The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

**GSK Medicine: dabrafenib**

**Study Number:** 200215

**Title:**
The epidemiology, management patterns, and direct costs of treating malignant melanoma in Canada: an observational study using the Canadian Melanoma Research Network (CMRN) Patient Registry and The Ontario Cancer Data Linkage Project (CD-link)

**Rationale:**
Melanoma is an aggressive type of skin cancer that is responsible for the majority of skin cancer-related deaths. Although evidence suggests that the incidence of metastatic melanoma is increasing in Canada, disease characteristics and economic burden of melanoma are not well understood. Detailed epidemiology, healthcare resource utilization and direct costs for managing patients particularly in unresectable (stage IIIC) and metastatic (stage IV) melanoma have not been previously described. This study aims to fill the epidemiological and resource utilization evidence gaps in the current understanding of metastatic melanoma by characterizing the burden of illness in a Canadian cohort, and estimating direct costs associated with disease management.

**Objectives:**
This explore the epidemiology, healthcare resource utilization and patterns, and direct costs associated with management and treatment of metastatic melanoma, through two main investigational objectives:
- To study the presentation, disease characteristics, and treatment patterns for metastatic melanoma in Ontario as part of an epidemiologic analysis, using three participating sites in the Canadian Melanoma Research Network (CMRN)
- To estimate the resource utilization and costs associated with the management and treatment of metastatic melanoma using the CD-link database

**Study Design:** Observational prospective, and retrospective study

**Indication:** metastatic melanoma

**Study Period:**
- Epidemiological study period from: April 2011 to April 30, 2013
- Resource utilization study period from: August 31, 2005 to August 31, 2012

**Study Investigators/Centres:**
- To study the burden of melanoma in Ontario, a cohort was identified from the CMRN which included patients from London Health Science Centre, Princess Margret Hospital and Sunnybrook Health Sciences Centre
- To study the healthcare resources utilized by melanoma patients, a cohort of melanoma patients were identified from the Ontario Cancer Data Linkage Project (CD-link) administrative database

**Data Source:**
- Canadian Melanoma Research Network Patient Registry (CMRN)
- CD-link database, through the Institute for Clinical Evaluative Sciences (ICES)

**Research Methods:**

1. **Epidemiologic analysis: melanoma-related disease characteristics**

This was a Canadian multicentre, observational, prospective and retrospective study of patients with metastatic melanoma, using data collected from the CMRN which included patients from London Health Science Centre, Princess Margret Hospital and Sunnybrook Health Sciences Centre.

The study investigated disease distribution by staging of melanoma patients by age, gender, body region, tumour site, initial stage, histological classification, mutation type, time to recurrence, sites of metastatic disease, resectability and previous adjuvant and systemic therapies.

**Inclusion and Exclusion Criteria:**
- All patients with confirmed melanoma seen at any one of the three participating treatment centers over either the retrospective or prospective duration of observation were eligible for entry into the database.
- Subjects with at least 12 months of follow up data were eligible for entry into the database.
- Patients who had less than 12 months follow up could be included but were delineated as such
- Anyone for whom the diagnosis of melanoma has not been histologically confirmed, or for whom such information cannot be accessed, were be excluded.

### 2. Melanoma-related healthcare resource utilization

Through the CD-link program, a cohort of individuals with a diagnosis of melanoma (ICD-9 code=172) was identified. These were subjects who received diagnoses between Aug 31, 2005 – Aug 31, 2012 (including pre-diagnosis treatments and follow up to 2013) with valid Oncology ICD-9 and histology codes. The CD-link database was linked to hospitalization, physician and homecare databases. The cohort of individuals with metastatic melanoma was generated by defining a cohort with a combination of at least one palliative, one medical oncology and one hospitalization code. At least one code from each of the three resource clusters was combined to identify the cohort.

