO performance status OR WHO-klasse OR WHO classificatie OR performance status WHO OR WHO-score OR WHO score OR WHO classificatie OR WHO PS OR PS WHO Karnofsky OR Karnofsky score OR karnofsky performance scale OR karnofsky index OR karnofsky performance OR karnofskyscore OR karnofski score OR karnofsky performance score OR who karnofsky OR karnofsky performance status OR karnovski score OR performance karnofsky OR kernovsky score OR karnowski score OR karnofsky landsky score OR kps OR kps score OR kps geschat		Before start date treatment	

Performance score text	Text search	Multiple choice options - WHO 0 (incl karnofsky 100) - WHO 1 (incl karnofsky 90-80) - WHO 2 (incl karnofsky 70-60) - WHO 3 (incl carnofsky 50-0)		n = WHO/ECOG performance status or karnofsky performance status according to multiple choice label WHO performance n OR WHO n OR WHO klasse n OR WHO score n OR ecog performance status n OR ecog score n OR ecog n OR performance score n OR karnofsky index n OR karnofsky n OR karnosky score n OR karnoskyindex n OR karnofsky-index n OR kanofsky performance status n OR karnosky scale n OR karnofsky performance status scale n OR KPS n	
LDH	Measurement		Most recent value	LDH	Before start date treatment
Previous systemic treatments	Medication request		Medication name	All treatments starting with ATC code L01, excluding topical applications	Before start date treatment

Supplementary Table S6.1B continues on next page.

Supplementary File S6.1B. *Continued*

Name data point	Type of data	Multiple choice labels	Collected answer	Searched terms/keywords	Keyword search restricted to	Time window	Comments
Stage	Text search	Multiple choice options: - III - IIIa - IIIb - IIIc - IIIc resectable - IIIc irresectable (excluded) - IV resected - unknown	Multiple choice option	Stadium III OR stadium 3 OR stage III or stage 3 Stadium IIIa OR tadium 3a OR stadium III a OR stadium 3 a OR stage IIIa OR stage 3a OR stage III a OR stage 3 a Stadium IIIb OR tadium 3b OR stadium III b OR stadium 3 b OR stage IIIb OR stage 3b OR stage III b OR stage 3 b Stadium IIIc OR tadium 3c OR stadium III c OR stadium 3 c OR stage IIIc OR stage 3c OR stage III c OR stage 3 c (Stadium IIIc OR tadium 3c OR stadium III c OR stadium 3 c OR stage IIIc OR stage 3c OR stage III c OR stage 3 c) AND (resectable OR resectabel) Stadium IIIc OR tadium 3c OR stadium III c OR stadium 3 c OR stage IIIc OR stage 3c OR stage III c OR stage 3 c AND (niet resectabel OR niet resectable OR irresectable) stadium IV OR stadium 3 OR stage IV OR stage 4 stadium OR adjuvant OR adjuvante		Before start date treatment	

Primary tumor location	Text search	Multiple choice options: - eye - acral - mucosal - extremities - body - unknown primary - unknown	Multiple choice option	(Eye OR eyeball OR optic OR ocular O oog OR ogen OR oculair OR oculaire) AND (melanoom OR melanoma OR melanomen) AND (primair OR primaire) Acraal OR acral lentiginous melanoma OR acraal melanoom OR acral lentiginou malinant melanoma OR ALM OR acrolentigineus melanoom (mucous membrane OR mucosa OR mucosal OR slijmvliesweefsel OR slijmvlies OR slijm vlies OR mucosaal) AND (melanoom OR melanoma OR melanomen) AND (primair OR primaire) (Leg or lower leg OR been OR benen OR onderbeen OR bovenbeen OR kuit OR dij OR arm OR armen OR bovenarm OR onderarm OR extremtiteit OR ledemaat OR ledematen OR extremiteiten OR bovenste extremeiteit OR onderste extremiteit OR scheen OR scheenbeen OR hand OR vinger OR teen) AND (melanoom OR	Before start date treatment

Supplementary Table S6.1B continues on next page.

