GetReal - Project No. 115546

WP1: Deliverable D1.5

Case Study on Metastatic Melanoma

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1. Executive Summary

A key objective of work package 1 (WP1) is to develop a framework for incorporating real world evidence (RWE) in decision-making. To this end, the work package is using case studies to explore how RWE could be used to help demonstrate relative effectiveness of new drugs. This document relates to a case study on metastatic melanoma. It outlines the natural history of the disease, treatment options and treatment pathway. Additionally, it contains a review of regulatory and HTA decisions for a recent drug indicated for metastatic melanoma and summarises the key challenges that were observed in establishing relative effectiveness of the drug.

The overall objective of the case study on metastatic melanoma is to better understand how decision-making in pharmaceutical research and development, regulatory approval and health technology assessment (HTA) recommendations could be improved by an expansion in the nature of the evidence available to decision makers. More specifically, the case study on metastatic melanoma has the following aims:

1. Explore options for combination of real world data (RWD) and randomized controlled trial (RCT) data to improve estimates of effectiveness for metastatic melanoma treatments at time of decision making. This may include the following sub-themes:

   a. Description of RWD from different registries and data from phase IV studies on ipilimumab (including usability testing)

   b. Comparison and synthesis of RWD from different registries and data from phase IV studies on ipilimumab

   c. Synthesis of RWD (from registries and/or phase IV studies) and RCT data to carry out predictive modelling of relative effectiveness of metastatic melanoma treatments. This includes, for example, prediction of long term outcomes from RWD (extrapolation)

   Each sub-theme includes issues related to data quality (e.g. completeness, comprehensiveness, comparability, transferability), definition of parameters and outcomes, as well as statistical methodologies available to perform data syntheses.

2. Explore the potential for data on metastatic melanoma patients collected from social media sources to be included as part of evidence base for relative effectiveness research.

3. Explore the possibilities for developing novel real-world study designs during drug development that better incorporate patient preferences.

In order to address these aims the case study working group will organize two workshops, the first of which was held on June 10th 2015 and the second will be held in April 2016.

Innovative Medicines Initiative

2. The Metastatic melanoma case study

2.1 Context

2.1.1 Natural History, Diagnosis and Staging of Disease

Melanoma is a form of skin cancer affecting melanocytes, with a relatively higher prevalence among the Caucasian population.(2) Prevalence rates of metastatic melanoma within industrialised nations has witnessed a steady rise in recent years, especially in countries within Oceania, Northern Europe, North America and Latin America.(2) One established risk factor for contraction of metastatic melanoma is exposure to UV radiation.(3, 4)

Melanoma first manifests as an asymmetric primary tumour characterised by an irregular border, variegated colour and a diameter larger than 0.6mm. In the case of nodular lymphoma, the primary tumour is also elevated above the skin surface, firm to the touch and increasing in size. Observation of such characteristics of skin abnormalities provide the basis for initial diagnosis of melanoma.(5)

Subsequent metastatic spread of tumours may arise from small tumour masses. This can develop via three main metastatic pathways, beginning with either satellite or in-transit metastasis, regional lymph node metastasis, or immediately with distant metastasis as first tumour recurrence (See figure 1).(6) About half of all patients with tumour progression develop regional lymph node metastases as first type of metastasis. In the other half, the first metastases are satellite or in-transit metastases, or distant metastases. Development of distant metastasis is discussed to be most often an early event in metastatic spread originating from the primary tumour. Once such metastasis has occurred, the melanoma is classified as metastatic melanoma.

