Title	A health technology assessment of the new drugs for inoperable or metastatic malignant melanoma patients
Norwegian title	Fullstendig metodevurdering av de nye legemidlene for pasienter med inoperabel eller metastaserende føflekkreft
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We would like to thank all contributers for their expertise in this project. Norwegian Knowledge Centre for the Health Services assumes final responsibility for the content of this report.

Norwegian Knowledge Centre for the Health Services
Oslo, November 2015

Key messages

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In this health technology assessment we have compared the relative effectiveness and cost-effectiveness of seven new drugs used for the treatment of advanced malignant melanoma patients in the Norwegian setting. The drugs are: cobimetinib, dabrafenib, ipilimumab, nivolumab, pembrolizumab, trametinib and vemurafenib. The clinical endpoints are overall survival, progression free survival, health related quality of life and serious adverse events.

Our results are based upon 17 randomized controlled trials, presented in 40 publications. Our conclusions for the relative effectiveness of the included drugs or combinations of drugs are based upon network meta-analyses using both direct and indirect evidence with dacarbazine as a common comparator. We ranked the different treatments in terms of their likelihood of leading to the best results for each endpoint. The rankings were interpreted cautiously taking into account the quality of the evidence. The cost-utility analysis was based on a probabilistic discrete-time Markov cohort model. Our findings:

- *For overall survival:* Nivolumab, pembrolizumab, nivolumab combined with ipilimumab, vemurafenib combined with cobimetinib, and dabrafenib combined with trametinib seemed to have a higher probability of good performance than the other available treatment strategies.
- *For progression free survial:* Dabrafenibin combination withtrametinib and vemurafenib combined with cobimetinib seemed to have a higher probability of good performance than the other available treatment strategies.
- *For health related quality of life*: Evidence from pairwise comparisons for four interventions reported better health related quality of life in the intervention groups.
- *For serious adverse events:* We could not establish any differences between the treatment strategies. However, pembrolizumab and nivolumab seemed to have a higher probability of fewer serious adverse events than the other treatment strategies.
- *We assessed the quality of the evidence* for overall survival and progression free survival from the network meta-analyses to be moderate or high for the majority of our comparisons. For serious adverse events, we assessed the quality to be low or very low in most of our assessments.
- *The analysis of cost-effectiveness* was conducted using the maximum pharmacy retail prices, due to the fact that any negotiated discounts are hidden from the general public as per contract between the Drug Procurement Cooperation system and the manufacturers.
- *None of the interventions are cost-effective at the maximum pharmacy retail* prices, and the budget impact if the interventions are accepted in clinical practice are substantial. Drug price reductions in the region of 63 to

91 percent would be necessary to improve the cost-effectiveness and minimize the budget impact.

Executive summary

Background

The Commissioners Forum, in the "National system for the introduction of new health technologies within the specialist health service" has requested a health technology assessment to compare effectiveness and cost-effectiveness of the new drugs used for inoperable or metastatic malignant melanoma patients in the Norwegian setting.

The drugs are: cobimetinib, dabrafenib, ipilimumab, nivolumab, pembrolizumab, trametinib and vemurafenib. These can be used as monotherapy or in combination with each other.

The incidence of malignant melanoma in Norway is among the highest in the world with approximately 1,500 persons diagnosed annually.

Objective

To assess the effectiveness and cost-effectiveness of seven new drugs used for inoperable or metastatic malignant melanoma patients relative to each other in the Norwegian setting.

Method

In this health technology assessment, clinical effectiveness was measured in terms of overall survival, progression free survival, health-related quality of life and serious adverse events. In the economic evaluation the primary endpoint was the incremental cost-effectiveness ratio with effectiveness measured in quality-adjusted life-years. Results were also presented in life years gained, in net health benefits, scatterplots, probability of being cost-effective and value of information analysis.

We performed a systematic search for randomized controlled trials in February 2015 in relevant bibliographic databases, Google Scholar and websites of selected health technology assessment agencies. We updated the search in September 2015. We contacted relevant pharmaceutical companies to obtain additional information.

Two reviewers worked independently to identify relevant publications. One review author extracted data from the included references and another review author verified the data.

We performed network meta-analyses where appropriate according to population, intervention, control and outcome. We ranked the different treatments in terms of their likelihood of leading to the best results for each endpoint. This we did by help of the surface under the cumulative ranking curve (SUCRA).

The quality of the direct evidence, indirect evidence, and the combined evidence from the network meta-analyses were evaluated by two review authors using the GRADE working group approach for network meta-analysis.

Our cost-utility analysis were based on a probabilistic discrete-time Markov cohort model with three health states, progression free survival, progressed disease and death. We adjusted the baseline transition probabilities with the hazard ratios from the network meta-analysis. Clinicians in the field provided information relevant for the estimation of costs as well as modelling assumptions.

Due to the fact that any negotiated discounts are hidden from the general public, as per contract between the Drug Procurement Cooperation system and the manufacturers, the analysis of cost-effectiveness was conducted using the official maximum pharmacy retail prices.

Results

Our results are based upon 17 randomized controlled trials, presented in 40 publications. Our conclusions for the relative comparisons of effectiveness for the included drugs or combinations of drugs are based upon network meta-analyses using both direct and indirect evidence with dacarbazine as a common comparator. We ranked the different treatments in terms of their likelihood of leading to the best results for each endpoint. The rankings were interpreted cautiously taking into account the quality of the evidence.

Our findings:

- *For overall survival:* Nivolumab, pembrolizumab, nivolumab combined with ipilimumab, vemurafenib combined with cobimetinib, and dabrafenib combined with trametinib seem to have a higher probability of good performance than the other available treatment strategies. We assessed the quality of the evidence to be moderate for nivolumab and vemurafenib combined with cobimetinib; low for nivolumab combined with ipilimumab, and dabrafenib combined with trametinib, and very low for pembrolizumab.

- *For progression free survival:* Dabrafenib combined with trametinib and vemurafenib combined with cobimetinib seem to have a higher probability of good performance than the other available treatment strategies. We assessed the quality of the evidence to be moderate in both cases.
- *For health related quality of life:* Due to insufficient data we did not perform a network meta-analysis for health related quality of life. Evidence from pairwise for four comparisons reported better health related quality of life in the intervention groups.
- *For serious adverse events*: We could not establish any differences between the available treatment strategies. However, the ranking suggests that pembrolizumab and nivolumab have a higher probability of fewer serious adverse events than the other available treatment strategies.We assessed the quality of the evidence to be low in both cases.
- *We assessed the quality of the evidence* for overall survival and progression free survival from the network meta-analyses to be moderate or high for the majority of our comparisons. For serious adverse events, we assessed the quality to be low or very low in most of our assessments.
- *The economic model predicts a median survival* of about 12.5 months for ipilimumab and about 19 months for nivolumab, pembrolizumab and the combination nivolumab and ipilimumab. The median survival for the BRAF/MEK inhibitors dabrafenib, vemurafenib and trametinib in monotherapy are about 11 months, and for the combinations dabrafenib and trametinib as well as vemurefanib and cobimetinib, 17.5 months. In comparison, the median survival of dacarbazine is 9 months.
- *None of the interventions are cost-effective at the maximum pharmacy retail prices*. The ranking of the interventions and the budget impacts may however change as a result of price changes.
- *The first incremental analysis includes all the interventions from the network meta-analysis*. Nivolumab has an incremental effect of 0.82 quality adjusted life years and an incremental cost-effectiveness ratio against dacarbazine of about NOK 1.1 million per quality adjusted life year gained. The combination vemurafenib and cobimetinib has an incremental effectiveness of 0.07 quality adjusted life years and an incremental cost-effectiveness ratio of about NOK 19.8 million per quality adjusted life year gained against nivolumab. The scatterplot indicates that there is much uncertaintly in the results, particularly for effectiveness.
- *When we restrict the incremental analysis to the BRAF and MEK inhibitors,* dabrafenib has an incremental effect of 0.36 quality adjusted life years and an incremental cost-effectiveness ratio compared to dacarbazine of approximately NOK 2.2 million per quality adjusted life year gained. The combination vemurafenib and cobimetinib has an incremental effect of 0.53 quality adjusted life years and incremental cost-effectiveness ratio compared to dabrafenib of about NOK 2.9 million per quality adjusted life year gained. The BRAF and MEK inhibitor monotherapies (dabrafenib, vemurafenib,

trametinib) all have very similar costs and effectiveness. The same applies to the BRAF/MEK combinations (dabrafenib and trametinib or vemurafenib and cobimetinib), but at a higher level of costs and effectiveness.

- *When the incremental analysis is limited to the immunotherapies*, nivolumab, pembrolizumab and the combination nivolumab and ipilimumab, all have similar levels of effectiveness and costs. In the cost-effectiveness acceptabilility curves, the new immunotherapies in monotherapy have a slight advantage over the combination nivolumab and ipilimumab for increasing willingness to pay values.
- *The expected value of partial perfect information analysis* identified the efficacy data used in the model as the dominating source of uncertainty, followed by the health related quality of life data, costs and serious adverse events.
- *The maximum pharmacy retail prices would have to be reduced by approximately* 79 percent for dabrafenib, 83 percent for the combination dabrafenib and trametinib, 81 percent for vemurafenib, 84 percent for the combination vemurafenib and cobimetinib, 83 percent for trametinib, 75 to 91 percent for ipilimumab, 63 percent for nivolumab and 64 percent for pembrolizumab in order to achieve incremental cost-effectiveness ratios of NOK 500.000 per quality adjusted life year gained against dacarbazine.
- *If the prices for the new interventions are reduced by 63 to 91 percent* (depending on intervention) from the maximum pharmacy retail price, the annual budgetary savings could be about NOK 249 million and the accumulated budgetary savings over a 5 year period NOK 1,248 million.

Discussion

We found only two head to head comparison for the included drugs as monotherapies, and five direct comparisons of combination treatment versus monotherapy. None of the included trials compared a BRAF inhibitor (dabrafenib or vemurafenib) head to head with a drug acting on the immune system. The best available comparisons are the indirect evidences via dacarbazine as a common comparator. All the interventions could be included in the network meta-analyses for overall survival, progression free survival and serious adverse events. Of the endpoints studied, we consider overall survival to be of higher importance than progression free survival, since progression free survival is a surrogate endpoint. Health related quality of life and serious adverse events are of importance for the patients. However, from the available literature we were not able to find data usable for our network meta-analysis for health related quality of life, and the quality of the evidence for serious adverse events were low or very low in most of our assessments.

We only included randomized controlled trials. Our endpoints were all well-defined and harmonized in their definitions across the trials.

Based on a qualitative assessment, the results of the pairwise estimates and network meta-analyses are consistent.

The number of avaliable interventions for patients with advanced malignant melanoma is evolving rapidly at the moment. Many of the interventions in this health technology assessment have just reached marketing authorization in Norway, and the available evidence from randomized controlled trials is quite limited. Hence, the clinical efficacy data in our report have the uncertainty that the majority of the evidence for the included comparisons were based upon a single study. It cannot be ruled out that new evidence from randomized controlled trials have the potential to change the ranking of the interventions both with regards to effectiveness and cost-effectiveness.

We believe that the economic model distinguish the interventions fairly well with regards to costs and overall survival, but not so well with regards to health related quality of life, which is a crucial input for life prolonging interventions. This emphazises the need to make separate judgments and not relying on the cost-effectiveness evidence alone.

We are extrapolating effectiveness data beyond the clinical trial follow-up period for nivolumab, pembrolizumab, the combinations nivolumab and ipilimumab and vemurafenib and cobimetinib. There is uncertainty with regards to the correct treatment duration, both for the new immunotherapies and the BRAF and MEK inhibitors. Also, the results are dependent on that the treatment effects are the same across the three incremental cost-effectiveness analyses.

To our knowledge a relative comparison for the different new drugs used for inoperable or metastatic malignant melanoma patients has not been done by any others, neither for effectiveness nor for cost-effectiveness.

Conclusion

All conclusions are given with respect to the current state of the evidence and with the reservation that new evidence from randomized controlled trials can change the ranking of the interventions both with regards to effectiveness and cost-effectiveness (one of the interventions still do not have marketing authorization).

None of the interventions are cost-effective at the maximum pharmacy retail prices. The budgetary impact of accepting some or all of the new interventions in clinical practice can be substantial, potentially diverting resources away from other interventions or treatment areas with better cost-effectiveness. The budgetary impact and incremental cost-effectiveness ratios can however be reduced through price reduc-

tions. We believe that drug price reductions in the region of 63 to 91 percent, depending on drug, would be necessary for the interventions to represent cost-effective use of resources in the Norwegian setting.

We find it difficult to separate the new immunotherapies nivolumab and pembrolizumab, or the combination nivolumab and ipilimumab with respect to cost-effectiveness. If the new immunotheraphies are accepted in clinical practice, we expect increased effectiveness compared to ipilimumab in monotherapy, but at an increased cost. The potential budgetary savings with price reductions from the maximum pharmacy retail price may be as high as NOK 109 million per year.

Based on the cost-effectiveness results, we cannot argue that any of the BRAF or MEK inhibitor monotherapies (dabrafenib, vemurafenib, trametinib), should be preferred over another, or that any BRAF/MEK combination (dabrafenib and trametinib or vemurafenib and cobimetinib), should be preferred over another. However, the combination therapies are more likely to give the highest quality adjusted life year gains in the long run, at an increased cost. For the BRAF/MEK inhibitors, the potential budgetary savings with price reductions may be as high as NOK 140 million per year.

Hovedfunn (norsk)

Tittel:
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Hvem står bak denne rapporten?

Eksempel text:
Kunnskapssenteret har skrevet rapporten på oppdrag fra Helse Sør-Øst RHF.

Når ble litteratursøket utført?

Søk etter studier ble avsluttet [måned, år].

I denne metodevurderingen har vi sammenlignet den kliniske effekten og kostnadseffektiviteten mellom syv nye legemidler som brukes i behandling av føflekkreft med spredning og/eller føflekkreft som ikke kan opereres. De syv legemidlene er: cobimetinib, dabrafenib, ipilimumab, nivolumab, pembrolizumab, trametinib og vemurafenib. De kliniske endepunktene er total overlevelse, progresjonsfri overlevelse, helserelatert livskvalitet og alvorlige bivirkninger.

Våre resultater er basert på 17 randomiserte kontrollerte studier som er beskrevet i 40 publikasjoner. Våre konklusjoner for klinisk effekt er basert på nettverks metaanalyser der vi har brukt både direkte og indirekte evidens, med dakarbazin som felles komparator. Vi har rangert de ulike legemidlene med hensyn til deres sannsynlighet for å lede til beste resultat for hvert endepunkt. Vi har gjort en forsiktig tolkning av rangeringen der vi har tatt hensyn til tillitten til resultatet. Kostnadseffektivitetsanalysen var basert på en Markov modell.

Våre funn:

- *For totaloverlevesle:* Nivolumab, pembrolizumab, nivolumab kombinert med ipilimumab, vemurafenib kombinert med cobimetinib, og dabrafenib kombinert med trametinib så ut til å virke bedre enn de andre tilgjengelige legemidlene alene eller i kombinasjon.
- *For progresjonsfri overlevelelse:* Dabrafenib kombinert med trametinib og vemurafenib kombinert med cobimetinib så ut til å virke bedre enn de andre legemidlene alene eller i kombinasjon.
- *For helserelatert livskvalitet*: Dokumentasjon fra parvise sammenligninger for fire av våre intervensjoner rapporterte bedre helserelatert livskvalitet i intervensjonsgruppene.
- *For alvorlige bivirkninger:* Vi fant ingen signifikante forskjeller mellom legemidlene alene eller i kombinasjon. Pembrolizumab og nivolumab så imidlertid ut til å ha en større sannsynlighet for færre alvorlige bivirkninger enn de andre legemidlene alene eller i kombinasjon.
- *Vi vurderte kvaliteten på dokumentasjonen* for totaloverlevelse og progresjonsfri overlevelse fra nettverksmetaanalysen til å være moderat eller høy for flertallet av våre sammenligninger. For alvorlige bivirkninger vurderte vi kvaliteten til å være lav eller svært lav i de fleste av våre vurderinger.
- *Analysene ble utført med apotekenes maksimale utsalgspris* siden fremforhandlede prisrabatter er unntatt offentlighet i henhold til avtaler mellom legemiddelinnkjøpssamarbeidet (LIS) og produsentene.
- Gitt apotekenes maksimale utsalgspris er ingen av legemidlene kostnadseffektive og budsjettkonsekvensene ved en eventuell innføring i norsk helsetjeneste er store. Prisene må reduseres i størrelsesorden 63 til 91 prosent for å bedre kostnadseffektiviteten og minimere budsjettvirkningene.

Sammendrag (norsk)

Bakgrunn

Bestillerforum i "Nasjonalt system for innføring av nye metoder i spesialisthelsetjenesten" har bedt om en fullstendig metodevurdering av den kliniske effekten og kostnadseffektiviteten mellom nye legemidler for pasienter med føflekkreft med spredning.

