Single Technology assessment

Nivolumab (Opdivo) for the treatment of recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck

16-10-2017

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 (NoMA) 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. NoMAcan, when necessary, provide guidance to pharmaceutical companies.

NoMAassesses 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. NoMAdoes not perform its own health economic analyses. If required, NoMAmay request additional information and perform additional calculations of the costs and cost effectiveness using the submitted model.

NoMAevaluates the relative efficacy and incremental costs in relation to a relevant comparator. NoMAdoes not assess the benefit risk balance already assessed under the market-authorization procedure. Information about this can is provided by EMA (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003985/WC500189765.pdf)

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. NoMAhas no decision-making authority in this system.

All assessments are published and available to the public (www.legemiddelverket.no).

ABSTRACT

Background

Opdivo (nivolumab) is a drug that has an approved therapeutic indication for several types of cancer. This single technology assessment concerns the treatment of recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck (SCCHN) in Norway. The general clinical efficacy and safety of nivolumab in treatment of recurrent or metastatic SCCHN is considered documented by the CHMP approval of the marketing authorisation in EU. The relative effectiveness of nivolumab compared to treatment alternatives in the Norwegian clinical setting as for today is evaluated in this assessment. NoMAs assessment is mainly, but not exclusively, based on the documentation submitted and presented by the pharmaceutical company Bristol-Myers Squibb (BMS).

Clinical efficacy in the Norwegian setting

The efficacy and safety of Nivolumab in SCCHN patients is documented with results from an open-label, randomized phase III study (CheckMate 141) which included previously treated patients with SCCHN who had tumour progression on, or within six months of platinum therapy in the primary, recurrent or metastatic setting. Nivolumab is compared to investigator's choice of treatment in CheckMate 141. NoMA considers the alternatives in the investigator's choice arm (docetaxel, methotrexate and cetuximab) to be representative for the Norwegian clinical setting. The results showed significantly better median overall survival compared to all investigator`s choice of treatments.

Severity and shortfall

Patients with metastatic or recurrent SCCHN who are no longer amenable to local surgical/radiation therapy experience substantial morbidity and high mortality. Severity calculations on population level for the current patient population indicates that recurrent or metastatic SCCHN is a disease with high degree of severity. The degree of severity is based on absolute shortfall, which is estimated to be in the range 15.6 -18.4 quality-adjusted life-years. The severity level of disease will influence the willingness to pay threshold for the drug, i.e. if the cost is considered reasonable in relation to the magnitude of clinical benefit of the treatment and improvements in quality of life.

Cost effectiveness

NoMA has evaluated if the costs related to the use of nivolumab is reasonable in relation to the magnitude of the clinical benefit of the treatment, presented in cost per QALY gained. Efficacy data from CheckMate 141 are used to evaluate the cost-effectiveness of nivolumab. NoMA has updated the original analysis submitted by the applicant (BMS) as it was considered necessary to change some of the input

data in the analysis. In NoMa's main analysis the incremental cost per QALY was 640 000 NOK based on the maximal pharmacy selling price (AUP). If NoMA's analysis is based on prices from the 2017 LIS-tender (LIS-AUP) the cost per QALY was [redacted] Based on this, it is NoMA's opinion that nivolumab most likely is a cost-effective treatment for metastatic or recurrent SCCHN compared with investigator's choice, when the analysis is based on LIS-AUP.

The budget impact of implementing nivolumab (Opdivo) for the current population with SCCHN is estimated to 6.6 MNOK in year 5 based on AUP and [redacted] based on LIS-AUP. There is uncertainty around this estimate.

NoMA's overall appraisal

NoMA´s overall evaluation, considering the severity of the illness, clinical relevant efficacy in the Norwegian setting and cost-effectiveness of nivolumab (Opdivo), is that nivolumab (Opdivo) compared to investigator`s choice seems to meet the conditions to be recommended for implementation in the Norwegian specialist healthcare system

OPPSUMMERING

Formål
Hurtig metodevurdering av legemiddelet Opdivo (nivolumab). Metodevurderingen er utført i henhold til følgende anmodning fra Bestillerforum Nye metoder; ID2016_070 Hurtigmetodevurdering av Nivolumab (Opdivo) til andrelinjebehandling av residiv eller metastatisk plateepitelkarsinom i hode- og halsregionen.

Bakgrunn
Opdivo (nivolumab) er et legemiddel godkjent til behandling av flere kreftformer. Denne metodevurderingen gjelder nivolumab som monoterapi i behandling av residiverende eller metastatisk platinum-resistent plateepitelkarsinom i hode- og halsregionen (SCCHN) i Norge. Klinisk effekt av nivolumab i behandling av residiverende eller metastatisk platinium resistent SCCHN er dokumentert gjennom utstedelse av markedsføringstillatelse. Relativ effekt av behandling med nivolumab, sammenlignet med dagens standardbehandling i norsk klinisk praksis, blir vurdert i Legemiddelverkets metodevurdering presentert i denne rapporten. Legemiddelverkets vurdering tar utgangspunkt i dokumentasjon innsendt av produsenten (BMS).

Effektdokumentasjon i henhold til norsk klinisk praksis
Dokumentasjon av effekt og sikkerhet i denne metodevurderingen er fra en randomisert, ublindet, multisenter fase III studie (CheckMate 141) som inkluderte pasienter med SCCHN som allerede hadde blitt behandlet i førstelinje og som nå innkom med sykdomsprogresjon i en primær, residiverende eller metastatisk sykdomstilstand. Pasientene hadde progrediert enten under behandling med platinumbasert kjemoterapi eller innen 6 måneder etter at de hadde mottatt slik behandling. I CheckMate 141 sammenlignes nivolumab mot «investigator's choice» terapi (IC) bestående av enten docetaksel, metotreksat eller cetuksimab. Legemiddelverket vurderer sammenligningen mot IC terapi som relevant for norsk klinisk praksis. Resultatene fra studien viser signifikant bedre median total overlevelse ved bruk av nivolumab sammenlignet med IC med 29% reduksjon i risiko for død basert på data fra intention to treat (ITT) populasjon. Det finnes ikke tilsvarende sammenligninger av nivolumab mot hver av de tre enkelte legemidlene som ingår i IC armen hver for seg.

Alvorlighet og helsetap
Pasienter med residiverende eller metastatisk SCCHN som ikke lenger er egnet for lokal kirurgisk behandling eller stråleterapi, opplever betydelig sykelighet og høy dødelighet. Alvorlighetsberegninger på gruppenivå av pasienter på dagens standardbehandling, tilsier at SCCHN er en meget alvorlig sykdom. Alvorlighetsgraden vil påvirke betalingsvillighet for legemiddelet, dvs. om kostnadene vurderes å stå i rimelig forhold til nytten av behandlingen. Absolutt prognosetap ble estimert til 15,6 – 18,4 kvalitetsjusterte leveår (QALY).

Kostnadseffektivitet

Legemiddelverket har vurdert om kostnadene ved bruk av nivolumab står i et rimelig forhold til den nytten behandlingen gir. Produsentens innleverte analyse omhandler bruk av nivolumab i andrelinje. Legemiddelverket har justert produsentens (BMS) analyse med de forutsetningene vi mener er mest plausible. I legemiddelverkets hovedanalyse er merkostnaden per vunnet kvalitetsjusterte leveår (QALY) 640 000 NOK basert på apotekets maksimale utsalgspris (AUP). Om legemiddelverket baserer sin analyse på dagens tilbudte rabatterte priser (LIS-priser) blir merkostnaden per QALY [redacted]. Basert på dette, er det legemiddelverkets vurdering at nivolumab mest sannsynlig vil være en kostnadseffektiv behandling av residiverende eller metastatisk SCCHN når det benyttes gjeldende LIS-priser i analysene.

Legemiddelverket antar at budsjettvirkningen for sykehusene ved å ta i bruk nivolumab i behandling av residiverende eller metastatisk SCCHN-pasienter vil være om lag 6,6 MNOK i år 5 basert på maks. AUP og [redacted] i år fem, basert på LIS-priser. Budsjettberegningene er forenklede og usikre.

Legemiddelverkets totalvurdering

Legemiddelverket mener at når man tar hensyn til alvorlighet, klinisk relevant effekt og kostnadseffektivitet oppfyller Opdivo (nivolumab) kriteriene for å kunne anbefales og tas i bruk selv om analysene er beheftet med noe usikkerhet.

EXECUTIVE SUMMARY

Rationale

Single technology assessment (STA) of nivolumab (Opdivo). NoMA has assessed the clinical efficacy, safety and cost-effectiveness of nivolumab according to the request specifications from Ordering Forum (request number ID2016_070). The request from Ordering Forum in full text is available from: https://nyemetoder.no/metoder/nivolumab-opdivo-indikasjon-vi.

Background

Nivolumab (Opdivo) is a drug that has a range of approved therapeutic indications for several types of cancer. This single technology assessment concerns the treatment of recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck (SCCHN) in Norway. The general clinical efficacy of nivolumab in treatment of recurrent or metastatic SCCHN has been assessed by EMA/CHMP through the process of approval of the marketing authorisation. The relative effectiveness of nivolumab compared to current treatment in the Norwegian clinical setting is evaluated in this assessment.

NoMA's evaluation is mainly, but not exclusively, based on the documentation submitted and presented by BMS.

Patient population in the Norwegian setting

BMS has estimated a yearly incidence of 25 patients with metastatic or recurrent SCCHN in Norway. Norwegian clinical experts find it most likely that 60-70 % of these patients are eligible for treatment with nivolumab.

Severity and shortfall

Patients with metastatic and recurrent SCCHN that are no longer amenable to local surgical/radiation therapy experience substantial morbidity and high mortality. Severity calculations on population level for the current patient population indicates that recurrent or metastatic SCCHN is a disease with a high degree of severity. Absolute shortfall is estimated to be in the range 15.6 - 18.4 QALY. The severity level of a particular disease will influence the willingness to pay for the drug, i.e. if the costs are to be considered reasonable in relation to the clinical benefit and safety of the treatment.

Treatment in the Norwegian setting

In Europe, there are no drugs approved by EMA for patients progressing on or after platinum-based therapy. Further treatment choice is individualized and based on several factors including previous

chemotherapy exposure, performance status, and comorbid conditions. Recommendations include best supportive care (BSC), but also chemotherapy with taxanes (paclitaxel, docetaxel), 5-FU, methotrexate, ifosfamide, bleomycin, gemcitabine, capecitabine, and vinorelbine and cetuximab. For patients not eligible for combination chemotherapy, European Society of Medical Oncology (ESMO) guidelines recommends weekly methotrexate.

Clinical efficacy in the Norwegian setting

The efficacy and safety of nivolumab in SCCHN is documented with results from one open-label, randomized phase III study (CheckMate 141) which included previously treated patients with SCCHN who had tumour progression on, or within six months of platinum therapy in the primary, recurrent or metastatic setting. Nivolumab is compared to investigator's choice of treatment in CheckMate 141 (docetaxel, cetuximab or methotrexate) NoMA considers the three alternatives in the investigator's choice arm to be representative for the Norwegian clinical setting. The results showed significantly better median overall survival in the nivolumab arm (7.7 months) compared to investigator`s choice (5.1 months)

Nivolumab showed a significant (29%) reduction in risk of death compared with investigator's choice therapy in the intent to treat (ITT) population (HR = 0.71; 95% CI: 0.55, 0.90; p=0.005).

The difference in the median progression free survival (PFS) was not statistically significant.

Cost effectiveness

NoMA has evaluated if the cost related to the use of nivolumab is reasonable in relation to the magnitude of the clinical benefit of the treatment. BMS has submitted a cost-utility analysis together with supporting data. In the cost-utility analysis submitted by BMS the efficacy data are from CheckMate 141. Equivalency in OS was assumed for all comparators in the IC arm. NoMA has updated the analysis submitted by BMS by changing several input data in the original analysis. In NoMA's main analysis the incremental cost per quality adjusted life year (QALY) was 640 000 NOK based on AUP. If NoMA's analysis is based on LIS-AUP from the 2017 tender the cost per QALY was [redacted]. Based on these results, it is NoMA`s opinion that nivolumab most likely is a cost-effective treatment for metastatic or recurrent SCCHN compared with IC, when based on LIS-AUP.