Melanoma is classified into four different clinical stages (stages I-IV) to describe its degree of severity.(7) These clinical stages correspond to particular TNM (Tumour thickness, lymphatic Nodes affected and distant Metastasis presence) pathological classifications. For an overview of TNM values and their meaning, please consult Balch et al.(7) Stage I and II melanoma are localized and may be ulcerated and may have a mitotic rate of $\leq 1/mm2 \geq$. More advanced melanomas, stage III and IV melanoma, have metastasized to other parts of the body.(7)
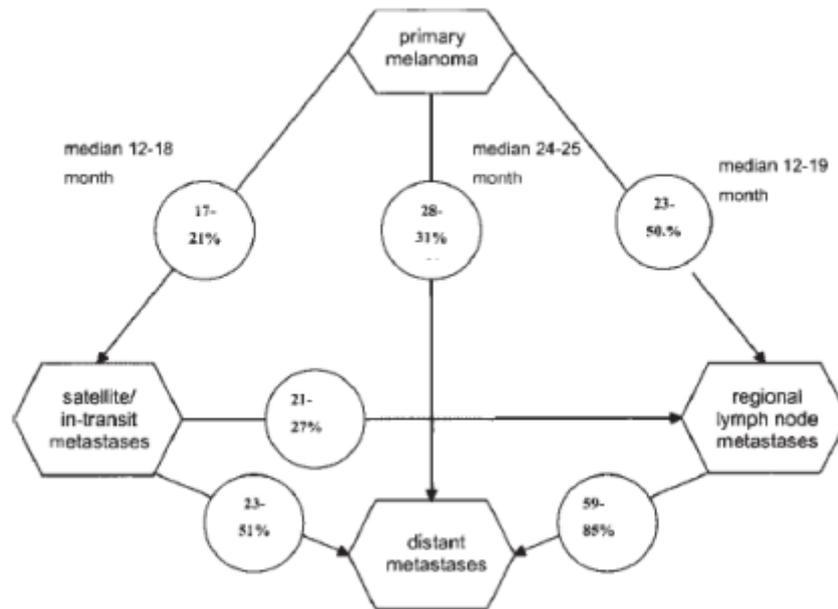
Figure 1. Three main metastatic pathways occur in primary cutaneous melanoma. The respective frequencies of their involvement are given within this graph. There is a certain percentage of transition from satellite/intransit metastasis to regional lymph node and to distant metastasis and from regional lymph node to distant metastasis (From Leiter et al. (6)).

With regard to the progression of patients from Stage I/II to Stage III, the stage of disease at diagnosis is the most important prognostic factor.(6, 8) Disease-independent significant prognostic factors include: tumour thickness, level of invasion, age, gender, anatomic site of primary tumour, and presence of ulceration. The male gender and primary tumour location on head/neck and trunk were associated with a decreased survival probability. Meanwhile, important prognostic factors for Stage III patients are tumour thickness, age and presence of ulceration, but the number of node metastases and type of recurrence remain the most significant prognostic factors for stage III patients.(6, 9-11)

As melanoma progresses several disease-associated symptoms increase, such as pain, weight loss, dyspnea, headache, loss of mobility, nausea, vomiting and fatigue.(12)

Decisions on the treatment of melanoma are based on several aspects, the tumour stage being the most important one. Furthermore, treatment depends on the presence of brain metastasis and of specific genetic mutations (e.g. BRAF and RAS mutations).

2.1.2 Current Treatment Landscape: Licensed Medications and Late-Stage Pipeline Agents
Prior to 2011, cytotoxic therapy, notably dacarbazine, formed the cornerstone of treatment. In 2011, two drugs were approved for the treatment of non-resectable metastatic melanoma. Ipilimumab (Yervoy; Bristol-Myers Squibb), is a first-in-class monoclonal antibody that targets cytotoxic T lymphocyte antigen 4 (CTLA4).[12] Vemurafenib (Zelboraf;

Roche/Genentech/ Daiichi Sankyo/Chugai), is an additional first-in-class agent which exerts its action on the serine/threonine-protein kinase B-Raf (BRAF) protein.[13] Vemurafenib targets the V600E mutation in the BRAF enzyme, which is found in 40–50% of patients.[14;15]

In May 2013, two additional targeted therapies, dabrafenib (Tafinlar; GlaxoSmithKline) and trametinib (Mekinist; GlaxoSmithKline) were approved. Dabrafenib exerts a similar mechanism of action as vemurafenib by targeting the BRAFV600E protein.[16] On the other hand, trametinib is a first-to-market MAPK/ERK (MEK) inhibitor that is approved for use in both BRAFV600E and the less common BRAFV600K-mutated malignant melanoma.[17] A combination of dabrafenib and trametinib was granted accelerated approval by the US Food and Drug Administration (FDA) for unresectable or metastatic BRAFV600E or BRAFV600K malignant melanoma, based on Phase I/II trials.[18]