De syv legemidlene er: cobimetinib, dabrafenib, ipilimumab, nivolumab, pembrolizumab, trametinib og vemurafenib. Disse kan brukes alene eller i kombinasjon med hverandre.

Insidensen av føflekkreft i Norge er en av de høyeste i verden med omtrent 1 500 nye tilfeller hvert år.

Problemstilling

Å sammenlikne effektivitet og kostnadseffektivitet av syv nye legemidler til pasienter med inoperabel eller metastatisk malignt melanom.

Metode

I denne metodevurderingen har vi målt klinisk effektivitet som totaloverlevelse, progresjonsfri overlevelse, helserelatert livskvalitet og alvorlige bivirkninger. I den økonomiske evalueringen er det primære endepunktet den inkrementelle kostnadseffektivitetsratioen med effekt målt i kvalitetsjusterte leveår. Resultatene er også presentert i vunne leveår og i sensitivitetsanalyser.

Vi utførte et systematisk litteratursøk etter randomiserte kontrollerte studier i relevante bibliografiske databaser, Google Scholar og hjemmesidene til noen utvalgte metodevurderingsinstitutter i februar 2015. Vi oppdaterte søket i september 2015. Vi kontaktet relevante farmasøytiske firmaer for å innhente ytterligere informasjon.

To forfattere identifiserte relevante publikasjoner uavhengig av hverandre. En forfatter hentet ut data fra de inkluderte publikasjonene og en annen verifiserte dataene.

Vi utførte nettverks meta-analyser der det var mulig med hensyn til populasjon, intervensjon, kontroll og endepunkt. Vi rangerte de ulike legemidlene brukt alene eller i kombinasjon med hensyn til deres sannsynlighet for å lede til beste resultat for hvert endepunkt. Vi gjorde dette ved hjelp av «surface under the cumulative ranking curve (SUCRA)".

To forfattere vurderte kvaliteten på dokumentasjonen for direkte, indirekte og samlet evidens fra nettverks meta-analysene ved metoden som er foreslått av GRADE-arbeidsgruppen (Grading of Recommendations Assessment, Development and Evaluation) for nettverks meta-analyser.

Kostnadseffektivitetsanalysen er basert på en Markov modell med tre helsetilstander, progresjonsfri overlevelse, progrediert sykdom og død. Vi justerte populasjonens bakgrunnsrisiko for død og progresjon med de estimerte hazard ratioer fra nettverks meta-analysen. Fageksperter bidro med råd i tilknytning til estimering av kostnader og modellantakelser.

Analysene er utført med apotekenes maksimale utsalgspris siden fremforhandlede prisrabatter er unntatt offentlighet i henhold til avtaler mellom legemiddelinnkjøpssamarbeidet (LIS) og produsentene.

Resultat

Våre resultater er basert på 17 unike randomiserte kontrollerte studier som er beskrevet i 40 publikasjoner. Våre konklusjoner for den relative effektiviteten av legemidlene vi har sett på er basert på nettverks meta-analyser der vi har brukt både direkte og indirekte evidens med dakarbazin som en felles komparator. Vi har rangert de ulike legemidlene alene eller i kombinasjon med hensyn til deres sannsynlighet for å lede til beste resultat for hvert endepunkt. Vi har gjort en forsiktig tolkning av rangeringen der vi har tatt hensyn til tillitten vi har til resultatet.

- *For totaloverlevelse:* Nivolumab, pembrolizumab, nivolumab kombinert med ipilimumab, vemurafenib kombinert med cobimetinib, og dabrafenib kombinert med trametinib ser ut til å virke bedre enn de andre tilgjengelige legemidlene alene eller i kombinasjon. Vi vurderte kvaliteten på dokumentasjone til å være moderat for nivolumab og vemurafenib kombinert med cobimetinib; lav for nivolumab kombinert med ipilimumab, og for dabrafenib kombinert med trametinib, og svært lav for pembrolizumab.

- *For progresjonsfri overlevelse:* Dabrafenib kombinert med trametinib og vemurafenib kombinert med cobimetinib ser ut til å virke bedre enn de andre legemidlene alene eller i kombinasjon. Vi vurderte kvaliteten på dokumentasjonen til å være moderat i begge tilfellene.
- *For helserelatert livskvalitet*: På grunn av mangelfull dokumentasjon har vi ikke gjort nettverks meta-analyse for helserelatert livskvalitet. Dokumentasjon fra parvise sammenligninger for fire av våre intervensjoner rapporterte bedre helserelatert livskvalitet i intervensjonsgruppene.
- *For alvorlige bivirkninger:* Vi fant ingen signifikante forskjeller mellom legemidlene alene eller i kombinasjon. Pembrolizumab og nivolumab ser imidlertid ut til å ha en større sannsynlighet for færre alvorlige bivirkninger enn de andre legemidlene alene eller i kombinasjon. Vi vurderte kvaliteten på dokumentasjone til å være lav i begge tilfellene.
- *Vi vurderte kvaliteten på dokumentasjonen* for totaloverlevelse og progresjonsfri overlevelse til å være moderat eller høy for flertallet av våre sammenligninger. For alvorlige bivirkninger vurderte vi kvaliteten til å være lav eller svært lav i de fleste av våre vurderinger.
- *I den økonomiske modellen er median overlevelse* for ipilimumab beregnet til 12.5 måneder. For de nye immunterapiene nivolumab, pembrolizumab og kombinasjonen nivolumab og ipilimumab er median overlevelse om lag 19 måneder. Median overlevelse for BRAF- og MEK- hemmerne dabrafenib, vemurafenib og trametinib i monoterapi er beregnet til omtrent 11 måneder og for kombinasjonsbehandlingene dabrafenib og trametinib samt vemurafenib og cobimetinib, omtrent 17.5 måneder. Til sammenlikning er median overlevelse med dakarbazin i monoterapi 9 måneder.
- Ingen av legemidlene er kostnadseffektive med apotekenes maksimale utsalgspris. Rangeringen av legemidlene med hensyn til kostnadseffektivitet og budsjettkonsekvensene av å innføre legemidlene i norsk helsetjeneste vil kunne påvirkes av prisendringer.
- *Når alle intervensjonene fra nettverks meta-analysen er inkludert i samme kostnadseffektivitetsanalyse*, ser vi at at nivolumab har en mereffekt i forhold til dakarbazin på 0.82 kvalitetsjusterte leveår og en kostnadseffektivitetsbrøk på 1.1 millioner kroner per vunnet kvalitetsjusterte leveår. Kombinasjonen vemurafenib og cobimetinib har en mereffekt i forhold til nivolumab på 0.07 kvalitetsjusterte leveår og en kostnadseffektivitetsbrøk på 19.8 millioner kroner per vunnet kvalitetsjusterte leveår. Sensitivitetsanalysene indikerer at det er mye usikkerhet i resultatene, særlig for effekten av legemidlene.
- *Når analysen av kostnadseffektivitet er begrenset til BRAF- og MEK-hemmerne,* har dabrafenib en mereffekt på 0.36 kvalitetsjusterte leveår og en kostnadseffektivitetsbrøk på 2.2 millioner kroner per vunnet kvalitetsjusterte leveår sammenliknet med dakarbazin. Kombinasjonen vemurafenib og cobimetinib har en mereffekt på 0.53 kvalitetsjusterte leveår og en kostnadseffektivitetsbrøk på 2.9 millioner kroner sammenliknet med

dabrafenib. BRAF- og MEK- hemmerne i monoterapi (dabrafenib, vemurafenib og trametinib) ligger på omtrent samme nivå med hensyn til kostnader og effekter. Det samme gjelder BRAF/MEK kombinasjonene (dabrafenib og trametinib eller vemurafenib og cobimetinib), men på et høyere nivå av kostnader og effekter.

- *Når analysen av kostnadseffektivitet er begrenset til immunterapiene, er det* vanskelig å skille nivolumab, pembrolizumab og kombinasjonen nivolumab og ipilimumab fra hverandre med tanke på kostnadseffektivitet. Nivolumab og pembrolizumab har sammenliknbare andeler som kostnadseffektive i kostnadseffektivitets-akseptabilitetskurvene, og kombinasjonen nivolumab og ipilimumab nærmer seg monoterapiene for økende betalingsvillighetsverdier.
- *I sensitivitetsanalysene* er det effektdataene på totaloverlevelse og progresjonsfri overlevelse som er de viktigste kildene til usikkerhet, etterfulgt av helserelatert livskvalitet, kostnader og alvorlige bivirkninger.
- *Prisanalysene viser at apotekenes maksimale utsalgspris må reduseres* med omtrent 79 prosent for dabrafenib, 83 prosent for kombinasjonen dabrafenib og trametinib, 81 prosent for vemurafenib, 84 prosent for kombinasjonen vemurafenib og cobimetinib, 83 prosent for trametinib, 75 til 91 prosent for ipilimumab, 63 prosent for nivolumab og 64 prosent for pembrolizumab, for at disse intervensjonene skal oppnå en kostnadseffektivitetsbrøk mot dakarbazin på 500,000 kroner per vunnet kvalitetsjusterte leveår.
- Dersom prisene på de ulike legemidlene reduseres med de nevnte reduksjonene på mellom 63 og 91 prosent fra apotekenes maksimale utsalgspris, kan de årlige budsjettbesparelsene beløpe seg til 250 millioner kroner samlet for immunterapiene og BRAF/MEK hemmerne. Den akkumulerte budsjettbesparelsen over en 5-års periode kan beløpe seg til omtrent 1.25 milliarder kroner.

Diskusjon

Vi fant kun to direkte sammenligninger for de inkluderte legemidlene når disse var gitt som monoterapier. Det var fem direkte sammenligninger av en kombinasjonsbehandling versus monoterapi. Ingen av de inkluderte studiene sammenlignet en BRAF-hemmer (dabrafenib eller vemurafenib) direkte med noen av legemidlene som virker på immunsystemet. De beste tilgjengelige sammenligninger er indirekte sammenligninger med dakarbazin som en felles komparator. Alle intervensjone kunne inkluderes i nettverks meta-analysene for totaloverlevelse, progresjonsfri overlevelse og for alvorlige bivirkninger. Av de undersøkte utfall, anser vi totaloverlevelse å ha større betydning enn progresjonsfri overlevelse, siden progresjonsfri overlevelse er et surrogate endepunkt. Helserelatert livskvalitet og alvorlige bivirkninger er viktige for pasientene. Fra den tilgjengelige litteraturen kunne vi imidlertid ikke finne data for helserelatert livskvalitet som vi

kunne nyttiggjøre oss i vår nettverks meta-analyse. Kvaliteten på dokumentasjonen for alvorlige bivirkninger var lav eller svært lav for de fleste sammenligningene.

Vi inkluderte kun randomiserte kontrollerte studier. Våre utfallsmål var godt definerte og harmoniserte i deres definisjoner i de inkluderte studiene.

Basert på en kvalitative vurdering fant vi at resultatene av de parvise estimatene og nettverksmeta-analysene er konsistente.

Flere av legemidlene i denne analysen har nylig fått markedsføringstillatelse. Av den grunn er mye av evidensen basert på enkeltstudier. Det kan ikke utelukkes at ny evidens fra randomiserte kontrollerte studier endrer rangeringen av tiltakene både med tanke på klinisk effekt og kostnadseffektivitet.

Ikke alle aspekter av legemidlene fanges like godt opp i kostnadseffektivitetsanalysen på grunn av begrensninger i tilgjengelige data. Den økonomiske modellen skal skille de ulike legemidlene ganske godt med hensyn til kostnader og totaloverlevelse, men fanger ikke like godt opp ulikheter i helserelatert livskvalitet, som er en viktig parameter for livsforlengende intervensjoner. Dette understreker behovet for å supplere beslutningsgrunnlaget også med annen evidens.

I tillegg bør det nevnes at vi ekstrapolerer effektdata ut over oppfølgingstiden i studiene for nivolumab, pembrolizumab og kombinasjonene nivolumab og ipilimumab, samt vemurafenib og cobimetinib. Det er i tillegg en del usikkerhet knyttet til riktig behandlingslengde, både for de nye immunterapiene og BRAF- og MEK- hemmerne. Våre resultater er avhengige av at behandlingseffektene ikke er forskjellige for ulike subpopulasjoner av vår målgruppe i de tre analysene av kostnadseffektivitet.

Så vidt vi vet har en relativ sammenlikning av alle de ulike nye legemidlene til pasienter med inoperabel eller metastatisk malignt melanom, ikke blitt gjort av noen andre, verken for effektivitet eller for kostnadseffektivitet.

Konklusjon

Alle konklusjoner er gitt med utgangspunkt i det vi hadde av informasjon om effekt og kostnader ved publisering og med forbehold om at ny dokumentasjon fra randomsierte kontrollerte studier, kan endre rangeringen av legemidlene både med hensyn til effektivitet og kostnadseffektivitet (et av legemidlene i analysen har ikke markedsføringstillatelse i Norge).

Gitt apotekenes maksimale utsalgspris, er ingen av legemidlene kostnadseffektive, og budsjettkonsekvensene ved en eventuell innføring i norsk helsetjeneste er betydelige. Det er risiko for at ressurser vris bort fra andre tiltak eller behandlingsområder

i spesialisthelsetjenesten med bedre kostnadseffektivitet. Vi mener at prisreduksjoner i størrelsesorden 63 til 91 prosent er nødvendige for at de nye legemidlene skal representere en mer kostnadseffektiv bruk av ressurser i norsk helsetjeneste, samt for å minimere budsjettvirkningene.

Vi kan ikke konludere på hvilken av de nye immunterapiene nivolumab og pembrolizumab eller kombinasjonen nivolumab og ipilimumab som er mest kostnadseffektiv. Hvis noen av disse nye immunterapiene tas i bruk i klinisk praksis kan man forvente økt effekt sammenliknet med ipilimumab i monoterapi, men til en økt kostnad. De potensielle budsjettmessige besparelsene ved prisreduksjoner for de nye imunterapiene beløper seg til omtrent 109 millioner kroner per år, hvis man legger til grunn et kostnadseffektivitetsnivå på 500,000 kroner per vunnet leveår.

Vi kan heller ikke skille mellom BRAF- og MEK- hemmerne i monoterapi (dabrafenib, vemurafenib og trametinib) eller mellom BRAF/MEK kombinasjonene dabrafenib og trametinib og vemurafenib og cobimetinib med tanke på kostnadseffektivitet. Kombinasjonsterapiene vil sannsynligvis gi de største helsegevinstene, men da til en betydelig økt kostnad. For BRAF- og MEK- hemmerne kan de potensielle budsjettbesparelsene ved prisreduksjoner være så høye som 140 millioner kroner per år.

Nasjonalt kunnskapssenter for helsetjenesten fremskaffer og formidler kunnskap om effekt av metoder, virkemidler og tiltak og om kvalitet innen alle deler av helsetjenesten. Målet er å bidra til gode beslutninger slik at brukerne får best mulig helsetjenester. Kunnskapssenteret er formelt et forvaltningsorgan under Helsedirektoratet, men har ikke myndighetsfunksjoner og kan ikke instrueres i faglige spørsmål.

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Glossary and abbreviations	
BRAF	Serin-threonine protein kinase B-RAF
CEAC	Cost-effectiveness acceptability curve. A type of probabilistic sensitivity analysis.
CI	**Confidence interval.** A measure of uncertainty around the results of a statistical analysis that describes the range of values within which we can be reasonably sure that the true mean effect lies. Wider intervals indicate lower precision; narrow intervals, greater precision.
CrI	Credible intervals
CUA	**Cost-utility analysis.** An economic evaluation where health consequences are measured in **QALY**s.
EORTC QLQ-C30	**The European Organization for Research and Treatment of Cancer core quality of life questionnaire**, the EORTC QLQ-C30, is a cancer-specific quality of life instrument applicable to a broad range of cancer patients.
EQ-5D	**European Quality of Life-5 Dimensions.** EQ-5D is a standardized instrument for use as a measure of health outcome.
EVPPI	Expected value of partial perfect information. A type of sensitivity analysis.
FACT-M	The Functional Assessment of Cancer-Therapy-Melanoma. Measuring quality of life in patients with melanoma.
GDT	Guideline development tool
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HR	**Hazard ratio.** Ratio of hazard rates. Ratios above 1 indicate increased instantaneous rate of an event. Ratios below 1 indicate a decrease in event rates.
HRQoL	Health related quality of life
HTA	Health Technology Assessment
ICER	**Incremental cost-effectiveness ratio**. The ratio of the difference in costs between two alternative health technologies to the difference in effectiveness between these two technologies. $ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$

ICTRP	International Clinical Trial Registry Platform
ITT	Intention to treat
LYG	Life-years gained
MD	Mean difference
MTM	Multiple Treatments Meta-analysis
NCT number	ClinicalTrials.gov registry number
NMA	Network meta-analysis
NHB	**Net Health Benefit.** In a decision-making process, a positive NHB suggests that the intervention represents good value for money $NHB = \Delta E - \frac{\Delta C}{\lambda}$
NMB	**Net Monetary Benefit.** In a decision-making process, a positive NMB suggests that the intervention represents good value for money. $NMB = \lambda \cdot \Delta E - \Delta C$
OS	Overall survival
PFS	Progression free survival
PSA	**Probabilistic sensitivity analysis.** An analysis of the uncertainty related to all parameters in a decision analytic model. Typically performed by Monte Carlo simulation, hence by drawing values from probability distributions for all parameters simultaneously
QALY	**Quality-adjusted life-year.** A measure of health outcomes that combines quantity and quality of life by assigning to each year of life a weight from 1 (perfect health) to 0 (state judged equivalent to death) dependent on the individual's health related quality of life during that year
RCT	**Randomised controlled trial.** An experiment in which investigators use randomisation to allocate participants into the groups that are being compared. Usually allocation is made at the level of individuals, but sometimes it is done at group level e.g. by schools or clinics. This design allows assessment of the relative effects of interventions.
RECIST	Response Evaluation Criteria in Solid Tumors
RHA Forum	The Regional Health Authorities Forum
RR	**Relative risk / risk ratio.** The relative risk is the absolute risk (AR) in the intervention group divided by the AR in the control group. It is to be distinguished from odds ratio (OR), which is the ratio of events over non-events in the intervention group over the ratio of events over non-events in the control group.

