Single Technology assessment

Talimogene laherparepvec (Imlygic/T-Vec) for the treatment of malign melanoma

01-03-2017

Norwegian Medicines Agency

PREFACE

Implementation of the National System for the introduction of new technologies in the specialist healthcare system will help ensure that assessment of appropriate new technologies happens in a systematic manner with respect to efficacy and safety, as well as impacts on health and society. The main aim of the new system is described in the National Health and Care Plan 2011-2015 and the White Paper 10 (2012-2013), Good quality - safe services. The regional health authorities, the Norwegian Knowledge Centre for Health Services, the Norwegian Medicines Agency and the Directorate of Health collaborate on tasks related to the establishment and implementation of the new system. Eventually, the National System for the introduction of new technologies in the specialist healthcare system will assist in the rational use of health care resources.

The Norwegian Medicines Agency has been assigned the responsibility to evaluate Single Technology Assessments of individual pharmaceuticals. A Single Technology Assessment is a systematic summary of evidence based on research on efficacy, safety and impact assessment. For pharmaceuticals, this will usually revolve around budgetary consequences or resource allocation. The burden of proof relating to the documentation of efficacy, safety and cost-effectiveness is borne by the MA-holder for the pharmaceutical under review. NoMA , when necessary, can provide guidance to pharmaceutical companies.

NoMA assesses the submitted evidence for all important clinical outcomes, resource use as well as the assumptions made in the analysis presented by the MA-holder and the presented results. NoMA does not perform its own health economic analyses. If required, NoMA may request additional information and perform additional calculations of the costs and cost effectiveness using the submitted model.

NoMA evaluates the relative efficacy and incremental costs in relation to a relevant comparator. NoMA does not assess the benefit risk balance already assessed under the market-authorization procedure. Information about this can is provided by EMA (SPC Imlygic).

Single Technology Assessment of pharmaceuticals is intended to support sound decision making on potential introductions of new technologies, and prioritization made at the Health Authority level. NoMA has no decision-making authority in this system.

All assessments are published and available to the public (The Norwegian Medicines Agency)

ABSTRACT

Rationale

Single technology assessment (STA) of Imlygic (T-vec). NoMA has assessed the clinical efficacy, safety and cost-effectiveness of Imlygic according to the request specifications from Ordering Forum (request number ID2015_018). Request form Ordering Forum can be found at www.nyemetoder.no. NoMA´s assessment is mainly, but not exclusively, based on the documentation presented by Amgen (market authorization holder, MAH).

Background

Imlygic is a cancer medicine used to treat adults with melanoma. The overall efficacy and safety of Imlygic for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease has been evaluated by the European Medicines Agency (EMA) (Imlygic EPAR). Approximately 15 adult patients are potentially suitable for the treatment of unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease each year in Norway. This number is tentative and based on feedback from Norwegian clinicians.

Clinical efficacy in the Norwegian setting

Amgen submitted one phase III pivotal trial (OPTiM) and one supportive phase II trial (Study 002/03) to document safety and clinical effectiveness of Imlygic. Amgen in addition, performed a systematic review of available literature (literature review) but could not identify additional studies with Imlygic to include in the submission.

NoMA considers OPTiM, the pivotal trial, to be relevant to the submission. The supportive study 002/03 is considered relevant to the documentation of safety.

NoMA considers the identification of relevant matching patients in the Norwegian setting challenging, this due to the relative narrow indication.

NoMA has consulted appointed clinicians regarding the current treatment of suitable patients in Norway. Their opinion is summarized as follows: “These patients are no longer treated with ipilimumab (monotherapy) today, but are instead treated with newer immunotherapies, BRAF inhibitors, radiation, isolated limb perfusion and electro chemotherapy.”

NoMA therefore considers that ipilimumab is no longer considered the first choice treatment for the intended patient population. Pembrolizumab and nivolumab should be considered more relevant comparators. Based on the indication´s wording patients with BRAF mutations, BRAF inhibitors could also potentially be relevant comparators for the submission. However, the choice of ipilimumab as comparator has been taken in consideration since at the time of submission it still was an alternative.

Based on this conclusion NoMA is critical to the choice of ipilimumab as comparator in this STA since a comparison to newer implemented immunotherapies is more appropriate.

Severity and shortfall

NoMA considers untreated metastatic melanoma to be a severe condition that meets the criterion of severe illness, or risk factors that in all probability lead to or exacerbate severe disease.

In this assessment, NoMA has not calculated the absolute shortfall (AS) of quality adjusted life years (QALYs) due to the lack of relevant documentation to estimate/calculate the prognosis in patients undergoing standard treatment.

Cost effectiveness

NoMA finds very difficult to value the ICER resulting from Amgen's base case due to the lack of robustness in the submitted documentation on relative effectiveness

NoMA´s overall appraisal

NoMA´s overall evaluation, taking into consideration the severity of the illness, clinical relevant efficacy in the Norwegian setting and cost-effectiveness of T-Vec together with the degree of uncertainty, is that is uncertain whether Imlygic fulfils or not the conditions to be recommended for implementation in the Norwegian specialist healthcare system.

Nevertheless, NoMA would like to highlight the fact that Imlygic has shown to be effective in the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease. Despite the lack of evidence for a systemic effect, some patients achieved long lasting responses. In the submitted documentation, an attempt was made to establish the relative effectiveness vs ipilimumab. The indirect evidence was not robust enough to establish the relative effectiveness or a cost-effectiveness ratio vs ipilimumab in the relevant patient population.

EXECUTIVE SUMMARY

Rationale

Single technology assessment (STA) of Imlygic (T-vec). NoMA has assessed the clinical efficacy, safety and cost-effectiveness of Imlygic according to the request specifications from Ordering Forum (request number ID2015_018) and. Request from Ordering Forum is detailed at www.nyemetoder.no.

NoMA´s assessment is mainly, but not solely, based on the documentation presented by Amgen.

Patient population in the Norwegian setting

Based on the opinion of clinical experts the proposed patient population would currently most likely be treated with immunotherapy, BRAF inhibitors, radiation, isolated limb perfusion and electro chemotherapy. When asked if they see a place for T-Vec in the treatment algorithm, they answered that T-Vec would likely not be the first choice. Additionally, based on the indication wording, only a very small number of patients will be considered suitable for this therapy in the current treatment landscape

Approximately 15 adult patients are potentially suitable for the treatment with Imlygic each year in Norway. This number is tentative and based on feedback from Norwegian clinicians.

Severity and shortfall

NoMA considers that untreated metastatic melanoma is a severe condition that meets the criterion of severe illness, or risk factors that in all probability lead to or exacerbate severe disease.

In this assessment, NoMA has not calculated the absolute shortfall for the patient population under consideration due to lack of relevant documentation to estimate the prognosis in patients undergoing standard treatment Appendix 1 Severity and shortfall, gives is a more detailed explanation of severity and QALY shortfall in untreated patients with melanoma.

Treatment in the Norwegian setting

Norwegian guidelines for the treatment of malign melanoma do not include the use of Imlygic.

NoMA has requested information from appointed clinicians regarding the treatment of suitable patients in Norway and summarized as follows:

"…These patients are no longer treated with ipilumumab (monotherapy) today, but are instead treated with newer immunotherapies, BRAF inhibitors, radiation, isolated limb perfusion and electro chemotherapy…"

After having consulted key appointed clinicians, NoMA concludes that ipilimumab is no longer considered the first choice treatment for the intended patient population. Pembrolizumab and nivolumab are considered more relevant comparators. Based on the indication´s wording patients with BRAF mutation, BRAF inhibitors could also potentially be relevant comparators for the submission.

However, the choice of ipilimumab as comparator has been taken in consideration since at the time of submission it still was an alternative.

Clinical efficacy in the Norwegian setting

Amgen submitted one phase III pivotal trial (OPTiM) and one supportive phase II trial (Study 002/03) to document safety and clinical effectiveness of Imlygic. Additionally, Amgen performed a systematic review of available literature but could not identify additional studies to include in the submission.

NoMA considers OPTiM, the pivotal trial, to be relevant for the documentation of clinical effectiveness of T-Vec and the supportive study 002/03 relevant to document safety.

Amgen constructed an artificial patient population for the comparator arm by pooling two ipilimumab studies and thereafter trying to match the population to the T-Vec population. To construct the patient population Amgen has used the KORN method, which is itself derived from an inappropriate population.

In absence of a direct comparison to an relevant active comparator, the fact that the granted indication is for a sub-population of the ITT population only and the difficulties to compensate for these factors in the health economic model, NoMA has to conclude that the presented documentation for relative effectiveness is not adequate to support a robust cost effectiveness ratio.

Safety

Based on the still limited documentation on safety it can be concluded that Imlygic has few serious side effects. The lack of long-term data is considered problematic.

NoMA considers that the safety data for T-Vec used in the HE- model compares favourably to safety data for ipilimumab. This is also the case with many of the new treatments when compared to ipilimumab e.g. pembrolizumab and nivolumab.