Table 1 NoMA`s main analysis (based on LIS AUP were available)

	Nivolumab	IC	Difference
Total cost (NOK)	[redacted]	[redacted]	[redacted]
Total QALYS	0,79	0,44	0,35
Total LY	1,25	0,71	0,54
ICER/QALY			[redacted]
ICER/LY			[redacted]

Table 2 NoMA`s main analysis (based on AUP)

	Nivolumab	IC	Difference
Total cost (NOK)	498 487	272 317	226 171
Total QALYS	0,79	0,44	0,35
Total LY	1,25	0,71	0,54
ICER/QALY			**637 856**
ICER/LY			421 883

Budget impact

The budget impact of implementing nivolumab (Opdivo) for the current population with SCCHN is estimated to 6.6 MNOK in year 5 based on AUP and [redacted] based on LIS-AUP. This estimation is simplified and uncertain.

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 nivolumab (Opdivo) is that nivolumab (Opdivo) compared to investigator`s choice seems to meet the conditions to be recommended for implementation in the Norwegian specialist healthcare system.

TABLE OF CONTENTS

PREFACE 2
ABSTRACT 3
OPPSUMMERING 5
EXECUTIVE SUMMARY 7
TABLE OF CONTENTS 10
LOGG 12
GLOSSARY 14
1 BACKGROUND 16
1.1 SCOPE 16
1.2 RECURRENT OR METASTATIC PLATINUM-REFRACTORY SQUAMOUS CELL CARSINOMA OF THE HEAD AND NECK (SCCHN) 17
1.3 SEVERITY AND SHORTFALL 17
1.4 TREATMENT OF RECURRENT OR METASTATIC PLATINUM-REFRACTORY SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (SCCHN) 18
1.4.1 Treatment guidelines 18
1.4.2 Biomarkers in SCCHN 19
1.4.3 SCCHN treatment with nivolumab (Opdivo) 19
1.4.4 Treatment with comparator 20
2 SUBMITTED DOCUMENTATION TO PROVE THE RELATIVE EFFECTIVENESS 23
2.1 OUTCOMES 25
2.1.1 Efficacy 25
2.1.2 Safety 29
2.1.3 Health-related quality of life 30
3 PICO 33
3.1 PATIENT POPULATION 33
3.2 INTERVENTION 35
3.3 COMPARATOR 37
3.4 OUTCOME /RESULTS 38
4 HEALTH ECONOMIC ANALYSES 41

4.1 THE MODEL, METHODS AND ASSUMPTIONS USED 41
4.1.1 Model´s perspective *42*
4.1.2 Resource-use and costs *42*
4.2 RESULTS 44
*4.2.1 BMS´ main analysis** *44*
4.2.2 NoMA´s analysis *45*
4.2.3 Sensitivity and scenario analyses *47*
4.3 NOMA'S CONCLUSION ON THE COST-EFFECTIVENESS CRITERION 49
5 BUDGET IMPACT ANALYSIS 50
5.1 APPROXIMATION OF THE NUMBER OF PATIENTS POTENTIALLY SUITABLE FOR THE TREATMENT 50
5.2 COST ESTIMATION 50
5.3 BUDGET IMPACT 50
6 DISCUSSION 53
7 CONCLUSION 54
APPENDIX 1: CALCULATION OF SEVERITY 56
APPENDIX 2 COMMENTS FROM THE APPLICANT 57
REFERENCES 58

LOGG

Bestilling:	ID-nr 2016_070: Nivolumab (Opdivo). Indikasjon VI. Andrelinjebehandling av residiv eller metastatisk plateepitelkarsinom i hode og halsregionen
Forslagstiller:	Statens legemiddelverk
Legemiddelfirma:	BMS
Preparat:	Opdivo
Virkestoff:	nivolumab
Indikasjon:	Squamous Cell Cancer of the Head and Neck (SCCHN) OPDIVO as monotherapy is indicated for the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy (see section 5.1).
ATC-nr:	L01XC17

Prosess

Dokumentasjon bestilt av Legemiddelverket	21.09.2016
Fullstendig dokumentasjon mottatt hos Legemiddelverket	20.03.2017
Klinikere kontaktet for første gang	26.04.2017
LIS/HINAS kontaktet for første gang av Legemiddelverket.	-
Legemiddelverket bedt om ytterligere dokumentasjon	Only minor questions
Ytterligere dokumentasjon mottatt av Legemiddelverket	-
Rapport ferdigstilt:	16-10-2017
Saksbehandlingstid:	210 dager
Saksutredere:	Krystyna Hviding Anja Schiel Anette Grøvan Camilla Hjelm
Kliniske eksperter:	Åse Bratland Oslo Universitetssykehus Åsa Karlsdottir, Haukeland universitetssykehus

	Jan Folkvard Evensen, (spesialist i onkologi, pensjonist fra medio 2017)
Kliniske eksperter har bidratt med avklaringer av sentrale forutsetninger i analysen (bl.a. sammenlignende behandling, pasientgrunnlag og overførbarhet av studiedata til norsk klinisk praksis). Legemiddelverket er ansvarlig for rapportens innhold. Kliniske eksperter har ikke vært involvert i noen konsensusprosess eller hatt noen «peer-review» funksjon ved utarbeidelse av rapporten. Clinical experts have contributed to clarifications of key assumptions in the analysis (in example comparative treatment, clinical patient group characteristics and transferability of study data to Norwegian clinical practice). The NoMAis responsible for the content of the report. Clinical experts have not been involved in any consensus process or had any peer review function when preparing the report.	

GLOSSARY

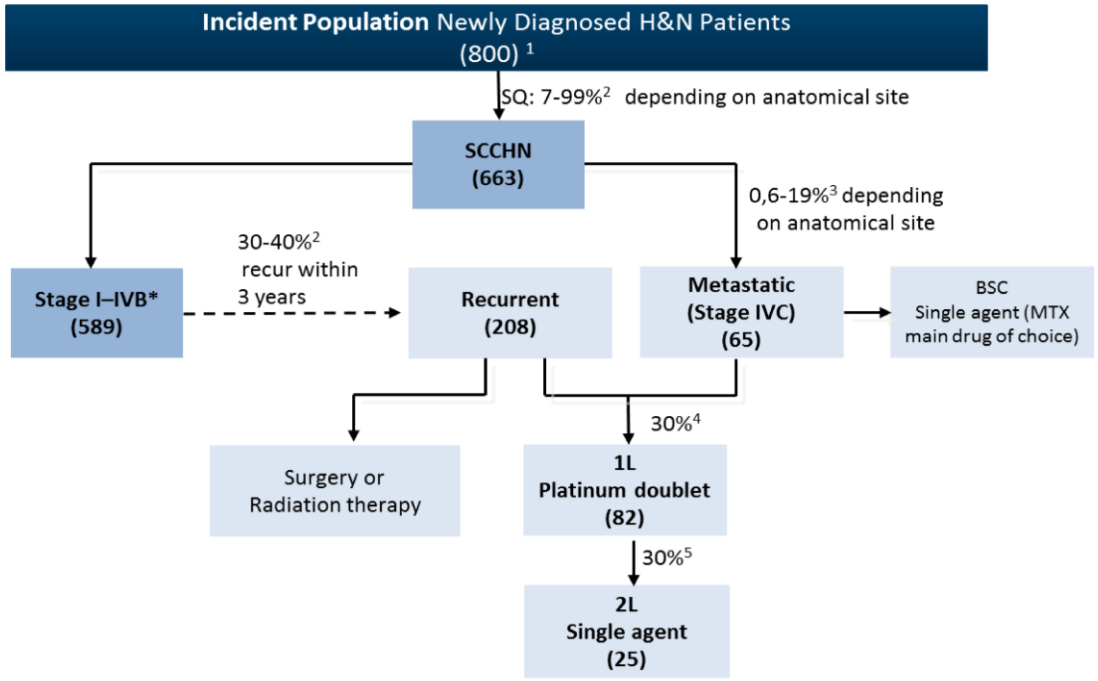
AUP	Pharmacy selling price
CI	Confidence interval
DOR	Duration of Response
ECOG	European Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ5D	EuroQol 5 dimensions
ESMO	European Society of Medical Oncology
HE	Health economic
H2H	Head-to-Head
HPV	Human Papilloma Virus
HRQoL	Health related Quality of Life
IC	Investigator`s choice
KOL	Key opinion leader
KM	Kaplan Meier
LIS-AUP	Tender pharmacy price
MAH	Market Authorisation Holder
MNOK	Million Norwegian kroner
NCCN	National Comprehensive Cancer Network
NoMA	Norwegian Medicines Agency
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PR	Partial response
PRO	Patient related outcomes
QALY	Quality-adjusted life year

QLQ	Quality of Life Questionnaire
Q2W	Every second week
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
STA	Single Technology Assessment
TRAE	Treatment-related adverse events

1 BACKGROUND

1.1 SCOPE

This single technology assessment concerns the treatment of recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck in Norway. BMS has estimated the yearly incidence as 25 individuals of this patient group in Norway.



Source: (Kreftregisteret 2014; Oncolex 2017; Helsedirektoratet 2015; National Cancer Registry Ireland 2011; Norwegian clinical experts 2016)

Note: * Patients in stage III < 70 years can get concomitant cisplatin, and if they progress within 6 months they are defined cisplatin refractory – candidate for new treatment in accordance with inclusion in 141

Abbreviations: H&N: head and neck, SCCHN: Squamous cell carcinoma of the head and neck, BSC: Best supportive care, MTX: Methotrexate, 1L: Firs line, 2L: Second line

Figure 1 Yearly SCCHN patient flow in Norway

1.2 RECURRENT OR METASTATIC PLATINUM-REFRACTORY SQUAMOUS CELL CARSINOMA OF THE HEAD AND NECK (SCCHN)

Squamous cell carcinoma of the head and neck (SCCHN) refers to a group of cancers originating in the squamous cells of the mouth, nose, and throat [1-3]. SCCHN of the oral cavity and oral pharynx most commonly occur in the tongue, tonsils and oropharynx, gums, floor, and other parts of the mouth. SCCHN tumours arising from the nasopharynx occur mostly in Asian population with 80 % prevalence.

The main risk factors for head and neck cancers of the oral cavity, oropharynx, hypopharynx, and larynx are tobacco use and alcohol consumption. Human papilloma virus (HPV) infection, especially HPV type 16, is a significant risk factor for oropharyngeal cancer. Other known risk factors are Epstein-Barr virus (EBV) infection, immune suppression either related to treatment or human immunodeficiency virus (HIV) infection, industrial and radiation exposure [3].

In Norway head and neck cancers represents approximately 2% of all cancers forms. The incidence of all head and neck cancers in Norway has slightly increased and in 2014, with 774 Norwegians diagnosed with head and neck cancers (505 men and 269 women). SCCHN amounts to approximately 90% of head and neck cancers. The most common sites in Norway are pharynx, larynx and tongue. Oropharyngeal cancer is the largest group in men and oral cavity cancer is the most common SCCHN in women. Age at diagnosis varies between the different sites. In Norway the mean age at diagnosis is 64 years [4].

At initial diagnosis, about a third of patients present with early stage (33%; Stage I/II), whereas the majority present with locally advanced disease (52-60%; Stage III/IV-A/IV-B). Only a small minority presents with metastatic disease (~10%; Stage IV-C). Approximately 50% of the SCCHN population initially treated with curative intent either will have refractory disease, or will eventually develop recurrent disease. With standard of care treatment, the 5-year survival is 80%, 50%, and 25% for early stage, locally advanced and metastatic disease, respectively.

The 5-year survival data by site from the Norwegian cancer registry show that among the different head and neck cancers larynx cancer has the best 5-year survival rate of 67.4% in men and 58.4% in women, respectively. Cancers of the pharynx has a five-year survival rate for men at 60% and 56.4% for women. Oral cancer has a five-year survival rate of 57.6% in men and 64.9% for women. There are wide variations in long- term survival >5 years between the different sites with range from over 90% to under 10%.

1.3 SEVERITY AND SHORTFALL

Patients with metastatic and recurrent SCCHN who are no longer amenable to local surgical/radiation therapy experience substantial morbidity and high mortality. Patients whose disease progresses within 6 months of platinum-based therapy, regardless of whether it was given for locally advanced or metastatic disease, have a poor prognosis. In this patient population, no OS benefit has ever been demonstrated,

and thus the choice of chemotherapy is not well defined. For these patients, the 1-year survival rate is 5-33% by various estimates with a median OS (mOS) of 6 to 8 months [5].

The Norwegian Medicines Agency (NoMA) has used a quantitative method for grading severity by estimating the absolute shortfall (APT) for the relevant patient group. APT represents, on average, the number of QALY lost for the relevant patient groups given current treatment in Norwegian clinical setting, compared to the general population. Based on this, APT due to metastatic and recurrent SCCHN was estimated to be in the range 15.6 - 18.4 QALY.