SAEs	Serious adverse events
SF-6D	**Short form -6D.** The SF-6D is a classification for describing health derived from a selection of SF-36 items. It is composed of six multi-level dimensions.
SMD	Standardised mean difference
SR	**Systematic review.** A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.
Statistically significant	Means that the findings of a study are unlikely to have arisen because of chance. Significance at the commonly cited 5% level ($P < 0.05$) means that the observed difference or greater difference would occur by chance in only 1/20 similar cases. Where the word "significant" or "significance" is used without qualification in the text, it is being used in this statistical sense.
SUCRA	Surface under the cumulative ranking curve
WHO	World health organization
WTP (λ)	**Willingness to pay**. A pre-specified limit of what society is willing to pay for a given health unit (e.g. QALY or life year). In Norway it is common to use NOK 500 000 per QALY or life year in economic evaluations.

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Preface

The Commissioners Forum, in the "National system for the introduction of new health technologies within the specialist health service" has requested a health technology assessment to compare effectiveness and cost-effectiveness of the new drugs used for inoperable or metastatic malignant melanoma.

Eva Pike was lead reviewer for the clinical evaluation and Einar Bjørner Torkilseng lead the health economic evaluation. We will thank the external experts Jarle Karlsen, MD Senior consultant oncology, Department of oncology St Olavs Hospital, Assistant professor NTNU/University Hospital of Trondheim, and Oddbjørn Straume, MD PhD Oncology Consultant, Haukeland University Hospital, Bergen. The experts were identified through their membership of their specialist association in the Norwegian Medical Association. Marta Sølvi Nyakas, MD, specialist in oncology, Oslo University Hospital, and Torbjørn Wisløf, Associate Professor, University of Oslo, performed peer review of the report. We thank them for valuable contribution.

The project group consisted of the following persons affiliated with the Norwegian Knowledge Centre for the Health Services:

- Eva Pike, Researcher,
- Einar Bjørner Torkilseng, Researcher,
- Ingvil Sæterdal, Researcher,
- Enrique, Jimenez, Researcher,
- Jan Odgaard-Jensen, M.Sc.,
- Ingrid Harboe, Research librarian,
- Marianne Klemp, Head of Health Economics and Drugs Unit,

The aim of this report is to support well-informed decisions in health care that lead to improved quality of services. The evidence should be considered together with other relevant issues, such as clinical experience and patient preference.

Gro Jamtvedt	Marianne Klemp	Eva Pike	Einar Bjørner Torkilseng
Department director	*Head of Unit*	*Lead reviewer Clinical evaluation*	*Lead health economist*

Objective

To assess the effectiveness and cost-effectiveness of the new drugs used for inoperable or metastatic malignant melanoma patients relative to each other.

Background

Malignant melanoma

Malignant melanoma is the most serious form of skin cancer (1). These cancerous growths develop when unrepaired DNA damage to skin cells (most often caused by ultraviolet radiation from sunshine or tanning beds) triggers mutations (genetic defects) that lead the skin cells to multiply rapidly and form malignant tumors. These tumors originate in the pigment-producing melanocytes in the basal layer of the epidermis (2). Malignant melanoma or melanoma are terms that are used interchangeably (1). Malignant melanoma is divided into four stages, where stage I is the least severe and stage IV the most severe. Stage III includes locally advanced (inoperable, regional disease), and stage IV includes distant metastasis (3, 4). The incidence of malignant melanoma in Norway is among the highest in the world (5) with 1,719 new cases in 2013 (6). Malignant melanoma is the cancer type that increases most in Norway (1). For persons aged between 15 and 49 years, this is the second most frequent cancer type for both sexes together (7). A family history of malignant melanoma may be present in 5-10% of the melanoma cases (3).

Treatment and prognosis

Surgery is the primary treatment for malignant melanoma and currently also the only potentially curative treatment (5). Early diagnosis and appropriate surgical treatment cures 80-90% of patients, while 10-20% experience a relapse as local/regional recurrence or distant spreading (5).

Patients with metastatic malignant melanoma have poor prognosis (7). The 5-year relative survival rate for distant melanoma (stage IV) for the period 2009-2013 was 12.3% for men and 24.5% for women (6). For selected patients with one single metastasis, surgery can be useful as the initial treatment (7). In cases with successful removal of all known metastases, the 5-year survival rate can improve to nearly 40% (7). When it is not possible to remove all metastatic tissue, the treatment will be palliative, and a 5-years survival of 7% has been shown (7). Radiation may provide good palliation and local control of inoperable metastases (7).

Drug treatment for patients with inoperable and/or metastatic malignant melanoma

Chemotherapy, as dacarbazine, has been the standard drug treatment for most patients (5). However, such chemotherapy has low response rates and has not been demonstrated to be life-extending (5). Recently, new drugs, that are not cytostatic, have been under development for the treatment of malignant melanoma. As a result of the clinical experiences with these new drugs, the drug treatment of metastatic malignant melanoma has changed in the last 2-3 years (5, 7).

The Norwegian guidelines for malignant melanoma (7) gives preliminary recommendations for drug treatment for stage IV and inoperable stage III patients. The guidelines recommends a revision when new evidence on clinical effectiveness and cost-effectiveness is available. This health technology assessment can serve as input for such a revision.

In this health technology assessment we have assessed seven new drugs relative to each other. We included the three new drugs that already had marketing authorization in Norway at the time when this health technology assessment was requested, ipilimumab, dabrafenib and vemurafenib. All three are indicated for treatment of advanced/metastatic melanoma. Dabrafenib and vemurafenib are only indicated for a specific population of melanoma patients carrying BRAF V600 mutations (8). Further, we include the following drugs that did not have marketing authorization in Norway at the time of the request: cobimetinib, nivolumab, and pembrolizumab (after request from RHA forum) and trametinib (on Norwegian Medicines Agency's list of requested rapid assessments). However, at the time of finalizing this report, all the drugs, except cobimetinib, had marketing authorization in Norway.

The new drugs have different mechanism of action: 1) affect the immune system (ipilimumab, nivolumab and pembrolizumab) (9); 2) inhibitors of mutated BRAF (serin-threonine protein kinase B-RAF) (dabrafenib and vemurafenib) (10, 11) or; 3) MEK inhibitors (inhibit the mitogen-activated protein kinase pathway) (cobimetinib and trametinib) (12, 13).

The drugs acting on the immune system do so by blocking mechanisms that limit activating of T cells. Activated T cells can be limited by 4 (CTLA-4) (cytotoxic T-lymphocyte-associated protein), a co-inhibitory molecule of the immune system; and by programmed cell death 1 (PD-1) with its ligands PD-L1 and PDL2, which is expressed in peripheral tissues and cancers (9). Ipilimumab acts by blocking 4 (CTLA-4), whereas nivolumab and pembrolizumab block the interaction of the PD-1 receptor with its two ligands PD-L1 and PD-L2 (9, 14).

Forty to fifty percent of the patients with metastatic malignant melanoma have activated mutations in serin-threonine protein kinase B-RAF (BRAF) (7). This knowledge has led to the development of the drugs, dabrafenib and vemurafenib,

that are BRAF inhibitors. The use of a MEK inhibitor (cobimetinib or trametinib) together with a BRAF inhibitor may reduce the resistance seen to single agent BRAF inbibitors (15). The MEK inhibitors, are however, also used as single therapies.

The Norwegian Medicines Agency (NMA), Canadian Agency for Drugs and Technologies in Health (CADTH), and National Institute for Health and Clinical Excellence (NICE), have performed single technology assessments on drugs used for metastatic melanoma, such as dabrafenib (16, 17), ipilimumab (18-21), trametinib (22) and vemurafenib (23, 24). However, none of these assessments compared the different new drugs for inoperable or metastatic malignant melanoma patients relatively to each other. We have therefore conducted this health technology assessment for the new drugs for these patients in a Norwegian setting.

Introduction to systematic reviews of clinical effectiveness

Systematic reviews of clinical effectiveness are products of a comprehensive process, including: literature search, study selection, risk of bias evaluations, data extraction, combining findings and quality of evidence evaluations.

Based on predefined research questions, an information specialist develops a search strategy to identify relevant publications in electronic databases for medical research. In addition, the literature search may include reviews of reference lists, contacting field experts and searching for unpublished studies. The aim is to identify all relevant literature and include trials based on predefined inclusion criteria, specifying relevant populations, interventions, comparisons, outcomes and study design. To reduce bias, two reviewers assess abstracts and potentially relevant full text publications independently for inclusion. The two reviewers also check that data from included studies are extracted correctly.

Further it is usual for systematic review to evaluate the included trials for risk of bias or quality. This information may be used in addition to similarity in participants, interventions, comparisons and endpoints, in the decision as to whether effect estimates from several trials can be combined statistically in a meta-analysis. The risk of bias or quality should be used along the effect estimates when a conclusion is made in a systematic review.

Introduction to Economic Evaluations of Health Care Programmes

The basic task of any economic evaluation is to identify, measure, value and compare costs and consequences of the alternatives being considered in an incremental analysis which means that the difference in cost is compared with the differences in consequences (25). Hence, results of economic evaluations can be expressed as an

incremental cost-effectiveness ratio (ICER), which is defined by the following equation:

$$ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$$

Because the health care sector, as the society in general, is restricted by scarce resources and budget constraints, economic evaluations are tools for decision makers facing questions of how to prioritize and maximize benefits from scarce resources. For an economic evaluation to be meaningful in a decision making process, the ICER must be judged with regards to a ceiling ratio that reflects the decision maker's maximum willingness to pay (WTP) for a health gain. The decision rule for an economic evaluation can therefore be expressed as:

$$\frac{\Delta C}{\Delta E} < \lambda$$

where λ equals WTP, and means that if the ICER of an intervention is below the ceiling ratio, introducing the intervention represents good value for money. Because the ICER have poor statistical properties, ICERs are often rearranged to express either net monetary benefit (NMB) or net health benefit (NHB), which yields the following decision rules related to NMB or NHB.

$$NMB: \lambda \cdot \Delta E - \Delta C > 0$$

$$NHB: \Delta E - \frac{\Delta C}{\lambda} > 0$$

An intervention can in other words be considered cost-effective if it yields a positive NHB or NMB.

Economic evaluations are often based on decision models (such as decision trees, Markov models etc) that calculate results based on various input parameters in the model. There are always uncertainties related to the values of these parameters, making sensitivity analyses an important feature of any economic evaluation that uses decision models as its framework. In short, sensitivity analysis illustrates how much the results vary when model parameters are being changed. Sensitivity analyses can be performed in many ways, with one-way or two-way sensitivity analysis being common approaches. This represents changing, respectively one or two model-parameters at a time while all the other model-parameters are held constant, to see how much impact the variation in these parameters has on the results. One-way sensitivity analyses are often presented as tornado-diagrams, which identify and illustrate the model-parameters that have the highest impact on the results.

Another important kind of sensitivity analysis is referred to as probabilistic sensitivity analysis (PSA). The advantage of PSA is that it makes it possible to take the uncertainties of all the model-parameters into account at the same time. The basic approach in PSA is to assign appropriate probability distributions to the model-param-

eters, which makes it possible to replace the "fixed" values of the parameters by values generated by random draws from the distributions. Doing this repeatedly, with a definite number of iterations, makes it possible to estimate probabilities of alternatives being cost-effective subject to different ceiling values of WTP. The calculation is based on the alternative that renders the highest values of NMB or NHB. PSA is often presented as scatterplots, which show point estimates of the ICER for all iterations in the cost-effectiveness plane, and also by cost-effectiveness acceptability curves (CEACs), that show the probability of the alternatives being cost-effective subject to changing values of WTP.

Another result from PSA is expected value of perfect information (EVPI). This is a number which says what value it would be for the society to have more accurate information about the decision, given a WTP. If EVPI for a given population seems large, it might be of interest to find out which parameters it would be most useful to get new and improved data on. Expected value of perfect information for parameters is a more time-consuming operation which can give information on which single parameters or groups of parameters it is most cost-effective to conduct new research on.

In short, making a model probabilistic, means that it is possible to estimate the uncertainty in the decision of implementing alternative interventions, and also provides a possibility of estimating the value of collecting additional information from new research.

Priority setting criteria

According to Norwegian policy documents ("prioriteringsforskriften") (26), a treatment should be prioritised if the following criteria are met:

1. *The disease is severe;* A disease is considered severe to the degree that it causes pain and discomfort, loss of physical, psychological and social function and if it limits the individual in his or her daily activities. Severity is also evaluated according to the risk increase the disease entails in terms of death, disability and discomfort, if treatment is postponed.

2. *The treatment is effective;* the patient should be expected to benefit from treatment, for instance in terms of survival or improved quality of life of certain duration. The treatment effectiveness should also be well documented.

3. *The treatment is cost-effective;* the added costs of the treatment should be reasonable compared to the added benefits.

There is no academic or political consensus regarding what constitutes a reasonable relationship between costs and effectiveness in Norway. For this reason, we use a

range of potential willingness-to-pay (WTP) values throughout our report, but with NOK 500,000 per quality adjusted life year gained as input in some of the price scenarios and budget impact analysis. For a decision maker which has to prioritise between interventions within a fixed budget, even NOK 500,000 per quality adjusted life year gained may be too high if the average cost per quality adjusted life year in the Norwegian health sector is lower. Generally, the risk of displacing interventions with a lower cost per quality adjusted life year, and a net health loss due to implementation of new interventions, increase when the incremental cost-effectiveness ratios are very high.

Clinical evaluation – Methods

We have performed a Health Technology Assessment consisting of a systematic review of effectiveness and a health economic evaluation. We have performed the health technology assessment in accordance with the handbook from the Norwegian Knowledge Centre (27).

Literature search

In cooperation with a research librarian, the project group developed search strategies that combined selected index terms and free text terms. We provide the complete search strategy in Appendix 1.

A methodology search filter was used to limit retrieval to randomized controlled trials. The search filter consisted of a combination of randomized controlled trial.pt. (publication type), randomized controlled trial (MeSH), and relevant text words.
We excluded trials of animals or animal experiments. We limited the search to trials published in year 2000 to 2015 since the interventional drugs have entered the market recently and we do not expect to find relevant trials published before 2000. No language restrictions were applied during the literature search, but we only included trials written in English or in any of the Scandinavian languages.

We performed a systematic search for literature 12-16th of February 2015 in the following databases:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) version 1946 to Present
- Embase version 1974 to present
- Cochrane Central Register of Controlled Trials (Central)
- Web of Science
- PubMed (epub ahead of print)

We also searched Google Scholar.
This searches were updated 25th of September 2015. The websites of selected health technology assessment agencies were searched 9th of September 2015. We contacted the pharmaceutical companies that have marketing authorization or represent the

interventional drugs to obtain additional information as published articles, abstracts/posters that fulfil our inclusion criteria.
We also checked for randomized controlled trials in the relevant systematic reviews, reviews or meta-analyses which we identified.

We looked for ongoing trials in ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP) 18th August 2015 .

Inclusion criteria

Population: Patients with inoperable or metastatic malignant melanoma aged 18 or older.

Interventions: Cobimetinib
Dabrafenib
Ipilimumab
Nivolumab
Pembrolizumab
Trametinib
Vemurafenib

The above interventions given as monotherapy (including add-on) or in combination with each other

Control: Any drug treatment or placebo

Endpoints: Overall survival (or time to death)
Progression free survival (PFS, Time To Progression etc.)
Health related quality of life (measured with EQ-5D, SF-6D or disease specific instrument such as FACT-M, EORTC QLQ-C30)
Serious adverse events

Study design: Randomized controlled trials

Languages: No language restrictions were applied during the literature search, but we only included trials written in English or any of the Scandinavian languages

Selection of articles

The review authors worked independently and in pairs and reviewed all citations generated by the search to identify potentially relevant publications based on title

and/or abstract. We retrieved full text articles of all potentially relevant references and worked independently and in pairs to assess whether these references should be included according to the inclusion criteria. We resolved disagreements by discussion.