Cost effectiveness

NoMA finds difficult to accept the ICER resulting from Amgen's base case due to the following problems (discussed exhaustively in this report):

- The absence of relevant evidence from a clinically appropriate comparator makes it impossible to estimate or predict the relative effectiveness and thereafter, the relative cost effectiveness of T-Vec vs. current clinical practice.
- The fact that Amgen constructed an artificial patient population for the comparator arm by pooling two ipilimumab studies and thereafter trying to match the population to the T-Vec population. To construct the patient population Amgen has used the KORN method, which is itself derived from an inappropriate population.
- The inappropriate use of registry data in the health economic model.
- The methodology used to model long-term curation.
- The use of limited and immature data on survival.

Budget impact

Based on the information from clinical experts, NoMA has attempted to calculate/evaluate possible budget impact of recommending use of T-Vec by the regional health authorities. However, this has proven

difficult given the many different treatment options currently available for patients with inoperable stage III and in-transit metastases. Instead of the budget impact, NoMA has decided to calculate the costs that will potentially be incurred if T-Vec replaces current treatment options i.e. all the potential patients (15 per year) are treated using T-Vec. Multiplying the mean acquisition cost for T-Vec with the potential patient population of 15 gives a total cost of NOK 17 million. However, this does not take into account the savings that may occur due to the costs forfeited because of replaced treatments.

NoMA´s overall appraisal

NoMA´s overall evaluation, taking into consideration the severity of the illness, clinical relevant efficacy in the Norwegian setting and cost-effectiveness of T-Vec together with the degree of uncertainty, is that is uncertain whether Imlygic fulfils or not the conditions to be recommended for implementation in the Norwegian specialist healthcare system.

Nevertheless, NoMA would like to highlight the fact that T-vec has shown to be effective in the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease. Despite the lack of evidence for a systemic effect, some patients achieved long lasting responses. The size of the relative effectiveness and thus the Incremental Cost Effectiveness ratio (ICER) cannot be established. based on the submitted information.

The budget impact of Imlygic will be relatively limited. A national centre for the treatment of suitable patient with T-vec can possibly limit even further the budget impact.

TABLE OF CONTENTS

LOG

Request nr:	ID2015_018
Proposer:	
Pharmaceutical company:	Amgen
Pharmeceutical product:	(Imlygic/T-Vec)
Active substance	Talimogene laherparepvec
Indication:	Imlygic is indicated for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease
ATC-nr:	L01XX51

Process

Documentation delivered to NoMA	14-12-2015
Total assessment time:	443 days
Appraisers	David Mwaura Anja Schiel Pilar Martin Vivaldi
Clinical experts:	Oddbjørn Straume Jarle Karlsen

Clinical experts have contributed with clarifications of central assumtions in the analysis (among other things, comparators, patient population, and generalizability of trial data to Norwegian clinical practice). The Norwegian medicines agency is responsible for the contents of the report. The clinical expertes have not been included in a consus process or had any peer review in the elaboration of this report

GLOSSARY

CR	Complete response
DOR	Duration of response
DRR	durable response rate
DTIC	intravenous dacarbazine
EMA	European Medicines Agency
ESMO	European Society of Medical Oncology
FDA	Food and Drugs Administration
H2H	Head to Head
HSV-1	herpes simplex virus type-1
ITT	Intention to Treat
KM	Kaplan Meier
MAH	Market Authorisation Holder
NCCN	National Comprehensive Cancer Network
NoMA	Norwegian Medicines Agency
ORR	Overall response rate
OS	Overall survival
PF	Progression free survival
PR	Partial response
STA	Single Technology Assessment
T-vec	Imlygic, talimogene laherparepvec

1 BACKGROUND

1.1 SCOPE

This single technology assessment concerns the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease with talimogene laherparepvec (hereafter T-vec) in Norway.

1.2 MELANOMA

Cutaneous melanoma, hereafter referred to as melanoma, is a malignancy of pigment producing cells called melanocytes in the skin[1]. The development of melanoma depends on intrinsic factors, such as skin type or gene mutations, and extrinsic factors, the most relevant of which is exposure to ultraviolet radiation [2].

Melanoma represents only a small proportion (<5%) of all skin cancer cases, making it a relatively rare disease compared with non-melanoma skin cancer (e.g. basal cell and squamous cell carcinoma). However, melanoma is the most deadly form of skin cancer, causing 90% of skin cancer-related deaths [1, 3-5]. By comparison, non-melanoma skin cancers are rarely fatal [6].

Melanoma is deadly because the disease progresses rapidly, can relapse suddenly [7], and is more likely than other skin cancers to metastasize (spread) to distant sites on the skin, lymph nodes, or internal organs (visceral) where it becomes difficult to treat [4]. The most common sites to which melanoma metastasizes are lymph nodes, lung, liver, and brain, but melanoma can metastasize to almost any organ and may affect many sites simultaneously [8-10].

In year 2012, about 1800 patients were diagnosed with melanoma in Norway and 314 died from the disease. Compared with other cancers, a relatively high proportion of people diagnosed with melanoma are younger adults and the average number of life-years lost is as high as about 20 years.

Due to T-vec's indication, Amgen has estimated that the number of melanoma patients suitable for treatment might be about 40. Appointed clinicians estimate that the potential number of patients suitable for this treatment in Norway is around 15.

1.3 SEVERITY OF UNTREATED MELANOMA

NoMA considers that untreated metastatic melanoma is a severe condition that meets the criterion of severe illness, or risk factors that in all probability lead to or exacerbate severe disease.

In this assessment, NoMA has not calculated the AS for the patient population under consideration due to the lack of relevant documentation to estimate the prognosis in patients undergoing standard treatment. Appendix 1 Severity and shortfall, gives a more detailed explanation of severity and QALY shortfall in patients with melanoma.

1.4 TREATMENT

1.4.1 Treatment with T-VEC

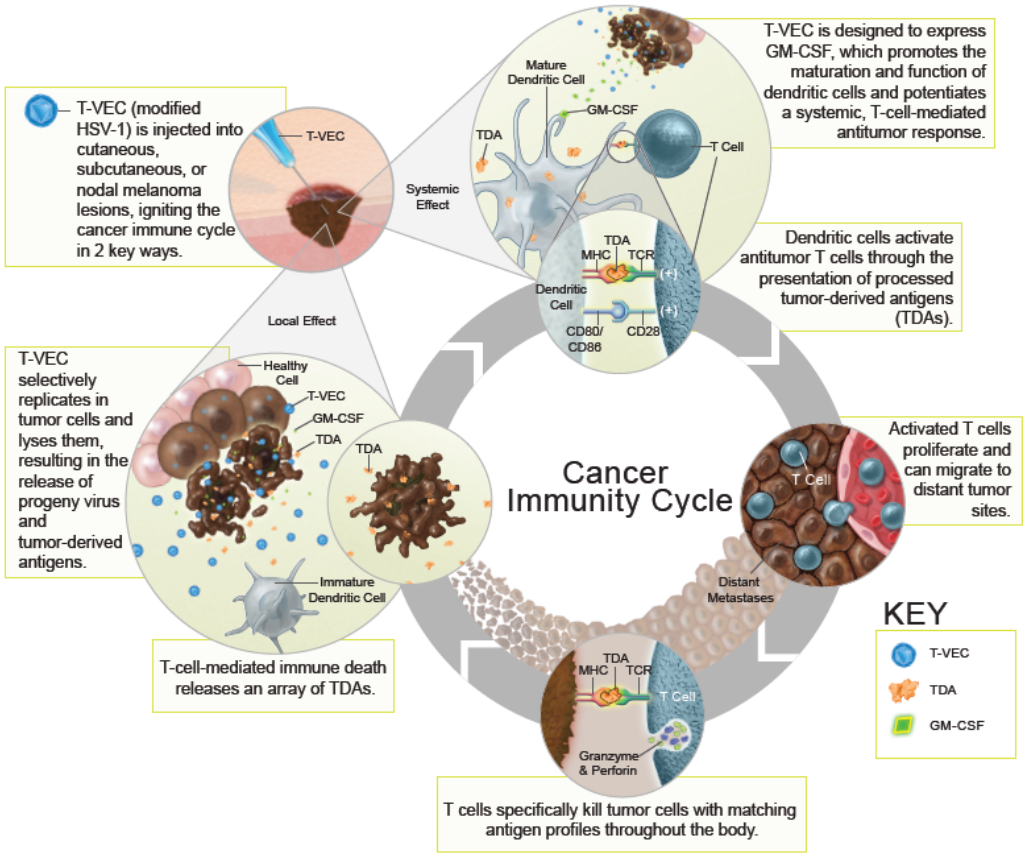
- Therapeutic indication

  T-vec is indicated for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease.

- Mechanism of action

  T-vec is an oncolytic immunotherapy derived from HSV-1. T-vec has been modified to replicate within tumours and to produce the immune stimulatory protein human GM-CSF. T-vec causes the death of tumour cells and the release of tumour-derived antigens as shown in Figure 1

Figure 1 Dual Mechanism of Action of T-VEC



HSV: herpes simplex virus type-1

- Posology and method of administration

Imlygic is to be administered by intralesional injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable or detectable by ultrasound guidance.
Treatment with T-vec should be initiated and supervised by a qualified physician experienced in the treatment of cancer. Patients treated with T-vec must be given the patient alert card and be informed about the risks of T-vec.