Several BRAF and MEK inhibitors are currently in late-stage clinical development or have recently received marketing authorisation.[19;20] The MEK inhibitor cobimetinib (Roche/ Genentech/ Exelixis) is approved for administration in combination with vemurafenib.[21] The MEK inhibitor binimetinib (MEK162; Novartis/Array) has potential for the treatment of *NRAS*-mutated malignant melanoma (accounting for approximately 15–25% of patients. Binimetinib is additionally being evaluated in a three-armed Phase III study in combination with the BRAF inhibitor encorafenib (LGX818; Novartis) versus encorafenib and vemurafenib monotherapies.[19;22]

Novel targeted monoclonal antibodies targeting programmed cell death protein 1 (PD1)-, a novel class of immune checkpoint inhibitors, have recently received marketing authorisation. In December 2014, nivolumab (Bristol-Myers Squibb/Ono) was approved in the USA for the treatment of advanced melanoma and in June 2015 in Europe.[23;24] Pembrolizumab (MK-3475; Merck) has also recently been granted marketing authorisation in the USA and Europe for the treatment of advanced, unresectable metastatic melanoma. [25;26]

Other immunotherapeutic approaches are being explored. The oncolytic immunotherapy talimogene laherparepvec (T-Vec; Amgen) is a modified version of herpes simplex virus type 1 (HSV1) that is modified to selectively replicate in tumour cells and activate a systemic immune response.[25] Talimogene has recently received marketing authorisation approval in the USA (October 2015) and Europe (December 2015).

Recent development involve exploring combinations of immunotherapies; one example being nivolumab in combination with ipilimumab (approved by the CHMP in March 2016).

2.1.3 Standard of Care and Current Practice

Although several treatments and therapies are available for patients with metastatic melanoma, guidelines mainly focus on follow-up care of patients. Several dermatologic and oncologic organizations, such as the European Society for Medical Oncology and the British Association of Dermatologists, have developed such guidelines.(28-30, 30) Follow-up care focuses on the detection of recurrences by determining the duration and frequency of follow-up, history & physical examinations.(29)

The National Comprehensive Cancer Network (NCCN) provides a guideline on standard of care and current practice for metastatic melanoma. For primary treatment of stage III in-transit melanoma the NCCN recommends clinical trial participation, lymph node dissection, wide excision, bacillus calmette-guerin, interferon alfa, IL-2 injection in the tumour, imiquimod cream, laser/ablative therapy, palliative radiation if unresectable, heated melphalan injection confined to the limb or systemic therapy. As adjuvant treatment next to this, clinical trial participation, observation or interferon alfa are recommended. In the case of clinical stage III melanoma, the primary treatment suggested is wide excision with lymph node dissection and for adjuvant treatment the NCCN recommends clinical trial participation, observation or interferon alfa and/or radiation therapy to nodal basin. The treatment options for stage IV melanoma patients are surgery, observation, systemic therapy, clinical trial participation, best supportive care and/or radiation therapy for symptoms or brain metastases.(31)

Additional guidelines on standard of care or current practices for metastatic melanoma seem non-existent, but several sources agree on the treatment options available to patients with metastatic melanoma, namely surgery, chemotherapy, radiation therapy, targeted therapy, immunotherapy or a combination of immunotherapy and chemotherapy (biochemotherapy). Furthermore these sources agree that patients with metastatic melanoma could benefit from experimental treatments available via clinical trials.(30, 32-34)

2.1.4 Ipilimumab as an Example: Overview, Marketing Authorisation and HTA Assessment

Ipilimumab is a monoclonal antibody initially granted marketing authorisation in Europe by the European Medicines Agency (EMA) in July 2011 within its proposed target population: "treatment of advanced (unresectable or metastatic) melanoma in adults". The proposed mechanism of action of ipilimumab involves its binding to CTLA-4, a protein found on a subset of activated T cells, to trigger an enhanced T-cell mediated immune response characterised by T cell activation, proliferation and infiltration into tumours leading to tumour cell death.(13) In the pivotal clinical study (MDX010-20), ipilimumab was shown to improve overall survival of patients with mild to moderate side-effects resulting from excessive immune activity such as severe reactions and inflammation.(13)

The positive efficacy results were supported by another phase 3 study (CA184-024) examining the effect of high-dose ipilimumab (10 mg/kg) in combination with dacarbazine on overall survival in untreated patients. In addition, two single arm, non-interventional studies in previously untreated US patients (CA184-332 and CA184-338) demonstrated the effectiveness of ipilimumab 3 mg/kg in a real-world setting. In combination with the existing RCT evidence, this led to the extension of the marketing authorisation to the first-line treatment of metastatic melanoma in October 2013. The Committee for Medicinal Products for Human use (CHMP) indicated that further data was required on the comparative efficacy (and safety) of 3 mg/kg and 10 mg/kg monotherapy in previously untreated patients and requested a randomised dosage comparison study from the manufacturer to evaluate this.(13)