The types of health system services utilized by this population were clustered into hospitalization, palliation, physician medical visits, medication, homecare, laboratory, diagnostics and other resources. Ontario level costs were obtained from publicly provincial sources including the Ontario Case Cost Initiative (OCCI), Ontario Drug Benefit Formulary (ODB), Ontario Health Insurance Plan (OHIP) and hospital sources for diagnostics. Costs were reported in 2013 Canadian dollars.

<table>
<thead>
<tr>
<th>Data Analysis Methods:</th>
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<tbody>
<tr>
<td>Descriptive statistics (counts, proportions, mean, median and standard deviation) and inferential statistics (paired t-tests, survival analysis, Cox proportional hazards, and covariate analysis) were employed based on variables of interest.</td>
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**Study Results:**

### 1. Epidemiologic analysis: melanoma-related disease characteristics

#### Patient characteristics

Using the CMRN Patient Registry, a cohort of 810 CMM patients was identified from three different treatment sites in Ontario, diagnosed from 1964 to 2013. The mean age of the cohort was 58.7±14.8 years with a male predominance (60% vs. 40%). At presentation, there was a broad spectrum of stage representation in melanoma, from stage 0 to stage IV. The mean time to recurrence for all patients included in the cohort was about 5 years.

Out of the 810 patients, at initial stage, 9 (1.1%) were stage 0, 83 (10.3%) were IA, 99 (12.2%) were IB, 73 (9.0%) were II, 12 (1.5%) were II A, 72 (8.9%) were II B, 62 (7.6%) were II C, 47 (5.8%) were III A, 29 (3.6%) were III B, 28 (3.5%) were III C, 4 (0.5%) had primary melanoma of the eye, 26 (3.2%) had no primary site determined at staging, and 200 (24.7%) were not classified due to unknown stage. There were 78 (9.6%) patients who were stage IV, of which 13 (1.6%) had a diagnosis of M1A distant skin metastasis, 16 (1.9%) had the M1B lung metastasis diagnosis, and 49 (6.1%) had M1C which was any other distant metastasis. In all patients, the limbs (27.2%), trunk (25.9%), head (16.9%) and neck (4.8%) were found to be the most common sites of primary disease. At presentation, out of the 810 patients in the cohort, 356 (44%) were metastatic compared to 454 (56%) non-metastatic, 704 (87%) were resectable compared to 104 (13%) non-resectable, 51 (6%) had a BRAF mutation and 367 (45%) were unresectable metastatic.

When comparing mean age across all disease stages (0 to IV), no statistically significant differences were found between groups (p=0.111). Similarly, when comparing mean age between metastatic and non-metastatic patients, resectable and unresectable patients, in patients with presence of BRAF mutation versus absence, no significant differences were found.

#### Treatment modalities

A total of 488 (60.2%) patients out of the 810, had previously used medications across different lines of treatment. The majority of patients (57%) were on a first-line therapy, 32% were on a second-line therapy and 11% were on a third-line therapy. Treatments in the first-line setting that were most commonly utilized were DTIC alone (27.9%), investigational drugs from clinical trial (22.1%), combination of carboplatin and paclitaxel (15.7%), ipilimumab (11.1%) and vemurafenib (9.6%). For second- and third-line treatments, the use of ipilimumab, investigational drug and the combination of carboplatin and paclitaxel were most common.

Of the 488 patients who had previously utilized treatment, 147 (30.1%) were metastatic, 90 (18.4%) were unresectable, 51 (10.4%) had the BRAF designation and 346 (70.9%) were unresectable metastatic. Of the 346 unresectable metastatic patients who were taking medications, 22.2% were on ipilimumab, 19.9% were on DTIC alone, 17.9% were on an investigational drug from a clinical trial. Most patients had taken DTIC alone as first-line therapy, ipilimumab as second- and third-line therapy.

In all 810 patients identified, treatment modalities such as radiotherapy, surgery and systemic therapy were commonly used across different stages. At presentation, more patients had undergone radiotherapy (90.1%) compared to surgery (37.6%) and systemic therapy (23.5%), and fewer patients had undergone all three treatments (8.9%). A total of 182 patients who were stage III and stage IV most commonly utilized both radiotherapy and surgery.