Table 1: Recommended dosing schedule for T-vec

Treatment visit	Treatment interval	Maximum total injection volume	Dose concentrations	Prioritization of lesions to be injected
Initial	-	Up to 4 mL	10^6 (1 million) PFU/mL	• Inject largest lesion(s) first. • Prioritise injection of remaining lesions based on lesion size until maximum injection volume is reached.
Second	3 weeks after initial treatment	Up to 4 mL	10^8 (100 million) PFU/mL	• First inject any new lesions (lesions that may have developed since initial treatment). • Prioritise injection of remaining lesions based on lesion size until maximum injection volume is reached.
All subsequent treatment visits (including re-initiation)	2 weeks after previous treatment	Up to 4 mL	10^8 (100 million) PFU/mL	• First inject any new lesions (lesions that may have developed since previous treatment). • Prioritise injection of remaining lesions based on lesion size until maximum injection volume is reached.

There are no reasons to believe that clinical posology might differs from the approved posology. Please refer to Summary of product characteristics for further information [11].
T-vec treatment can be reinitiated if new lesions appear following complete

response and the physician considers that the patient will benefit from treatment.

Accidental exposure may lead to transmission of T-vec and herpetic infection. Healthcare professionals and close contacts (e.g. household members, caregivers, sex partners or persons sharing the same bed) should avoid direct contact with injected lesions or body fluids of treated patients during the entirety of the treatment period and up to 30 days after the last treatment administration. Accidental needle stick and splash-back have been reported in healthcare professionals during preparation and administration of T-vec.

- *Undesirable effects*

The safety of T-vec was evaluated in the pivotal study where 292 patients received at least 1 dose of T-vec.

The most commonly reported adverse reactions (≥ 25%) in T-vec-treated patients were fatigue (50.3%), chills (48.6%), pyrexia (42.8%), nausea (35.6%), influenza-like illness (30.5%), and injection site pain (27.7%). Overall, ninety eight per cent (98%) of these adverse reactions reported were mild or moderate in severity. The most common grade 3 or higher adverse reaction was cellulitis (2.1%).

Please refer Summary of product characteristics for further information [11].

1.4.2 Treatment guidelines

Both the European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) have revised their clinical guidelines for melanoma since the introduction of the newer therapies [12, 13]. The main changes to the guidelines have the positioning of immunotherapy and kinase inhibitors as the backbone of systemic therapy.

Since 2011, newer agents as monotherapy or in combinations have been approved for the treatment of advanced melanoma.

Treatment guidelines in Norway [14]

Patients with metastatic unresectable Stage IV/III disease are, according to the Norwegian national treatment program [14], in general recommended to be included in clinical trials or receive systemic pharmacological treatment if patient condition allows. It is recommended to test the tumours for BRAF mutation.

The guidelines recommend use of ipilimumab within the phase IV study program in Norway, or receive DTIC/Temodal. The guidelines also states that for first or second line treatment of BRAF mutated tumours, vemurafenib or dabrafenib have been demonstrated effective.

Neither the Norwegian guidelines nor ESMO guidelines for the treatment of melanoma include the use of T-vec.

NoMA has requested information from appointed clinicians and summarized the information as follows:

Mainly patients with in-transit metastases and the small group of patients with inoperable stadium III melanoma are eligible for treatment with T-vec.

These patients are no longer treated with ipilimumab (monotherapy) today. Instead, they are treated with newer immunotherapies, BRAF inhibitors, radiation, isolated limb perfusion and electro chemotherapy.

1.4.3 Comparator

Given the information above NoMA is critical to the choice of ipilimumab as comparator in the HE-model since a comparison to more relevant newer immunotherapies seems more appropriate. However, the choice of ipilimumab as comparator has been taken in consideration since at the time of submission it still was an alternative.

2 SUBMITTED DOCUMENTATION TO PROVE THE RELATIVE EFFECTIVENESS

Amgen submitted one phase III pivotal trial (study 005/05, OPTiM study) [15] and one supportive phase II trial (study 002/03) [16] to document safety and clinical effectiveness of T-Vec. (Table 2).

Amgen has in addition performed a systematic review of available literature but could not identify additional studies with Imlygic to include in the submission.

2.1 OVERVIEW OF RELEVANT CLINICAL STUDIES

Only two studies have been identified by Amgen as relevant for the submission

Table 2 Overview of Relevant Clinical Studies

	Study 1 (OPTiM Study 005/05)	**Study 2 (002/03)**
Study design	Randomized, phase 3, active-controlled study	Single-arm study
Duration of treatment	Minimum 6 months (or up to 18 months if the subject was receiving clinical benefit)	Up to 47 weeks
Setting	Multicenter; 4 countries	Multicenter; 2 countries
Treatment groups	2:1 randomization T-VEC (n = 295) GM-CSF (n = 141)	T-VEC (n = 50)
Population	Unresectable stage IIIB, IIIC, or IV melanoma	Unresectable stage IIIC or IV melanoma
Primary endpoint	DRR	ORR
Secondary endpoints	Best overall response, OS, disease burden, response onset, time-to-treatment failure, duration of response, response interval	Time to tumor response, time to disease progression, OS
Primary references	(Kaufman 2014) (Andtbacka 2014) (Andtbacka 2015) (Harrington 2015b) (Harrington 2016a)	(Senzer 2009)

Abbreviations: DRR, durable response rate; GM-CSF, granulocyte–macrophage colony stimulating factor; ORR, objective response rate; OS, overall survival; T-VEC, talimogene laherparepvec.

Sources: (Senzer et al, 2009; Andtbacka et al., 2015; Harrington et al., 2015b; Harrington 2016a

Assessment of the literature review

The clinical literature review identified 66 RCTs, and 174 non-RCTs published between 1990 to September 1, 2015. The RCTs were mostly high-quality phase II and III RCTs, conducted in relatively similar patient populations. Evidence regarding 16 of the 19 drugs of interest was identified. Overall survival, progression-free survival, complete and partial response, and frequency of adverse events (AEs) were consistently reported across trials. The non-RCT evidence was mostly single-arm, non-comparative studies with sparse reporting of data for patient and treatment characteristics.

In the literature review the following is concluded: 'Given the low risk of heterogeneity, the review demonstrates the potential for an assessment of baseline risk and observed treatment effects across studies by means of a network meta-analysis (NMA) comparing other drugs of interest for advanced, malignant melanoma to Amgen's T-VEC.' NoMA considers that a comparison to more relevant newer immunotherapies seems feasible given this statement.

Pharmaco-economic studies

Fifty-one economic evaluations and 73 cost and resource use studies were identified by economic review. Lastly, the literature review identified 85 Patient reported outcome studies in melanoma patients. Quality-of-life was assessed most often using the European Organisation for Research and Treatment of Cancer Quality-of Life Questionnaire (EORTC QLQ)-C30 instrument (21%), which has been validated for use in cancer patients.

None of the identified studies included T-Vec in their analysis. OPTiM used the FACT_BRM questionnaire, not the frequently used EORTC QLQ-C30. Direct comparison between the pharmaco-economic studies and the current submission is therefore difficult.

Ongoing studies

Three studies are ongoing and fully enrolled, investigating bio-distribution and shedding of T-VEC (NCT02014441, primary analysis January 2016), the role of immune response in unresected melanoma (NCT02366195, primary analysis June 2017) and most importantly a head to head study versus ipilimumab in unresected melanoma (NCT01740297, primary analysis August 2016).

Four studies are ongoing and recruiting, the most important for this submission being a H2H study versus pembrolizumab in unresected melanoma (NCT02263508, primary analysis May 2018).

A registry study aiming to evaluate survival and long-term safety is currently ongoing. It is expected completed by 2023.

NoMA's assessment of the submitted evidence

NoMA considers the pivotal trial to be relevant to the submission. Study 002/03 is of limited value for the documentation of clinical effectiveness of T-Vec but is relevant to the documentation of safety.

The submission is based on the sub-group of patients relevant to the marketing authorisation, yet this deviates from the ITT in the OPTiM study. The primary endpoint, durable response rate (DRR) is not easily comparable to the more frequently used primary efficacy endpoints in other studies, such as ORR, PFS, DOR and OS.

OPTiM compared T-Vec with GM-CSF therapy, a non-approved therapy (but at the time of study initiation considered potentially relevant comparator) and not one of the more relevant comparators for this patient population (this will be discussed in detail in section 3.3).

NoMA is critical to the choice of ipilimumab as comparator in the HE-model since a comparison to more relevant newer immunotherapies seems feasible. However, the choice of ipilimumab as comparator has been taken in consideration since at the time of submission it still was an alternative.

Additionally, ongoing studies that investigate head to head efficacy versus active comparators potentially would allow a more robust assessment of the relative effectiveness of T-vec.

3 PICO[1]

3.1 PATIENT POPULATION

The submission is relevant for patients with unresectable melanoma, stage IIIB to stage IV, with non-visceral disease and injectable lesions, which is in line with the indication wording.

The patient population in the Norwegian setting

Based on the opinion of clinical experts the proposed patient population would currently most likely be treated with immunotherapy, BRAF inhibitors, radiation, isolated limb perfusion and electro chemotherapy. When asked if they see a place for T-Vec in the treatment algorithm, they felt that T-Vec would likely be not a first choice and based on the indication wording only a very small number of patients might be considered for treatment with T-Vec in the current treatment landscape.

The patient population in the submitted clinical studies related to Norwegian setting.

