

NEW PHARMACEUTICALS FOR UNRESECTABLE OR METASTATIC MALIGNANT MELANOMA

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■ KEY MESSAGES

- ➔ The Norwegian Knowledge Centre for the Health Services assessed in November 2015 the effectiveness and cost-effectiveness of seven new drugs for the treatment of unresectable or metastatic malignant melanoma in the adult population. Their review included evidence from 17 RCTs.
- ➔ For overall survival (over a 2 year time horizon), nivolumab or pembrolizumab as monotherapies as well as the combinations of nivolumab+ipilimumab, vemurafenib+cobimetinib and dabrafenib+trametinib have the highest probabilities of being superior to the other treatment strategies.
- ➔ For safety, nivolumab and pembrolizumab have the lowest probability of serious adverse events but the quality of the evidence was rated as low.
- ➔ The cost-effectiveness evaluation including all interventions showed that at list prices in Norway, all new treatments had ICERs above € 100 000 per QALY.



■ SUMMARY OF THE PUBLICATION

- Pike E, Torkilseng EB, Sæterdal I, Jimenez E, Odgaard-Jensen J, Harboe I, Klemp M. A health technology assessment of the new drugs for inoperable or metastatic malignant melanoma patients. Report from Kunnskapssenteret no. 22–2015. Oslo: Norwegian Knowledge Centre for the Health Services, 2015..

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Quality of the publication

Two KCE researchers independently appraised the quality of this review using the AMSTAR tool. The score obtained by the review is 9/11.

Context

Malignant melanoma is a rare cancer, representing the most aggressive type of skin cancer. It affects a relatively young population and its incidence is expected to increase in the future.^[1] A patient with a stage IV (metastatic) or unresectable melanoma presents a median overall survival of around 8-18 months.^[2] Recent advances in pharmacological therapies have raised hope to improve survival. However, the rapid evolution with multiple innovative, high-priced options (used as mono or in combination) has also created a challenging context for decision making.

The objective of the review was to assess the relative effectiveness and cost-effectiveness of seven new pharmacological treatments (i.e. cobimetinib, dabrafenib, ipilimumab, nivolumab, pembrolizumab, trametinib and vemurafenib), as monotherapy or in combination, in adult patients with unresectable or metastatic malignant melanoma.

What is KCE has read for you?

KCE has read for you synthesises a recently published high-quality systematic review or health technology assessment with relevance for the Belgian health system. The original publication was appraised and contextualised by KCE researchers.

KCE has read for you is not based on original research conducted by KCE.

More details on methodology can be found on the KCE website

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This document includes:



- **Key findings** of the publication under evaluation
- **A contextualisation** within the Belgian healthcare system



Not included:

- Recommendations
- Detailed descriptions



Trustworthy original publication

The methodological quality of the systematic review was assessed with the AMSTAR tool

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Method

The authors performed in September 2015 a systematic literature review of randomized controlled trials (RCTs).

The possible risk of bias of the included studies was assessed using the Handbook of the Norwegian Knowledge Centre for the Health Services,^[3] while the overall quality of the evidence for each outcome was evaluated using GRADE methods.

When evidence from included trials was available, the authors conducted pairwise meta-analyses of monotherapies or combination therapies. In addition to this, they performed network meta-analyses using dacarbazine as common comparator. The different therapeutic interventions were subsequently ranked according to their likelihood to lead to the best results for each endpoint.

The main outcomes considered for the evaluation of the effectiveness were: overall survival, progression free survival, health-related quality of life (HRQoL), as well as safety.

For the economic evaluation, effectiveness was measured in quality-adjusted life years (QALYs) as well as in life years gained (LYG) over a 10-year time horizon.

Results

Results are based on 17 RCTs in adults with inoperable or metastatic malignant melanoma

Efficacy

Direct evidence (head to head comparisons) on overall survival, progression free survival and serious adverse events was available for only three monotherapies (pembrolizumab versus ipilimumab and nivolumab versus ipilimumab). These comparisons showed an advantage of pembrolizumab and nivolumab for all endpoints (quality of evidence mostly moderate or high). Five direct comparisons of combination therapies versus monotherapies were found, although only one included all endpoints of interest. In all cases, an advantage was attributed to the combination therapies.

Indirect evidence (network meta-analyses using dacarbazine as common comparator) showed that:

1. For overall survival, nivolumab or pembrolizumab in monotherapy, and the combination of nivolumab + ipilimumab; vemurafenib + cobimetinib, and dabrafenib + trametinib had a higher probability of good performance than any other treatment strategy (see Table 1 for results and quality of evidence).
2. For progression free survival, the highest probability of good performance was obtained for dabrafenib + trametinib, and vemurafenib + cobimetinib. The quality of the evidence for most comparisons in the network meta-analysis was moderate or high.
3. For HRQoL, the evidence was insufficient, i.e. a network meta-analysis was not possible.