Supplementary File S6.1B. *Continued*

Name data point	Type of data	Multiple choice labels	Collected answer	Searched terms/keywords	Keyword search restricted to	Time window	Comments
				Melanoma OR melanomen) AND (primair OR primaire) (Romp OR buik OR rug OR onderrug OR flank OR flanken OR bovenbuik OR bovenrug OR onderbuik) AND (melanoom OR melanoma OR melanomen) AND (primair OR primaire) (primair OR primaire) AND (tumor OR melanoom OR melanomen OR tumorlocatie) AND (onbekend OR niet bekend OR onduidleijk OR onduidelijk OR zonder OR occult OR occulte) (Melanoom OR melanomen OR melanom)			

Histology	Text search	Multiple choice options: - superficial spreading - Nodular - Acral Lentiginous - Spindle cell - Unclear	Multiple choice option	Superficieel spreidend nodulair ALM OR acrolentigineus melanoom OR acrolentigineus Spindle cell carcinoma OR sacomatoid carcinoma OR spoelcelcarcinoom OR spoelcelca OR spoelcel OR spoelcelmelanoom Melanoom OR melanoma OR melanomen	Before start date treatment
BRAF mutation	Text search	Multiple choice options: - Positive - Negative - Unclear	Multiple choice option	BRAF positief OR braf v600e-mutatie positief OR braf v600e mutation positiveOR braf v600e positief OR braf analyse positief OR braf gemuteerd OR braf POS BRAF negatief OR braf v600e-mutatie negatief OR braf v600e negatief OR braf analyse negatief OR braf neg OR geen braf mutatie BRAF	Before start date treatment
NRAS mutation	Text search	Multiple choice options: - Positive - Negative - Unclear	Multiple choice option	NRAS positief OR NRAS analyse positief OR NRAS gemuteerd OR klasse 5 pathogene variatie in NRAS OR NRAS pos NRAS negatief OR geen NRAS OR NRAS neg NRAS	Before start date treatment

Supplementary Table S6.1B continues on next page.

Supplementary File S6.1B. *Continued*

Name data point	Type of data	Multiple choice labels	Collected answer	Searched terms/keywords	Keyword search restricted to	Time window	Comments
KIT mutation	Text search	Multiple choice options: - Positive - Negative - Unclear	Multiple choice option	KIT*		Before start date treatment	*Since KIT mutations are rare, we started with sorting all patients with a "KIT" mutation mention as "negative", and verified/ corrected if this was (not) the case.
Ulceration	Text search	Multiple choice options: - Yes - No - Unclear	Multiople choice option	- Ulceratie - Geen ulceratie		Before start date treatment	

Adverse events					
Pyrexia	Text search Vital signs	Multiple choice options: - Any grade - Grade 3-4 - no	Multiople choice option	Fever OR febrile OR high body temperature OR pyrexia OR hyperthermia OR tempereature elevation OR feverish OR high temperature OR pyrexie OR hyperthermie OR lichaamstemperatuur verhoging OR hoge temperatuur OR temperatuursverhoging OR koortsig OR koortsachtig OR koorts OR temperatuur hoog OR verhoging lichaamstemperatuur OR hoog temperatuur OR koorst OR lichaamstemperatuur verhoogd OR temperatuur stijging OR koortsige OR koortsen OR verhoogde lichaamstemperatuur OR febriel OR fever with chills OR koortsrillingen OR koorts met koude rillingen OR koorts met koude rilling temperature > 38 degrees Geen koorts	Between start date treatment AND stop date treatment + 1 month

Supplementary Table S6.1B continues on next page.