The OPTiM Study 005/05 included patients with stage IIIB, IIIC, and IV melanoma that were not considered to be surgically resectable. The indication for T-VEC only includes patients with no visceral disease, and this indication is primarily based on analysis of the subset of the patients without visceral disease in the OPTiM Study 005/05 trial. Refer to SPC [11] for a more detailed summary of patient baseline.

The patient population considered relevant to the submission with respect to the indication wording is a heterogeneous sub-group of melanoma patients. Comparison of this specific sub-group with patients from other clinical studies and the extrapolation to the Norwegian setting is difficult.

Patient population in the health economic model related to the Norwegian setting and clinical studies

The patient population treated with T-Vec in the health economic model is directly derived from the OPTiM study.

Amgen assumes that patient characteristics in terms of age, sex, height and weight from the OPTIM study generally represent patients with advanced melanoma

The study population in the comparator treatment arm (ipilimumab) has a higher percentage of patients with stage IV melanoma and hence a higher mortality risk than the T-Vec arm. Amgen has tried to calibrate for this using the KORN model in order to have comparable input estimates

For the comparator arm (patients treated with ipilimumab), time to event were constructed by digitizing survival curves from two studies, pooling the data and then using an algorithm (KORN algorithm) to correct for baseline difference, this to allow an indirect comparison between T-vec and ipilimumab studies.

Amgen has submitted an indirect treatment comparison [17] that describes how studies were selected and the algorithm implemented.. Amgen has selected two studies that were included into the Meta-

[1] Patients, Intervention, Comparator, Outcome.

analysis based on 'recommendation' rather than based on the original result of the literature search. In addition, results for these studies have been pooled,.

The way Amgen has constructed the ipilimumab arm is not considered technically acceptable. NoMA is critical to the use of the Korn algorithm. The algorithm was not developed for the purpose it is used for here but rather to be used in optimising trial designs in melanoma patients. It is based on information for stage IV patients and has not been validated for use in earlier stages. NICE accepted the use of the Korn method in appraisals TA268 and TA319 because those studies were conducted in appropriate late stage populations. In addition a modified version of the Korn-algorithm has been used which further complicates the assessment of its appropriateness. Finally NoMA considers pooling of data, which is only acceptable if both study populations are very homogenous, as problematic. No documentation is provided showing that this assumption is valid.

Conclusions on the population

NoMA concludes that Amgen's attempt to correct for the differences between patient populations by the use of the Korn algorithm is technically weak and increases the uncertainty around the heterogeneity of the different study populations.

NoMA considers that it is uncertain whether results from the OPTIM study or the indirect treatment comparison will be transferable to the Norwegian patient population.

3.2 INTERVENTION

Intervention in the Norwegian setting

NoMA find no reasons for the Norwegian clinical practice to differ from authorized posology and administration.

Intervention in the submitted clinical studies related to Norwegian setting.

In the clinical studies relevant for this submission T-vec is dosed in accordance to the approved posology and administration.

Intervention in the health economic model related to the Norwegian setting and clinical studies

T-Vec is used in accordance with the OPTiM study in the health economic model.

Conclusions on the intervention

NoMA considers the use of T-vec in clinical setting, studies and model as reasonable.

NoMA considers it reasonable to assume that clinical practice would not deviate from the authorized posology.

3.3 COMPARATOR

Comparator in the Norwegian setting

It seems, according to key Norwegian clinicians, that ipilimumab is no longer considered the first choice treatment for the intended patient population. Pembrolizumab and nivolumab must be considered more relevant comparators. Based on the indication wording including patients with BRAF mutations , BRAF inhibitors could also potentially be relevant comparators for the submission. However, the choice of ipilimumab as comparator has been taken in consideration since at the time of submission it still was an alternative.

Comparator in the submitted clinical studies related to Norwegian setting.

The comparator used in the OPTiM study is GM-CSF, injected at a dose of 125 µg/m2/day SC for 14 days, followed by a 14-day rest period. GM-CSF is not considered an active comparator in the health economic model as submitted by Amgen. NoMA agrees that the data generated in the GM-CSF control arm can be used as a proxy for placebo in the current submission.

Comparator in the health economic model related to the Norwegian setting and clinical studies

Ipilimumab and T-vec are used in the model in accordance with the SmPC. The health economic model uses, in absence of head-to-head data, constructed data for ipilimumab as active comparator (section 3.1).

Amgen has not explored BRAF-inhibitors as potential comparators.

Conclusions on the Comparator

As mentioned earlier, ipilimumab is not considered to be the most appropriate comparator in this patient population. Currently PD-1 inhibitors (pembrolizumab and nivolumab) have replaced ipilimumab as first choice in treatment of melanoma patients.

Despite the fact that T-Vec can be used for the same patient population as the BRAF inhibitors, the health economic model does not allow comparison to these relevant comparators.

Overall conclusions by NoMA

NoMA concludes that the provided STA is based on the comparison to a likely outdated comparator, ipilimumab. In addition, NoMA is critical to the lack of robustness in the modelling of the ipilimumab comparator arm used in the model.

NoMa acknowledge the difficulties discussed by Amgen with respect to conducting a more conventional indirect comparison, but considers that the approach presented is not robust and results in an unrealistic prediction of relative effectiveness - in particular in comparison to other submissions that used ipilimumab in their modelling.

3.4 OUTCOMES

3.4.1 Efficacy

The primary endpoint of OPTiM was durable response rate (DRR): partial response (PR) or complete response (CR) that lasted continuously for ≥ 6 months. Responses were per modified World Health

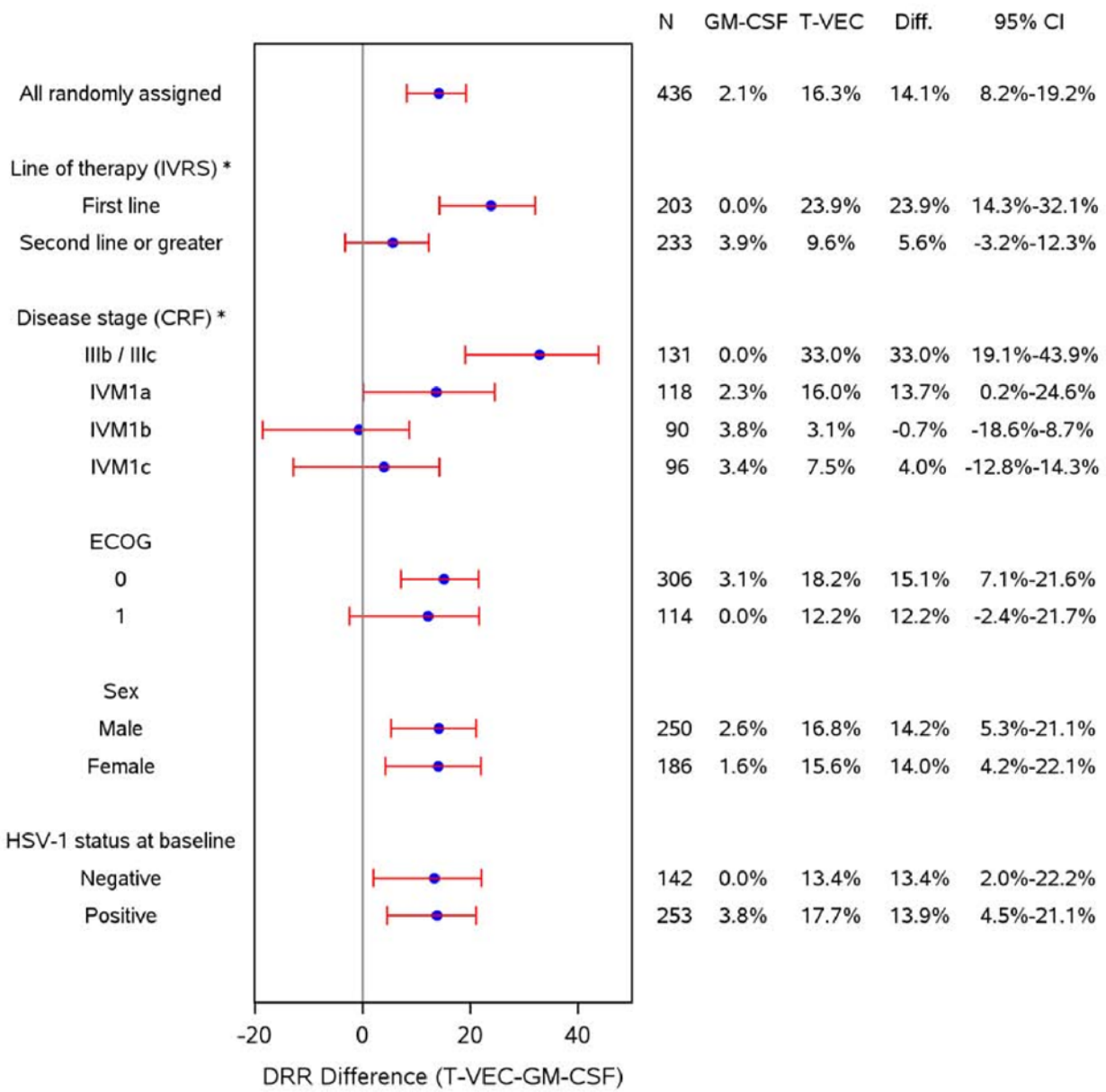
Organization (WHO) criteria by blinded central review. Key secondary endpoints included overall response rate (ORR) and OS [15].