Table 3 Severity calculations

Age	60-64
Expected QALE for average population without disease (undiscounted)	18,8 – 16,1
Expected QALE with the disease without the new treatment (undiscounted) (prognosis)	0,45
Number of QALYs lost due to illness (absolute forecast loss)	15,6 – 18,4

1.4 TREATMENT OF RECURRENT OR METASTATIC PLATINUM-REFRACTORY SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (SCCHN)

1.4.1 Treatment guidelines

Currently, there are no national guidelines available, as the Norwegian “Handlingsprogrammet for hode-halskreft” is under evaluation. The final guideline is expected in 2017.

Treatment options for squamous head and neck cancer vary according to the specific sites involved. Patients with metastatic and recurrent SCCHN that are no longer amenable to local surgical/radiation therapy experience substantial morbidity and high mortality and palliative chemotherapy is given to control the disease and improve quality of life. Platinum-based chemotherapy is commonly used for recurrent or metastatic head and neck cancer. Patients whose disease progresses within 6 months of platinum-based therapy, regardless of whether it was given for locally advanced or metastatic disease, have a poor prognosis. In this patient population, no OS benefit has ever been demonstrated, and thus the choice of chemotherapy is not well defined. Treatment choice depends on prior treatment, progression-free interval since last platinum-based therapy, and comorbidities.

Nivolumab is the first drug registered for treatment of the relevant patient group.

1.4.2 Biomarkers in SCCHN

There are several biomarkers currently being studied in SCCHN. Many of the biomarkers are useful for prognostic purposes, but biomarkers that can be used to determine which patients will most likely respond to a specific treatment are still not defined. (Sacco 2015; Suh 2014).

• Programmed cell death ligand (PD-L1) is currently under investigation as a predictive and/or prognostic biomarker in SCCHN. In CheckMate 141 tumour PD-L1 status was evaluable in 260 patients (72.0%); of these, 57.3% had PD-L1 expression ≥1% (n=149), and 42.7% had PD-L1 expression <1% (n=111)

• HPV and p16 positivity is associated with a favourable prognosis mainly in oropharyngeal cancer (Suh 2014; Tinhofer 2015)

• The E6 and E7 HPV antigens involved in the oncogenesis of epithelial tissue also are associated with favourable outcomes (Park 2011)

• EGFR overexpression is common in HPV-tumours, TP53 mutations, are present in approximately 50% of SCCHN tumours, and EBV positivity is associated with an unfavourable prognosis (Suh 2014)

1.4.3 SCCHN treatment with nivolumab (Opdivo)

Nivolumab currently has a marketing authorisation in Norway for treatment of squamous-cell carcinoma of the head and neck after platinum-based therapy. It has been studied in a randomized controlled trial compared with investigator's choice of therapy of cetuximab, methotrexate or docetaxel in patients with recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck.

- Opdivo is indicated as monotherapy for the treatment of recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck (SCCHN).
- Nivolumab is developed for the treatment of different types of tumours and currently approved for the treatment of metastatic malignant melanoma, non-small-cell lung cancer (NSCLC), renal cell carcinoma (RCC) and Hodgkin lymphoma.
- Mechanism of action

  Nivolumab is a programmed death receptor 1 (PD-1) immune checkpoint inhibitor. The PD-1 receptor is a key regulator of T-cell activity that controls tumour-specific inhibition of T-cell responses to tumours. Engagement of the PD-1 co-inhibitory receptor on activated T cells through programmed death ligands 1 and 2 (PD-L1 and PD-L2) results in inhibition of T-cell proliferation, survival and cytokine secretion. Nivolumab is a human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that potentiates T-cell responses through dual ligand blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

- Posology

Nivolumab is provided as a solution for injection as an intravenous infusion and is supplied in the following concentrations as single-use vials: 100 mg/10 ml (10 mg/ml) and 40 mg/4 ml (10 mg/ml). Nivolumab is administered as an intravenous infusion over a period of approximately 60 minutes. The recommended dose and schedule of nivolumab monotherapy for the SCCHN indication is 3 mg/kg administered as IV infusion Q2W, which is consistent with existing approved dose and schedule of nivolumab monotherapy in adults. No separate dose finding study for the treatment of SCCHN had been conducted for nivolumab monotherapy.

Escalation or reduction of dose is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.

Treatment with nivolumab should be continued as long as clinical benefit is observed or until the treatment is no longer tolerated by the patient. Dosing delay or discontinuation may be required based on individual safety and tolerability.

- Undesirable effects reported in CheckMate 141

  The rates of treatment-related adverse events of any grade were similar in the two groups, but fewer events of grade 3 or 4 were reported in the nivolumab group than in the investigator's choice therapy group (15.3% vs. 36.0%). Treatment discontinuations due to any grade AE (all causality) were similar between groups (21.6% nivolumab versus 24.3% IC), but proportions were lower in the nivolumab arm compared to IC of therapy (3.8% versus 9.9%) for drug-related AEs of any grade. Most frequently reported AE of Grade 3-4 were anaemia (5.9%), dyspnoea (5.5%), hyponatremia (4.7%), dysphagia (3.8%), and pneumonia (3.8%). Two deaths were reported in the nivolumab arm that were considered to be related to study drug toxicity (Grade 3 pneumonitis and Grade 5 hypercalcaemia).

  The most frequently reported AEs of any cause in the nivolumab arm were (any grade): fatigue (26.3%), nausea (19.1%), anaemia (18.6%), decreased appetite (18.6%), malignant neoplasm progression (18.2%), and constipation (15.3%).

  Depending on severity, nivolumab should be withheld or permanently discontinued for immune-mediated pneumonitis, colitis, hepatitis, hypophysitis, adrenal insufficiency, hyperglycemia, nephritis and renal dysfunction, rash, encephalitis, or other immune-mediated adverse reactions. Nivolumab should be permanently discontinued for any life-threatening or Grade 4 adverse events.

  In general, no new safety concerns with nivolumab were identified in CheckMate 141, with a similar safety/tolerability profile observed to that seen in trials of nivolumab monotherapy in other cancer types.

1.4.4 Treatment with comparator

There is no established pathway of care in recurrent or metastatic platinum-refractory SCCHN. No other drugs are approved by EMA when platinum-based therapy is no longer clinically appropriate. Further treatment choice is determined by previous chemotherapy exposure, performance status, and other

comorbidity conditions. The European society for medical oncology (ESMO) clinical practice guidelines for SCCHN were published in 2010 [1]. Recommendations in guidelines vary from best supportive care (BSC), or chemotherapy with taxanes (paclitaxel, docetaxel), 5-FU, methotrexate, ifosfamide, bleomycin, gemcitabine, capecitabine, and vinorelbine or cetuximab. For patients not eligible for combination chemotherapy, ESMO guidelines recommends weekly methotrexate. The same guidelines state that it is unclear whether taxanes are useful in this context or not. Cetuximab alone seems to have a favourable toxicity profile with activity that is comparable to methotrexate alone (ESMO). Second or third line chemotherapies are not mentioned in these guidelines [1].

According to Norwegian clinical expertise there is no defined standard treatment practice for the recurrent or metastatic platinum-refractory SCCHNs patient group in Norway. The most frequently used therapies are docetaxel, paclitaxel, cetuximab or methotrexate for patients not eligible for chemotherapy.

The following comparators are considered as most relevant for this rapid STA assessment:

- Cetuximab (Erbitux)
- Methotrexate
- Docetaxel (Taxotere)
- Paclitaxel (Taxol)

The IC arm (Investigator's choice) of the CheckMate 141 trial reflects current Norwegian practice since the patients were treated with either docetaxel, methotrexate or cetuximab. The IC arm was therefore accepted by NoMA as the main comparator in the cost-utility analysis. There are no head-to-head comparisons between nivolumab and docetaxel, or methotrexate or cetuximab. It is anticipated that all three therapies have similar effect on overall survival in relevant patient group since all three are included in the IC–arm as parallel options. The safety profile is different due to different modes of action.

Therapeutic indication

- Cetuximab 400 mg/m2 IV once, then 250 mg/m2 weekly is indicated for the treatment of patients with squamous cell cancer of the head and neck in combination with radiation therapy for locally advanced disease, and in combination with platinum-based chemotherapy for recurrent and/or metastatic disease followed by cetuximab as maintenance therapy until disease progression. (premedication with dexamethasone, diphenhydramine, and ranitidine) [4]

- Methotrexate 40 mg/m ^{2} IV weekly (3wk equals 1 cycle) as monotherapy

- Taxotere (docetaxel): docetaxel 75 mg/m IV every 3 week is indicated in combination with cisplatin and fluorouracil for the indication of treatment of patients with locally advanced SCCHN [6].

- Taxol (paclitaxel) Paclitaxel 200 mg/m ^{2} IV every 3wk

In Norway, there is some variation in the choice of second line chemotherapy e.g. whether paclitaxel or docetaxel is used, or whether single agent or combination therapy with platinum-based chemotherapy such as carboplatin is being preferred. Cetuximab may be used in combination with paclitaxel. As cytotoxic chemotherapy is the most routinely used treatment approach, recurrent or metastatic platinum-refractory SCCHN patients may experience further deterioration in health related quality of life due to drug-related adverse events (AEs) in addition to the impact of worsening disease symptoms.

There is an unmet medical need for effective treatments that can maintain levels of quality of life for recurrent or metastatic patients who are refractory to platinum-based therapy. All active therapy options are so far associated with significant toxicity and relatively low response rates.

2 SUBMITTED DOCUMENTATION TO PROVE THE RELATIVE EFFECTIVENESS

The main submitted documentation is based on results from study (CA209141) CheckMate 141 [7]. This is an open-label randomized phase III trial comparing nivolumab to investigator's choice (IC) in previously treated patients with SCCHN of the oral cavity, pharynx or larynx, 18 years or older who had tumour progression on, or within six months of platinum therapy in the primary, recurrent or metastatic setting. Patients were enrolled in the study regardless of their tumour PD-L1 status or human papilloma virus (HPV) status. The table below shows the study design in more details.

Table 4 CheckMate 141 study design (MAH submission file)

Study (acronym, ID no.)	CheckMate 141 CA209141
Location/place of study/country	55 sites in 15 countries (Argentina, Brazil, Canada, France, Germany, Hong Kong, Italy, Japan, Korea, Netherlands, Spain, Switzerland, Taiwan, United Kingdom, and United States of America)
Design/study type	Phase III, randomized, open-label study
Duration of the study	Study initiation date was 29 May 2014. The clinical database was locked for interim analysis at 18 December 2015. For the addendum analysis the database was locked at 20 September 2016
Randomisation method	2:1 randomisation to nivolumab or investigator's choice therapy. Stratification by prior cetuximab treatment (yes/no)
Blinding method (investigator, patient, outcomes assessor)	Per protocol, investigators were to indicate their choice of therapy for each patient (cetuximab, methotrexate, or docetaxel) prior to randomization
Intervention (n=)	240
Comparison/control (n=)	121
Primary outcome (including measurement tools and measurement times)	Overall survival (defined as the time from randomization to the date of death from any cause)
Secondary outcome (including measurement tools and measurement times)	Progression-free survival (time from randomization to the date of disease progression or death) Objective response rate (according to RECIST, version 1.1.)
Follow-up time	Followed every 3 months until death, loss to follow-up, or withdrawal of consent. The updated analysis represents a minimum of 11.4 months of follow-up

Source: (Bristol-Myers Squibb 2016f; Bristol-Myers Squibb 2016g; Ferris 2016a)

The trial randomized 361 patients 2:1 to receive either nivolumab 3 mg/kg intravenously every two weeks (n=240) or investigator's choice with cetuximab, methotrexate or docetaxel (n=121) until documented disease progression or unacceptable toxicity. The primary endpoint of this pivotal trial was OS, and secondary endpoints included PFS and ORR. Safety, DOR, and HRQOL were assessed only as exploratory endpoints.

Patients received nivolumab 3 mg/kg as a 60 min intravenous infusion every 2 weeks, or investigator's choice therapy, consisting of weekly intravenous administrations of methotrexate (40–60 mg/m² of body surface area), docetaxel (30–40 mg/m²), or cetuximab (250 mg/m² after a loading dose of 400 mg/m²) until disease progression, intolerable toxicity, or withdrawal of consent.

Nivolumab treatment could be continued beyond disease progression, as assessed clinically or radiographically, if the investigator determined that it was providing clinical benefit [8].