Predictions from cohort model (Markov) showed a median survival of about 12.5 months for ipilimumab and about 19 months for nivolumab, pembrolizumab and the combination nivolumab + ipilimumab. The median survival was about 11 months for the BRAF/MEK inhibitors dabrafenib, vemurafenib and trametinib as monotherapies, and 17.5 months for the combinations dabrafenib + trametinib as well as vemurafenib + cobimetinib.

In comparison, the median survival of dacarbazine was 9 months. These predictions were based on certain assumptions (see full report for details) and should therefore be interpreted with caution.

Table 1: Hazard ratios (and 95% CI) for overall survival over a 2 year period from pair-wise comparisons and network meta-analysis (from: the Norwegian Knowledge Centre for the Health Services report)

Intervention	HR vs dacarbazine (pairwise comparison)	HR vs dacarbazine (Network MA)	Ranking	Quality of evidence from network MA
Nivolumab	0.42 (0.30; 0.59)	0.45 (0.30; 0.71)	0.85	Moderate
Pembrolizumab	-	0.46 (0.26; 0.99)	0.81	Very low
Nivolumab+Ipilimumab	-	0.48 (0.28; 0.90)	0.78	Low
Vemurafenib+cobimetinib	-	0.50 (0.26; 0.96)	0.73	Moderate
Dabrafenib+trametinib	-	0.55 (0.37; 0.84)	0.68	Low
Ipilimumab+Dacarbazine	0.72 (0.59; 0.88)	0.70 (0.47; 0.99)	0.41	High
Ipilimumab	-	0.69 (0.44; 1.26)	0.40	Very low
Ipilimumab+glycoprotein 100	-	0.72 (0.40; 1.55)	0.36	Very low
Dabrafenib	0.77 (0.52; 1.14)	0.73 (0.49; 1.10)	0.35	Moderate
Trametinib	0.78 (0.57; 1.07)	0.78 (0.49; 1.22)	0.30	Low
Vemurafenib	0.76 (0.63; 0.92)	0.77 (0.54; 1.10)	0.29	Moderate
Dacarbazine	-	1	0.05	-

MA : meta-analysis; HR: hazard ratio





Safety

Despite sixteen trials reporting serious adverse events, clear conclusions regarding differences between the treatment alternatives could not be established due to the quality of the evidence which was low or very low in all cases.

Cost-effectiveness

The evaluation including all interventions showed that, at list prices, all new drugs had incremental cost effectiveness ratios (ICERs) above the 100 000 Euros/QALY, and 95 000 Euros/LYG.

If introduced in clinical practice, their budget impact is likely to be substantial. Significant price reductions may be needed in order to mitigate these effects.

BELGIAN CONTEXT

In 2013, there were 2635 new diagnoses of malignant melanoma made in Belgium, 59% in women and 41% in men, but only 6% of them would belong to the target population for the pharmaceuticals under review (~ 158 patients/year). The overall number of deaths due to malignant melanoma in Belgium in 2012 was 291.^[4]

Five out of the seven treatments included in the review by the Norwegian Knowledge Centre for the Health Services are already reimbursed in Belgium. Trametinib is under revision (INAMI/RIZIV) while no decision has yet been taken for the reimbursement of cobimetinib.

Further research would be of value to confirm the available clinical effectiveness evidence as well as to assess the impact of these therapies in HRQoL or their adverse event profile.

REFERENCES

- 1. Belgian Cancer Registry. *Cancer burden in Belgium 2004-2013*, Belgian. Brussels 2015. 
- 2. Finn L, Markovic S N, Joseph R W. *Therapy for metastatic melanoma: the past, present and future*. BMC Medicine 2012; 10(23):1-10.
- 3. Norwegian Knowledge Centre for the Health Services (Nasjonalt kunnskapssenter for helsetjenesten). *Slik oppsummerer vi forskning. Håndbok for Nasjonalt kunnskapssenter for helsetjenesten 3.2. rev. utg. Oslo: Nasjonalt kunnskapssenter for helsetjenesten; 2013.*
- 4. Belgian Cancer Registry. *Incidence Fact Sheets, Malignant Melanoma. Incidence Year 2013*. 2015. 

a. What is the Norwegian Knowledge Centre for the Health Services?

The Norwegian Knowledge Centre for the Health Services is an independent research centre organised under the Norwegian Directorate of Health. Its mission is to support the development of quality in health services.

b. What is GRADE?

GRADE (Grading of Recommendations Assessment, Development and Evaluation) offers a system for rating quality of evidence in, amongst other, systematic review.

More information on GRADE can be found

- in the GRADE website 
- and in the KCE process book 