DRR as endpoint is acceptable but difficult to compare to other studies due to the fact that it is rarely reported. OPTiM resulted in a highly significant difference in DRR in favour of T-Vec in the ITT population. Despite this, the indication wording is the result of the large heterogeneity in clinical effectiveness seen in the subgroups i.e. by disease stage, Figure 2. The heterogeneity in response was seen for DRR and relevant secondary endpoints such as ORR and OS, Figure 3.

OPTiM was not able to provide robust support for a survival gain in the ITT population and failed to show any survival benefit for patients with disease stage IVM1b-c.

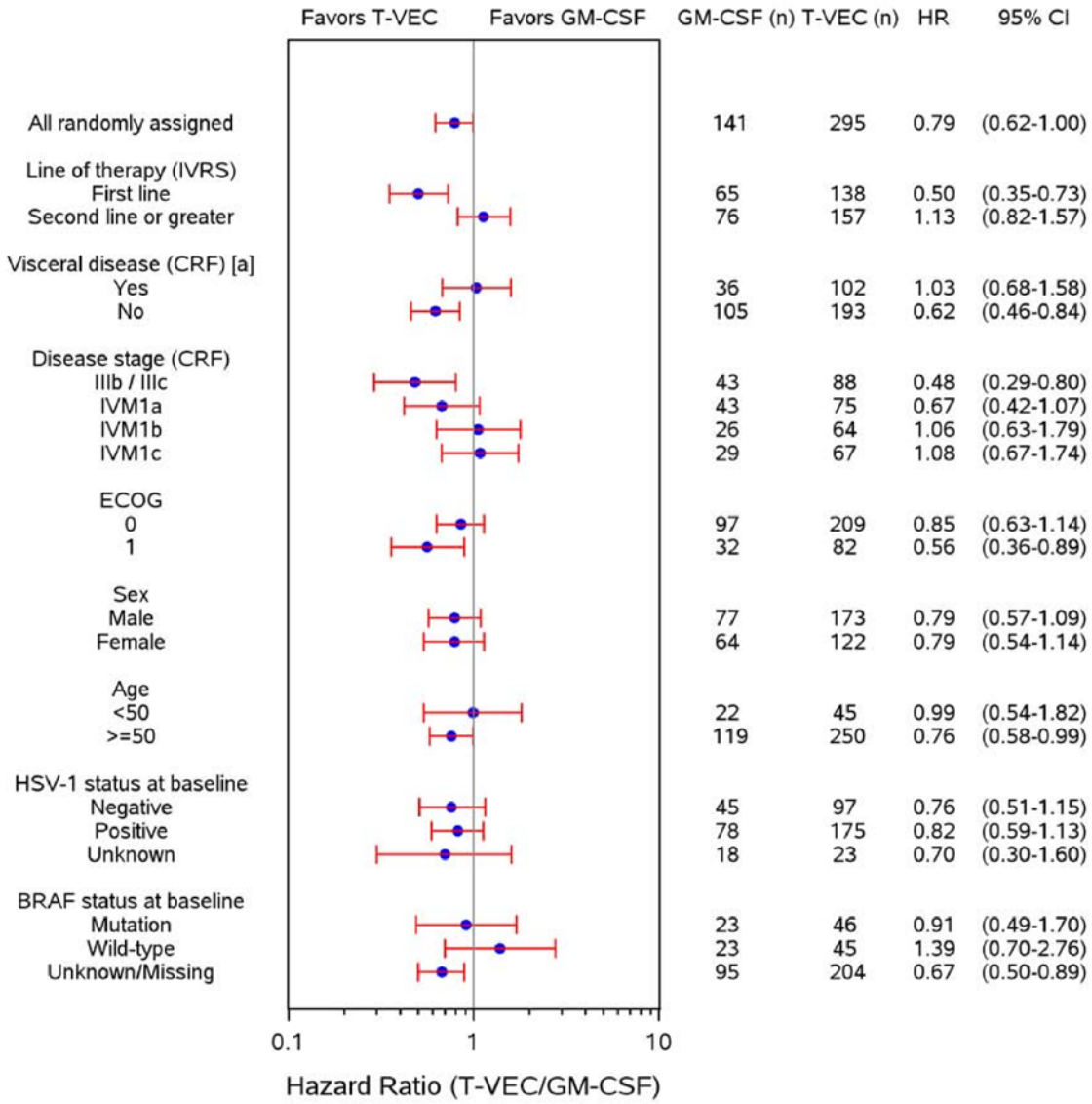
Main efficacy results:

Figure 2: Durable Response Rate per EAC Key Stratification Factors and Covariates in the Intent to Treat Population



* Gail & Simon quantitative treatment by covariate interaction test P-value <= 0.05.
T-VEC=Talimogene Laherparepvec
ITT population includes all subjects who have been randomized to receive study treatment. Subjects will be analyzed using the randomized treatment.
Durable response rate (DRR) is defined as the percent of subjects with complete response (CR) or partial response (PR) maintained continuously for at least 6 months (183 days) from when an objective response was first observed and initiating at any point within 12 months of starting therapy. This reflects all new sites of disease as well as all disease sites identified at baseline. NE = not estimable.
The confidence interval is calculated using Wilson's score method with continuity correction.

Figure 3: Hazard Ratio Plot with Log Scale - Overall Survival Hazard Ratio Key Stratification Factors and Covariates in the Intent to Treat Population



[a] If current sites of disease =brain/lung/liver/other visceral metastases , then visceral disease=Y. Otherwise visceral disease =N.
T-VEC=Talimogene Laherparepvec
Subjects that have not been recorded as dead are included as censored.
ITT population includes all subjects who have been randomized to receive study treatment. Subjects will be analyzed using the randomized treatment.
Overall survival is calculated as the number of months from randomization date to death date or last known to be alive date. One month = 365.25/12 days.

Use of efficacy data in the health economic model

Amgen has used DRR effect data from the ITT population as proxy for the patients covered by the indication wording. This introduces uncertainty since there was considerable heterogeneity in response rates among the sub-groups. One can argue that this is a conservative approach since patients in stage IV1b and c had lower DRRs, but group sizes for IIIb/c and IV1a differed and this should be reflected correctly in the health economic model.

Data provided on survival are limited and not mature. The study did not include a systematic follow-up since some patients could enter an extension phase. Therefore, a considerable number of patients were censored for survival, a fact that weakens the strength of the evidence. Amgen has used parametric modelling in combination with external data to provide estimates for the health economic model. NoMA is critical to the chosen modelling; this is further discussed in section 4.1.

Overall survival is estimated using three components:

- Short-term survival estimates are from the OPTIM study for T-Vec and a pooled analysis[18] [19-22] for ipilimumab up to a pre-determined cut-point. A test called the Chow break-point test was used to do this.
- Survival from the cut-point up until the last KM data point was estimated through regression-based parametric models.
- Longer-time survival (up to 30 years) was modelled using AJCC registry data, which was adjusted and then applied to the study cohort based on disease stage, age and sex for 11 years after the trial. This is followed by the use of data from UK life tables for the rest of the patient's lifetime.

PFS short-time survival was estimated using data from the OPTIM study for T-Vec and the pooled analysis data for ipilimumab. Survival beyond the last available KM data point until the end of the analysis was estimated through regression-based parametric models.

Overall conclusions by NoMA

In absence of clinical evidence including a direct comparison to an active comparator, the fact that the granted indication is for a sub-population of the ITT only and the difficulties to compensate for these factors in the health economic model, NoMA concludes that the submitted documentation does not support adequately the size of the relative effectiveness presented in the submission.

3.4.2 Safety

Based on the still limited documentation on safety it can be concluded that T-Vec has few serious side effects. The lack of long-term data is considered problematic.

- Submitted clinical documentation

Overall AE frequencies were comparable between the total safety population and the IIIB-IVM1a sub-group.

- Health economic model

The incidence rates for Adverse Events associated with Imlygic are sourced from the OPTIM trial while AEs for ipilimumab are sourced from the pivotal studies for ipilimumab [23, 24].

Only grade 3 AEs or above affecting at least 2 % of patients in each treatment arm are included in the model. All other AEs are assumed to have minimal impact on costs or quality of life. There is only one grade 3 AE (cellulitis) reported to have affected at least 2 % av patients receiving Imlygic treatment (see table below).

The incidence of AEs is assumed to be annual in the model i.e. one episode of each AE per patient experiencing the AE. Further, the duration of AEs is assumed to be one day.

- *Table 3: Incidence and Disutilities of Grade 3 or 4 Adverse Events (>2%)*

Grade 3 or 4 Adverse Events (>2%)	T-VEC	IPI	Utility Decrement[c]
Anemia		3,1[b]	0,09
Cellulitis	2,1[a]		0,12
Colitis		5,3[b]	0,26
Constipation		2,3[b]	0,14
Diarrhea		5,3[b]	0,11
Dyspnea		3,9[b]	0,11
Fatigue		6,9[b]	0,05
Headache		2,3[b]	0,16
Nausea		2,3[b]	0,00
Vomiting		2,3[b]	0,26

[a]Andtbacka *et al.*, 2014 [25], [b]Hodi *et al.*, 2010 [26], [c] Amgen, 2014b [27]

Conclusions on the use of safety data in the health economic model

Amgen has used the results of the safety population[2] in the OPTIM trial as a proxy for the IIIB-IVM1a subgroup, in the health economic model. Based on the comparability of results presented for both populations NoMA considers this approach as acceptable.