Disease assessments were performed with CT or MRI at baseline, and every 6 weeks beginning at week 9. Imaging data were assessed by the investigators to establish tumour response according to RECIST version 1.1. Patients were followed for overall survival every 3 months until death, loss to follow-up, or withdrawal of consent.

On 18-Dec-2015, the database was locked for interim analysis, which demonstrated that the study had meet its primary outcome of improved overall survival (HR 0.70; 97.73% CI: 0.51, 0.96; p=0.0101) [7]. The data cut-off point for the analyses of overall survival, progression-free survival, and safety was Dec 18, 2015 (planned interim analysis). Response and PRO data were based on a May 5, 2016, database lock. [7, 8].

BMS has provided NoMA with updated results from a later data cut-off of 20th September 2016, and these latter results are those included in the submitted analysis. Data from this last cut-off are only partly published at ASCO 2017 (poster presentation). Recently quality of life data from CheckMate 141 were published [8]. Some of the updated efficacy data are still unpublished.

The results from CheckMate 141 used in the analysis are described in details in part 3.4.

Ongoing studies related to SCCHN

There are 21 ongoing clinical studies of nivolumab for SCCHN, including both interventional and non-interventional studies. For more information, see clinicaltrials.gov[1]

[1] https://clinicaltrials.gov/ct2/results?cond=HNSCC&term=nivolumab&cntry1=&state1=&Search=Search

NoMA's assessment of the submitted evidence

According to quality assessment of CheckMate141 there are some issues that could influence the validity of the findings of the trial such as lack of blinding and imbalances in the drop-outs rates between treatment and comparator. The baseline characteristics of patients considering prognostic factors were relatively well balanced between the treatment arms, with exception for some histological differences of the tumour and number of current and previous smokers. The results are also prone to bias since the trial was open label and clinicians were able to exercise their own judgment in both concomitant and subsequent treatment. The study population is most probably younger than the median expected age of the Norwegian population, but as long as the patients have a good health status (ECOG 0-1) the results should be transferable.

It is challenging for NoMA that some of the final data used by BMS in the analysis are still not published and remain confidential on the request of BMS.

2.1 OUTCOMES

2.1.1 Efficacy

Submitted clinical documentation

The clinical documentation is mainly based on the trial CheckMate 141. In the submitted paper [7] efficacy data from a data cut off 18th December 2015 from this trial is presented. BMS has later in the process submitted a poster from ASCO 2017 which includes updated data from CheckMate 141 with cut off 20th September 2016.

The primary endpoint of this pivotal trial was OS, and secondary endpoints included PFS and ORR, safety, DOR, and HRQOL were assessed as exploratory endpoints. Study outcomes were defined as follows:

- Primary outcomes

Overall survival (OS): Defined as the time from randomisation to date of death from any cause. Survival time for patients who had not died was censored at the last known alive date. OS was censored at the date of randomisation for patients who were randomized but had no follow-up.

- Secondary outcomes

Progression-free survival (PFS): Defined as the time from randomisation to first date of documented progression, by the investigator (as per RECIST 1.1 criteria), or to death due to any cause, whichever occurred first.

Objective response rate (ORR): Defined as the proportion of randomized patients who achieved a best overall response (BOR) , complete response (CR) or partial response (PR), based on RECIST 1.1 criteria, as per investigator assessment.

- Exploratory endpoints

Duration of response (DOR): DOR was defined as the time between the date of first confirmed response (CR or PR) to the date of the first documented progression as determined by the investigator (per RECIST 1.1), or death due to any cause, whichever occurred first.

Time to response (TTR): Defined as the time from randomisation to the date of the first response (CR or PR), as assessed by the investigator. TTR was evaluated for responders (i.e. patients with a BOR of confirmed CR or PR) only

- Safety

Toxicity was assessed according to Common Terminology Criteria for Adverse Events version 4.0 at each visit during the treatment phase and for 100 days after discontinuation.

- Patient-reported outcomes (PROs)

Patient-reported outcomes (PROs) were assessed as an exploratory endpoint using both cancer specific instruments as the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30), the EORTC head and neck cancer-specific module (EORTC QLQ-H&N35), and the generic three-level European Quality of Life–5 Dimensions (EQ-5D) questionnaire [8]. The objective was to assess changes from baseline in symptoms and functioning from baseline over time between the treatement arms. The PROs were assessed at baseline, week 9, and every 6 weeks thereafter. Small sample sizes and missing data in the investigator's choice arm made it difficult to compare treatment arms after week 15 [8]

The primary and secondary outcomes are in line with recommendations from CHMP/EMA for studies with cancer drugs. It is especially important that the CheckMate 141 included overall survival as primary endpoint, and that the OS data were mature at the point of analysis.

Submitted model

The model is based on efficacy data from CheckMate 141 from the cut off 20th September 2016. OS and PFS data from this study is used to define the cohort´s distribution between the stages over time. Since the actual follow-up time in CheckMate 141 is shorter than the required time horizon in the health economic (HE) model, time-to-event data are extrapolated by fitting parametric functions.

PFS

The choice of a parametric survival model was informed by visual inspection of the log-cumulative hazards, log-cumulative logs and the standardized normal curve plots. Those graphs showed that curves were not parallel which indicates violation of the proportional hazard assumption. In the absence of proportional hazards, modelling cannot be based on hazard ratios. Therefore, BMS used two different approaches: a single survival model where a single parametric curve is fitted to both arms (nivolumab and

IC arm) based on adjustment for effect by a fixed coefficient, and independent survival model (independent parametric survival curves are fitted separately to the nivolumab and IC arm). The single survival model provided a poor fit to the data, therefore an independent survival model by treatment arm was chosen for the analysis

To secure consistency across all endpoints, independent survival models are used for all clinical endpoints (OS and TTD in addition to PFS).

A number of parametric functions have been explored by BMS.

The choice of parametric function for the extrapolation of PFS for the nivolumab arm, was based on the best visual and statistical fit (lowest AIC/BIC value) of the non-spline models, which according to BMS was the generalized gamma function. BMS further argues for the generalized gamma because it provided the same "restricted mean" as the KM data (21.42 months vs. 21.16 months). The latter argument is questionable, as very few patients remain at risk in the original KM data set, consequently the mean is not the relevant point estimator here. As a scenario analysis an alternative extrapolation was done based on the log-normal function.

Based on the same criteria, the choice of parametric function for the extrapolation of PFS for the IC arm is the log-logistic function with a log-normal function used as a scenario analysis.

In BMS´ base case the treatment duration in the model is based on time in PFS, hence the choice of algorithm for parametrisation of PFS data influences both the estimated clinical effects and the treatment costs (drug acquisition cost, administration cost and monitoring costs). The model offers an alternative modelling of treatment duration as TTD.

<u>OS</u>

It is anticipated in that all three therapies included in IC-arm (docetaxel, cetuximab and methotrexate) have similar efficacy in terms of OS. The direct evidence from clinical trials that assess relative efficacy of docetaxel, methotrexate and cetuiximab versus one another or nivolumab is limited and there are differences in safety profile. ITT results from the IC arm of CheckMate 141 are considered applicable to all three comparators included in this appraisal.

An identical selection process as for PFS has been implemented to select the appropriate algorithm for the parametrisation of the survival data. Also for OS evidence was present to indicate that the proportional hazard assumption is not holding.

The parametric distribution for OS considered best fit in the nivolumab arm was the log-normal function. An additional scenario using log-logistic was provided.

For the IC arm a log-logistic function was identified as best fit. As a scenario analysis log-normal was selected.

NoMA´s evaluation of efficacy

In this submission, as in past submissions, BMS tested different spline models as well as the usual conventional algorithms. BMS disregarded the spline models despite the fact that those models often have superior AIC/BIC scores. NoMA has criticized these models in the past for their overfit, and BMS has in line with this critique concluded that those models give too much weight to the least reliable part of the data set, i.e. the tail.

NoMA considers the strategy for selection of the most appropriate acceptable parametric model. BMS provided, on NoMA's request, the possibility to model PFS, OS and TTD based on the actual KM data with extrapolation starting beyond a fixed time point or percentage of patients still at risk. NoMA is of the opinion that these options provide better estimates than the full parametrisation in BMS' base case. The final choice is based on the visual inspection of all available parametrisations. In all tested options some part of the curves were either over- or under- estimated.

The impact of the choice of parametrisation is less problematic when the model is largely based on the true KM data. Based on this NoMA has chosen to model OS, PFS and TTD based on KM + parametric tail, instead of a full parametric modelling. For OS KM is used up to 19 months, for PFS/TTD KM is used up to 10 months.

NoMA agrees that both treatment arms need to be extrapolated individually but does not support BMS' argumentation to choose different algorithms for the nivolumab and IC arms. In the nivolumab arm the generalized gamma model was selected as the BMS' base case curve for PFS. Log-logistic model was the BMS` choice for the IC arm. NoMA considers choosing the same algorithm a more robust approach for modelling of both PFS and OS.

The log-logistic and log-normal functions belong to the same family of functions and will likely provide relatively similar results. Both algorithms are characterised by long tail sections that can lead to unrealistic long-term predictions. BMS argued that the effect of this can be neglected in this model and by exploring shorter and longer time horizons NoMA found support for this assumption. Based on this assessment NoMA agrees that the choice of either algorithm can be accepted. Log-logistic parametrisation will be used in NoMA's base case.

To summarize, NoMA accepts the use of clinical data from CheckMate 141 to model OS and PFS in the submitted model. PFS is also accepted as a proxy for time on treatment. However, NoMA has found it necessary to make some changes in BMS` submitted main analysis. The following changes have been made by NoMA:

- Full parametric modelling of all data has been changed to KM data with extrapolation from a certain point (19 m for OS and 10 md for PFS/TTD).
- The extrapolation of PFS for nivolumab has been changed from generalized gamma to a log logistic function.
- The extrapolation of OS for nivolumab has been changed from log normal to a log logistic function.

2.1.2 Safety

Submitted clinical documentation

The safety documentation for nivolumab in SCCHN patients is based on reported adverse events during the CheckMate trial. The table below presents adverse events reported in 5 % or more of the patients in CheckMate 141.

Table 5 Treatment related adverce events CheckMate 141, presented in poster at ASCO 2017 [9]

	Nivolumab (n = 236)		Investigator's choice (n = 111)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE, n (%)	146 (61.9)	36 (15.3)	88 (79.3)	40 (36.0)
TRAEs in ≥15% of patients				
Fatigue	37 (15.7)	5 (2.1)	20 (18.0)	3 (2.7)
Nausea	22 (9.3)	0	23 (20.7)	1 (0.9)
Anemia	12 (5.1)	3 (1.3)	19 (17.1)	6 (5.4)
Asthenia	10 (4.2)	1 (0.4)	17 (15.3)	2 (1.8)
Select TRAEs, n (%)				
Skin	40 (16.9)	0	14 (12.6)	2 (1.8)
Endocrine	22 (9.3)	1 (0.4)	1 (0.9)	0
Gastrointestinal	20 (8.5)	1 (0.4)	17 (15.3)	2 (1.8)
Hepatic	7 (3.0)	2 (0.8)	5 (4.5)	1 (0.9)
Pulmonary	7 (3.0)	2 (0.8)	1 (0.9)	0
Renal	3 (1.3)	0	2 (1.8)	1 (0.9)
Hypersensitivity/infusion reactions	3 (1.3)	0	2 (1.8)	1 (0.9)

Submitted model

In BMS` base case treatment specific utilities are used in the progression free health states derived from CheckMate 141. This is assumed to include the adverse events related to the treatments in the model.

The model also provides an option which includes state specific utilities. In this case the disutility related to adverse events is based on the incidence of adverse events reported in CheckMate 141 and disutility values derived from a literature review. The duration of each disutility value is modelled as one 4-week-cycle.

Table 6 Grade 3 or greater frequency ≥ 5%, all causes AEs included in the economic model

Type of adverse event	Nivolumab	Investigator's Choice
Anaemia	5.93%	8.11%
Dyspnoea	5.51%	1.80%
Fatigue	3.39%	6.31%
Hyponatremia	4.66%	8.11%
Malignant neoplasm progression	18.64%	22.52%
Neutropenia	0.00%	7.21%

NoMA's evaluation of safety

The safety profiles included in the HE analysis are based the same population as the efficacy data, and NoMA accepts the use of these data. However, these safety data have not been thoroughly evaluated as they have very little impact on the results. Notably, there is a difference between the reported AEs presented at ACSO 2017 and the frequencies of AEs in the submitted model. This is explained by the inclusion of all-cause AEs in the model, while only the treatment related AEs were presented at ASCO.