Ipilimumab has undergone health technology assessment (HTA) with several European agencies, receiving approval for reimbursement within its European marketing authorisation in 2011 by Haute Autorite de Santé (HAS), 2012 by Zorginstituut Nederland (ZIN), The Dental and Pharmaceutical Benefits Agency (TLV) and the National Institute for Health & Care Excellence (NICE), and in 2013 by the Scottish Medical Consortium (SMC) (Table 2). Ipilimumab is now reimbursed for second-line treatment of advanced melanoma in nearly all EU countries. Nearly all submissions relied on assessment of the pivotal MDX010-20 trial supplemented by a couple of phase 2 trials.

Recurring uncertainties in the submission highlighted by nearly all HTA bodies centred on the choice of the comparator used in the pivotal trial and the limited duration of the study requiring cautious interpretation of extrapolated survival data. In the NICE appraisal, the independent evidence review group (ERG) noted that the pivotal study did not include any of the comparators stated in the final scope issued by NICE and instead relies on the gp100 vaccine - whose effect on outcomes was not completely understood.(35) Similarly, the HAS Transparency Committee stated that gp100 was an experimental peptide vaccine which did not have a marketing authorisation and was not available on the French market, making the therapeutic contribution of ipilimumab difficult to quantify given the choice of this comparator.(36)

Regarding extrapolation of long-term outcomes, the SMC highlighted uncertainty surrounding the estimation of the long-term effects of the ipilimumab in the submission, claiming that the robustness of the extrapolated data was uncertain given that few patients (2%) experienced a complete response to treatment.(37) However, a subsequent re-analysis presented at ESMO in 2013 that pooled all Yervoy clinical data showed a survival plateau at approximately 20% of patients starting at 36 months and extending to 10 years.(38) A network meta-analysis at the time of HTA submission also showed that gp100 produced similar treatment outcomes to those of existing treatments.(35) Following the extension of the marketing authorisation for use as a first-line treatment in advanced metastatic

melanoma, re-appraisal of the medicine as a first-line treatment was given a positive recommendation by NICE, TLV and the SMC.

Comparators for ipilimumab include best supportive care, carboplatin-based chemotherapy and dacarbazine. Additionally, alternative treatments for untreated patients with BRAF V600 mutation-positive melanoma include vemurafenib, dabrafenib and trametinib. Clinical trials of new agents were also historically used as a common treatment option in second line treatment and beyond.

Table 1: EMA approved therapies for metastatic melanoma

Medicine Name	Product Number	Common name	Marketing Authorisation Holder	Status	Initial EMA MA date	Indication
IntronA	PL 11587/0008	dacarbazine	medac	Authorised	28/11/1997	Various indications including metastatic melanoma, advanced Hodgkin's disease, and advanced adult soft tissue sarcomas.
Mekinist	EMEA/H/C/002643	trametinib	Glaxo Group Ltd	Authorised	30/06/2014	Treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation
Tafinlar	EMEA/H/C/002604	dabrafenib	GlaxoSmithKline	Authorised	26/08/2013	Treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
Yervoy	EMEA/H/C/002213	ipilimumab	Bristol-Myers Squibb Pharma EEIG	Authorised	13/07/2011	Yervoy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults
Zelboraf	EMEA/H/C/002409	vemurafenib	Roche Registration Ltd.	Authorised	17/02/2012	Vemurafenib is indicated in monotherapy for the treatment of adult patients with BRAF-V600-mutation-positive unresectable or metastatic melanoma.