Safety data for ipilimumab is from the results of the total safety population in the pivotal ipilimumab study [23].

NoMA´s overall appraisal on safety

NoMA considers the safety data used in the model acceptable.

NoMA is also cognisant of the fact that long-term safety data based on long-term exposure to T-Vec is currently limited. This is especially relevant given that T-Vec is an oncolytic virus that has biologic

[2] The safety population in the OPTIM trial refers to all randomized patients that also received treatment

properties similar to wild type HSV-1 as regards viral shedding. This has the potential to transmit infection from patients to carers and those in close contact – a risk that is not shared with the other melanoma drugs. NoMA is also aware of the ongoing registry study commissioned by EMA to monitor long-term safety of patients who have received T-Vec treatment which is anticipated to be available in February 2017 [28].

NoMA considers that the safety data for T-Vec used in the HE- model compares favourably to safety data for ipilimumab.

3.4.3 Health related quality of life

Submitted clinical documentation

The Functional Assessment of Cancer Therapy-Biologic Response Modifier (FACT-BRM) questionnaire was used in the OPTIM study to elicit health-related quality-of-life data (HRQoL). The questionnaire has a 40-item scale for measuring HRQoL in cancer patients receiving treatment with biological response modifiers [29].

HE model

The HRQoL data from FACT-BRM questionnaire collected in the OPTIM trial has not been used in the cost-effectiveness analysis. Amgen has chosen to use utility data from a health economic evaluation submission to NICE for Dabrafenib [30]. Hence the utility value for non-progressive disease used in the model is 0,77 while the utility value for progressed disease is 0,68.

The utilities in the model are based on progression status. It is assumed that patients with non-progressive disease have the same HRQoL regardless whether they have complete response, partial response or stable disease. Patients with progressed disease are assigned lower utility values compared to those with non-progression.

The model also includes disutilities associated with grade 3 or 4 Adverse Events (AE). These disutility values are derived from a preference elicitation study commissioned by Amgen itself [31].

Adverse event	Mean utility value (standard error)	95% confidence interval	Source
Anaemia	0,09 (0,003)	0,083 to 0,097	Amgen
Cellulitis	0,12 (0,005)	0,111 to 0,129	
Colitis	0,26 (0,010)	0,241 to 0,280	
Constipation	0,14 (0,005)	0,130 to 0,151	
Diarrhea	0,11 (0,004)	0,102 to 0,118	
Dyspnea	0,11 (0,004)	0,102 to 0,118	
Fatigue	0,05 (0,002)	0,046 to 0,054	
Headache	0,16 (0,006)	0,148 to 0,172	
Nausea	0,26 (0,010)	0,241 to 0,280	
Vomiting	0,26 (0,010)	0,241 to 0,280	

Conclusions on HRQoL used in the HE model

NoMA considers the use of utility estimates from another assessment report [30] as having less face validity because the utility values used in the model do not adequately represent the health benefit accrued. i.e they do not differentiate between the complete response state from partial response and stable disease states.

NoMA considers the HRQoL data used in the model are a source of further uncertainty. NoMA would like the HRWoL data in the model to be sourced from previous HTA´s assessments from NoMA in the same therapeutic area.

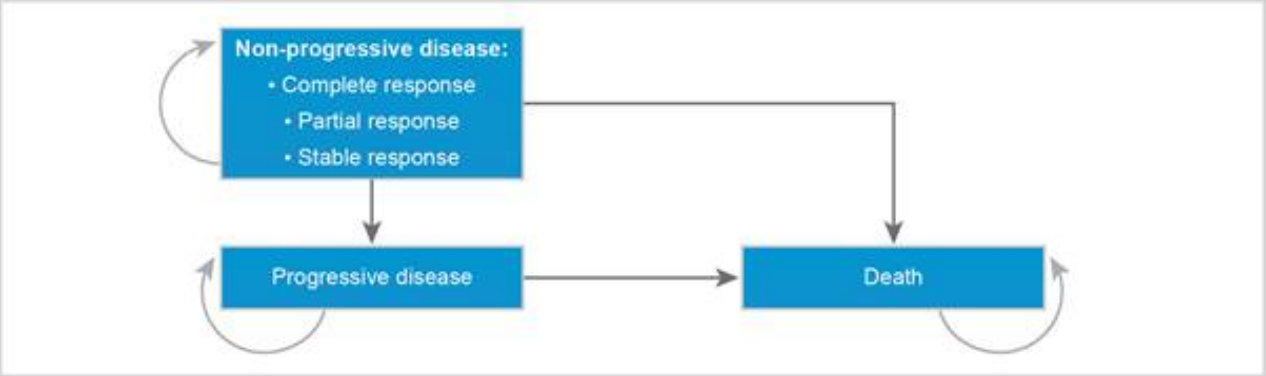
4 HEALTH ECONOMIC ANALYSES

This section presents a summary of the economic evidence submitted by Amgen in support of the use of T-Vec for the treatment of patients with non-visceral metastatic melanoma, and NoMA's assessment of the evidence. NoMA evaluates two key components in this section; the input data used not already assessed in the previous sections, and the economic model used. A typical health economic model will include the calculation of costs, life-years gained, and quality-adjusted-life-years gained (QALYs).

4.1 THE MODEL, METHODS AND ASSUMPTIONS USED

The model used by Amgen to compare the cost effectiveness of T-Vec vs. ipilimumab is a semi-Markov model in Excel that allows for the extrapolation of observed OS and PFS. The model comprises three mutually exclusive health states; non-progressive disease; progressive disease; and the absorbing state – death.

The model uses 1-week cycles and the time horizon is set at 30 years. Patients enter the model in the non-progressive disease state and can either remain in the same state or move to a worse health state in subsequent cycles.



Five disease management-phases (which are independent of treatment arm) derived from the three health states are included in the model. These are intended to address the differences in HQoL, disutility associated with AE's and the costs incurred when transitioning from one health state to another. The management phases include:

- Routine treatment received while in the non-progressive disease stage
- Health care received when switching to Best-Supportive-Care (BSC) as a result of disease progression
- BSC treatment-period which takes place in the period between progression and palliative care
- Palliative care which takes place up to 3 months before death.
- Terminal care which takes place immediately prior to death

The model does not make distinction between the palliative phase and the BSC phase and both phases have the same resource use and costs.

Amgen assumes that patient characteristics in terms of age, sex, height and weight from the OPTIM study generally represent patients with advanced melanoma. Further, all patients who progress are assumed to receive the same best supportive care while those who die are assumed to receive terminal care prior to death.

Estimates on resource use are from an expert while the unit costs of different health care resources are from published tariffs.

Norwegian limited social perspective where direct health care costs relating to treatment and management of side effects/deterioration are included. VAT is excluded.

Discounting is set at 4% for both costs and effects as stipulated in NoMA's guidelines

The time horizon used in the model is 30 years

NoMA's appraisal on the model

The model structure used by Amgen is well described and a common feature in other melanoma disease models is used. NoMA has assessed variants of the model structure in other Single Technology Assessments (STA's).

NoMA considers the model transparent in that it has been possible to follow, adjust and change some input parameters for assessment as needed.

However, NoMA considers the method used by Amgen in the estimation of efficacy input parameters (as discussed in chapter 2) as very problematic.

NoMA is critical to the use of clinical trial data in combination with multiple sources of registry data within the health economic model. The comparability of patients treated in randomized clinical trials and registries can be questionable. No attempts have been made to select matching patients.

NoMA considers the choice of analysis and the discounting rate to be appropriate and in line with NoMA guidelines and other melanoma assessments.

Amgen's base case uses a time horizon of 30 years.

4.1.1 Resource-use and costs

Direct costs

Drug costs (ex VAT)

Amgen has calculated the utilization costs for T-Vec based on the mean volume of drugs used and the length of time used receiving treatment in the OPTIM study. Utilization costs for ipilimumab are sourced from published listed sources.

The drug acquisition cost for T-vec used in the model is NOK 23 519,12 for a 1 ml vial containing 10^6 PFU/ml or 10^8 PFU/ml.

The total T-vec cost is a summation of

the mean observed dose in the initial cycle multiplied by the price per vial,

the estimated dose in each subsequent cycle multiplied by the price per vial and by the total number of weekly cycles following the first cycle.

Drug utilization including wastage has been estimated directly from the OPTIM study. The total mean volume used is 37,95 ml which includes an initial dose of 2,86 ml followed by a three week break and then a mean of 27,44 weeks on subsequent treatment (weekly dose of 1,28 ml). The total treatment duration used in the model is 30,44 weeks.