2.1.3 Health-related quality of life

Submitted documentation

In CheckMate 141 patient-reported outcomes were assessed by the European organisation for research and treatment of cancer (EORTC) quality of life questionnaire core 30 (QLQ-C30) and quality of life questionnaire head and neck specific module (QLQ-H&N35) instruments and European Quality of life-5 Dimensions – 3 levels (EQ-5D-3L) questionnaire. Patient reported HRQoL was an exploratory endpoint in CheckMate 141.

The CheckMate 141 trial collected patient reported outcomes including the EQ-5D-3L after randomization, but prior to the first dose of study therapy, then every six weeks as of week 9, and then at follow-up visits 1 and 2. During follow-up EQ-5D-3L assessments were taken approximately 35 and 115 days after the last dose of study treatment, and continued to be taken every three months at subsequent follow-up visits. The results of the analysis with the UK value set is presented in Table 7 below.

Table 7 Utility index values colleced in CheckMate 141, UK tariff (EQ-5D, data cut off th May 2016 Source: BMS))

Treatment arm and tumor respons category	Overall	Nivolumab	Investigator`s choice
Overall (n = 258) (95% CI)	[redacted]	[redacted]	[redacted]
PF (95 % CI)	[redacted]	[redacted]	[redacted]
PD (95 % CI)	[redacted]	[redacted]	[redacted]

PF: progression free survival, PD: progressed disease

HE model

In the submitted analysis the utility index values are based on the collected EQ-5D data using the UK tariff. In BMS´ base case treatment specific utilities for the progression free health state and overall utilities for the progression health state derived from the CheckMate 141 are used.

The model also has two other options based on the EQ-5D values from CheckMate 141: treatment specific utilities for both stages (PF and PD), and overall stage-specific utilities that are not treatment-specific. In the latter option, the model also includes adverse events utility, as shown in Table 8 below. The disutility values are derived from a targeted literature review. The duration of each disutility value is one cycle (4 weeks).

Table 8 Disutility related to each adverse event (Source: BMS)

Type of adverse event	Mean disutility	Source
Anaemia	-0.125	(LLyod A 2008)
Dyspnoea	-0.29	(Grutters 2010)
Fatigue	-0.0735	(Nafees 2008)
Hyponatreaemia	-0.1910	Assumed to be the same as hypomagnesemia reflecting a 24% decline in utility (from PF utility) (Hannouf 2012)
Malignant neoplasm progression	0.000	Assumption
Neutropenia	-0.0897	(Nafees 2008)

The incidences of AEs are modelled as presented in Table 6.

NoMA´s evaluation of Health related quality of life

Since CheckMate 141 was an open-label study it is NoMA's opinion that the lack of blinding may bias the patient-reported health related quality of life. Due to this, NoMA has chosen to change the utilities in the analyses so that the same values are used in both arms, the overall values for the stage PF[redacted]) and PD [redacted] as presented in Table 7 above.

Conclusion for HRQoL

NoMA finds the health related quality of life to be collected from a relevant patient population and with a relevant method. However, since the quality of life is obtained from an open-label study, NoMA does not find it optimal to use intervention-specific utilities. Due to this, NoMA has chosen to use overall utility index values for the stages in the model. NoMA approves of using the UK tariff.

In relation to the disutility included to the AEs in the model, these only have a marginal effect on the results, and have not been thoroughly evaluated.

3 PICO[2]

3.1 PATIENT POPULATION

The patient population in the Norwegian setting

According to Oncolex the median age for patients with cancer in head/neck in Norway is 64 years [4]. Clinical experts NoMA consulted confirmed that the relevant population`s average age most likely is in the range 60-64 years, with majority of patients < 64 years. More men than women get cancer in the head or neck, but there are some differences between the different sites of the disease.

NoMA anticipates that nivolumab in the Norwegian clinical practice will be used in line with the approved therapeutic indication. I.e." *… as monotherapy for the treatment of recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck (SCCHN)".*

In line with the therapeutic indication, the majority of the clinical experts NoMA has consulted recommend the use of nivolumab regardless of PD-L1 status based on the available clinical efficacy data. Testing of PD-L1 status is not a standard procedure for patients with SCCHN in Norway.

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

The CheckMate 141 study included patients 18 years or older with disease progression during or after a prior platinum-based therapy regimen (≤ 6 months). The average age in CheckMate141 was 59.1 years while the Norwegian patients might be older. Included patients had an ECOG performance status score of 0 or 1 and adequate bone marrow, hepatic, and renal function; and measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST), version 1. Patients were enrolled regardless of their tumour PD-L1 status or human papilloma virus (HPV) status. These enrolment criteria are most probably are line with expected selection criteria in clinical practice.

The following patients were excluded from the study: patients with active autoimmune disease, medical conditions requiring immunosuppression, recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment according to predefined conditions, and either were off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents.

These restrictions are most probably in line with expected clinical practice, but all SCCHN patients are assessed individually and there is an unmet need for effective treatment.

The baseline demographics for the patients in this study are shown in the table below.

[2] Patients, Intervention, Comparator, Outcome.

Table 9 Baseline demographics for patients in CheckMate 141 (source: BMS)

Study (acronym, ID no.)	Intervention	Comparator	Total
CheckMate 141 (CA209141)	**Nivolumab (N=240) n (%)**	**Investigator's choice (N=121) n (%)**	**Total (N=361) n (%)**
Mean age (years)	59.0	59.4	59.1
Median age (years)	59.0 (29-83)	61.0 (28-78)	60.0 (28-83)
<65	172 (71.7)	76 (62.8)	248 (68.7)
≥65	68 (28.3)	45 (37.2)	113 (31.3)
Gender (%)			
Male	197 (82.1)	103 (85.1)	300 (83.1)
Female	43 (17.9)	18 (14.9)	61 (16.9)
Smoking/tobacco use			
Current/former	191 (79.6)	85 (70.2)	276 (76.5)
Never	39 (16.3)	31 (25.6)	70 (19.4)
ECOG PS, %			
0	49 (20.4)	23 (19.0)	72 (19.9)
1	189 (78.8)	94 (77.7)	283 (78.4)
≥2	1 (0.4)	3 (2.5)	4 (1.1)
Not reported	1 (0.4)	1 (0.8)	2 (0.6)
Number of prior systemic regimens, %			
1	106 (44.2)	58 (47.9)	164 (45.4)
2	80 (33.3)	45 (37.2)	125 (34.6)
≥3	54 (22.5)	18 (14.9)	72 (19.9)
Site of primary tumour			
Oral cavity	108 (45.0)	67 (55.4)	175 (48.5)
Pharynx	92 (38.3)	36 (29.8)	128 (35.5)
Larynx	34 (14.2)	15 (12.4)	49 (13.6)
Other	6 (2.5)	3 (2.5)	9 (2.5)
PD-L1 quantifiable	161 (67.1)	99 (81.8)	260 (72.0)
≥1%	88 (54.7)	61 (61.6)	149 (57.3)
<1%	73 (45.3)	38 (38.4)	111 (42.7)
Not evaluable	79 (32.9)	22 (18.2)	101 (28.0)
HPV-16 status[a]			
Positive OPSCC	63 (26.3)	29 (24.0)	92 (25.5)

Note: [a] Per protocol, HPV status testing was only required for patients with oropharyngeal disease. The HPV-negative OPSCC + non-OPSCC subgroup also includes 3 subjects with sample dates after the first dose date (considered non-evaluable) and 1 subject who was tested for HPV but had a non-evaluable test result).

European Cooperative Oncology Group; PD: progressive disease; PR: partial response; PS: performance status; SD: stable geal squamous cell carcinoma

The baseline characteristics were well balanced between the arms with exception for smoking/tobacco users. There is some inbalance in the number of current/former smokers enrolled in the nivolumab arm compared to IC arm (79.6 % vs. 70.2%). More patients with PD-L1 > 1 % were enrolled in IC-arm compared to nivolumab (61.6 % vs. 54.7 %). Since PD-L1 expression might be related to the outcome the differenece has been explored by BMS in later analysis.

Patient population in the HE-model related to the Norwegian setting and clinical studies

The patient population in the submitted model is based on the population in CheckMate 141 as presented above.

NoMA´s evaluation of the patient population

The patient population in CheckMate 141 might have a slightly lower average age than in the relevant population in Norwegian clinical setting. The proportion of men in the study (83%) might also be higher than reported numbers in registry data. There are also some differences between the sites of the primary tumor disease, but the numbers are low and uncertain. Altogether, NoMA considers the population in the clinical study and the health economic model to be sufficiently representative of the current patient population, and accepts this population.

3.2 INTERVENTION

Intervention in the Norwegian setting

Nivolumab (Opdivo) is expected to be used according to the approved therapeutic indication concerning head and neck cancer, as presented in section 1.4.3.

Intervention in the submitted clinical studies related to Norwegian setting.

Patients that were randomized to the nivolumab arm in the CheckMate 141 study (n= 240) received a nivolumab dose of 3 mg per kilogram bodyweight every 2 weeks.

The median duration of treatment in CheckMate 141 was 1.9 months in both arms in the study. At the data cut-off September 2016, 6.8 % (n = 16) in the nivolumab arm and 0.9 % (n = 1) in the IC arm were still receiving study treatment. The CheckMate 141 protocol indicated treatment until disease progression, unless patients receiving nivolumab had investigator-assessed clinical benefit despite RECIST 1.1 defined progression [7].

Intervention in the HE-model related to the Norwegian setting and clinical studies

The intervention in the model is treatment with nivolumab. The modelled posology is in line with the approved therapeutic indication.

In BMS´ base case, the duration of treatment with nivolumab is modelled as the same length as PFS (treat to progression). An alternative modelling of treatment duration in the model is based on specific modelling of time to treatment discontinuation (TTD).

BMS states in their submission that there is uncertainty around how long patients will use nivolumab in clinical practice. In CheckMate 141´s study protocol patients were treated with nivolumab or IC treatment until disease progression. However, there was an exception from this, as patients in the nivolumab arm with investigator-assessed clinical benefit despite progression could continue with nivolumab as defined in the study protocol (RECIST v.1.1).

Figure 2**Feil! Fant ikke referansekilden.** below presents the PFS KM and the TTD KM from CheckMate 141. The figure shows that KM data for TTD and PFS are quite similar for the nivolumab arm in the study.

Figure 2 PFS KM vs. TTD KM within the nivolumab arm (CheckMate 141, source: BMS)

As for OS and PFS (will be presented later in this chapter), independent models were fitted to each treatment arm for TTD. The choice of parametric function was based on the visual fit to the KM data, lowest combined AIC/BIC value and “restriced means” comparisons.

NoMA´s evaluation of the intervention

NoMA accepts the submitted modelling of the intervention. It is considered plausible to estimate the intervention based on clinical data from CheckMate 141. The extrapolation of data is addressed in section 2.1.1. Treatment duration modelled in line with PFS is acceptable despite some limitations. NoMA agrees

with BMS that there is uncertainty around the duration of treatment, and will explore the effect of using TTD data to estimate treatment duration as sensitivity analyses.

3.3 COMPARATOR

Comparator in the Norwegian setting

There is no defined standard of treatment practice for SCCHN patient group in Norway. The current treatment recommendations in the ESMO guidelines include: taxanes (docetaxel, paclitaxel), methotrexate and cetuximab. Correspondence with Norwegian clinical experts confirms that all these treatments are considered as relevant alternatives for Norwegian practice. See 1.4.4 for further information about NoMa's evaluation of the IC arm in light of current clinical practice.

Comparator in the submitted clinical studies

Patients who were randomized to the IC arm in CheckMate 141 (n= 121) received a single agent therapy of the investigator's choice between methotrexate (40–60 mg per square meter of bodysurface area weekly), docetaxel (30-40 mg per square meter of bodysurface area weekly) or cetuximab (250 mg per square meter of bodysurface area weekly after a loading dose of 400 mg per square meter).

The distribution between the alternatives in the IC arm were 44.6 % docetaxel, 43.0 % methotrexate and 12.4 % cetuximab.

Comparator in the HE-model

The comparator in the model is based on the IC arm from CheckMate 141.

The model assumes the same clinical effect for all these three options, but different drug acquisition cost and slightly different administration costs.

In the BMS base case treatment duration for the IC arm is based on the data for PFS (time to progression) from CheckMate 141. The model also has the option to use time to treatment discontinuation (TTD).