Assessment of methodological quality

We assessed the included trials for possible risk of bias according to our Handbook (27). Two of the review authors performed and agreed upon the assessments working independently. We resolved disagreements by discussions or, if required, by consulting one of the other review authors.

Data extraction

One review author extracted data from the included references and another review author verified the data.

We extracted the following data: Information about the study (authors, year of publication, setting, study design, clinical trial identification number and funding); participant characteristics (gender, age, disease stage, known mutations, previous drug treatment); intervention and control characteristics (which drugs, doses, length of use); endpoints (which endpoints were examined, methods used to analyse outcome data, length of follow up and loss to follow up).

Statistical analyses and presentation of results

Measures of treatment effect

We expressed the comparative effectiveness of the treatments as the relative risk (RR) of dichotomous endpoints, hazard ratio (HR) for time-to-event endpoints and mean difference (MD) for continuous endpoints. If a continuous outcome had been measured/reported using different instruments/scales in the included randomized controlled trials we calculated the standardised mean difference (SMD). For all endpoints 95% confidence intervals (CI, results from pairwise meta-analyses) or credible intervals (CrI, results from network meta-analyses) were calculated for the RR, HR, MD or SMD. The credibility interval is the Bayesian analogue to the confidence intervals used in traditional frequentist statistical approaches. We considered a result "significant" if the CrI did not include RR/HR = 1 or MD/SMD=0.

Meta-analyses

If appropriate according to population, intervention, control and outcome, we performed meta-analyses. First, we conducted pairwise meta-analyses for each available endpoint for all possible combinations of interventions and controls with available

evidence from included trials. Random effect models were assumed. Estimates of RR, HR, MD, or SMD with corresponding 95% CI were provided. These analyses were performed using the software RevMan 5.3.

Second, we performed a network meta-analysis (NMA) for each endpoint individually. We did this by combining direct and indirect effects of the interventions of interest for each endpoint. The analysis was based on Multiple Treatments Meta-analysis (MTM) as described by Salanti (28). We used the arm-based network meta-analysis method (a Bayesian method based on Markov Chain Monte Carlo simulation). All NMAs were performed using Winbugs version 1.4.3 (Imperial College and MRC, UK). The statistical analysis was based on binomial likelihoods (dichotomous endpoints) and normal likelihood (continuous endpoints), with vague priors for the trial baselines, basic parameters (normal distribution with mean 0 and standard deviation 0.0001) and the random effects standard deviation (uniformly distributed in the interval 0 to 2), and takes the correlation structure induced by multi-arm trials into account. For time-to-event endpoints (overall survival and progression free survival), with HR as the measure of effect, we used the method described by Woods et al (29) to combine hazard ratios, cumulative number of events, and median survival statistics. We used a random effects model. We checked for incoherence between direct and indirect evidence by "node-splitting" (30). We calculated the direct and indirect estimates of effect and the corresponding Bayesian "P-values" for incoherence.

We also ranked the different treatments in terms of their likelihood of leading to the best results for each endpoint. We based the rankings on the surface under the cumulative ranking curve (SUCRA) (31). We interpreted the rankings cautiously taking into account the quality of the evidence.

The estimated treatment effect based on the direct evidence from the NMA (presented in the summary of findings tables (SoF tables) in Appendix 8 may differ somewhat from the results from the pairwise comparisons obtained from RevMan in Appendix 6. The differences are due to the use of different methods (RevMan and NMA), but both are based upon the same pairwise dataset from the included trials.

Where data were available, we intended to carry out subgroup analyses for different categories of the population (for example patients that are BRAF V600 mutation positive; previously untreated/treated patients) and; different uses of the drug (for example as mono-or combination therapy). However, we decided not to carry out these analyses due to scarcity in data.

The dose-comparison trials of Hamid 2011 (32) and Robert 2014 (33) showed that the effect of ipilimumab and pembrolizumab did not seem to depend upon the doses given. As a consequence we have combined different doses of ipilimumab and pembrolizumab into one group. We have treated different doses of the other interventions in a similar way, this was however, only relevant for trametinib.

Dealing with missing data

For the endpoint progression free survival, we assumed that participants who dropped out experienced disease progression if a hazard ratio between intervention and control was not reported. For all other endpoints, we did not perform imputations for missing data. We based the statistical analyses on the intention-to-treat principle (all participants analysed in the group to which they were allocated, and all available data included in the analyses).

Grading the quality of evidence

Two review authors assessed the overall quality of evidence for each endpoint using GRADE (Grading of Recommendations Assessment, Development, and Evaluation). We followed the guidelines provided by the GRADE working group (34) and categorized our confidence in quality of the effect estimates into four levels: high, moderate, low and very low.

The quality of the direct evidence, indirect evidence, and the combined evidence from the NMAs was evaluated using the GRADE approach for network meta-analyses (35).
We used the Guideline Development Tool (GDT) (36), while evaluating the quality of the direct evidence.

Clinical evaluation - Results

Result of literature search

The literature searches were performed in February 2015, and updated in September 2015. The complete search strategies are shown in Appendix 1. We searched only for randomized controlled trials, and identified 621 titles in February and additionaly 83 in the update search in September 2015. From these 704 titles we found 93 titles to be potentially relevant and we reviewed the full text publications. However, for 56 of these references no full text was available, and we reviewed the available abstracts. From these we included 17 full text publications and seven abstracts. Further, we found two full texts by manual search in PubMed after inputs from the abstracts from the latest meetings for the American Society of Clinical Oncology (ASCO) and the European Cancer Congress (ECC). From the manufactures we received 75 titles (26 full text publications and 49 abstracts/posters). From these we included five full publications, five abstracts and four posters.

Finally, 40 publications (24 full text publications and 16 abstracts/posters) met the pre-specified inclusion criteria.Those publications represent 17 unique clinical trials. The excluded publications, from our own search, and from the ones received from the manufactures, including reasons for the exclusions, are given in Appendix 2.

Our searches in websites of sister health technology assessment agencies in August 2015 did not identify further trials, for details see Appendix 3.

Possible relevant ongoing trials are listed in Appendix 4.

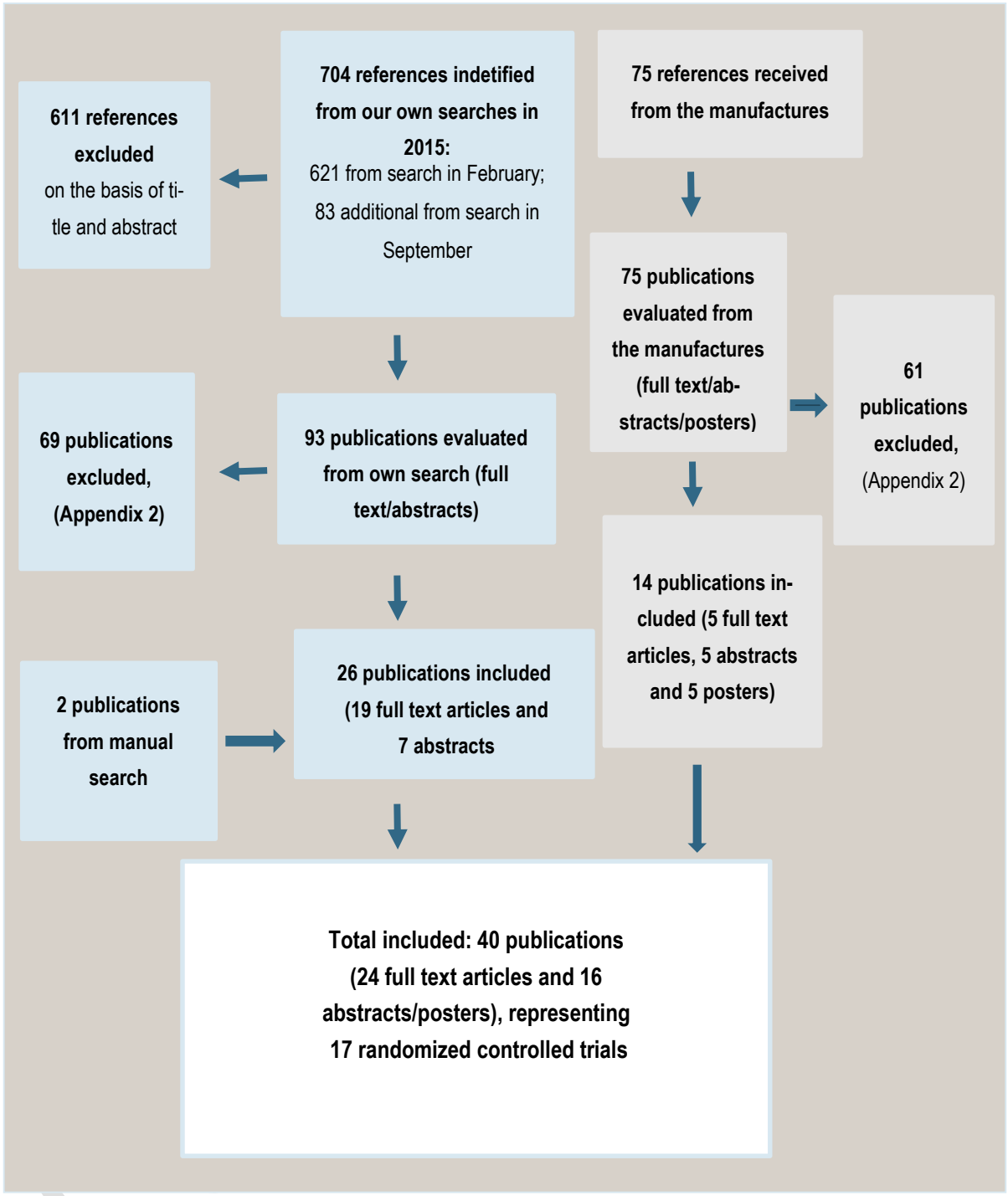

Figure 1 Flowchart of identification of documentation

Description of included trials

Seventeen randomized controlled trials with specific NCT numbers (ClinicalTrials.gov registry number) were included (9-15, 37-46). These trials were published from 2010 to 2015 in a total of 40 publications (9-15, 37-68). Of these, 24 were published as final full text publications and 16 were published as abstracts or posters. The abstracts and posters were either updates of the mother trials with respect to

the endpoints overall survival, progression free survival or serious adverse events; or the presentations of health related quality of life data. Most of the publications were of new date, with 24 of the 40 publications published from 2014 and later, the newest full text publication was published in October 2015 (47), and the newest abstracts/posters were from ASCO 2015 (American Society of Clinical Oncology 2015). An overview of the included publications are shown in the Tables 1 to 5.

Population

The included trials included patients ≥18 years, with inoperable or metastatic malignant melanoma. Twelve of the trials reported that the diagnosis was histologically confirmed (9, 12, 13, 15, 38-41, 43-46). Fifteeen (9-15, 37-40, 43-46) of the 17 trials specified that the included patients should have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Normal organ function was specified as an inclusion criteria in seven of the trials (10-12, 37, 38, 45, 46) and a life expectancy of 3 or 4 months in four of the trials (10, 37, 40, 41).

The median age ranged from 49 to 67, and the proportion of males ranged from 49% to 74.3%. In two of the included trials the range in age was from 17-86 (10) and from 15-89 (38), even though both trials had ≥18 as their inclusion critera. The majority of the trials (ten of 17) were done on patients previously pharmacologically untreated. Four of the trials included both previously treated and untreated patients (9, 13, 45, 46) and three of the trials included only patients that were previously pharmacologically treated (37, 38, 69). The previous treatment regimen in Hodi et al reported to contain one or more of the following: dacarbazine, temozolomide, fotemustine, carboplatin, or interleukin -2. In Weber et al the patients with BRAF wild type tumours must have had progression after anti-CTLA-4 treatment, such as ipilimumab, and patients with BRAF V600 mutation positive tumour mutation must have had progression on anti-CTLA-4 treatment and a BRAF inhibitor. Ribas et al (38) included patients previously treated with ipilimumab, and if BRAF V600 mutant-positive, previously treated with a BRAF or MEK inhibitor or both.
Patients with identified BRAF V600 mutation, either specifically identified as BRAF V600E (10, 11) or BRAF V600E or V600K (12, 13, 15, 45, 46) were included in the seven trials with BRAF and/or MEK inhibitors as the intervention. Patients that were included in the trials where the intervention acts on the immune system, had not identified any BRAF mutation, except in four trials (38, 39, 43, 44) that identified both patients with and without BRAF mutation.

Interventions

All the seven interventions defined in our inclusion criteria are represented in the included randomized controlled trials, i.e. cobimetinib, dabrafenib, ipilimumab, nivolumab, pembrolizumab, trametinib and vemurafenib. Cobimetinib was however only studied in combination with vemurafenib (12). Since the seven included interventions were used both as monotherapy (9-11, 14, 38, 39, 46, 69), monotherapy as add-on (37, 39-42), and in combination with each other (12, 13, 15, 39, 44, 45), we

had 11 different treatment strategies available. More details can be seen in Tables 1-5.

Comparator

Dacarbazine was used as the comparator in seven of the trials (10, 11, 14, 38, 40, 46, 69), including three trials were the control groups were the investigator choice of chemotherapy: dacarbazine or paclitaxel (46), dacarbazine or paclitaxelin combination withcarboplatin (69), or dacarbazine as one of five investigator-choice chemotherapies (38, 69) to be equivalent to dacarbazine.
The other comparators used in the included trials were ipilimumab for six of the trials (9, 37, 39, 41, 42, 44), nivolimumab in one trial (39), dabrafenib in two trials (15, 45), and vemurafenib in two trials (12, 13).

Since all the interventions, except cobimetinib, were compared to dacarbazine, directly or indirectly, this was used as our common comparator in our NMA. The three arms using investigator choice of chemotherapy (38, 43, 46) were considered to be equivalent to dacarbazine. Consequently, these three arms were included as dacarbazine arms in the statistical analyses.

Endpoints

Of the 17 included trials, eight reported on all our predefined endpoints: overall survival, progression free survival, health related quality of life and serious adverse events (11, 12, 14, 37, 40, 44, 47, 52); three trials did not report on overall survival (38, 42, 43), two did not report on progression free survival (41, 42), seven did not report health related quality of life (9, 10, 39, 41, 42, 45, 69), and one did not report any serious adverse events (46).

The endpoints were well defined and harmonized in their definitions across the included trials. A few trials lack to define some of the endpoints, or differ slightly in their definitions, but the trials that defined their endpoints, did it in the same way: Overall survival was defined as the time from randomization to death from any cause. Progression free survival was defined as the time from randomization to the earliest date of disease progression or death due to any cause. Disease progression was defined by RECIST (Respons Evaluation Criteria in Solid Tumors), version 1.1 (70) in 12 (9, 10, 12-15, 38, 39, 41, 43, 44, 46) of the trials. Health related quality of life was measured by EORTC-QLQ-C30 in ten trials (38, 47, 48, 51, 53, 57, 64, 66, 68, 71) , by EuroQoL EQ-5D in three trials (47, 53, 71), of which one (71) lacked results, and by FACT-M in one trial (47). Serious adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. (72) for the majority of the trials (9-15, 38, 39, 43, 44, 46).

In most of the trials progression free survival was assessed by the investigator (14 of 15 trials), in eight of these trials this assessments were also confirmed by an independent review committee (9, 11-13, 38, 45, 46, 69). Four of these trials reported

data from both assessments. In one progression free survival was only assessed by an independent review committee) (40).

Overall survival was measured with a follow up time from 5 months (11) to 5 years (50). When one study reported from more than one follow up time points, we choose to extract from the first report measuring 2 years survival (if available) as well as from the latest available data. In our network meta-analyses we use the 2 years data.

Design

All the trials were randomized controlled trials, mostly of phase III, three trials were phase II (38, 41, 45), and one was phase I (42). Most of the trials (10 of 17) were open-labelled, the other seven trials were double-blinded (12, 14, 15, 37, 39, 40, 44). All were multicentre trials, the majority were performed in North America and Europe. A total of 7482 patients were included in the 17 trials, with a range from 59 to 945 patients in the respectively trials. The follow-up of overall survival was from 5 months (11) to five years (50).

Seven of the trials allowed patients in the control group to cross over to the intervention group after progression (38, 41, 44, 55, 61, 62, 68). McArthur 2014, (an update of Chapman 2011) reported results for overall survival and progression free survival both as censored at the time of cross over, and without censoring at the time of cross over. In our analyses we only included the data without censoring at the time of cross over, since this method was used in the other trials.