Supplementary File S6.1B. *Continued*

Name data point	Type of data	Multiple choice labels	Collected answer	Searched terms/keywords	Keyword search restricted to	Time window	Comments
Artralgia	Text search	Multiple choice options: - Any grade - Grade 3-4 - No	Multiople choice option	Arthralgia OR joint pain OR aching joints OR articular pain OR painful joint OR pijnlijk gewricht OR pijn in gwricht OR artralgie OR pijn gewricht OR pijnlijke gewrichten OR gewrichtspijn OR gewricht pijnlijk OR pijnlijk gewrichten OR pijnljike gewricht OR gewrichten pijnlijk OR gewrichten doen pijn OR aralgie OR arhalgie		Between start date treatment AND stop date treatment + 1 month	

Colitis	Text search	Multiple choice options: - Any grade - Grade 3-4 - No	Multiople choice option	Colitis OR ontsteking van het colong OR collitis NOT "besproken zoals colitis, huisafwijkingen, hepatisis" OR "bijwerkingen, met name diarre/e/colitis, shcildklier OR het immuunsysteem, te weten colitis, hepatitis." *	Between start date treatment AND stop date treatment + 1 month	*EHR files with these keywords were excluded, as these were often used in EHR files indicating that a patient received the AE information prior to treatment.
Diarrhea	Text search	Multiple choice options: - Any grade - Grade 3-4 - No	Multiople choice option	Diarrhea OR diarrhee OR diarre OR diaree OR diarree OR def OR defecatie OR diare NOT (onverklaard) diarree?: nee OR geen diarree OR defecatie: vast patroon * Geen diarree OR defecatie: vast patroon	Between start date treatment AND stop date treatment + 1 month	*EHR files with these keywords were excluded from this multiple choice option as these were indicative for not having diarrhea

Supplementary Table S6.1B continues on next page.

Supplementary File S6.1B. *Continued*

Name data point	Type of data	Multiple choice labels	Collected answer	Searched terms/keywords	Keyword search restricted to	Time window	Comments
Hypothyroidism	Text search Measurement Text search Medication request	Multiple choice options: - Any grade - Grade 3-4 - No - Unclear	Multiople choice option	Hypothyroidism OR hypothyreoisis OR hypothyroid OR hypothyroidie OR deficientie schildklier OR hypothyreoidie OR hypothyreose OR schieldklier deficientie OR insufficientie schildklier OR schildklier insufficientie OR hypothyroidie Free T4 <9 Levothyroxine OR thyroxine OR L-thyroxine OR schildklier levothyroxine		Between start date treatment AND stop date treatment + 1 month	
Hyperthyroidism	Text search Measurement Text search Medication request	Multiple choice options: - Any grade - Grade 3-4 - No - Unclear	Multiople choice option	Hyperthyroidism OR hyperthyroid OR hyperthyreose OR hyperthyreoidie OR hyperthyrodie OR hyperthyroidie OR basedow Free T4>24 Levothyroxine OR thyroxine OR L-thyroxine OR schildklier levothyroxine		Between start date treatment AND stop date treatment + 1 month	

	Pneumonitis	Text search	Multiple choice options: - Any grade - Grade 3-4 - No	Multiople choice option	Pneumonitis OR pulmonary inflammation OR long ontsteking OR ontsteking long OR longontstekingen OR longonsteking Orpneumonia OR pulmonitis OR longontsteking OR inflammatie van de long OR lage luchtweginfectie OR longinfect OR pneumonie	Between start date treatment AND stop date treatment + 1 month	
	Diabetes Mellitus I	Text search Medication request	Multiple choice options: - Any grade - Grade 3-4 - No	Multiople choice option	Diabetes mellitus OR diabetes OR DM OR NIDDM OR IDDM OR diabets OR diabeet OR suikerziekte OR dmt1 OR dm1 OR mellitus diabetes NOT "let op: DM-patienten hebben een" OR "bv. Lichte DM, behandelde HT" OR DM schema: NVT* Insulins OR insulin-analogs	Between start date treatment AND stop date treatment + 1 month	*EHR files with these keywords were excluded, as they are often used sentences including "DM"but not indicating DM

Supplementary Table S6.1B continues on next page.