NoMA's evaluation of the Comparator

NoMA accepts the submitted modelling of the comparator treatment. The IC arm (Investigator's choice) of the CheckMate 141 trial is considered sufficiently relevant from a Norwegian perspective, based on input from clinical experts. Clinical expert opinion is that docetaxel and methotrexate have similar efficacy although there are differences in safety profiles. There is limited direct evidence from clinical trials that assess the relative efficacy of docetaxel and methotrexate or cetuximab either versus one another or versus nivolumab. The ITT results from the IC arm of CheckMate141 are therefore applicable to all three comparators included in this appraisal.

3.4 OUTCOME /RESULTS

See section 2.1 for definitions of all outcomes used in CheckMate 141.

On Jan 26, 2016, the independent data monitoring committee reviewed the data at the planned interim analysis and declared overall survival superiority for nivolumab over investigator's choice therapy. The protocol was amended to allow patients in the investigator's choice group to cross over to nivolumab. All patients not on active therapy are being followed for survival.

In CheckMate 141, overall survival was significantly longer for patients treated with nivolumab than for those treated with investigator's choice. Grade 3 or 4 treatment-related adverse events were less frequent with nivolumab versus investigator's choice. The study reported that mean changes from baseline in patient-reported outcome (PRO) domains assessed on the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) and the EORTC head and neck cancer–specific module (EORTC QLQ-H&N35) were stable for patients treated with nivolumab and deteriorated for patients treated with investigator's choice. Nivolumab delayed time to deterioration of patient-reported quality-of-life outcomes compared with single-agent therapy of investigator's choice in patients with platinum-refractory recurrent or metastatic squamous cell carcinoma of the head and neck [8].

Some of the submitted results from the database lock 20th of September 2016 are not yet published.

Published results from database lock on 18-Dec-2015 for interim analysis, demonstrated that the study had meet its primary outcome of improved overall survival (HR 0.70; 97.73% CI: 0.51, 0.96; p=0.0101)[7]. Since the primary endpoint was met, the study was stopped early and a final CSR was created based on the 18-Dec-2015 database lock.

The submitted updated data show significantly longer median OS for patients treated with nivolumab compared with investigator's choice in the intent to treat population: 7.7 months (95% CI: 5.68 months to 8.77 months) vs. 5.06 months (95% CI: 4.04 months to 6.24 months) (p=0.0048). In absolute terms patients in nivolumab arm had 2.7 month longer median overall survival. Nivolumab-treated patients had a significant (29 %) reduction in risk of death and superior OS compared with investigator's choice therapy observed in the ITT population level with (HR = 0.71 [95% CI: 0.55, 0.90] (HR 0.71; 95% CI: 0.55, 0.90; p=0.0048).

The figure below shows a Kaplan-Meier plot of Overall survival in all randomized subjects in CheckMate 141. The figure is taken from MAH submission file to illustrate the OS.

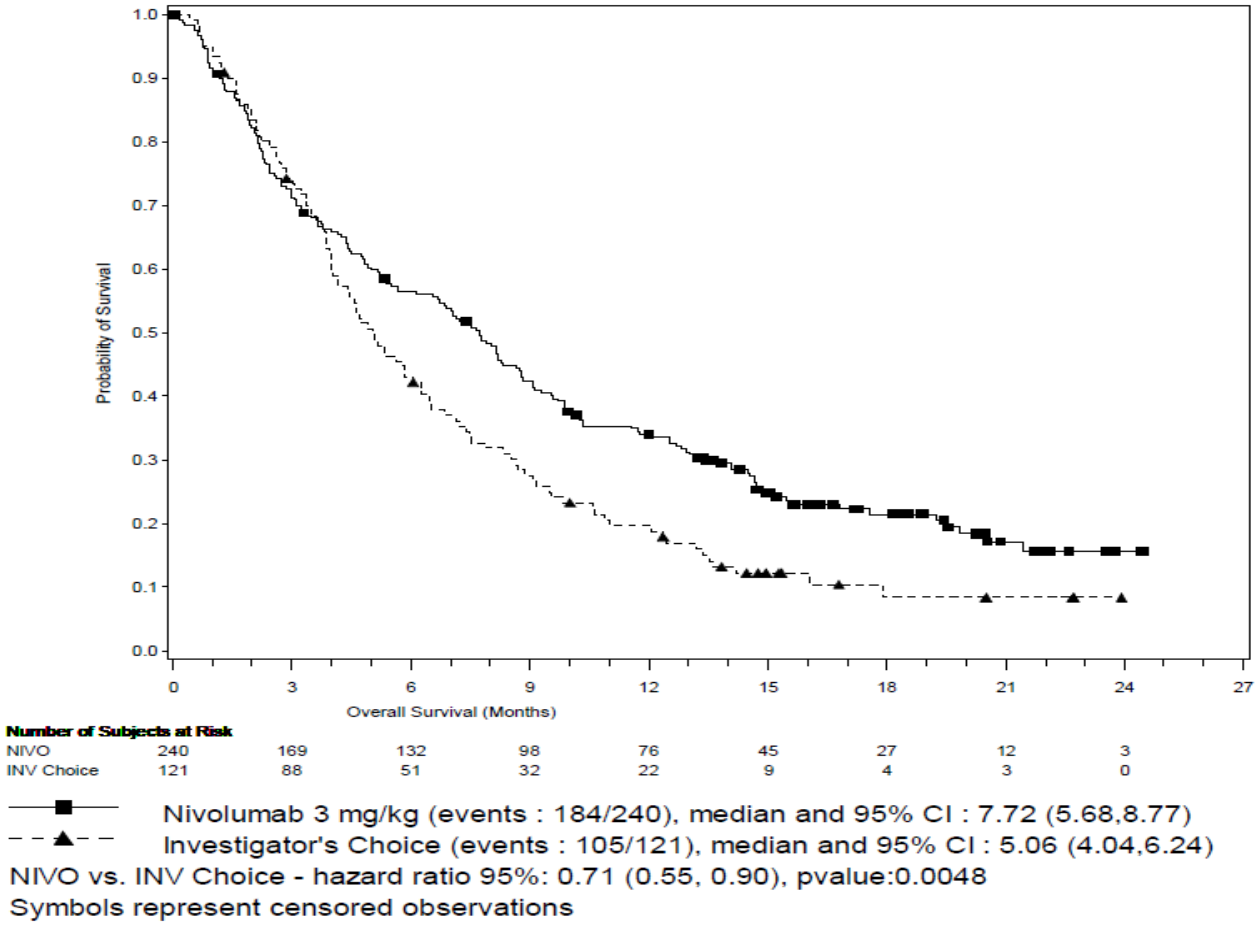


Figure 3 KM plot of overall survival in all randomized subjects in CheckMate 141 (Source: BMS` submission)

Median PFS did not differ significantly between treatment arms (2.04 months [95% CI: 1.9, 2.1] for nivolumab vs 2.33 months [95% CI: 1.9, 3.1] for investigator's choice). The estimated rates of PFS remained slightly lower in the nivolumab group than in the investigator's choice group at 3 months, but were two to three folds higher at 6 months, 9 months, and 12 months in the nivolumab arm compared to investigators choice arm.

A total of 347 patients (nivolumab, n=236; investigator's choice therapy, n=111) received at least one dose of study medication in the as-treated population for safety analyses. The safety profile for nivolumab was favourable compared to investigator's choice therapy, and consistent with prior studies; no new safety signals were noted. There were fewer treatment-related AEs of any grade (61.9% vs 79.3%) and grade 3 or 4 (15.3% vs 36.0%) in the nivolumab arm versus the investigator's choice arm, respectively [9].

The ORR (CR+PR) in patients who received nivolumab was 13.3% compared to 5.8% in the investigator's choice arm. Six (2.5%) of the patients in the nivolumab arm achieved a CR and 26 patients (10.8%)

achieved PR compared to one patient (0.8%) achieving CR and six patients (5.0%) achieving PR in the investigator's choice arm. The median time to response was approximately 2 months in both arms (Bristol-Myers Squibb 2016f).

The exploratory endpoints show that nivolumab is effective regardless of PD-L1 status. Although there was a greater magnitude of effect for PD-L1 expressors (PD-L1 ≥1%; HR=0.53; 95% CI: 0.37; 0.77) the interactions were not statistically significant and were not corrected for multiple comparisons (Bristol-Myers Squibb 2016f)

Patients in the investigator's choice group reported clinically meaningful worsening of physical, role, and social functioning (as assessed by means of the QLQ-C30), as well as of pain, sensory problems, and social-contact problems (as assessed by means of the QLQ-H&N35). These differences were also statistically significant compared to nivolumab where the measures remained stable or showed slight improvements. However, it is NoMA´s opinion that the lack of blinding in the study may bias the patient-reported health related quality of life.

4 HEALTH ECONOMIC ANALYSES

This section presents a summary of the economic evidence submitted by BMS in support of the use of nivolumab (Opdivo) for treatment of recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck, and NoMA's assessment of the evidence. NoMA evaluates two key components in this section; input data used which are not already assessed above, and the applied health economic. A typical health economic model will include the calculation of costs, life-years gained, and quality-adjusted-life-years gained (QALYs).

In the submitted evidence, treatment with nivolumab is compared with treatment with IC (investigator's choice, which includes certuximab, methotrexate or docetaxel). The submitted health economic evaluation is a CUA (cost-utility-analysis).

4.1 THE MODEL, METHODS AND ASSUMPTIONS USED

Model´s description

The submitted model is a partitioned survival model with three stages: PF/progression free, PD/progressed disease and death.Figure 4 below presents an overview of the model structure.

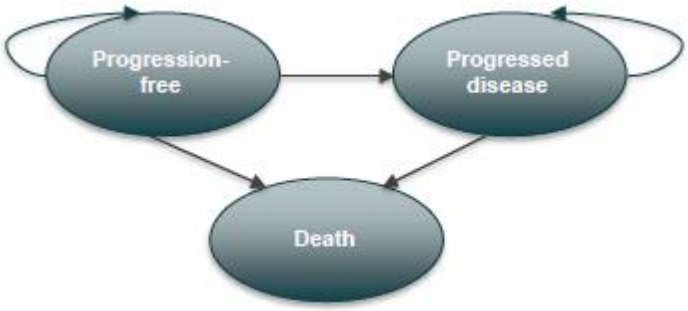


Figure 4 Structure of the economic model (source: BMS)

The model is cohort-based, and the distributions between the stages over time are estimated based on parameterized PFS and OS data from CheckMate 141. This is presented and discussed in section 2.1.1. The model has a cycle length of 4 weeks.

The model adjusts for age specific mortality. However, the background mortality is not included in addition to the probability of death derived from the OS data, but the model has adjustments that secures that the probability of dying never goes below the mortality in the general population.

NoMA's appraisal of the model

A three stage partitioned survival model, as presented above, is commonly used in economic evaluation of anti-cancer treatments, and NoMA accepts the use of the submitted model in this evaluation.

4.1.1 Model´s perspective

The perspective is the Norwegian healthcare perspective, the time horizon is 15 years and the discount rate is set to 4 % for costs and health outcomes.

NoMA's appraisal of the models perspective

NoMA accepts the perspective and the applied discount rates, as they are in line with our guidelines for health economic evaluations. NoMA also accepts the time horizon, as the model in line with the nature of the disease models very low overall survival in the latter years of the time horizon in the model.

4.1.2 Resource-use and costs

Direct costs

Submitted documentation

Drug acquisition cost

The analysis includes direct drug acquisition costs for nivolumab and IC (docetaxel, cetuximab and methotrexate). No vial sharing is assumed. In the submitted analysis, the costs of drugs are based on AUP.

Drug costs nivolumab

In regard to the direct drug cost for nivolumab, the calculation is based on the median patient weight in CheckMate 141 which was 66,0 kg. Due to this, the costs are based on the assumption that 50 % of the patients are under 66,0 kg (requiring a dose of 200 mg) and 50 % are above 66,0 kg (requiring a dose of 220 mg). The mean weight in CheckMate 141 was 66,9 kg.

Drug costs IC

The drug cost in the IC arm is based on a weighted average based on docetaxel (44.6%), methotrexate (43.0%) and cetuximab (12.4%).

Cost for subsequent treatment

The analysis also includes drug acquisition costs for subsequent treatment. The proportion of patients receiving subsequent treatment were based on numbers from CheckMate 141, where 29.6 % in the nivolumab arm received subsequent treatment vs. 32.2 % in the IC arm. It was assumed that the mean

PFS from the IC arm was a reasonable estimate of the duration of the subsequent treatment (3.5 months). The distribution between the different treatment options for the two arms were based consultations with clinical experts, giving the following assumption: for the nivolumab arm 70 % BSC and 30 % cetuximab, and for the IC arm: 70 % BSC, 15 % cetuximab and 15 % nivolumab.