Risk of bias for the endpoints in the included trials

We assessed the risk of bias for the endpoints in the included randomized controlled trials to be from low to high risk, mostly of low risk of bias. Eight of the trials (9, 12, 14, 15, 39, 40, 42, 69) had low risk of bias for all the reported endpoints. Progression free survival had low risk of bias in all the trials. We assessed the risk of bias to be high for overall survival, health related quality of life, and serious adverse events in the trials that allowed cross over from the controlled group to the intervention group after progression, here we graded down for the domain “Other risk of bias”, for health related quality of life we also graded down to high risk of bias in the open-labeled trials. The risk of bias assessments are shown Appendix 5.

Statistical analysis in the included trials

For all the included trials the efficacy analyses were performed on the intention-to-treat population, whereas the safety population included all patients who had received at least one dose of study drug. One study, however, did not use the intention-to-treat population (41).

A tabulated overview of the included randomized controlled trials

In tables 1-5 below, we present an overview of the included randomized controlled trials for the different types of interventions. The randomized controlled trials where

the intervention acts on the immune system, either by blocking 4 (CTLA-4), or by blocking the interaction of the PD-1 receptor with its two ligands PD-L1 and PD-L2, respectively are seen in Table 1 and Table 2.
An overview of the randomized controlled trials for the included BRAF inhibitors is given in Table 3. Table 4 shows the included randomized controlled trials for the BRAF inhibitors in combination with the MEK inhibitors, and Table 5 gives an overview of the included randomized controlled trials where the MEK inhibitors were used as monotherapies. In the tables we have used different colours, in order to make it easier to identify reports from the same trial, i.e. have the same ClinicalTrials.gov registry number (NCT number). More details on the included trials are shown in Appendix 5.

Table 1 Overview of the included randomized controlled trials where the intervention acts on the immune system via blocking of 4 (CTLA-4)

Study/full text or abstract	Intervention (number of patients)	Comparator (number of patients)	Population characteristics: Previously pharma-cologically treated or untreated/ BRAF status identified or not	Endpoints	Follow-up in months for overall survival (Survial rates)	Cross-over design or not
Hodi 2010, NCT 00094653, full text (37)	Ipilimumab + gp100 (n=403)	Ipilimumab alone, versus gp100 alone (n=137)	Previously treated/BRAF status not identified	OS, PFS, SAEs	12, 18, 24	No cross over
Revicki 2012, NCT 00094653, full text (48)	As above	As above	As above	HRQoL		As above
Robert 2011, NCT00324155, full text (40)	Ipilimumab + Dacarbazine (n=250)	Dacarbazine (n=252)	Previously untreated/ BRAF status not identified	OS, PFS, SAEs	12, 24 and 36	No cross over
Maio 2012, 4 yrs update, ab-stract (49)	As above	As above	As above	OS 4 years	48	As above
Maio 2015, five years survival, full text (50)	As above	As above	As above	OS 5 years	12, 24, 36, 48 and 60	As above
Kotapati 2011, abstract (51)	As above	As above	As above	HRQoL		As above
Hersh 2011 NCT00050102, full text (41)	Ipilimumab + Dacarbazine (n=36)	Ipilimumab (n=40)	Previously untreated/ BRAF status not identified	OS, SAEs	12, 24, 36	Cross over
Weber 2013, full text (42)	Ipilimumab+ either dacarba-zine or car-boplatin/paclitaxel (n=19)	Ipilimumab (n=20)	Previously untreated/BRAF sta-tus not identified	SAEs		No cross over

Table 2 Overview of the included randomized controlled trials where the intervention acts on the immune system via blocking of the interactionof the PD-1 receptor with its two ligands PD-L1 and PD-L2

Study/ full text or abstract	Intervention (number of patients)	Comparator (number of patients)	Population characteristis: Previous treated or untreated/ BRAF mutation identified or not	Endpoints	Follow-up in months for overall survival (Survival rates)	Cross over design or not
Robert 2015/ CheckMate 066, NCT01721772, full text (14)	Nivolumab (n=210)	Dacarbazine (n=208)	Previously untreated/ *without* BRAF mutation	OS, PFS, SAEs	12	No cross over
Long 2015, abstract (71)	As above	As above	As above	HRQoL		As above
Weber 2015/CheckMate 037, NCT 01721746, full text (69)	Nivolumab (n=272)	Chemotherapy (dacarbazine or paclitaxel+ carboplatin) (n=133)	Previous treated/ Patients both with wild type and BRAF V600 mutation, analyzed together	PFS, SAEs		No cross over
Postow 2015/CheckMate 069, NCT01927419, full text (44)	Nivolumab+ ipilimumab (n=95)	Ipilimumab (n=47)	Previously untreated / Patients with BRAF V600, and subgroup of wild type, analyzed seperately	OS, PFS, SAEs	11	Cross over
Abernethy, 2015, abstract (53)	As above	As above	As above	HRQoL		As above
Larkin, 2015/CheckMate 067, NCT01844505 full text (39)	Nivolumab + Ipilimumab (n=314)	Ipilimumab monotherapy (n=315)/ Nivolumab monotherapy (n=316)	Previously untreated/ with identified BRAF status	OS, PFS, SAEs	12	No cross over
Robert 2015/KEYNOTE-006, NCT01866319, full text (9)	Pembrolizumab (n=556)	Ipilimumab (n=278)	Not more than 1 previous systemic therapy/ BRAF V600 and wild	OS, PFS, SAEs	12	No cross over
Ribas 2015/KEYNOTE-002, NCT01704287(38)	Pembrolizumab (n=361)	Investigator-choice chemotherapy (paclitaxel + carboplatin, paclitaxel, carboplatin, dacarbazine, or oral temozolomide (n=179)	Previous treated/BRAF status identified	PFS, HRQoL, SAEs		Cross over

Table 3 Overview of the included randomized controlled trials were the intervention is a BRAF inhibitor

Study/ full text or abstract	Intervention (number of patients)	Comparator (number of patients)	Population characteristis: Previous treated or untreated/ BRAF mutation identified or not	Endpoints	Follow-up in months for overall survival (Survival rates)	Cross over design or not
Hauschild 2012, BREAK-3, NCT01227889, full text (11)	Dabrafenib (n=187)	Dacarbazine (n=63)	Previously untreated/ BRAF V600E mutation	OS, PFS, SAEs	5	Cross over to dabrafenib after progression
Hauschild 2013, update, abstract (54)	As above	As above	As above	OS, PFS, SAEs	12	As above.
Hauschild 2014, update, poster (55)	As above	As above	As above	OS and SAEs	24	As above.
Grob 2014, update, poster (56)	As above	As above	As above	3-yrs survival	12, 24 and 36	As above.
Grob 2014, full text (57)	As above	As above	As above	HRQoL		As above.
Chapman 2011, BRIM-3, NCT01006980, full text (10)	Vemurafenib (n=337)	Dacarbazine (n=338)	Previously untreated/ BRAF V600E mutation	OS as interim, PFS final, SAEs	6	No cross over at the analyze date December 2010. Amendment for cross over Jan 2011, hence the follow-ups are with cross-over.
McArthur 2011, update, abstract (58)	As above	As above	As above	OS	6	Cross over from dacarbazine to vemurafenib after progression.
Hauschild 2011, update, abstract (59)	As above	As above	As above	OS	6	As above
Chapman 2012, update, abstract (60)	As above	As above	As above	OS	12	As above

McArthur 2014 , update, full text (61)	As above	As above	As above	OS	6, 12, 18	Cross over. Analyze both with and without censoring at crossover

Table 4 Overview of the included randomized controlled trials were the intervention is a BRAF inhibitor in combination with a MEK inhibitor

Study/ full text or abstract	Intervention (number of patients)	Comparator (number of patients)	Population characteristis: Previous treated or untreated/ BRAF mutation identified or not	Endpoints	Follow-up in months for overall survival (Survival rates)	Cross over design or not
Flaherty 2012, NCT01072175, full text (45)	Dabrafenib + trametinib (n=108)	Dabrafenib (n=54)	Both previously untreated/treated /BRAF V600 mutations	Median OS not reached, PFS	No data for OS after 12 months	Cross over from dabrafenib to combination group after progression
Flatherty 2014, update, abstract (62)	As above	As above	As above	Updated OS, 2 years	12 and 18	Cross Over
Daud ASCO 2015, update, poster (63)	As above	As above	As above	Updated OS, 3 years	36	As above
Long 2014/ NCT01584648, full text (15)	Dabrafenib + trametinib (n=211)	Dabrafenib (n=212)	Previously untreated/ BRAF V600E or K mutation	OS, PFS, SAEs	6 months OS not reached	No cross over
Long 2015, update, full text (52)	As above	As above	As above	OS, PFS, SAEs	12 and 24	As above
Schadendorf 2015/abstract (64)	As above	As above	As above	HRQoL		As above
Larkin 2014/ CoBRIM NCT01689519, full text (12)	Vemurafenib + cobimetinib (n=247)	Vemurafenib (n=248)	Previously untreated/ BRAF V600 mutation	OS interim at 9 months, PFS , SAEs	9	Cross over not permitted
Larkin, Asco 2015, update, abstract (65)	As above	As above	As above	Updated PFS, 14 months		As above
Dreno 2015, update, abstract (66)	As above	As above	As above	HRQoL		As above
Robert 2015/Combi-V NCT01597908, full text (13)	Dabrafenib + trametinib (n=352)	Vemurafenib (n=352)	Previously untreated and not/BRAF V600E or K mutation	OS at preplanned interim, PFS SAEs	12	Open for cross over, but none crossed

Grob 2014/Combi-V, full text(47)	As above	As above	AS above	HRQoL		As above

Table 5 Overview of the included randomized controlled trials were the intervention is a *MEK inhibitor as monotherapy*

Study/ full text or abstract	Intervention (number of patients)	Comparator (number of patients)	Population characteristics: Previously treated or untreated/ BRAF status identified or not	Endpoints	Follow-up in months for overall survival (Survival rates)	Cross over design or not
Flaherty 2012, METRIC NCT01245062, full text (46)	Trametinib (n=214)	Dacarbazine or paclitaxel (n=108)	Both previously treated and not/ BRAF V600E or K mutation	OS, PFS, SAEs	6	Crossover from chemo-therapy to trametinib after progression
Schadendorf 2013, update, poster (67)	As above	As above	As above	OS	12 and 24	As above
Schadendorf 2014, full text (68)	As above	As above	As above	HRQoL		As above

OS: Overall survival; PFS: Progression free survival; HRQoL: Health related quality of life; SAEs: Serious adverse events

Presentation of results based on endpoints

Overall survival

Pairwise comparisons

Fourteen of the 17 included trials reported overall survival, either from the mother study or in an updated publication (9, 12-14, 37, 39-41, 44, 52, 55, 61, 62, 67). Among these 14 trials, there was only two head to head comparison of two mono-therapies: pembrolizumab versus ipilimumab (9); and nivolumab versus ipilimumab (39). In both cases a difference in overall survival in favour of the intervention group (pembrolizumab and nivolumab respectively) could be established. Further, six of the trials directly compared a combination-therapy versus a monotherapy; these were nivolumab in combination with ipilimumab versus ipilimimab (39, 44), nivolumab in combination with ipilimumab versus nivolumab (39), dabrafenib in combination with trametinib versus dabrafenib alone (52, 62); vemurafenib in combination with cobimetinib versus vemurafenib (12); and dabrafenib in combination with trametinib versus vemurafenib (13). For three of these comparisons (39, 44) (52, 62) (13) a difference in favour of the combination group could be established.

For the comparisons nivolumab in combination with ipilimumab versus ipilimumab (39, 44), and dabrafenib in combination with trametinib versus dabrafenib (52, 62), the results are based on meta-analyses, for the remaining comparisons only results from one single trial was available.

For the combination dabrafenib in combination with trametinib versus vemurafenib (Combi-v study) (73) the evidence used in our report are the overall survival rates at 12 months. At the time of finalizing this report we have been made aware of 2 year estimates of overall survival from this trial (73). These data confirmed an overall survival in favour of the combination group.

Dacarbazine was used as comparator in five of the trials (14, 40, 55, 61, 67), including one study (67) where dacarbazine or paclitaxel were used as the comparator . For three of these five trials (14, 40, 61) a difference in overall survival could be established in favour of the intervention (ipilimumabin combination withdacarbazine, nivolumab, and vemurafenib respectively).

More details for all the pairwise comparisons are shown in Appendix 5 and 6, the latter showing all hazard ratios based upon RevMan analyses.

Network meta-analyses

The evidence network for overall survival (OS) is shown in Figure 2.

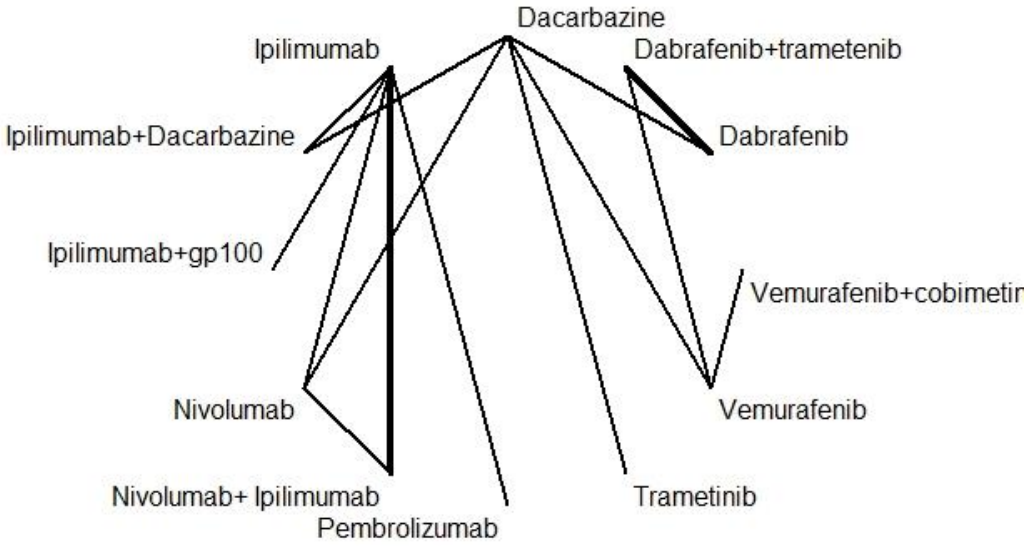

Figure 2 Evidence network for overall survival

A summary of results comparing pairwise meta-analyses performed in RevMan and random effects network meta-analysis for the comparisons between the interventions and the common comparator dacarbazine are presented in Table 6. In addition, a ranking of the included treatments is presented using the surface under the cumulative ranking curve (SUCRA). The results of the pairwise estimates from RevMan and NMA are consistent. That is, the results from network meta-analysis and pairwise comparisons are similar in magnitude and direction.

Table 6 Hazard ratios for overall survival from pairwise comparisons and network meta-analysis

Intervention	Hazard ratio relative to dacarbazine (pairwise comparison)	Hazard ratio relative to dacarbazine (Network meta-analysis)	SUCRA	Quality of Evidence from the network meta-analysis
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+gp100	-	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	-

The full network-meta-analysis results comparing all available treatment strategies are presented in Appendix 7.

Based on the results of the NMA, we find that nivolumab, pembrolizumab, nivolumab combined with ipilimumab, vemurafenib combined with cobimetinib, and dabrafenib combined with trametinib has better overall survival than dacarbazine. The ranking as measured by the SUCRA suggests that nivolumab, pembrolizumab, nivolumab combined with ipilimumab, vemurafenib combined with cobimetinib, and dabrafenib combined with trametinib have a higher probability of good performance than the other available treatment strategies.

Hazard ratios and quality ratings for direct and indirect comparisons for overall survival from the network-meta-analysis are shown in Table 7. Here we present results from all the comparisons with available direct evidence. A formal test, using "node-splitting", for consistency between direct and indirect evidence reveals no significant difference between the direct and indirect evidence (p-values>0.3) in the network meta-analyses.