#### Disease presentation and factors affecting survival (stage of disease, BRAF mutation status, brain metastasis)

Of the 182 stage III and IV patients only, 65% were metastatic and 58% were unresectable. The proportion of newly diagnosed patients vs. recurrent patients at presentation was 48% and 52%, respectively, showing no statistical significance (p=0.350).

When comparing the presence versus absence of BRAF mutation in the 367 unresectable metastatic patients only, 11% were BRAF positive with the majority (19.5%) of patients falling in the stage IV MIC classification. There was no significant difference between group and gender proportion in this group of patients. In unresectable metastatic patients, the most common histological presentations were superficial spreading (42.3%) and nodular (18.5%).

Out of the 367 unresectable metastatic patients, 29.2% tested for BRAF mutation and 38% of these patients tested positive. Of the patients who tested positive for BRAF mutation, the proportion of surviving unresectable, metastatic patients was 83.8% with a mean survival time and 95% CI of 108.6 (81.1-136.1) months. The overall survival in this population was 50% with a mean...
survival time and 95% CI of 76.8 (69.5-84.1) months.

Cumulative survival decreased more steadily in patients with BRAF mutation compared to those without the mutation, causing a rapid decline in survival over months. Survival in unresectable metastatic patients from the initial 810 patients cohort was about 50% with an estimated mean survival time and 95% CI of 78.9 (70.4 – 87.5) months.

The proportion of patients in the same population of unresectable metastatic disease (n=367) who had brain metastases was 17.8% at presentation and 82.2% subsequently. The proportion of unresectable metastatic patients surviving with brain metastasis is about 50.9% at presentation and 50.8% at subsequent presentation. The mean survival time and 95% CI was 25.4 months (12.5 – 38.4) at presentation and 53.7 months (41.6 – 65.7). On average, unresectable metastatic patients with brain metastasis had significantly lower survival time compared to other patients.

The proportion of surviving patients across progressing disease stages decreased, with the highest percent of survival in stages 0 – IIC (79.9%), and III (71.0%), followed by IV (52.0%). The mean survival time and 95% CI by disease stage for stage 0-IIC, III and IV were 113.3 (95.5-130.9), 76.3 (59.2-93.2), and 59.9 (38.2-81.7) months, respectively. The mean time to recurrence across all disease stages was 47.4 (39.0 – 55.7) months.

Disease-free survival in the overall population of 810 patients, at one year was 73.1% and 65.8% after two years. It was not possible to determine survival from the other potential prognostic from the registry.

2. Melanoma-related healthcare resource utilization

Patient Characteristics

A cohort of 2,748 individuals was identified in the algorithm-defined diagnosis of advanced metastatic melanoma. The majority (65.6%) of individuals were male and the majority of individuals were over 65 years of age (>50%). The mean age of the cohort was 67±14 years. The survival of the cohort was assessed over the phases of care in the study period. Less than 45% of the cohort was alive 3 years after the metastatic melanoma diagnosis. After a follow up of 8+ years, there were no patients remaining in the dataset either due to censoring or subject deaths.

Healthcare resource utilization costs

With respect to utilization of healthcare services, there were a number of different clusters of attributable costs. Resource utilization and costs were tabulated for the entire cohort of 2,748 patients, which included a population of individuals who were using healthcare resources as well as those who were not over the course of the study. The overall average cost per individuals diagnosed with metastatic melanoma within the study horizon was calculated to be $37,489, ranging from $3,722 to $882,775. The median was $25,641. Cost drivers were hospitalizations, physician medical visits, diagnostics and medications. When only patients with resource utilization were included, the average cost for patients requiring hospitalization was $24,600, for palliation, the average cost was $858 and for subjects with physician medical visits, the average cost was $4,699. Eighty-three percent of the subjects received at least one attributable medication from the ODB, costing on average $2,720.