Supplementary File S6.1B. *Continued*

Name data point	Type of data	Multiple choice labels	Collected answer	Searched terms/keywords	Keyword search restricted to	Time window	Comments
Fatigue	Text search	Multiple choice options: - Any grade - Grade 3-4 - No	Multiople choice option	Fatigue OR loss of energy OR lack of energy OR energie afgenomen OR futloosheid OR lusteloosheid OR verlies van energie OR gevoel van energieloosheid OR lusteloos OR moeheid OR vermoeid OR uitzonderlijk moe OR futloos OR vermoedheid OR vermoeide OR vermoeiden OR vermoeit OR vermoei OR afgenomen energie OR vermoeien OR moe OR malaise OR suf OR duf OR geen energie OR hagnerig OR zwak OR slap OR uitgeput OR verzwakt OR loom OR moeie OR extreme vermoeidheid?: ja NOT vermoeidheid?: nee* Vermoeidheid?: nee		Between start date treatment AND stop date treatment + 1 month	*EHR files with these keywords were excluded, indicating no fatigue

Nausea	Text search Medication request	Multiple choice options: - Any grade - Grade 3-4 - No	Multiople choice option	Nausea OR nauseous OR nauseated OR misselijkheid OR onpasselijk OR onpasselijk gevoel OR misselijk OR misselijke OR vomiting OR emesis OR gebraakt OR regurgitatie maaginhoud OR braken OR braakt OR kots OR kotsen OR overgeven OR braaksel OR braakte OR vomeren OR spugen OR oprisping NOT "u misselijk bent of moet overgeven" OR "- misselijkheid / braken - tandbeschadiging" Aprepitant OR fosaprepitant OR netupitant OR granisetron OR ondansetron OR palonosetron	Between start date treatment AND stop date treatment + 1 month	*EHR files with these keywords were excluded, it only indicated that a patient received AE information

Supplementary Table S6.1B continues on next page.

Supplementary File S6.1B. *Continued*

Name data point	Type of data	Multiple choice labels	Collected answer	Searched terms/keywords	Keyword search restricted to	Time window	Comments
Headache	Text search	Multiple choice options: - Any grade - Grade 3-4 - No	Multiople choice option	Headache OR cephalgia OR cephalalgia OR head pain OR hoofd pijn OR cefalgie OR pijn hoofd OR hoofdpijn OR hoofdpijnen OR cefalalgie OR migraine OR headache migraine OR migrainous headache OR migraine type headaches OR migraine headache OR migrainehoofdpijn OR migraineuze hoofdpijn OR syndroom migraine OR hoofdpijn migraine OR migrianehoofdpijnen OR migraine hoodpijn OR migraine syndroom OR migraineuze hoofdpjnen OR migrianes NOT "geen hoofdpijn Geen hoofdpijn		Between start date treatment AND stop date treatment + 1 month	
Chills	Text search	Multiple choice options: - Any grade - Grade 3-4 - No	Multiople choice option	Shivering OR rillingen OR rillen OR rilling OR bibber OR bibberen OR beven OR rilde OR bibberde OR beefde OR chills OR chill OR koude rillingen OR koude rilling		Between start date treatment AND stop date treatment + 1 month	

Hepatitis	Text search	Multiple choice options: - Any grade - Grade 3-4 - No	Multiople choice option	Hepatitis OR ontsteking van de lever OR ontstekingsproces van lever OR niet-specifiek hepatitis OR ontsteking lever OR lever ontsteking NOT "een colitis, hepatitis, schildklierafwijkingen, vitiligo, etc."*	Between start date treatment AND stop date treatment + 1 month	*EHR files with these keywords were excluded since it only indicated that a patient received AE information
Dyspnea	Text search	Multiple choice options: - Any grade - Grade 3-4 - No	Multiople choice option	Dyspneu OR shortnes of breath OR breathlessness OR breathless OR difficulty breathing OR DIB OR SOB OR kortademigheid OR kortademigheid adem OR dyspnoea OR dyspneu OR ademnood OR moelijk ademen OR adem kortademigheid NOT "geen dyspneu" OR "heeft u last van kortademigheid in rust of bij lichte inspanning?: nee"	Between start date treatment AND stop date treatment + 1 month	*EHR files with these keywords were excluded, indicating no dyspnea

Supplementary Table S6.1B continues on next page.