Table 2: Summary of Regulatory and HTA Opinions on Ipilimumab

Regulatory Milestone (EMA):	HTA Milestone	Relative Effectiveness - Key Issues:
MA granted within manufacturer proposed target population: "patients with a diagnosis of unresectable stage III or IV melanoma who, in response to at least 1 cycle first-line therapy, have relapsed following an objective response, failed to demonstrate an objective response" (EPAR, 2011). Subsequently expanded to first-line therapy (EPAR, 2013).	*Approved as an option for previously treated advanced (unresectable or metastatic) melanoma (NICE, SMC, HAS, ZIN).*	
13 July 2011 **MA granted:** Advanced (unresectable or metastatic) melanoma in adults who have received prior therapy **Studies:** 1.) MDX010-20 (Phase 3) 2.) seven phase 2 studies **Basis for MA:** Overall survival (OS) advantage of ipilimumab at the recommended dose of 3 mg/kg in patients with previously-treated advanced (unresectable or metastatic) melanoma was demonstrated. **Issues:** -Not clear of additional benefits and/or adverse events (AEs) that the higher dose (10 mg/kg) of Yervoy would give. -CHMP requested dosing study (3 vs. 10 mg/kg of ipilimumab). -Risk Management Plan (RMP), which included a risk minimisation plan and a multi-arm, non-interventional study was introduced by CHMP to ensure safe and effective use of ipilimumab.	**14 December 2011** **HAS:** treatment of advanced melanoma in adults as second-line treatment; approved for inclusion on list of reimbursable medicines within MA; IAB level = IV (minor improvement) **Studies:** 1.) MDX010-20 (Phase 3) 2.) two phase 2 studies: CA184022, CA184004 **23 January 2012** **ZIN:** treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy **December 2012** **NICE TA268:** for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy **Studies:** 1.) MDX010-20 (pivotal phase 3) 2.) two phase 2 studies: **8 April 2013** **SMC:** advanced (unresectable or metastatic) melanoma in adults who have received prior therapy **Studies:** 1.) MDX010-20 (Phase 3) 2.) phase 2 study: CA184-025 3.) expanded access program: CA184-089	*Comparators:* **NICE:** – The ERG noted that the pivotal study does not include any of the comparators stated in the final scope issued by NICE and instead relies on gp100 vaccine. – Clinical advisors to the ERG mentioned that the direction of the effect that the gp100 vaccine may potentially have on outcomes is not known **HAS:** – Transparency Committee stated that gp100 is an experimental peptide vaccine which has no MA and is not available on the French market; the therapeutic contribution of ipilimumab is difficult to quantify given the choice of comparator. **SMC:** – Pivotal study did not have a placebo control group so assumptions must be made regarding efficacy compared with BSC. *Outcomes:* **ZIN:** – Estimating the one-year survival rates of patients with melanoma remains difficult, so it is not clear if the one-year survival rates found in the phase-3 study correspond to daily practice. **NICE:** – The Committee noted uncertainty regarding continuing benefit in overall survival after the original 56 month length of the MDX010-20 trial – The Committee was unclear as to how prolonged complete disease response following treatment may be due to lack of long-term data and small sample size in this subset of patients – The Committee noted that a curative treatment would be expected to result in the disappearance of all visible disease (complete response), but only a small percentage

Regulatory Milestone (EMA):	HTA Milestone	Relative Effectiveness - Key Issues:
		(less than 1%) of patients in the ipilimumab arms of the MDX010-20 trial showed a complete disease response. – Number of respondents to QoL questionnaires dropped off considerably after week 12 in the MDX010-20 trial and there was little difference between the utilities assigned to the progression-free and the progressive disease health states. **SMC:** – Uncertainty surrounding the estimation of the long-term effects of the medicine: robustness of extrapolated data is uncertain given that very few patients (2%) experienced a complete response to the treatment.
5 December 2013 **Extension of indication:** treatment of previously untreated adult patients with advanced (unresectable or metastatic) melanoma (i.e. first-line treatment of metastatic melanoma with ipilimumab). **Studies:** 1.) CA184024 (Phase 3) **Basis of MA:** Overall survival (OS) advantage of ipilimumab	**13 June 2014** **NICE: TA319 –** draft guidance recommending ipilumumab as first-line treatment for previously untreated unresectable stage III or IV melanoma. **10 November 2014** **SMC:** ipilimumab as a first-line treatment of advanced melanoma.	*Outcomes:* **NICE:** – EORTC-QLQ-30 utility data were collected in the CA184-024 trial but there were lower completion rates among surviving patients at certain time points. The ERG was concerned at the lack of direct EQ-5D data. – The ERG expressed concern that the approach used for the propensity score analysis by the manufacturer was inconsistent with the previous appraisal.

2.2 Outline of the metastatic melanoma case study

The overall objective of this WP1 GetReal case study is to better understand how decision making in pharmaceutical research and development, regulatory approval and health technology assessment (HTA) recommendations could be improved by an expansion in the nature of the evidence available to decision makers. The case study will focus on metastatic melanoma, though will aim to produce results transferable to other diseases more generally.