The total costs associated for the entire cohort by phase of care, namely pre-diagnosis and follow up years one through to eight and beyond, found that costs were highest in the early phases of care compared with late phases as a result of patient survival. The overall cost for the cohort at the end of the first year was $43,278,269 for 2,734 individuals compared with $704,577 for 186 individuals by eight years and over. The average annual cost per subject over the time horizon was $6,551. The first year after diagnosis was the most expensive year at a cost per subject of $15,830, followed by $8,166 in year 2 and down to $3,788 by 8 years and beyond. The most expensive types of care received by patients at the end of the first year included hospitalizations (costing $30,467,311 for 2,121 patients), medical visits (1,345,057 for 2,629 patients) and medications ( $2,850,804 for 1,824 patients).

The total costs for the entire cohort by the phase of care for those subjects who were alive at the end of that time horizon also found costs to be highest at early phases of care compared to late phases. The most expensive types of care received by patients at the end of the first year included hospitalizations ($26,822,857 for 1,483 patients), medical visits ($1,931,067 for 509 patients), diagnostics care ($1,253,430 for 612 patients) and medications ($570,563 for 458 patients).

A total of 127 patients had coded brain metastasis. For this cohort, the mean cost was $60,759 (range $12,801-$206,640) which is about $23,270 greater than the mean cost per patient in the entire cohort ($37,489).
Using the total OHIP paid cost reported in the dataset instead of the publicly available cost, it was determined that the overall average cost per individual in the entire cohort of 2,748 decreased slightly from $38,380 to $33,680. Cost drivers of care were again hospitalizations, physician medical visits, diagnostics and medications. In the cohort with at least one type of resource utilization (excluding patients with no resource utilization), mean cost per individual was found to be $34,840.

**Limitations**

1. **Epidemiologic analysis: melanoma-related disease characteristics**
   - The primary limitation is the retrospective nature of an analysis on a limited cohort of patients
   - The inclusion of patients into the registry was based on the availability of data and was not intended to provide a comprehensive overview of all patients or a specific subset of patients. Patient selection was therefore intrinsically biased by data availability and was limited to 3 geographical sites.
   - Missing data was also an inherent problem of the study which relied upon the presence of information in patient records
   - Furthermore, the time limits of the study reduced the ability to observe the impact of new diagnostic and treatment modalities. Patients who had BRAF testing within the time period observed were not as comprehensive as current methods.

2. **Melanoma-related healthcare resource utilization**
   - The cohort was not defined according to recorded stage characteristics of melanoma but instead by surrogate indicators based on expert clinical opinions and algorithms, making the cohort not entirely representative of the CMRN database.
   - In terms of drug utilization, a number of antineoplastics (e.g., temozolomide, interferon, etc) used in the management were captured, but there was no data available on systemic chemotherapy agents in the database. The drug database only had information on individuals over the age of 65 and those on social assistance but a majority of the population under investigation is under 65 years.
   - Moreover, newer drugs such as vemurafenib and ipilimumab were not yet utilized by this population and therefore not available for costing. The cost estimate for medications may represent an underestimate at this time. These data will be available in the future and will be available for analysis at that time.
   - Only the resources deemed attributable by the medical oncologists for the management of advance metastatic melanoma were identified and included in the analysis. It is possible that resources outside of the ones identified could also be used by this cohort, however, these resources were validated by clinicians treating metastatic melanoma patients.

**Conclusion:**
The burden of illness and healthcare resource utilization in metastatic melanoma has not been previously described in a Canadian cohort. This study aimed to examine disease characteristics and associated cost of managing patients in metastatic melanoma. The study found unresectable metastatic melanoma patients to have significantly lower survival compared to other melanoma patients across different disease stages. Cost drivers in the advanced metastatic melanoma cohort were hospitalizations, physician visits and diagnostics.