Supplementary File S6.1B. *Continued*

Name data point	Type of data	Multiple choice labels	Collected answer	Searched terms/keywords	Keyword search restricted to	Time window	Comments
Cough	Text search	Multiple choice options: - Any grade - Grade 3-4 - No	Multiople choice option	Coughing OR cough OR hoest OR hoesten OR gehoest OR hoeste OR hoestte OR kuchen OR kuch NOT geen hoest OR "heeft u last van hoesten of keelpijn?: nee" OR geen hoesten OR geen dyspneu of hoesten* Geen hoest OR geen hoesten OR geen dyspneu of hoesten		Between start date treatment AND stop date treatment + 1 month	*EHR files with this sencente were excluded, indicating no cough
Pruritus	Text search	Multiple choice options: - Any grade - Grade 3-4 - No	Multiople choice option	Pruritus OR pruritis OR itching OR itchy OR jeukende huid OR jeuk OR jeukend OR jeuken Geen jeuk OR geen pruritus OR geen pruritis		Between start date treatment AND stop date treatment + 1 month	
Asthenia	Text search	Multiple choice options: - Any grade - Grade 3-4 - No	Multiople choice option	Asthenia OR zwakte OR asthenie OR krachteloosheid OR zwakheid OR zwak NOT geen zwakte OR geen asthenie Gene asthenie OR geen zwakte		Between start date treatment AND stop date treatment + 1 month	

Rash	Text search	Multiple choice options: - Any grade - Grade 3-4 - No	Multiople choice option	Exanthema OR skin eruption OR cutaneous eruption OR eruption OR skin rash OR exanthem OR rash OR huiduitslag OR vluchtig exantheem en overige niet-specifieke erupties OR effluorescentie OR huideruptie OR exantheem OR uitslag huid OR huid uitslag NOT geen uitslag OR geen rash* Geen uitslag OR geen rash	Between start date treatment AND stop date treatment + 1 month	*EHR files with this sencente were excluded, indicating no rash
Abdominal pain	Text search	Multiple choice options: - Any grade - Grade 3-4 - No	Multiople choice option	Abdominal pain OR darmpijn OR abdominale pijn OR buikpijn OR pijn abdominaal OR abdominaal pijn OR pijn buik OR buik pijn OR pijn in buik OR pijn in onderbuik NOT geen buikpijn* Geen buikpijn	Between start date treatment AND stop date treatment + 1 month	*EHR files with these keywords were excluded, indicating no abdominal pain

Supplementary File S6.2a.

Treatment-limiting adverse event per individual patient	Nivolumab n=9									Total
	1	2	3	4	5	6	7	8	9	
Colitis	1	1								2
Pneumonitis		1	1							2
Hepatitis				1	1					2
Thyroiditis				1	1					2
Myalgia				1						1
Myocarditis				1						1
Arthralgia						1				1
Hypocortisolism							1			1
Polymyalgia rheumatica								1		1
Meningitis									1	1
Adrenalitis									1	1
Total	1	2	1	4	2	1	1	1	2	

Supplementary File S6.2b.

Treatment-limiting adverse event per individual patient	Pembrolizumab n=3			Total
Colitis	1			1
Arthralgia		1		1
Myalgia		1		1
Pneumonitis			1	1
Total	1	2	1	

Supplementary File S6.2c.

Treatment-limiting adverse event per individual patient	Dabrafenib plus trametinib n=8								
	1	2	3	4	5	6	7	8	Total
Pyrexia	1	1	1	1	-	-	1	-	5
Chills	1	1	1	-	-	-	-	-	3
Nausea	1	1	1	-	-	-	-	-	3
Myalgia	1	-	-	-	-	1	-	-	2
Headache	1	-	-	-	-	-	-	-	1
Liver function disorders	1	-	-	-	-	-	-	-	1
Fatigue	-	1	-	-	-	-	-	1	2
Syncope	-	1	-	-	-	-	-	-	1
Skin disorder	-	-	-	1	1	1	1	-	4
Allergic reaction	-	-	-	-	1	-	-	-	1
Tachycardia	-	-	-	-	1	-	-	-	1
Decreased appetite	-	-	1	-	-	-	-	-	1
Arthralgia	-	-	-	-	-	1	-	-	1
Malaise	-	-	-	1	-	-	-	1	2
Total	6	5	4	3	3	3	2	2	