The type of evidence considered during the case study will include those obtained from randomised clinical trials (RCTs) in metastatic melanoma, the use of observational/real world studies to supplement clinical trial data, and the use of quantitative methods to synthesise (and extrapolate from) these different sources of data.

2.2.1 Objectives

The overall case study objectives include:

1. Explore options for combination of real world data (RWD) and RCT data to improve estimates of effectiveness for metastatic melanoma treatments at the time of decision making. This may include the following sub-themes:
    a. Description of RWD from different registries and Ipilimumab phase IV studies data (including usability testing)
    b. Comparison and synthesis of RWD from different registries and Ipilimumab phase IV studies data
    c. Synthesis of RWD (from registries and/or phase IV studies) and RCT data to carry out predictive modelling of relative effectiveness of metastatic melanoma treatments. This includes, for example, prediction of long term outcomes from RWD (extrapolation)

    Each sub-theme includes issues related to data quality (e.g. completeness, comprehensiveness, comparability, transferability), definition of parameters and outcomes, as well as statistical methodologies available to perform data syntheses.

2. Explore the potential for data on metastatic melanoma patients collected from social media sources to be included as part of evidence base for relative effectiveness research.
3. Explore the possibilities for developing novel real-world study designs for use during drug development that better incorporate patient preferences.

It is important to note that these three objectives should not be viewed as separate aims but as jointly contributing to understanding how decision making in pharmaceutical research and development, regulatory approval and HTA recommendations could be improved by an expansion in the nature of the evidence available to decision makers.

2.2.2 Disease area

This case study focuses on metastatic melanoma – previously untreated and previously treated patients are in scope. There is no other exclusion on the basis of any characteristics of the patient and disease, including mutation status of the tumour.

2.2.3 Specific medicines

BMS is the only GetReal industry partner able to provide individual patient data (IPD) on metastatic melanoma treatments within the project timelines, the team's use of ipilimumab data does not imply that this product is the focus of research work. Instead, the focus is on the methodology of combining IPD from RCT's and phase IV studies with patient registry data.

2.2.4 Effectiveness challenges

There are several key effectiveness challenges that are expected to be addressed in this case study. These effectiveness challenges relate to the ones observed or known at the time of initial regulatory and HTA decision making. These challenges include:

1. In the absence of a comparative study of the new treatment in its relevant regimen relative to existing treatments, how can decision makers make an assessment of the relative effectiveness of the new treatment?
2. Where the data on which decisions will be made are immature and/or where decision makers are interested in longer term outcomes, how can decision makers assess the relative effectiveness of the new treatment?
3. How can RWD and other methods be used to extrapolate beyond clinical trial data and project long term outcomes?
4. Where the definition of endpoints important to decision makers (e.g. overall survival (OS), progression-free survival (PFS), quality of life (QoL)) differs between different datasets, how can decision makers assess the relative effectiveness in these endpoints?

These challenges link to the objectives of the case study as listed in the introduction and first section. Each of these challenges can be addressed by examining the possibilities for combination of RWD and RCT data, as well as examining issues around the design of these studies. As decision makers will also be influenced by the methodology relating to the synthesis of different types of data, it is expected that the methodological aspect of the objectives will be a key component in addressing the effectiveness challenges listed.

Effectiveness challenges in the ipilimumab example

Some effectiveness challenges in HTA assessments are specific to the ipilimumab example. Alongside each challenge potential simulation options are given to be further explored at the first workshop of metastatic melanoma case study.

Issue 1: Inappropriate comparator selection in gp100 in 2nd line pivotal studies
- Network meta-analyses to justify the comparator (2nd line) and to establish the comparative efficacy of ipilimumab in 1st line (For 1st line indirect comparison using the CA184-024 and BRIM 3 trials was undertaken after comment that no direct data was available from NICE).
- Incorporation of existing registry and other observational data into analyses to demonstrate the similarity of outcomes between gp100 and existing treatments

Issue 2: Extrapolation of OS data from short-term RCTs in 1st and 2nd line patient populations
- Use of real world registry data out to 15 years to validate the extrapolation
- Use of the pooled analysis of all ipilimumab clinical data to support the durability of survival and the lack of relationship to response
- Exploration of non-traditional, non-parametric approaches to extrapolating trial data to better reflect the underlying heterogeneity of the patient population and its impact on outcomes
- Exploration of approaches that incorporate the changing underlying hazards into the survival extrapolation