Administration cost

The same unit cost per administration is used for all the drugs in the analysis, however due to different time per infusion, there are marginal differences in the total cost estimated per infusion related the differences in time spent. There is also included cost related to treatment monitoring.

Disease management costs

Disease management costs are assigned in the model per cycle in the PF and the PD stages. The size of these costs are approximately 2100 NOK in PF and 2900 NOK in PD. These costs are based in unit costs sourced from the disease related groups (DRG) tariff [10] and from Aleris' pricelist oncology [11].

Adverse advent costs

All causes adverse events grade 3 or higher with a 5 % or above incidence in the CheckMate 141 study are included in the analysis base case. The total costs related to adverse events are under 400 NOK for the whole horizon for both arms in the model, and do not influence the results.

End of life costs

End of life cost are included as a one off cost of approximately 100.000 NOK. This cost is based in unit cost for hospitalization, advanced medical home care and hospice care sourced from diagnose related groups tariff *Innsatsstyrt finansiering* [10] and from *Normaltariffen 2016 [12].*

NoMA's assessment

NoMA has updated the analysis with the LIS AUP for nivolumab and based the drug acquisition costs on the average weight in CheckMate 141 instead of the median weight approach, in line with the estimation of the other drug acquisition costs in the model.

NoMA has also updated the docetaxel price to LIS AUP and the AUP for cetuximab (minor change for the latter). The price for methotrexate is changed to a price for a smaller vial (still sufficient for the relevant dose) and changed to LIS AUP price.

Concerning the drug acquisition cost for the subsequent treatment, NoMA finds these estimates uncertain, both the assumed duration of this treatment and the distribution between the different treatment options. In addition the *clinical effect* of the subsequent treatments as estimated by the clinical expert is not included in the analysis, only the costs. NoMA has chosen to base the subsequent drug acquisition cost on the use of subsequent treatment seen in CheckMate 141 in order to not include treatment cost without also including the clinical effect.

The unit cost per administration is according to NoMA's published cost list. The differences in costs due to different amount of time spent on administration and monitoring and adverse events are marginal, and do not influence the results. Therefore, these costs are not evaluated further.

The end of life costs are higher than in most earlier economic evaluations related to anti-cancer treatment. However, this cost does only to a small degree influence the results and has not been evaluated further.

Indirect costs

The analysis does not include indirect costs.

4.2 RESULTS

4.2.1 BMS´ main analysis*

BMS` main analysis is based on max. AUP prices. If this analysis is updated with current LIS-AUP prices the ICER (cost per QALY) is approximately [redacted].

Table 10 BMS`main analysis

	Nivolumab	IC	Difference
Total cost (NOK)	542 442	283 651	258 791
Total QALYS	0,79	0,47	0,32
Total LY	1,17	0,71	0,46
ICER (QALY)			**801 598**
ICER(LY)			561 286

* Based on max AUP prices.

4.2.2 NoMA´s analysis

Based on NoMA's assessments in the previous chapters our main analysis differs from BMS` main analysis. NoMA's main analysis is based on the same assumption as BMS' main analysis, except the changes presented in Table 13**. <u>A central change from BMS' main analysis to NoMA's analysis, is that the drug acquisition prices are changed from AUP to LIS-AUP for most of the drugs included in the analysis, including nivolumab.</u>** This results in a substantially lower ICER.

Table 11 NoMA`s main analysis (based on LIS AUP were available)

	Nivolumab	IC	Difference
Total cost (NOK)	[redacted]	[redacted]	[redacted]
Total QALYS	0,79	0,44	0,35
Total LY	1,25	0,71	0,54
ICER (QALY)			[redacted]
ICER (LY)			[redacted]

Table 12 NoMA`s main analysis (based on max. AUP)

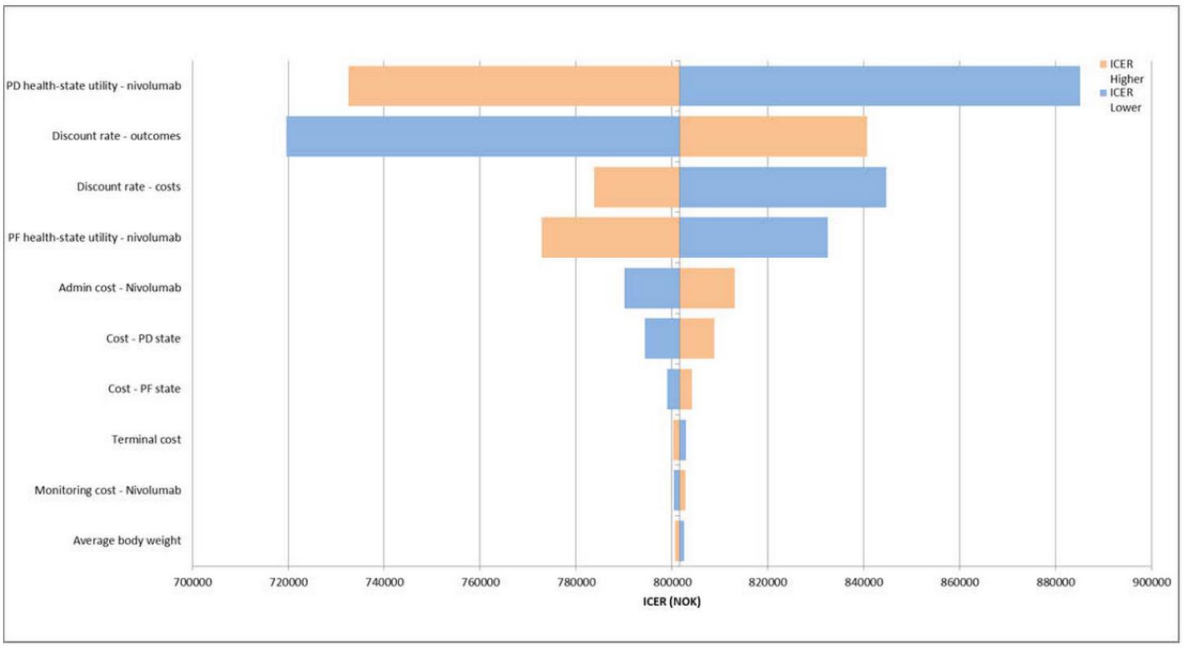
	Nivolumab	IC	Difference
Total cost (NOK)	498 487	272 317	226 171
Total QALYS	0,79	0,44	0,35
Total LY	1,25	0,71	0,54
ICER (QALY)			**637 856**
ICER (LY)			421 883

Table 13 Presentation of NoMA's changes in the analysis and the effect on ICER (QALY)

Input	**NoMA`s input**	**ICER- incremental cost per QALY (NOK)**
BMS' base case		***801 598***
Drug consumption nivolumab	Consumption based on average weight in CheckMate 141 (BMS base case: median weight approach)	850 630
Parametrisations ,both OS and PFS	KM data with tail (BMS: full parametrisation)	831 266
Parametrization OS	Log logistic for nivolumab (BMS: log normal)	721 326
Parametrization PFS	Log logistic for nivolumab (BMS base case: generalized gamma)	606 700
Utilities	Stage specific utilities (BMS base case: treatment specific)	620 893
Subsequent treatment (costs)	Subsequent treatment as seen in CheckMate 141 (BMS: estimates based on KOL)	637 856
NoMA's base case (based on AUP prices)		***637 856***
Updated drug prices	LIS AUP prices where relevant	[redacted]
NoMA's base case (based on LIS-AUP)		[redacted]

4.2.3 Sensitivity and scenario analyses

BMS has submitted the following tornado diagram from their base case analysis.



Abbreviations: ICER: incremental cost-effectiveness ratio; PD: progressed disease; PF: progression-free; QALY: quality-adjusted life year

Figure 5 Tornado plot of the deterministic sensitivity analysis, nivolumab vs. IC. Showing impact on ICER (Source: BMS)

As can be seen from the diagram above, the utility index values for both PF and PD are amongst the parameters with greatest influence on the resulting ICER in BMS' base case. However, the effect of different parametric functions in the extrapolation is not explored in this sensitivity analysis, neither is the drug acquisition costs of nivolumab (Opdivo). NoMA has performed a one-way sensitivity analysis on how the price of nivolumab affects the ICER. This is shown in Figure 6.

NoMA has further evaluated the effect of changes of different variables and input data in the model. The main results are presented in Table 14 below. These analysis are based on NoMA's base case analysis.

Table 14 Sensitivity analysis done by NoMA

Adjusted variable/parameter	Changes done	ICER- incremental cost per QALY (NOK)
Treatment time (base case: as PFS)	Treatment time modelled based on TTD data -functions as BMS base case -based on generalized gamma function	[redacted]
Time horizon (base case: 15 years)	Reduced horizon to 10 years	[redacted]
Time horizon	Extended horizon to 20 years	[redacted]
Costs end of life (base case: 105.947 NOK)	Reduced to 0 NOK	[redacted]
Stage related costs PF (base case: 2114)	Increased with 50 %	[redacted]
Stage related cost PF	Reduced with 50 %	[redacted]
Stage related costs PD (base case: 2900 NOK)	Increased with 50 %	[redacted]
Stage related costs PD	Reduced with 50 %	[redacted]
Utilities Base case: Overall utilities	BMS base case choice for utilities. Treatment specific utilities for PF	[redacted]
Utility PF	Increased with 25%	[redacted]
Utility PF	Reduced with 25 %	[redacted]
Utility PD	Increased with 25 %	[redacted]
Utility PD	Reduced with 25 %	[redacted]

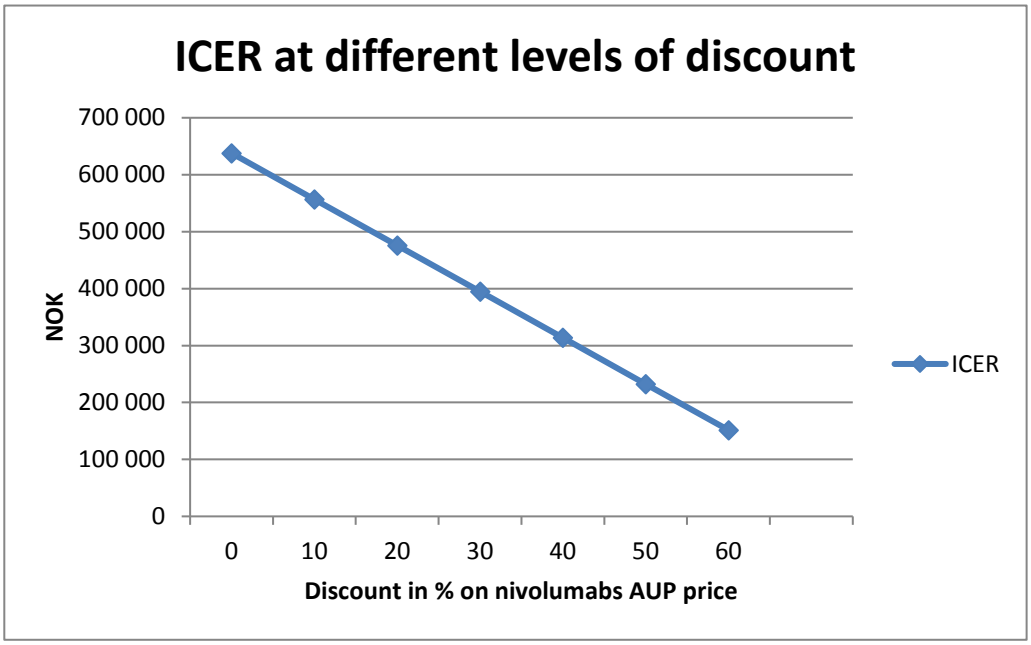


Figure 6 ICER at different levels of discount on nivolumab. Based on AUP prices for nivolumab and all the other drugs in the HE analysis.

4.3 NoMA's conclusion on the cost-effectiveness criterion

NoMA has evaluated whether the costs of using nivolumab is reasonable compared to the magnitude of the benefits of the treatment. The incremental cost per quality adjusted life year (QALY) for nivolumab for treatment of recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck in Norway is [redacted] NOK when compared to investigators choice (IC) and based on the current LIS-AUP price. Based on AUP the cost per QALY is 640 000 NOK.

Based on these analyzes, NoMA concludes that it is most likely that nivolumab is a cost effective treatment of recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck when compared to investigators choice.