Table 7 Estimates of overall survival and quality ratings for direct and indirect comparisons from network meta-analysis

Comparison (study)	Direct evidence		Indirect evidence		Network meta-analysis	
	Hazard ratio (95% CI)	Quality of Evidence	Hazard ratio (95% CI)	Quality of Evidence	Hazard ratio (95% CI)	Quality of Evidence
Ipilimumab + dacarbazine versus dacarbazine (40)	0.72 (0.59-0.88)	High	0.48 (0.12-1.83)	Very low	0.70 (0.47-0.99)	High
Dabrafenib versus dacarbazine (55)	0.77 (0.52-1.14)	Low	0.68 (0.03-6.09)	Moderate	0.73 (0.49-1.10)	Moderate
Vemurafenib versus dacarbazine (61)	0.76 (0.63-0.92)	Moderate	0.84 (0.03-17.26)	Low	0.77 (0.54-1.10)	Moderate
Trametinib versus dacarbazine or paclitaxel (67)	0.78 (0.49-1.22)	Low	-	-	0.78 (0.49-1.22)	Low
Nivolumab versus dacarbazine (14)	0.42 (0.30-0.59)	Moderate	5.74 (0-17860)	Very low	0.45 (0.30-0.71)	Moderate
Ipilimumab +gp100 versus ipilimumab (37)	1.04 (0.69-1.60)	Moderate	-		1.04 (0.69-1.60)	Moderate
Ipilimumab + dacarbazine versus ipilimumab (41)	0.91 (0.00-880.1)	Very low	1.22 (0.35-3.25)	Moderate	1.01 (0.53-1.62)	Moderate
Pembrolizumab versus ipilimumab (9)	0.66 (0.45-1.00)	High	-		0.66 (0.45-1.00)	High
Nivolumab + ipilimumab versus ipilimumab (39, 44)*	0.75 (0.60-0.92)	Low	0.69 (0.24-2.61)	Low	0.69 (0.47-0.97)	Low
Dabrafenib + trametinib versus dabrafenib (52, 62)**	0.79 (0.61-0.92)	Moderate	0.40 (0.00-4983)	Low	0.74 (0.56-1.02)	Moderate
Vemurafenib + cobimetinib versus vemurafenib (12)	0.65 (0.37-1.13)	Moderate	-		0.65 (0.37-1.13)	Moderate
Dabrafenib + trametinib versus vemurafenib (13)	0.69 (0.53-0.90)	Moderate	0.74 (0.01-597.5)	Low	0.71 (0.49-1.04)	Moderate
Nivolumab + ipilimumab versus nivolimumab (39)	1.01 (0.78-1.30)	Low	1.49 (0.19-19)	Low	1.05 (0.72-1.65)	Low
Nivolumab versus ipilimumab (39)	0.74 (0.59-0.94)	Moderate	0.46 (0.06-3.16)	Very low	0.65 (0.42-0.91)	Moderate

*Meta-analysis of two trials (39, 44)
**Meta-analysis of two trials (52, 62)

More details about the estimates of overall survival and quality rating (GRADE) for direct and indirect evidences are shown in the Summary of Finding Tables in Appendix 8.

Sensitivity and subgroup analyses
Due to paucity in data we have not performed any sensitivity or subgroup analyses. However, we here present some descriptive results:

- *Trials that reported overall survival also beyond 2 years:*

Additionally to the overall survival data from the first published report measuring 2 years survival (or less) as shown in Table 7, four trials (15, 40, 55, 62) measured overall survival beyond 2 years follow-up. For these trials we have extracted the latest available overall survival data, which were up to 3 years for two comparisons: dabrafenib versus dacarbazine (56) and dabrafenibin combination with trametinib versus dabrafenib (52, 63) and up to five years for the comparison ipilimumab in combination with dacarbazine versus dacarbazine (50). The results for overall survival measured based on follow-up to 3 and 5 years did not differ substantially from the first report measuring up to two years, for more details see Appendix 9.

- *Drugs that act specifically on the BRAF mutations versus drugs that act on the immune system*

None of the included trials compared a BRAF inhibitor (dabrafenib or vemurafenib) head to head with a drug acting on the immune system. The best available comparisons are the indirect via dacarbazine as a common comparator. From Table 6 above we see the ranking of those drugs as measured by SUCRA.

- *Trials including previously treated, previously untreated or both patient groups*

Eight (10-12, 14, 15, 40, 41, 44) of the 13 trials reporting overall survival included previously pharmacologically untreated patients with metastatic or unresectable melanoma. Only one of the 13 trials that reported overall survival included patients previously treated (37), and four trials included patients that were both previously treated or untreated (9, 13, 45, 46). In our network meta-analyses we have not taken into account whether the patients were previously treated or not.

Progression free survival

Pairwise comparisons
Fifthteen of the 17 included trials reported progression free survival, either from the mother study or in an updated publication (9, 13, 14, 37-40, 44-46, 52, 54, 61, 65,

69). Among these 15 trials, there were only two head to head comparison of two monotherapies (9, 39), and for both these comparisons a difference in progression free survival in favour of the intervention (pembrolizumab and nivolumab respectively) could be established when compared to ipilimumab.

Further, six of the trials compared directly a combination therapy versus a monotherapy; these were ipilimumab in combination with nivolumab versus ipilimumab (39, 44), dabrafenib in combination with trametinib versus dabrafenib (45, 52), dabrafenib in combination with trametinib versus vemurafenib (13), and vemurafenib in combination with cobimetinib versus vemurafenib (65). For all these comparisons a difference in progression free survival in favour of the combination group could be established.
For two of the comparisons, ipilimumab in combination with nivolumab versus ipilimumab (39, 44), dabrafenib in combination with trametinib versus dabrafenib (45, 52), the results are based on meta-analyses, for the remaining comparisons only results from one single trial was available.

Dacarbazine was used as comparator in seven of the trials (14, 38, 40, 46, 54, 61, 69) including three trials where dacarbazine were used as one of two possible options in the control group either as dacarbazine or paclitaxel (46), or as dacarbazine or paclitaxel in combination with carboplatin (69); or as one of five possible options in the control group (38). In five of the seven trials (38, 40, 46, 54, 61) a difference in progression free survival in favour of the intervention could be established. A meta-analysis of two of the trials (14, 69) did not identify differences in progression free survival between nivolumab and control.

More details for all the pairwise comparisons are shown in Appendix 5. Trial description, dataextraction and Risk of Bias tables), and Appendix 6 showing all hazard ratios based upon RevMan analyses.

Network meta-analyses
The evidence network for progression free survival (PFS) is shown in Figure 3.

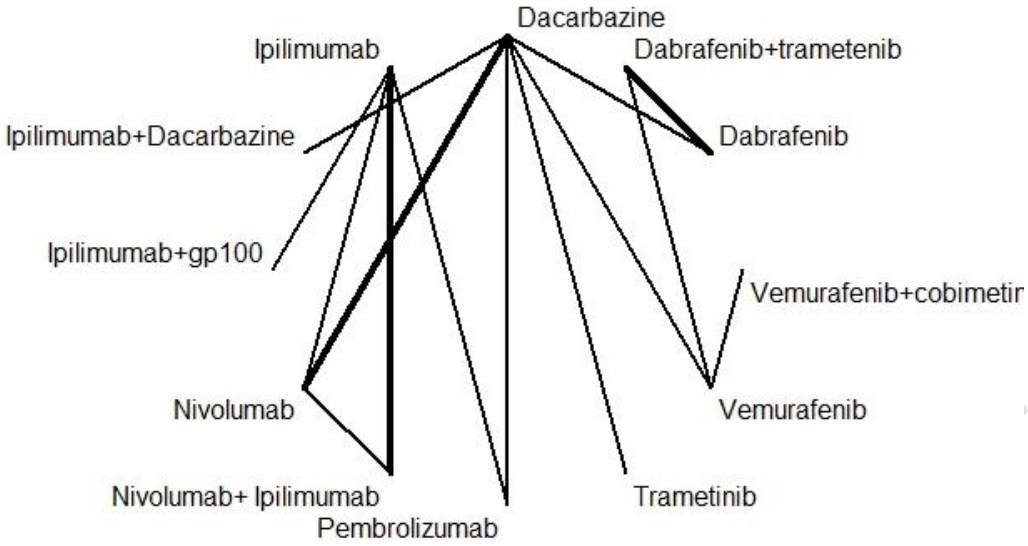

Figure 3 Evidence network for progression free survival

A summary of results comparing pairwise meta-analyses and random effects network meta-analysis for the comparisons between the interventions and the common comparator dacabazine are presented in Table 8. In addition, a ranking of the included treatments are presented using the SUCRA. The results from the direct pairwise comparison performed in RevMan and network meta-analysis are seen to be consistent. That is, the results from the network meta-analysis and pairwise comparisons are similar in magnitude and direction.

Table 8 Hazard ratios for progression free survival from pairwise comparisons and network meta-analysis

Interventions	Hazard ratio relative to Dacarbazine (pairwise comparison)	Hazard ratio relative to Dacarbazine (network meta-analysis)	SUCRA	Quality of Evidence from the network meta-analysis
Dabrafenib+trametinib		0.21 (0.12-0.37)	0.9249	Moderate
Vemurafenib+cobimetinib		0.22 (0.11-0.48)	0.8880	Moderate
Nivolumab+ Ipilimumab		0.35 (0.21-0.66)	0.6090	Low
Dabrafenib	0.37 [0.23, 0.60]	0.37 (0.22-0.63)	0.5639	Moderate
Vemurafenib	0.38 [0.32, 0.45]	0.38 (0.24-0.62)	0.5266	High
Trametinib	0.45 [0.33, 0.61]	0.45 (0.25-0.82)	0.3733	Moderate
Pembrolizumab	0.45 [0.38, 0.53]	0.47 (0.30-0.76)	0.3183	High
Nivolumab	0.57 [0.31, 1.08]	0.50 (0.36-0.82)	0.2341	Moderate
Ipilimumab+Dacarbazine	0.76 [0.63, 0.92]	0.76 (0.45-1.33)	0.0389	Moderate
Ipilimumab+gp100		1.05 (0.53-2.40)	0.0122	Moderate
Ipilimumab		0.84 (0.54-1.52)	0.0093	Moderate
Dacarbazine	-	1	0.0060	

The full network meta-analysis results comparing all available treatment strategies are presented in Appendix 7.

Based on the results from the network meta-analysis, we find that dabrafenib combined with trametinib, vemurafenib combined with cobimetinib, nivolumab combined with ipilimumab, dabrafenib, vemurafenib, trametinib, pembrolizumab and nivolumab has better progession free survival than dacarbazine. In addition, we find that: ipilimumab has poorer progression free survival than dabrafenib, vemurafenib, vemurafenib combined with cobimetinib, dabrafenib combined with trametinib, pembrolizumab, and nivolumab combined with ipilimumab. Dabrafenib, vemurafenib, nivolumab, and vemurafenib combined with cobimetinib, has better progression free survival than ipilimumab. Vemurafenib combined with cobimetib has better progression free survival than nivolumab and ipilimumab combined with dacarbazine. Dabrafinib combined with trametinib has better progression free survival than dabrafenib, vemurafenib, nivolumab, ipililumab combined with dacarbazine, ipilimumab, and pembrolizumab. The ranking as measured by the SUCRA suggests that dabrafenibin combination withtrametinib and vemurafenib combined with cobimetinib has a higher probability of better performance than the other available treatment strategies.

Hazard ratios and quality ratings for direct and indirect comparisons for progression free survival from the network meta-analysis analyses are shown in Table 9. Here we

present results from all the comparisons with available direct evidence. A formal test, using "node-splitting", for consistency between direct and indirect evidence reveals no significant difference between the direct and indirect evidence (p-values>0.10) in the network meta-analyses.

Table 9 Estimates of progression free survival and quality ratings for direct and indirect comparisons from network meta-analysis

Comparison (study)	Direct evidence		Indirect evidence		Network meta-analysis	
	Hazard ratio (95% CI)	Quality of Evidence	Hazard ratio (95% CI)	Quality of Evidence	Hazard ratio (95% CI)	Quality of Evidence
Ipilimumab + dacarbazine versus dacarbazine (40)	0.76 (0.45-1.33)	Moderate	-		0.76 (0.45-1.33)	Moderate
Dabrafenib versus dacarbazine (54)	0.37 (0.23-0.60)	Moderate	0.38 (0.06-6.39)	Moderate	0.37 (0.22-0.63)	Moderate
Vemurafenib versus dacarbazine (61)	0.38 (0.32-0.45)	High	0.38 (0.07-2.54)	Moderate	0.38 (0.24-0.62)	High
Trametinib versus dacarbazine or paclitaxel (46)	0.45 (0.25-0.82)	Moderate	-		0.45 (0.25-0.82)	Moderate
Nivolumab versus dacarbazine (14) or versus dacarbazine or paclitaxel+ carboplatin (69)*	0.49 (0.40-0.60)	Moderate	0.38 (0.00-5.93)	Low	0.50 (0.36-0.82)	Moderate
Dabrafenib + trametinib versus dabrafenib (45, 52)**	0.60 (0.50-0.73)	Moderate	0.57 (0.02-27.62)	Moderate	0.58 (0.39-0.85)	Moderate
Vemurafenib + cobimetinib versus vemurafenib (65)	0.58 (0.33-1.03)	Moderate	-		0.58 (0.33-1.03)	Moderate
Dabrafenib+ trametinib versus vemurafenib (13)	0.56 (0.46-0.68)	Moderate	0.56 (0.09-3.79)	Moderate	0.56 (0.34-0.88)	Moderate
Ipilimumab +gp100 versus ipilimumab (37)	0.75 (0.42-1.42)	Moderate	-		0.75 (0.42-1.42)	Moderate
Pembrolizumab versus ipilimumab (9)	0.58 (0.50-0.67)	High	0.42 (0.02-2.90)	Moderate	0.56 (0.32-0.86)	High
Nivolumab + ipilimumab versus ipilimumab*** (44)	0.42 (0.31-0.57)	Moderate	0.39 (0.11-1.47)	Low	0.42 (0.27-0.63)	Moderate
Nivolumab + ipilimumab versus nivolumab (39)	0.74 (0.00-79.61)	Low	0.56 (0.04-6.60)	Moderate	0.70 (0.40-1.14)	Moderate

Nivolumab versus ipili-mumab (39)	0.57 (0.43-0.76)	Moderate	0.69 (0.09-6.67)	Low	0.60 (0.38-0.97)	Moderate
Pembrolizumab versus chemotherapy****(38)	0.45 (0.38-0.53)	High	0.59 (0.05-6.12)	Moderate	0.47 (0.30-0.76)	High

*Meta-analysis of two trials (14, 69)
** Meta-analysis of two trials (45, 52)
*** Meta-analysis of two trials (39, 44)
***Investigator-choice chemotherpy (paclitaxel plus carboplatin, paclitaxel, carboplatin, dacarbazine, or oral temozolomide)

More details about the estimates of progression free survival and quality rating (GRADE) for direct and indirect evidences are shown in the Summary of Finding Tables in Appendix 8.

Sensitivity and subgroup analyses
Due to paucity in data we have not performed any sensitivity or subgroup analyses. However, we here present some descriptive results:

- *Drugs that act specific on the BRAF mutations versus drugs that act on the immune system*

None of the included trials compared a BRAF inhibitor (dabrafenib or vemurafenib) head to head with a drug acting on the immune system. The best available comparisons are the indirect via dacarbazine as a common comparator. From Table 8 above we see the ranking of those drugs as measured by SUCRA.

- *Trials including previously treated, previously untreated or both patient groups*

Seven (14, 40, 44, 52, 54, 61, 65) of the 13 trials reporting progression free survival included previously pharmacologically untreated patients with metastatic or unresectable melanoma. Only two of the 13 trials that reported progression free survival included patients previously treated (37, 69), and four trials included patients that were both previously treated or not (9, 13, 45, 46). In our network meta-analyses we have not taken into account whether the patients were previously treated or not.

Serious adverse events

Pairwise comparisons
Sixteen of the 17 included trials reported serious adverse events, either from the mother study or in an updated publication (9, 12-14, 37-42, 44, 45, 52, 56, 61, 69). Among these 16 trials, there were two head to head comparison of two monotherapies (9, 39), for both these comparisons fewer serious adverse events in intervention

group (pembrolizumab and nivolumab respectively) than in to the ipilimumab group could be established. Further, six of the trials compared directly a combination-therapy versus a monotherapy; these were nivolumab in combination with ipilimumab versus ipilimumab (39, 44), nivolumab in combination with ipilimumab versus nivolumab (39), dabrafenib in combination with trametinib versus dabrafenib (45, 52) vemurafenib in combination with cobimetinib versus vemurafenib (12); and dabrafenib in combination with trametinib versus vemurafenib (13). For two of these comparisons a differences between groups in the number of participants experiencing serious adverse events could be established: fewer serious adverse events for nivolumab than for nivolumab in combination with ipilimumab (39); and fewer serious adverse events for dabrafenib in combination with trametinib than for vemurafenib (13). For the comparisons nivolumab in combination with ipilimumab versus ipilimumab (39, 44), and dabrafenib in combination with trametinib versus dabrafenib (45, 52) the results are based on meta-analyses, for the remaining comparisons only results from one single trial was available.

Dacarbazine was used as comparator in six of the trials (14, 38, 40, 56, 61, 69), including two trials where dacarbazine were used either as one of two possible options in the control group (dacarbazine or paclitaxel in combination with carboplatin) (43), or as one of five possible chemotherapies in the control group (38). For three of these comparisons (38, 40, 43) a difference between groups could be established in the number of participants experiencing serious adverse events. This was in favour of dacarbazine when compared to ipilimumab in combination with dacarbazine (40), in favour of nivolumab when compared to dacarbazine or paclitaxel in combination with carboplatin (43), and in favour of pembrolizumab when compared to dacarbazine as one of five possible chemotherapies (38). For the comparison nivolumab versus dacarbazine (14, 69), the results are based on a meta-analysis, for the remaining comparisons only results from one single trial was available.