Issue 3: Absence of understanding of how reported AEs are managed in practice
- Use of data collected in an expanded access program to show that immune-related adverse events diminish as treating physicians gain experience in using ipilimumab
- Reanalyses of the QoL data collected in the pivotal studies to show that there was no ongoing decline in QoL

Issue 4: Absence of RCT data for first-line treatment at approved dosage (3mg/kg)
- Propensity scoring analyses to help construct a comparative efficacy assessment in ipilimumab 1st line
- Use of observational trial data to show effectiveness of ipilimumab 3 mg/kg in 1st line US patients
- Analyses of the similarity of 1st and 2nd line treatment populations to determine whether data from 2nd line 3 mg/kg studies is indicative of effectiveness in 1st line setting

2.2.5 Data sources

It is expected that a range of data sources will be used:

a. Melanoma patient registries – the case study team is currently exploring the possibility of obtaining data for the case study from registries in the Netherlands, France, and Italy. Data on patient characteristics, disease characteristics, patient outcomes (response rate, progression-free survival,

overall survival, quality of life) and use of prior and concomitant treatments would form a minimum data set.

b. Clinical trial data from BMS – it is proposed that BMS will provide patient level data from key clinical trials for analysis by the academic partners of the case study core team. The minimum data set would consist of patient and disease characteristics, inclusion criteria, patient outcomes (response rate, progression-free survival, overall survival, quality of life if available) and treatment intensity. The proposed studies are:

   i. MDX-020 (Phase 3) – ipilimumab 3 mg/kg alone vs.ipilimumab 3 mg/kg + gp100 vs. gp100 alone in previously treated metastatic melanoma patients

   ii. MDX-024 (Phase 3) – ipilimumab 10 mg/kg + DTIC vs. DTIC alone in previously untreated metastatic melanoma patients

   iii. CA184-143 (Phase 4) – ipilimumab: management of melanoma in real practice (includes non-ipilimumab patients as well)

   iv. CA184-332 (Phase 4) – a real world observational study of patients with advanced melanoma receiving first-line ipilimumab in a community setting in the USA

   v. CA184-338 (Phase 4)– a multi-site retrospective observational study of US patients with unresectable or metastatic melanoma receiving ipilimumab as first-line therapy

2.2.6 How does RWD address the effectiveness challenges tested?

The use of real world data to address these challenges is being tested in several ways during the case study. These include:

1. Inclusion of real world data from different registries to provide data on effectiveness where none exists in the RCTs to strengthen evidence around the effectiveness of treatments for metastatic melanoma – this relates to data from the Dutch, French and Italian registries.

2. Inclusion of real world data from different sources to provide data on effectiveness where none exists in the RCTs – this relates to the inclusion of phase IV studies CA184-332 and CA184-338 (please see above).

3. Validate and/or improve estimations of relative effectiveness of metastatic melanoma treatments based upon registry data & phase IV study data synthesised from different sources.

4. Perform predictive modelling of relative effectiveness of metastatic melanoma treatments based upon synthesised registry data and RCT data.

5. Inclusion of data from registries and phase IV studies to strengthen the link from early outcomes (e.g. response rates, PFS) to longer term outcomes (e.g. OS)

6. Verify and/or indicate which appropriate patient-centred outcomes should best be

measured during the conduct of real-world studies.

7. Potential different designs of real world studies that better accommodate patient perspectives, the potential use of these real world studies in the clinical development process and the integration of these real world studies with RCTs.

2.2.7 Anticipated issues of importance to decision-making stakeholders

There are issues of importance to all key stakeholders involved in the GetReal consortium and the metastatic melanoma case study. These include pharmaceutical manufacturers and their internal R&D groups, HTA agencies and payers, regulatory agencies and patient organisations. The key issues of importance to each group are explored below in turn.

1. <u>Pharmaceutical R&D</u>: What is the value of inclusion of RWD from patient registries earlier on during drug development to improve estimations of relative effectiveness? How acceptable is the use of RWD from such registries to make estimates of relative effectiveness for HTA/RA stakeholders? What is the usability of RWD derived from registries in different member states for the estimation of the effectiveness of drugs on an European level? How can patient perspectives be better incorporated in the design and implementation of RWS (whether registries or other)?