Table 4: Mean usage and treatment duration of Imlygic

Drug		Strength (1-mL Vial)	Mean Dose per Patient (Including wastage)
T-VEC	Initial dose	10^6 PFU/mL	2,86 mL
	Subsequent weekly dose	10^8 PFU/mL	1,28 mL[a]
	Subsequent dose total	10^8 PFU/mL	35,09 mL[a]
	Total mean volume used		37,95 mL
	Mean treatment duration		30,44 weeks

Ipilimumab:

Ipilimumab is available in two vial sizes of 10 ml and 40 ml at a strength of 5mg/ml, and is administered in 3 week cycles. The treatment duration/number of cycles used in the model is sourced from the ipilimumab submission to NICE in 2011 [32]. This seems inn accordance with suggested dose regime in the SPC.

The acquisition cost for ipilimumab used in the model is calculated by multiplying the number of vials used per administration based on the calculated dosage, the unit cost of the vials based on the publicly listed price in Norway and the total number of administrations.

Table 5: Drug Acquisition Costs and Treatment Duration for ipilimumab

Ipilimumab[a]		
Price per Pack/Vial (NOK)	35 303,9[b]	141 116.7[b]

Ipilimumab[a]		
Pack/Vial Size	10 mL vial (5 mg/mL)	40 mL vial (5 mg/mL)
Dose	261 mg/3 weeks	
Packs/Vials per Dose	1,22	1,0000
Cost per Dose (NOK)	184 187,50	
Treatment Duration (weeks)	10,50	
Number of Cycles	3,5	
Total Acquisition Cost (NOK)	644 656,26	

[a]NICE, 2011; NICE, 2014b, [b]NoMA (Legemiddelverket)

Administration costs

The administration costs for both Imlygic and ipilimumab are assumed similar to the unit cost of outpatient administration of a single chemotherapy regimen in the treatment of melanoma. Thus the administration cost used in the model is NOK 1 200 per administration.

Resource unit costs

The table below shows the unit costs representing the resource utilization used in the model to characterize the disease management phases. The unit costs are based on tariffs and reference costs published by NoMA and Norwegian Directorate of Health. All unit costs are based on the price levels of 2014.

In the model, a one-off cost for terminal care (NOK 80 183,04) based on ipilimumab submission to the Swedish Medicines Agency (TLV) is used.

Health-state costs

The costs associated with each of the health states are shown in the table below.

Table 6: Health-state costs used in the model

Health State	Item	Cost	Weekly Cost
Non-progressive disease	Routine treatment	NOK 7 276,59 (monthly)	NOK 1 679,21
Progressive disease	On-progression cost	NOK 37 178,18 (one-off)	–
	Best supportive care	NOK 9 365,29 (monthly)	NOK 2 161,22
	Palliative care	NOK 9 365,29 (monthly)	NOK 2 161,22
Death	Terminal care	NOK 80 183,04 (one-off)	–

Adverse events costs

Only grade 3 or higher AEs with an incidence of at least 2 % are used in the model. Amgen has calculated the cost of managing an AE as a weighted average between inpatient and outpatient treatment settings. The adverse events are assumed to only occur once in the model. The cost associated with managing AEs used in the model is assumed to be NOK 6 467,86.

NoMA's conclusion on direct costs data used in the HE model

NoMA has not validated these costs given the inappropriateness of the efficacy inputs discussed earlier in chapter 3.

Indirect costs

Indirect costs are not included in Amgen's base case.

4.2 RESULTS

NoMA finds it very difficult to evaluate the ICER resulting from Amgen's base case due to the problems that have been discussed exhaustively in earlier chapters. These are summarized as follows:

- Absence of relevant evidence from a relevant comparator that makes it impossible to estimate or predict the relative effectiveness and thereafter the relative cost effectiveness of T-Vec vs. current Norwegian clinical practice.
- Amgen's construction of a comparator based on the pooling of two ipilimumab studies and thereafter trying to match the population to the T-Vec population using the KORN
- method - which is itself derived from an inappropriate population.
- The inappropriate use of registry data in the health economic model.
- The methodology used to model long term curation.
- The use of limited and immature data on survival.

NoMA has therefore decided not to carry out any further evaluation or validation of the robustness of the modelled analysis.

NoMA has carried some sensitivity analyses. *The huge confidence interval estimates for the ICER per additional QALY (from NOK 211 788 to NOK 1 463 053) shows the uncertainty inherent in the estimation of an appropriate ICER. Additionally, NoMA considers the above results still very uncertain and hence should be interpreted with a lot of caution given that the main critique about the use and comparability of the data on relative effectiveness of T-Vec vs. ipilimumab is maintained.*

4.3 NoMA´S CONCLUSION ON THE COST-EFFECTIVENESS CRITERION

NoMA considers the submitted documentation insufficient to establish a reliable ICER.

5 BUDGET IMPACT ANALYSIS

Amgen has estimated the subset of melanoma patients that are eligible for treatment with Imlygic in Norway i.e. adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease. Amgen estimates that there might be about 40 new patients potentially eligible for Imlygic each year. Amgen assumes that treatment with Imlygic will replace treatment with Yervoy.

The budget impact analysis is calculated for the first 5 years based on two scenarios: the assumption that Imlygic is recommended for use by the regional health authorities vs. the assumption that the current status quo is maintained. The budget impact is the difference between the two scenarios

5.1 ESTIMATION OF THE POTENTIAL NUMBER OF PATIENTS ELIGIBLE FOR TREATMENT

Table 7 presents Amgen's estimation of the number of patients that are expected to receive treatment with Imlygic the next five years if the treatment is adopted by the regional health authorities. Table 8 shows the estimation if treatment with Imlygic is not adopted by the regional health authorities in the next five years.

Table 7 Number of patients the next five years if Imlygic is recommended for use by the regional health authorities

	2016	2017	2018	2019	2020
Imlygic	0	13	26	34	39
Yervoy	70	59	49	44	41
Total	70	72	75	78	80

Table 8 Number of patients the next five years if Imlygic is not adopted

	2016	2017	2018	2019	2020
Imlygic	0	0	0	0	0
Yervoy	70	72	75	78	80
Total	70	72	75	78	80

5.2 COST ESTIMATION

NoMA considers the costs estimation made by Amgen as uncertain and has therefore made a budget impact based only on drug (T-vec an Yervoy) acquisition costs.

The total mean volume used is 37,95 ml which includes an initial dose of 2,86 ml followed by a three week break and then a mean of 27,44 weeks on subsequent treatment (weekly dose of 1,28 ml). The total treatment duration used in the model is 30,44 weeks. Total acquisition cost (NOK) 1 115 689 (incl VAT)

The acquisition cost for Ipilimumab used in the health economic model is calculated by multiplying the number of vials used per administration based on the calculated dosage, the unit cost of the vials based on the publicly listed price in Norway and the total number of administrations. Total acquisition cost (NOK) 805 820

5.3 BUDGET IMPACT

The expected budget impact of adopting Imlygic, takin in account Amgen´s patient estimation but only treatment drugs costs is presented in Table 9.

Table 9 The expected budget impact in MNOK

	2016	2017	2018	2019	2020
Total drug costs if Imlygic is adopted	56	61,7	67,5	71,9	75,6
Total drug costs without adoption of Imlygic (current situation)	56	57,9	59,9	62	64,2
The budget impact of recommending adoption	0	3,8	7,6	9,9	11,3

NoMA's assessment of Amgen's budget impact analysis

NoMA accepts Amgen's argument that only drug acquisition costs are the main relevant costs for this budget impact analysis.

NoMA expects the acquisition cost for Yervoy to be lower given that actual drug cost is not publicly listed and is lower than the maximum price. This will in effect give a higher total budget impact than the one presented by Amgen.

According to the clinical experts, it is primarily patients with inoperable stage III and in-transit metastases that are eligible for treatment with T-Vec. The experts estimate that the group of patients with inoperable stage III metastases is very little and hence the main patient population will be those with in-transit metastases. However, not all patients with in-transit metastases will be eligible for treatment with Imlygic.

The eligible patient population, according to the clinical experts, is today primarily treated using immunotherapies. Alternatively, patients can also be treated using BRAF inhibitors, radiation, surgery, isolated limb perfusion and electro-chemotherapy. According to the clinical experts, about 15 patients are eligible per year.

Based on the information from clinical experts, NoMA has attempted to calculate/evaluate possible budget impact of recommending use of T-Vec by the regional health authorities. However, this has proven difficult given the many different treatment options currently available for patients with inoperable stage III and in-transit metastases. Instead of the budget impact NoMA has decided to calculate the costs that will potentially be incurred if Imlygic replaces current treatment options i.e all the potential patients (15 per year) are treated using Imlygic. The mean acquisition costs per patient for Imlygic are derived from the results of Amgen's cost effectiveness analysis. The mean treatment drug acquisition cost per patient is estimated in the model to be 1 115 688 NOK (incl 25% VAT). Multiplying this number with the potential patient population of 15 gives a total cost of approximately og NOK 17 Million (incl 25% VAT). However, this does not take into account the savings that may occur due to the costs forfeited because of replaced treatments. Budget impact calculations are uncertain and simplified.

6 CONCLUSION

Based on the submitted documentation NoMA considers that:

NoMA considers that untreated metastatic melanoma is a severe condition that meets the criterion of severe illness, or risk factors that in all probability lead to or exacerbate severe disease.

In absence of a comparison to an active comparator, the fact that the granted indication is for a sub-population of the ITT only and the difficulties to compensate for these factors in the health economic model, NoMA has to conclude that the presented documentation for relative effectiveness is not adequate .