5 BUDGET IMPACT ANALYSIS

5.1 APPROXIMATION OF THE NUMBER OF PATIENTS POTENTIALLY SUITABLE FOR THE TREATMENT

BMS has based the budget analysis on the estimated number of patients presented in section 1.1. Based on a yearly incidence of 663 patients with SCCHN in total, it is estimated that 25 patients a year will be patients with metastatic and platinum-refractory SCCHN who are eligible for treatment. Annual patient growth is assumed to be 2 %.

Table 15 BMS' estimated patient population per year

Number of new patients each year	Year 1	Year 2	Year 3	Year 4	Year 5
ITT	25	25	26	26	27

5.2 COST ESTIMATION

The cost in BMS' submitted budget analysis is based on the following input and assumptions:

- Max. AUP prices including VAT.
- Duration of treatment as modelled as PFS in the health economic model.
- Average weight 66.9 kg
- Nivolumab takes a market share of 50% (50 % of the eligible patients presented in Table 15).

Table 16 BMS` estimated patient share (in a scenario where nivolumab in assumed implemented)

Market share ITT	Year 1	Year 2	Year 3	Year 4	Year 5
Cetuximab	25 %	25 %	25 %	25 %	25 %
Docetaxel	5 %	5 %	5 %	5 %	5 %
Paclitaxel	15 %	15 %	15 %	15 %	15 %
Methotrexate	5 %	5 %	5 %	5 %	5 %
Nivolumab	50 %	50 %	50 %	50 %	50 %
Total	100 %	100 %	100 %	100 %	100 %

5.3 BUDGET IMPACT

The expected budget impact of adopting nivolumab (Opdivo) for treatment of the relevant cancer of head and neck, estimated from BMS, is presented in the table below.

Table 17 Results BMS' submitted budget impact analysis (MNOK).

	Year 1	Year 2	Year 3	Year 4	Year 5
Total drug costs if nivolumab is implemented	5,5	5,6	5,7	5,9	6,0
Todays practice (current situation) without nivolumab	1,2	1,2	1,3	1,3	1,3
The budget impact of recommending adoption	4,3	4,4	4,4	4,6	4,7

NoMA's assessment of BMS' budget impact analysis

NoMA has found it necessary to update the budget impact analysis. The analysis is based on the same input data and assumption as BMS' submitted analysis, except the following change:

- The assumed marked share for nivolumab if nivolumab is implemented is increased to 70 % (based on feedback from clinical expert).

The results are presented both based on LIS-AUP and on AUP.

NoMA's updated budget impact analysis based on LIS-AUP is presented in Table 18.

Table 18 NoMA`s updated budget impact analysis (MNOK) based on LIS-AUP

	Year 1	Year 2	Year 3	Year 4	Year 5
Total drug costs if nivolumab is implemented	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Todays practice (current situation) without nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The budget impact of recommending adoption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NoMA`s updated budget impact analysis based on max. AUP is presented in Table 19.

Table 19 NoMA`s updated budget impact analysis (MNOK)based on AUP.

	Year 1	Year 2	Year 3	Year 4	Year 5
Total drug costs if nivolumab is implemented	7.3	7.4	7.6	7.8	7.9
Todays practice (current situation) without nivolumab	1.2	1,2	1,3	1,3	1,3
The budget impact of recommending adoption	6.1	6.2	6.3	6.5	6.6

Conclusion

The budget impact of implementing nivolumab (Opdivo) for the current population with SCCHN is estimated to 6.6 MNOK in year 5 based on max. AUP and [redacted]NMOK based on LIS-AUP. This estimation is simplified and uncertain.

6 DISCUSSION

This single technology assessment concerns the treatment of recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck in Norway. BMS has estimated the yearly incidence as 25 individuals of this patient group in Norway.

Currently, there are no national guidelines available concerning treatment of this patient group, as the Norwegian "Handlingsprogrammet for hode-halskreft" is under evaluation. It is anticipated to be finished later in 2017.

Patients with metastatic and recurrent SCCHN who are no longer amenable to local surgical/radiation therapy experience substantial morbidity and high mortality. Patients whose disease progresses within 6 months of platinum-based therapy, regardless of whether it was given for locally advanced or metastatic disease, have a poor prognosis. For these patients, the 1-year survival rate is 5-33% by various estimates with a median OS of 6 to 9 months. NoMA considers metastatic and recurrent SCCHN to be a severe disease that leads to substantial loss of both quality of life and expected length of life.

In line with the therapeutic indication and the majority of the consulted clinical experts anticipates that nivolumab in the Norwegian clinical practice will be used in line with the approved therapeutic indication. i.e." *… as monotherapy for the treatment of recurrent or metastatic platinum-refractory squamous cell carciNoMAof the head and neck (SCCHN)".* Testing of PD-L1 status is not a standard procedure for patients with SCCHN in Norway.

In Europe, no drugs have previously been approved by EMA for patients progressing on or after platinum based therapy. Nivolumab is therefore the first drug registered for treatment of the current patient group. To document the relative effectiveness of nivolumab, BMS has submitted results from the study CheckMate 141 [7]. This is an open-label randomized phase III trial comparing nivolumab to investigator`s choice (IC) in previously treated patients with SCCHN of the oral cavity, pharynx or larynx who had tumour progression on, or within six months of platinum therapy in the primary, recurrent or metastatic setting. NoMA considers CheckMate 141 to be of sufficient quality and sufficiently representative for the Norwegian clinical setting, and accepts the use of these data to document the relative effectiveness.

The primary end point in CheckMate 141 was overall survival, and the results show significantly higher median OS for nivolumab compared the investigator`s choice (IC) in the ITT population. The median was 7.72 months and 5.06 months for the nivolumab arm and the IC arm respectively. Median PFS was not significantly different between the two arms. Both results are from data cut off 16th September 2016.

The health economic analysis is a cost-utility analysis, which is based on a submitted model. This model is a three-staged, partitioned survival model, based on the efficacy data from CheckMate 141. NoMA has accepted the submitted model, which was found sufficiently transparent and flexible. However, it was considered necessary to make some changes in BMS` main analysis, and due to this NoMA did an updated health economic analysis. In BMS` main analysis the ICER is 800 000 NOK per QALY, but in this analysis the drug prices are based on AUP. However, when the LIS-AUP prices are used in NoMAs' analysis, the ICER is substantially lower, [redacted] NOK, most due to lower LIS-AUP than AUP. When the analysis is based on LIS-AUP, the results are quite robust to changes of the most central input data, as choice of parametric functions and utility values. The analysis are still, however sensitive to changes in drug acquisition cost for nivolumab. In addition, the duration of treatment with nivolumab influences the results.

7 CONCLUSION

Based on the submitted documentation NoMA considers that:

The criterion for disease severity is fulfilled

NoMA considers that recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck is a severe condition that meets the criterion of severe illness, or risk factors that in all probability lead to or exacerbate severe disease.

The criterion for relative efficacy is fulfilled.

NoMA considers that the submitted documentation is sufficient to establish reliable efficacy data for nivolumab which are relevant for the Norwegian clinical setting.

The criterion for cost-effectiveness is fulfilled.

NOMA considers the submitted documentation sufficient to establish a reliable ICER. The established ICER is within a range that is normally considered cost-effective taken the disease severity into account. Based on this appraisal the criterion for cost- effectiveness seems to be met.

NoMA´s overall evaluation, taking into consideration the severity of the illness, clinical relevant efficacy in the Norwegian setting and cost-effectiveness of nivolumab (Opdivo), together with the degree of uncertainty, is that nivolumab (Opdivo) does fulfil the conditions to be recommended to be implemented in the Norwegian specialist healthcare system.

Norwegian Medicines Agency, 16-10-2017

Kristin Svanqvist (e.f.)

Executive officers

Krystyna Hviding

Anja Schiel

Anette Grøvan

Camilla Hjelm

APPENDIX 1: CALCULATION OF SEVERITY

The Norwegian Medicines Agency (NoMA) has used a quantitative method for grading severity calculated from the current treatment (includes a variety of options, as discussed in section 1.4.1).

NoMA's calculations are based on the absolute forecast loss (APT). APT is the actual health loss measured in undiscounted quality-adjusted life-years (QALYs) due to the disease without the new treatment. QALE is the expected remaining life-time measured in undiscounted quality-adjusted life-years (QALYs) for the current average population in question.

To calculate expected quality-adjusted life time, one has used a base from Swedish data indicating quality of life per age category (age in years) and Norwegian mortality tables published by Statistics Norway.

Table 1 Severity calculations

Age	60-64
Expected QALE for average population without disease (undiscounted)	18,8 – 16,1
Expected QALE with the disease without the new treatment (undiscounted) (prognosis)	0,45
Number of QALYs lost due to illness (absolute forecast loss)	15,6 – 18,4

Calculation of severity based on current treatment, indicates an absolute forecast loss of approx.

15,6-18,4 QALY.

APPENDIX 2 COMMENTS FROM THE APPLICANT

Bristol-Myers Squibb

Kommentarer til hurtig metodevurdering av nivolumab (Opdivo) til andrelinjebehandling av residiv eller metastatisk plateepitelkarsinom i hode og hals (ØNH)

Legemiddelverkets totalvurdering er at prioriteringshensynene alvorlighetsgrad, nytte og kostnadseffektivitet er oppfylt for Opdivo for denne indikasjonen. Sensitivitetsanalysene viser at konklusjonen er robust for endringer i flere sentrale forutsetninger.

Som ved tidligere metodevurderinger av Opdivo på andre indikasjoner, valgte Legemiddelverket å se bort fra dokumentasjon knyttet til klinisk relevante endringer i helserelatert livskvalitet. Den helserelaterte livskvaliteten ble dokumentert som en del av den kliniske studien CheckMate 141 og er publisert i Lancet[1]. Resultatene viste klinisk meningsfull forbedring i den helserelaterte livskvaliteten til pasienter som fikk Opdivo og en klinisk relevant reduksjon for pasienter som fikk standardbehandling. Dersom disse dataene hadde blitt tatt til følge ville det påvirket kostnadseffektiviteten i positiv retning.

[1] Harrington KJ, Ferris RL, Blumenschein G, Jr., Colevas AD, Fayette J, Licitra L, et al. Nivolumab versus standard, single-agent therapy of investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck (CheckMate 141): health-related quality-of-life results from a randomised, phase 3 trial. Lancet Oncol. 2017;18(8):1104-15.

REFERENCES

1. Grégoire, V., et al., *Squamous cell carcinoma of the head and neck: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Annals of Oncology, 2010. **21**(suppl_5): p. v184-v186.
2. Lefebvre, J.-L., *Current clinical outcomes demand new treatment options for SCCHN.* Annals of oncology, 2005. **16**(suppl_6): p. vi7-vi12.
3. institute, N.C. *Head and neck cancers* 2016; Available from: www.cancer.gov/types/head-and-neck/head-neck-fact-sheet.
4. *Onclolex*. Available from: http://oncolex.no/Hodehals.
5. Sacco, A.G. and E.E. Cohen, *Current treatment options for recurrent or metastatic head and neck squamous cell carcinoma.* Journal of clinical oncology, 2015. **33**(29): p. 3305-3313.
6. Rapidis, A., et al., *Docetaxel in the treatment of squamous cell carcinoma of the head and neck.* Therapeutics and clinical risk management, 2008. **4**(5): p. 865.
7. Ferris, R.L., et al., *Nivolumab for recurrent squamous-cell carcinoma of the head and neck.* N Engl J Med, 2016. **2016**(375): p. 1856-1867.
8. Harrington, *Nivolumab versus standard, single-agent therapy of investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck (CheckMate 141): health-related quality-of-life results from a randomised, phase 3 trial.* Lancet Oncol. , 2017. **18**(8): p. 1104-1115.
9. *Nivolumab vs investigator`s choice for platinum-refractory recurrent or metastatic (R/M) squamous cell carsinoma o the head and neck (CheckMate 141): Outcomes in first-line R/M Patients and updated safety and efficacy*. Link from QR code collected 29.sept 2017:[Available from: http://www.bmsmedicalpublications.com/posters/NIV-2017-030524.pdf
10. Helsedirektoratet. *Innsatsstyrt finansiering 2016*. Available from: www.helsedirektoratet.no/finansieringsordninger/innsatsstyrt-finansiering-isf-og-drg-systemet/innsatsstyrt-finansiering-isf#regelverk-isf-2016.
11. Aleris. *Aleris Pricelist Oncology 2016*. Available from: www.aleris.no/Vi-tilbyr/sykehus-medisinske-tjenester/Pasient/Pasientinformasjon/Prislister/Prisliste-Kreftsenter.
12. Assosiation, N.P., *Normaltariffen 2016.*