The most common serious adverse events (grade 3 or 4) reported from the studies were gastrointestinal, immune-related, endocrine and hepatic events for ipilimumab; gastrointestinal and hepatic for pembrolizumab; gastrointestinal, fatigue, anaemia for nivolimumab. Dabrafenib and vemurafenib both reported squamous cell carcinoma/keratoacanthoma. Trametinib reported hypertension. Combination treatment of ipilimumab and nivolimumab reported gastrointestinal and hepatic events. The combination treatment of dabrafenib and trametinib reported squamous cell carcinoma/keratoacanthoma, pyrexia, gastrointestinal and hepatic events. Vemurafenib in combination with cobimetinib reported increased creatinine kinase and hepatic events. Dacarbazine reported mostly blood related events (thrombocytopenia, neutropenia, leukopenia, anaemia), immune related events, gastrointestinal, and fatigue.

More details for all the pairwise comparisons are shown in in Appendix 5 and 6, the latter showing all hazard ratios based upon RevMan analyses.

Network meta-analyses

The evidence network for serious adverse events is shown in Figure 4.

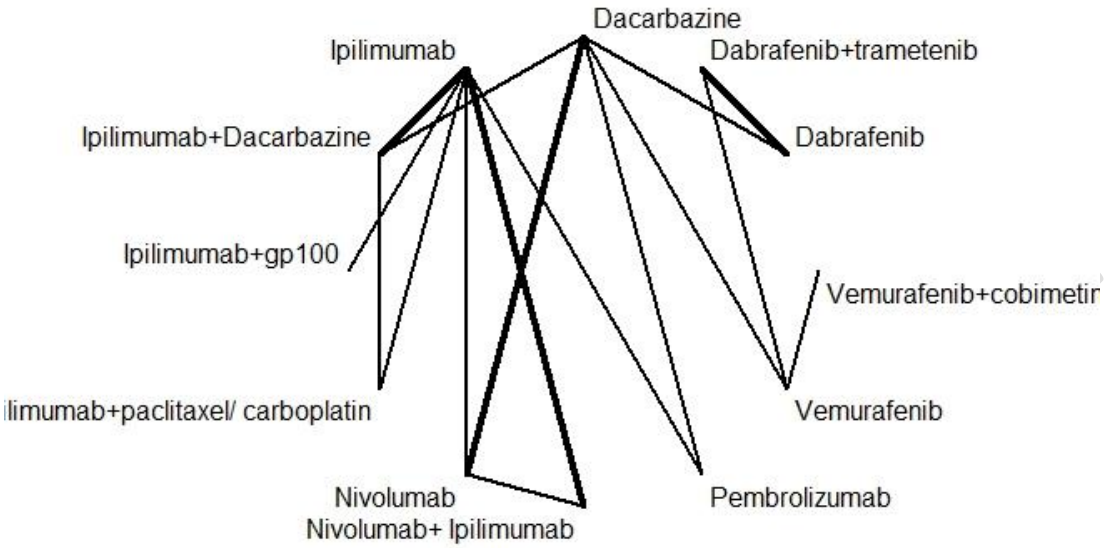

Figure 4 Evidence network for serious adverse events

A summary of results comparing pairwise meta-analyses and random effects network meta-analysis for the comparisons between the interventions and the common comparator darcabazine is presented in Table 10. In addition a ranking of the included treatments is presented using the SUCRA. The results from the pairwise estimates performed in RevMan and network meta-analyses are consistent when it comes to the ability to conclude, but the estimated direction of the difference relative to dacarbazine seems to differ between the pairwise comparisons and the network meta-analysis for vemurafenib and dabrafenib (for neither of the treaments, neither the pairwise comparisons nor the network meta-analysis could establish a difference relative to dacarbazine).

Table 10 Hazard ratios for serious adverse events from pairwise comparisons and network meta-analysis

Intervention	Relative risk relative to dacarbazine (pairwise comparison)	Relative risk relative to dacarbazine (network meta-analyses)	SUCRA	Quality of Evidence for the network meta-analysis
Pembrolizumab	-	0.49 (0.19-1.27)	0.88	Low
Nivolumab	0.51 [0.17, 1.58]	0.61 (0.29-1.26)	0.80	Low
Dacarbazine	-	1	0.60	-
Ipilimumab	-	0.87 (0.36-2.08)	0.59	Very low
Ipilimumab+gp100	-	0.85 (0.20-3.64)	0.58	Very low
Vemurafenib	0.77 [0.48, 1.24]	1.02 (0.36-2.84)	0.47	Very low
Dabrafenib	1.35 [0.82, 2.24]	1.03 (0.38-2.95)	0.46	Very low
Dabrafenib+trametinib	-	1.03 (0.34-3.20)	0.46	Very low
Vemurafenib+cobimetinib	-	1.10 (0.23-5.08)	0.43	Very low
Nivolumab+ Ipilimumab	-	1.28 (0.46-3.88)	0.31	Very low
Ipilimumab+paclitaxel/ carboplatin	-	1.41 (0.37-5.10)	0.29	Low
Ipilimumab+Dacarbazine	2.05 [1.63, 2.57]	1.51 (0.58-3.57)	0.22	Low

The full network-meta-analysis results comparing all available treatment strategies are presented in Appendix 7.

Based on the results of the network meta-analysis, we could not establish any differences between the available treatment strategies. However, the ranking as measured by the SUCRA suggests that pembrolizumab and nivolumab has a higher probability of fewer serious adverse events than the other available treatment strategies, even though we could not establish any differences.

Hazard ratios and quality ratings for direct and indirect comparisons for overall survival from the network meta-analyses are shown in Table 11. Here we present results from all the comparisons with available direct evidence. A formal test, using "node-splitting", for consistency between direct and indirect evidence did not establish any significant differences between the direct and indirect evidence (p-values >0.12), but at the same time the estimates from the direct and indirect evidence pointed in opposite directions.

Table 11 Estimates of serious adverse events for direct and indirect comparisons from network meta- analysis

Comparison (study)	Direct evidence		Indirect evidence		Network meta-analysis	
	HR (95% CI)	Quality of Evidence	HR (95% CI)	Quality of Evidence	HR (95% CI)	Quality of Evidence
Ipilimumab + dacarbazine versus dacarbazine (40)	2.05 (0.61-6.77)	Low	0.87 (0.19-3.66)	Very low	1.51 (0.58-3.57)	Low
Dabrafenib versus dacarbazine (56)	1.37 (0.38-5.04)	Very low	0.55 (0.08-3.96)	Very low	1.03 (0.38-2.95)	Very low
Vemurafenib versus dacarbazine (61)	0.77 (0.21-2.75)	Very low	1.88 (0.25-13.93)	Very low	1.02 (0.36-2.84)	Very low
Nivolumab versus dacarbazine (14) or versus dacarbazine or paclitaxel+ carboplatin (69)*	0.53 (0.20-1.30)	Very low	1.01 (0.19-5.92)	Low	0.61 (0.29-1.26)	Low
Ipilimumab + gp100 versus ipilimumab (37)	0.98 (0.31-3.13)	Low	-	-	0.98 (0.31-3.13)	Low
Ipilimumab + dacarbazine versus ipilimumab (41, 42)**	1.30 (0.47-3.49)	Very low	3.04 (0.61-16.13)	Low	1.74 (0.72-3.86)	Low
Ipilimumab + paclitaxel/carboplatin versus ipilimumab (42)	1.5 (0.4-5.1)	Low	1.9 (0.0 - INF)	Very low	1.63 (0.50-4.99)	Low
Pembrolizumab versus ipilimumab (9)	0.60 (0.15-2.38)	Low	0.52 (0.08-3.21)	Very low	0.57 (0.22-1.46)	Low
Nivolumab +ipilimumab versus ipilimumab (44)***	1.6 (0.7 - 3.7)	Very low	0.8 (0.0 - INF)	Moderate	1.48 (0.67-3.48)	Moderate
Dabrafenib + trametinib versus dabrafenib (45, 52)****	1.13 (0.47-2.71)	Very low	0.46 (0.05 - 4.21)	Very low	1.00 (0.46-2.16)	Very low
Vemurafenib+ cobimetinib versus vemurafenib (12)	1.08 (0.34-3.37)	Moderate	-	-	1.08 (0.34-3.37)	Moderate
Dabrafenib + trametinib versus vemurafenib (13)	0.82 (0.24-2.76)	Moderate	2.03 (0.26-14.99)	Very low	1.01 (0.39-2.79)	Moderate
Ipilimumab + paclitaxel/carboplatin versus ipilimumab +dacarbazine (42)	1.2 (0.3-4.3)	Low	0.9 (0.0 - INF)	Very low	0.94 (0.31-2.93)	Low
Nivolumab + ipilimumab versus nivolimumab (39)	1.38 (0.33-5.71)	Moderate	5.00 (0.53-51.46)	Very low	2.08 (0.82-5.92)	Moderate
Nivolumab versus ipilimumab (39)	0.78 (0.22-2.72)	Moderate	0.46 (0.10-2.00)	Very low	0.71 (0.30-1.64)	Moderate
Pembrolizumab versus chemotherapy*****(38)	0.46 (0.12-1.88)	Low	0.54 (0.09-3.36)	Very low	0.49 (0.19-1.27)	Low

*Meta-analysis of two trials (14, 69)

** Meta-analysis of two trials (41, 42)
*** Meta-analysis of two trials (39, 44)
**** Meta-analysis of two trials (45, 52)
*****The two doses of pembrolizumab are analyzed together

More details about the estimates of serious adverse events and quality rating (GRADE) for direct and indirect evidences are shown in the Summary of Finding Tables in Appendix 8.

Sensitivity and subgroup analyses
Due to paucity in data we have not performed any sensitivity or subgroup analyses. However, we here present some descriptive results:

- *Drugs that act specific on the BRAF mutations versus drugs that act on the immune system*

None of the included trials compared a BRAF inhibitor (dabrafenib or vemurafenib) head to head with a drug acting on the immune system. The best available comparisons are the indirect via dacarbazine as a common comparator. From table xx above we see the ranking of those drugs as measured by SUCRA.

- *Trials including previoulys treated, previously untreated or both patient groups*

Nine (12, 14, 40-42, 44, 52, 56, 61) of the 14
trials reporting SAEs included previously pharmacologically untreated patients with metastatic or unresectable melanoma. Only two of the 13 trials that reported serious adverse events included patients previously treated (37, 69), and three trials included patients that were both previously treated or not (9, 13, 45). In our network meta-analyses we have not taken into account whether the patients were previously treated or not.

Health related quality of life

Pairwise comparisons
Ten of the 17 included trials reported health related quality of life (38, 47, 48, 51, 53, 57, 64, 66, 68, 71). In all cases, except for Ribas 2015 (38), the health related quality of life were not reported in the mother publication, but in a separate publication reporting the HRQoL data. In all the ten trials the instrument use was the European Organization for Research and Treatment of cancer Quality of Life Questionnaire (EORCT-QLQ-C30), three of these trials also used the EuroQol (EQ-5D) Questionnaire (47, 53, 71). However, Long 2015 did not present any results from the EuroQol (EQ-5D). One of the trials (47) further used the Functional Assessment of Cancer Therapy-Melanoma (FACT-M).
The evidence available were mostly of poor quality, as six of the trials did not present the uncertainty (SD, SE, CI or p-value) associated with the results. Therefore,

we cannot use the results from the trials in our network meta-analysis, and a cautious interpretation of the conclusions presented in the publications are needed. However, the four studies that reported confidential interval (38, 47, 57, 68), reported better health related quality of life in the intervention group as compared to the control group (dabrafenib versus dacarbazine, trametinib versus dacarbazine/paclitaxel, pembrolizumab versus investigator choice of chemoterapy and dabrafenib + trametinib versus vemurafenib respectively).
None of the ten trials presented any head to head comparison of two monotherapies. For the comparisons that reported results with confidential interval there was one trial that compared directly a combination- therapy versus a monotherapy: dabrafenib in combination with trametinib versus vemurafenib (47).

Dacarbazine was used as comparator in five of the trials (38, 51, 57, 68, 71), including one study (68) where dacarbazine or paclitaxel were used as the comparator, and another (38) where dacarbazine was used as one of five possible investigator-choice chemotherapies. For the three trials that reported confidential intervals, the health related quality of life were in favour of the intervention group (dabrafenib, trametinib or pembolizumab respectively) (38, 57, 68).

Appendix 10 presents a descriptive overview of the evidences for health related quality of life. More details of the studies are found in Appendix 5.

Network meta-analyses

Due to insufficient data we have not perform network meta-analyses for health related quality of life.

Economic evaluation - Methods

General

This methods section will describe our cost-utility analysis (CUA) of interventions targeting patients with metastatic and/or unresectable malignant melanoma.

We refer to the interventions by their active ingredient. The interventions are dacarbazine, ipilimumab, dabrafenib, vemurafenib, trametinib, cobimetinib, pembrolizumab and nivolumab, either as monotherapy or in combinations.

All costs are in 2015 Norwegian kroner (NOK) and reflects the health care perspective. Both costs and effects are discounted by 4% annually as currently recommended by the Norwegian Ministry of Finance and guidelines for health economic evaluation in the health sector (74).

The health care perspective is relevant for prioritization of interventions within a fixed budget if the aim of the decision maker is to maximize health (no expansion of the budget is assumed). The methodological guidelines for economic evaluation in the health sector recommends a societal perspective that includes consequenses for all parts of the economy, including time costs, the deadweight loss of taxation, any productivity changes, and excluding transfers such as value added tax . This perspective is more appropriate if an expansion of the budget is assumed and in settings where prioritization of interventions across sectors of the economy is relevant (e.g. for public health interventions).

Model Structure

We have used a probabilistic discrete-time Markov cohort model to record the transition between health states, each of which are associated with a health-related quality of life weight and a cost. The time horizon is 10 years with a monthly cycle-length.

The model has three mutually exclusive disease-related health states: Progression-free disease (PFS) (1), Progressed disease (PD) (2) and Death (3) (Figure 5). All patients start in the progression-free disease state. For every model cycle, the arrows

indicates that a proportion of the patients may remain in the same health state, another proportion may experience progression and another may die, determined by the transition probabilities.

Disease regression in the form of transition from progressed disease to progression free survival is by assumption not possible. The model does not include treatment sequences.

We used R version 3.2.2 (75) for the estimation of the cumulative density functions and baseline transition probabilities, and Treeage Pro 2015 © (76) for the decision modelling.

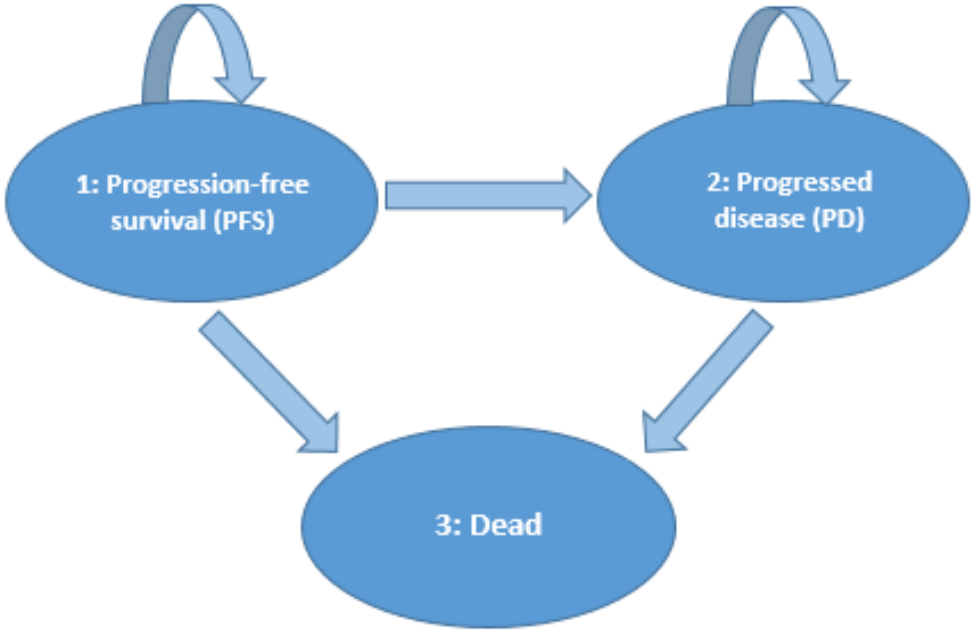

Figure 5 Diagram of the health states and possible transitions in the Markov model

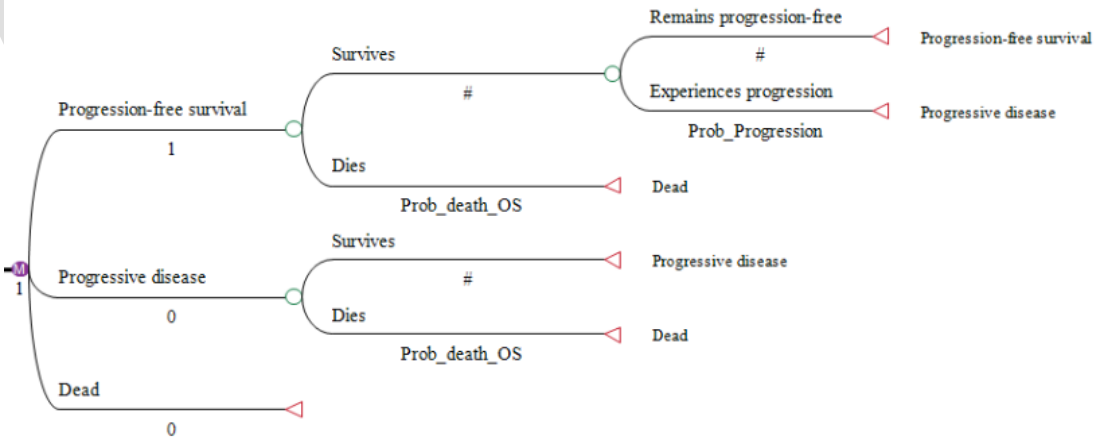

Figure 6 Decision tree structure for the Markov model

Model Parameters

See appendix 16 for a complete list of all the model parameters and distributions.