NoMA considers the submitted documentation insufficient to establish a reliable ICER.

NoMA´s overall evaluation, taking into consideration the severity of the illness, clinical relevant efficacy in the Norwegian setting and cost-effectiveness of T-Vec together with the degree of uncertainty, is that is uncertain whether Imlygic fulfils or not the conditions to be recommended for implementation in the Norwegian specialist healthcare system.

Nevertheless, NoMA would like to highlight the fact that Imlygic has shown to be effective in the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease. Despite the lack of evidence for a systemic effect, some patients achieved long lasting responses. Unfortunately, based on the submitted information, the size of the relative effectiveness and thus the cost-effectiveness cannot be established.

Budget impact calculations are uncertain and simplified. The budget impact of Imlygic will be relatively limited. A national centre for the treatment of suitable patient with T-vec can possibly limit even further the budget impact.

NoMA, 01-03-2017

Kristin Svanqvist (e.f.)

David Mwaura

Anja Schiel

Pilar Martin Vivaldi

APPENDIX 1 SEVERITY AND SHORTFALL

NoMA has made a tentative estimate of the prognosis i.e. the future health loss related to metastatic melanoma. The estimation and calculations have been done at the group level, taking into consideration therapies currently available.

Calculations are based on the concepts of absolute shortfall .

- Absolute shortfall is the total amount of future health, measured in quality-adjusted life years (QALYs) that patients are expected to lose due to their condition.

Absolute shortfall corresponds to the difference between the expected sum of QALYs the average population without disease has vs. the prognosis patients undergoing treatment with the current standard of treatment have.

NoMA uses Swedish data indicating the quality of life per age category (age in years) and Norwegian mortality data in order calculate the expected number of QALYs without disease - often described as Quality-Adjusted-Life- expectancy (QALE).

Prognosis calculations for the relevant patient population is based on the health economic model submitted by Amgen. NoMA's estimation is based on a patient population with a mean age of 64 years. Ipilimumab is the assumed standard therapy for this patient population. NoMA submits also that the figures are uncertain and must be interpreted cautiously.

Table 10: Calculation of disease severity

Age	64
Expected QALE without illness (not discounted)	14,9
Expected QALE with illness (not discounted) (prognosis)	4,87
Number og lost QALYs As a result of the illness (absolute shortfall)	10,04

NoMA's estimation above implies an absolute shortfall of approximately 10 QALY's. NoMA considers therefore that metastatic melanoma qualifies as a severe disease when current standards of treatment are taken into consideration. NoMA would also like to point out that the above estimation differs considerably from the severity results estimated in the pembrolizumab (Keytruda) assessment report [33]. The absolute shortfall in the report is estimated to be approximately 15.86 QALY's, while the proportional shortfall is approximately 90 %. NoMA assumed the difference is a result of the problems discussed at length in this report – see chapters 2 and 3.

NoMA believes that untreated metastatic melanoma is a severe condition that meets the criterion of severe illness, or risk factors that in all probability lead to or exacerbate severe disease.

APPENDIX 2 COMMENTS FROM AMGEN (ATTACHED SEPARATELY)

No comments have been submitted to NoMA by March 17th 2017.

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Norway Response

Introduction

Melanoma represents only a small proportion (< 5%) of all skin cancer cases, making it a relatively rare disease compared with nonmelanoma skin cancer (eg, basal cell and squamous cell carcinoma). However, melanoma is the most deadly form of skin cancer, causing 90% of skin cancer-related deaths (Boring et al. 1994, Garbe and Leiter 2009, American Cancer Society 2016). Despite recent entrants in immuno-oncology, approximately 60% of patients with unresectable and metastatic melanoma will not respond to the new treatments and only approximately 1 in 10 (10%) will have a complete response (Hodi 2010, Robert 2015a, Weber 2015, Robert 2015b, Chapman 2011, Hauschild 2012, Flaherty 2012, Long 2014). Newer therapies can result in toxicities (for example immune related adverse events), which complicates treatment and affects health-related quality of life for many patients already struggling with metastatic melanoma.

IMLYGIC® is the only immunotherapy approved specifically for unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease and has a unique place in the cancer immunity cycle (IMLYGIC SPC). In the indicated population, IMLYGIC® showed overall response rates (ORR) of more than 40% and has shown complete response rates of 16.6% resulting in patients who are disease free. IMLYGIC® showed durable response rates (DRR) of 25.2% compared to 1.2% for granulocyte-macrophage colony-stimulating factor (GM-CSF) (Harrington et al., 2016) and provided an additional 25 months median overall survival (OS) versus (GM-CSF; final analysis) (Andtbacka et al. 2014). Moreover, IMLYGIC® has a favorable safety profile with low treatment discontinuation rates due to adverse events (Andtbacka et al., 2015).

Comparative effectiveness

Given the timing of the original submission, ipilimumab was included as the comparator in the cost-effectiveness analysis. IMLYGIC is the only drug that has data in Stage IIIb/c-IVM1a melanoma. In the OPTiM study, upon which EU approval was based, patients with early metastatic disease comprised nearly 60% of the study population. Other therapies (ipilimumab, pembrolizumab, and nivolumab and BRAF/MEK inhibitors) have broader indications (stage IIIB/C-IVM1a/b/c), for which the majority of data from pivotal studies are from patients with stages IVM1b and IVM1c disease (eg, 90% of patients in the MDX010-20 study of ipilimumab, Hodi et al., 2010). This is an important distinction, which contributed to the approach used for the indirect treatment comparisons provided in in the submission.

With no relevant head-to-head RCT evidence, together with the fact that the OPTiM study is the only study with data in stage IIIB/C-IVM1a, and no common comparator linking to other published trials or publicly available data, a traditional NMA was not feasible. An evaluation of alternative methods for comparing survival outcomes for IMLYGIC versus ipilimuab was conducted. This included methods that use individual patient level data to adjust the outcomes of interventions to match comparator populations, and those that use prognostic equations to adjust comparator populations. The methodology based on adjusting the comparator populations using the Korn prognostic equation was considered the most suitable approach, as it captures the impact of key prognostic variables, importantly the presence of visceral disease. We conducted sophisticated analyses in order to compare IMLYGIC to ipilimumab despite the fact that the studied populations were not comparable (See Section 2.2.2.2 in original submission, Quinn et al., 2016).

We acknowledge the limitations of the KORN methodology, however, given the data limitations; we maintain that it was the most appropriate approach. Indeed, UK NICE complemented Amgen "…on the thorough approach to the problem of estimating the effectiveness of TVEC versus ipilimumab in earlier stage disease" and did not propose an alternative solution to address the limitations (which they often do). In addition, the NICE clinical experts consider OPTIM the best available evidenced on Stage IIIB/C-IVM1a. Furthermore, the committee concluded that the availability of a new treatment option with a novel mechanism of action and improved tolerability would be valuable for people with metastatic melanoma (NICE FAD).

The committee acknowledged Amgen's efforts to compare vs ipilimumab but noted the uncertainty largely due to lack of data for ipilimumab on the relevant stage. To reduce the uncertainty, we performed the following analyses:

1. [redacted]
   (Opplysningene er forretningshemmeligheter etter legemiddelloven § 30 jf. forvaltningsloven § 13 første ledd nr. 2)

2. We demonstrated that GM-CSF is at least as clinically effective as recognised treatments (DTIC) and BSC (gp100) (Quinn et al., 2017) and therefore the OPTiM GM-CSF arm can be used conservatively as a proxy for DTIC and BSC, allowing evaluation of cost effectiveness of IMLYGIC versus these treatments. We showed IMLYGIC is highly cost effective versus recognised treatments (DTIC) and BSC with much lower ICERs than those demonstrated for ipilimumab, further supporting the case that IMLYGIC is cost effective versus ipilimumab. This analysis benchmarks the cost effectiveness of IMLYGIC versus the approach taken for ipilimumab, removing the uncertainty associated with the lack of evidence for ipilimumab in the earlier stage disease population, and adds further certainty to the assessment of the cost effectiveness of IMLYGIC. The NICE committee noted that the ICERs vs dacarbazine (DTIC)(GBP 23,900 – 24,100 per QALY) were substantially lower than those of ipilimumab vs DTIC from previous assessments (approx. GBP 47,000)(NICE FAD).

We maintain that the estimated deterministic ICER of IMLYGIC versus ipilimumab is NOK 307,040 per QALY gained (Table 21, original submission). Given the analyses outlined above where IMLYGIC has demonstrated more favourable ICERs versus the same comparators as those reported for ipilimumab, we feel these add to the evidence base and reduce the uncertainty around the cost-effectiveness of IMLYGIC versus ipilimumab.

Our objective is to give melanoma patients access to one more treatment option in Norway as soon as possible. We urge you to be pragmatic and make IMLYGIC available to melanoma patients. Importantly, given IMLYGICs novel MOA, place in the cancer immunity cycle and indication for *unresectable* stage IIIB/C-IVM1a metastatic patients with *injectable tumors*, a very small number of melanoma patients will be eligible for IMLYGIC treatment (Chen and Mellman 2013, IMLYGIC SPC). Based on the estimates of the population size and eligible patients we expect only 15 patients in the first year, to be candidates for IMLYGIC in Norway resulting in a manageable budget impact. In addition, its use will be limited to specialized prescribers and centers.

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