2. <u>HTA Agencies</u>: To what extent can RWD be used to validate and/or improve generalisability of relative effectiveness estimates submitted as part of HTA submissions? How acceptable is the use of RWD to do so? What is the usability of RWD derived from registries in different member states for the estimation of the effectiveness of drugs on an European level?

3. <u>Regulatory Agencies</u>: To what extent can RWD be used to validate and/ or improve generalisability of relative effectiveness estimates submitted as part of marketing authorisation applications? How acceptable is the use of RWD to do so? What is the usability of RWD derived from registries in different member states for the estimation of the effectiveness of drugs on an European level?

4. <u>Patient Organisations</u>: How should RWD collection be designed to meet the demands of participating patients, specifically late stage melanoma patients? How can RWD be used to accelerate access to innovative and effective medicines for patients?

5. <u>Registry owners</u>: How can the data generated through individual registries be used to more effectively assess the value of a new treatment at the time of initial marketing authorisation? How can these data be used alongside data from other registries or cohort studies in order to increase the impact?

The first workshop will identify the key concerns of each stakeholder, prioritise and potentially add further concerns or issues to be addressed as part of the case study.

2.2.8 Analytical or simulation methods to be used

The methods that are expected to be used to address the main aim of the case study – to

understand how real world data can be integrated to better assess the relative effectiveness of new treatments at the time of initial regulatory and HTA decision making – are not confirmed prior to the first workshop. However, there are several options that may be considered:

1. Evidence synthesis using IPD data from patient registries (including a data quality assessment)
2. Using IPD data to investigate the relationship between and within patient populations in RCTs and RWD
3. Evidence synthesis combining data from phase III/IV studies and registries data
4. Predictive modelling of relative effectiveness (via network meta-analysis, propensity scoring, or other method)
5. Prediction of long term effects RCT data, using RWE

As part of this process and prior to the first workshop, BMS will provide the results of analyses submitted to regulatory and HTA agencies in support of ipilimumab. These include the results of network meta-analyses and matched adjusted indirect comparisons, predictive modelling using the Korn clinical algorithm and propensity scoring methods, extrapolation of survival outcomes using different parametric and non-parametric methods, and linkages between intermediate and final clinical endpoints. These analyses can act as a starting point for suggestions made at the workshop.

With regards to the two other objectives of this case study, it is clear that some research work will be conducted prior to the first workshop. For example, in order to better understand the potential for data from social media to be used to supplement existing real world data (or how it could be developed to meet such a goal), a literature review will be conducted. Similarly, to better understand the needs of patients from trial design, a patient survey, focus group, and expert panel discussion on the focus group findings will be conducted.

2.2.9 Key consultees

The case study team for the case study involves ZIN and BMS as the co-leads, GSK, NICE and the University of Leicester to provide technical guidance and advice. The case study team will collectively set the direction and strategy for the case study, including the development of workshop agenda and materials and the engagement of external consultees who are of relevance to the workshop objectives.

It is expected that any simulations or quantitative analyses required as part of the case study will be conducted by the University of Leicester with support from BMS where necessary. It is also possible that an additional analysis group will be involved if there are more analyses to be conducted.

In addition, there are several additional groups who should be part of the case study, especially with respect to the workshops. These include:

1. Additional EFPIA partners (e.g. Roche, GSK/ Novartis)
2. Representatives of other GetReal work packages – WP2 (Clementine Nordon), WP3 (Mira Zuidgeest), WP4 (Chrissie Fletcher)
3. Representatives from the EMA to provide the regulatory perspective
4. Representatives of HTA/payer organisations outside GetReal – the priorities would be a representative from IQWiG, AIFA and potentially TLV
5. Patient representatives (e.g. Melanoma Patient Network Europe)
6. Individual clinicians and medical societies (e.g., European Society for Medical Oncology)
7. Policymakers – including representatives from DG Sanco and/or individual members of the EU Parliament
8. Registry participants – Institute for Medical Technology Assessment in Rotterdam, Melbase in France and the University of Naples in Italy.

3. Deviations from Description of Work
There are no deviations from the description of work.

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Ethics: Do you consider the deliverable is in compliance with the GetReal Ethics section in DoW

√ Yes

☐ No (if not please add comments):

☐ Not applicable

☐ No: major changes needed, please comment (re-review required)

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