Transition probabilities

For the baseline overall suvival and progression free survival we fitted cumulative density functions from the dacarbazine arm of a randomized controlled trial, published in Robert 2011 (40) and Maio 2015 (50) (Table 12).

The choice of cumulative density function was based on the best fit as evaluated by the Akaike information criterion (AIC). Since use of this criteria gives no formal test of the quality of the absolute fit to the data, we checked how well the parametric function for overall survival fitted the patient-level data we used as well as the overall survival of Norwegian stage III and IV malignant melanoma-patients as reported by the Cancer Registry. The data we used seems to fit reasonably well the Kaplan-Meier curves for the patient level data, as well as the survival of Norwegian malignant melanoma stage IV patients, at year 1,2,3 and 4 following diagnosis. Appendix 10 gives more details.

We were unable to distinguish between mortality before and after progression in the model without compromising the accuracy of the model estimation of overall survival. We therefore assumed that the probability of death was independent of progression status.

We used the transition probability formula suggested by Briggs (77) in order to estimate the transition probability from alive to death (the transitions 1 to 3 and 2 to 3) and from progression free survival to progressed disease (1 to 2). From the fundamental relationships for probabilities of mutually exclusive events, it follows that the transition probability from progressive free survival to progressive disease (1 to 2) is one minus the probability of death minus the probability of staying in the progressive free survival health state.

Although the above relationship should hold in theory, we were not able to calculate the transition probabilities in this way with the parametric functions at hand. The decision tree (Figure 6) shows that the transitions from progression free survival to progressive disease or death in fact was calculated in two steps, first with regards to death (overall survival) and then for progression, conditional on survival. Appendix 12 gives more explanations for the choices made.

Table 12. Fitted distributions for the dacarbazine-arm in Robert 2011/Maio 2015 (NCT00324155)

Active ingredient/s	Progression free survival	Overall survival
Dacarbazine	Log-logistic	Log-logistic
*Parameters**	*2.13 , 3.16*	*1.52 , 9.03*

* Parameters are defined as in R: Shape and scale.

Treatment effects

We used the hazard ratios relative to dacarbazine from the network meta-analysis (Table 13) to adjust the transitions from alive to dead (1 to 3 and 2 to 3) and progression free survival to progressed disease (1 to 2).

Use of the hazard ratio assumes that the relationship between the times-to-events (survival and disease progression) of dacarbazine and each of these treatments is constant over time.

In the base case analysis, the hazard ratios are applied up to two years, assuming no treatment effects past two years of treatment for any of the interventions. When treatment stops, the hazard ratios are one and consequently we assume the same mortality as the dacarbazine-population past two years for all interventions. Any accumulated survival and progression benefits would however have an impact also after treatment discontinuation, until simulation ends at 10 years (the time horizon of the model).

Table 13. Hazard ratios used in model to modify the probability of death and progression in the model.

Active ingredient/s	Overall survival (95% CI)	Progression free survival (95% CI)
Ipilimumab	0.69 (0.44-1.26)	0.84 (0.54-1.52)
Dabrafenib	0.73 (0.49-1.10)	0.37 (0.22-0.63)
Dabrafenib+ trametinib	0.55 (0.37-0.84)	0.21 (0.12-0.37)
Ipilimumab+ Dacarbazine	0.70 (0.47-0.99)	0.76 (0.45-1.33)
Nivolumab	0.45 (0.30-0.71)	0.50 (0.36-0.82)
Nivolumab+ Ipilimumab	0.48 (0.28-0.90)	0.35 (0.21-0.66)
Pembrolizumab	0.46 (0.26-0.99)	0.47 (0.30-0.76)
Trametinib	0.78 (0.49-1.22)	0.45 (0.25-0.82)
Vemurafenib	0.77 (0.54-1.10)	0.38 (0.24-0.62)
Vemurafenib+cobimetinib	0.50 (0.26-0.96)	0.22 (0.11-0.48)

Costs

We received input regarding the course of the disease and the current course of treatment in Norway from Jarle Karlsen (oncologist, St. Olav Hospital, Trondheim) and Oddbjørn Straume (oncologist, Haukeland University Hospital, Bergen), both appointed by the four regional health authorities. We combined their feedback with price and fee information from different sources to estimate the costs associated with each treatment strategy. We included the following costs:

- BRAF gene mutation diagnostic testing
- Drug acquisition costs
- Oral drug dispensing costs
- Administration of parenteral therapies
- Monitoring costs before and after disease progression
- Hospital treatment of serious adverse events (SAEs)

We assumed that patients with advanced malignant melanoma would generally be entitled the health exemption card, and resultably counted the patient's copayments as a cost from the health care perspective.

BRAF gene mutation diagnostic testing
It has become current practice in Norway to test all unresectable and/or metastatic malignant melanoma patients for the BRAF gene mutation. Information on the mutation status of the patient can be used to determine whether the patient should receive immunotargeted- or BRAF gene mutation targeted therapy.

In our model, the only treatment arm not tested for genetic mutations is the dacarbazine-arm. This arm was included as a comparator to reflect the situation as if the new therapies were not an option. In such a context, the results of the test would not add valuable information as the treatment would be the same independently of the test result.

Based on communication with head of unit for molecular pathology at Oslo University Hospital, Lene Eggen, we assumed that all patients are tested with a BRAF qPCR test and around 15% also with a BRAFpyro. The BRAF gene mutation rate among Norwegian malignant melanoma patients is around 50%. All patients who do not have the BRAF gene mutation are subsecquently tested for neuroblastoma RAS viral oncogene homolog (NRAS) gene mutation.

Oslo University Hospital provided us with test cost data that indicated that the real costs associated with each BRAF qPCR is around three times higher than the reimbursement they receive from the public budget. However, since they did not have similar estimates for the two other tests, we used the reimbursement fees for those tests. Our average cost estimate for the cost of testing is NOK 4,089 per patient (Table 14).

Table 14. Costs associated with BRAF gene mutation testing

Test	Reimbursement rate (NOK)	Real expenses to lab (NOK)	Share of patients undertaking this test (%)	Expected real cost (NOK)	Total average cost per patient (NOK)
BRAF qPCR	1,027	3,000	100%	3,000	4,089
BRAF pyro	1,676	Unknown	15%	251	
NRAS	1,676	Unknown	50%	838	

Source: Lene Eggen, interim head of unit, Unit for molecular pathology, OUS.

Medicine costs

The medicine costs depends on the acquisition price, the dosages and duration of treatment.

The price paid by the regional health authorities consists of the maximum pharmacy retail price, adjusted for any discount negotiated through the Drug Procurement Co-operation system (LIS). We could not use any discounted prices for any of the new interventions in our analysis because they are not open to the public as per contract between LIS and the producers. We therefore used the maximum pharmacy retail price as of October 2015 in the base case analysis (78). However, we used the LIS-discounted price for dacarbazine since it is publicly available.

The dosages we used corresponds to the information in the summary of Product Characteristics (SPC) and an overview of the dosages used is provided in appendix 12.

In clinical practice, the actual cumulative dose may however be lower than the planned cumulative dose, for instance due to drug intolerance. The relative dose intensity of dabrafenib in the Combi-D study was about 88% (Personal communication with Petter Foss, Head of Market Access Oncology, Norway). We used the same relative dose intensity for dabrafenib in combination withtrametinib, trametinib, vemurafenib and vemurafenib in combination with cobimetinib in the model, based on expert advice from Oddbjørn Straume.

Based on experience from clinical practice in Norway, the number of doses each patient receives on average with ipilimumab are likely to be less than four. Of the first 100 Norwegian patients treated with ipilimumab, 61 received at least four doses and 17 received less than four doses. But since data were missing for 22 patients at the time of writing we were not able to calculate a weighted average with Norwegian data (Personal communication with Oddbjørn Straume). From the relative dose intensity information reported in Postow 2015 (79), we calculated a weighted average for ipilimumab in monotherapy of 3.5 doses and in combination therapy (with nivolumab) of 3.2 doses.

For the PD-1 immunotherapies, nivolumab and pembrolizumab, we were advised from our clinical experts to assume that treatment could be provided both in the progression free and progressed health states. In addition we assumed a gradual decline in the proportion being treated over time of those alive, according to information given in the appendix to Larkin 2015 (80) at 12 months of follow-up, and assuming no treatment after two years.

There is no accumulation of medicine costs past two years due to the assumption that treatment stops at this time. Table 15 summarises the assumptions we have made in the base case model.

Table 15 Overview of assumptions made about treatment in the model

Active ingredient	Information about treatment and treatment duration	Percentage of planned doses
	Oral medicines	
Dabrafenib	Treatment in PFS-health state to month 24, then no treatment. Dosages according to SPC.	88%***
Dabrafenib + trametinib		88%
Trametinib		88%
Vemurafenib		88%
Vemurafenib + cobimetinib		88%
	Parenteral medicines	
Ipilimumab	3,5 doses*	88% (Assuming 4 planned doses)
Ipilimumab+dacarbazine	Ipilimumab: 3,5 doses* Dacarbazine: Treatment in PFS-health state to month 24, then no treatment.	Ipilimumab: 88% (Assuming 4 planned doses)
Ipilimumab+nivolumab	Ipilimumab: 3,2 doses* Nivolumab: Treatment in PFS and PD to month 24, then no treatment	Ipilimumab: 80% (Assuming 4 planned doses) Nivolumab: Proportion of those alive, under treatment, reduced per month by: 1-12 months: 5,4%**. 13-24 months 3,2%** >24 months: No treatment
Nivolumab	Treatment in PFS and PD to month 24, then no treatment	Proportion of those alive, under treatment, reduced per month by**: 1-12 months: 4,4%** 13-24 months 3,9%** >24 months: No treatment
Pembrolizumab	Same as for nivolumab.	Same as for nivolumab.

*Based on relative dose intensity information for ipilimumab in monotherapy and in combination with nivolumab as reported in Postow 2015 supplementary appendix, table S3 (79).

** The monthly percentage reduction matches the reported proportion of those being treated and alive in Larkin 2015 supplementary appendix, table S1, at 12 months (80). For nivolumab in monotherapy, the proportion at 12 months was 51%. For nivolumab in combination with ipilimumab, the proportion was 41%. After 12 months, the monthly percentage reduction results in that no patients are treated past 24 months.

***Based on information on relative dose intensities in the Combi-D study.

Table 16 summarizes the medicine costs estimates per model cycle (month), with the exception of ipilimumab, where the total drug cost is valid only for the first model cycle.

For more details about the drug costs, see appendix 13.

Table 16. Drug costs per cycle (VAT included).

Treatment	First month	Months beyond the first
Dabrafenib	80,962	80,962
Dabrafenib + trametinib	169,949	169,949
Dacarbazine	1,259	1,259
Ipilimumab*	740,863	0
Ipilimumab* + dacarbazine	740,863 1,259	1,259
Ipilimumab* + nivolumab	677,360 28,817	28,817
Nivolumab	86,452	86,452
Pembrolizumab	92,909	92,909
Trametinib	88,987	88,987
Vemurafenib	83,538	83,538
Vemurafenib + cobimetinib**	172,525	172,525

* Ipilimumab: Full cost in the first month of treatment in the model. Assumed 3,2 doses per patient on average in combination therapy with nivolumab and 3,5 doses per patient on average in monotherapy and in combination with dacarbazine.

** Cobimetinib does not have marketing authorization in Norway. We assumed that the per cycle cost of cobimetinib would be the same as for trametinib.

Drug dispensing costs

We estimated that 80% of the patients receiving medicines in tablet form would prepare their doses alone (personal communication with Jarle Karlsen and Oddbjørn Straume), while the other 20% would get help from either a nurse (inpatients and homecare patients) or the hospital's pharmacy (outpatients). Dispensing and con-

trolling every dose requires two people (one pharmacist and one pharmacy-technician or another pharmacist) to spend 5 minutes of work each (personal communication with G. S. Furuhaug, pharmacist at the Oslo university hospital). Assuming an average gross wage of NOK 205/hour (i.e. NOK 3.4/minute), the dispensing costs are approximately NOK 17/dose per person involved. The cost estimate does not include overhead costs. The estimates does not include overhead costs due to lack of information. Table 17 shows the estimates for the relevant drugs.

Table 17. Dispensing costs per model cycle for oral medicines.

Treatment	Doses per day	Time usage per dose (minutes)	Wage per minute (NOK)	Share of doses dispensed by health personnel	Dispensing costs per day	Average dispensing costs per model cycle (NOK)
Cobimetinib + vemurafenib	2 [b]	10	3.42	20%	13.67	416
Dabrafenib	2	10	3.42	20%	13.67	416
Dabrafenib + Trametinib	2 [c]	10	3.42	20%	13.67	416
Trametinib	1	10	3.42	20%	6.83	208
Vemurafenib	2	10	3.42	20%	13.67	416

[a] Patients are not treated every day during each model cycle, as there are 7 days off every 21 treatment days.

[b] Assumption based on the number of doses per day needed for vemurafenib

[c] Assumption based on the number of doses per day needed for dabrafenib

Parenteral drugs administration costs

Dacarbazine, ipilimumab, nivolumab and pembrolizumab are intravenous therapies, i.e. the patient receives the relevant dose intravenously through a catheter, administered by a nurse that supervises the whole procedure, in a room dedicated to this purpose at a hospital or outpatient clinic. For all therapies given intravenously we assumed that administration costs per dose to the hospital were reflected by 7 % of the reimbursement rate for the DRG code 809H, which amounts to NOK 1,312. This estimate takes into account all costs other than drug acquisition associated with each intravenous procedure, i.e. wages, material, overheads but not capital costs

(amortization, interest expenses, building and equipment rental costs).[1] The results are summarized in Table 18.

Table 18. Administration costs per medicine injection per model cycle

Treatment	Cost per treatment	Number of doses per model cycle	Administration costs (NOK/ model cycle)
Dacarbazine	1,312	1.33 [a]	1,749
Ipilimumab	1,312	3.5 [b]	4,592 [b]
Ipilimumab + nivolumab	1,312	Ipilimumab:3.2 [b] Nivolumab:2 [c]	Ipilimumab: 4,198 [b] Nivolumab: 2,624
Ipilimumab + dacarbazine	1,312	Ipilimumab: 3.5 [b] Dacarbazine:1.33 [d]	Ipilimumab: 4,592 [b] Dacarbazine: 1,749
Nivolumab	1,312	2 [e]	2,624
Pembrolizumab	1,312	1.33 [f]	1,749

[a] *Assuming an injection of 850 mg/m2 on the first day, and then one intravenous injection every 3 weeks.*

[b] *All doses were "administered" during the first model cycle.*

[c] *One nivolumab dose every 2 weeks and all four ipilimumab doses administered during the first month.*

[d] *One dacarbazine injection of 850 mg/m2 on the first day, and then one intravenous injection every 3 weeks.*

[e] *One dose every 2 weeks.*

[f] *One dose every 3 weeks.*

Drug-therapy related serious adverse events (SAEs)

We chose to include serious adverse events requiring hospitalization, i.e. adverse events grade 3 and 4. The monthly costs related to serious adverse events are determined by the cost of hospitalisation and the average monthly probability of such an event.

The cost of an adverse event related hospitalization were assumed to be equal to 100% of the reimbursement rate for the DRG code 453B[2], i.e. NOK 20,814. We estimated the average monthly rate of a serious adverse event from patients included in the dacarbazine arm of the NCT00324155 trial published in Robert 2011 (40) and Robert 2015 (14), the only publications without cross-over after progression where in addition dacarbazine was administered as monotherapy. The average montlhy rate of 1.64% is the arithmetic average of the monthly frequency of experiencing serious adverse events.

[1] Based on information from Norwegian Directorate of Health, Department of Economy and Analysis. Wages and other costs share of DRG cost for DRG 809H.

[2] DRG code for complication associated with other treatment.

We adjusted the baseline risk of an adverse event with the relative risk of adverse event versus dacarbazine identified in our meta-analysis (Clinical Evaluation results chapter). Table 19 summarizes the expected cost per model cycle for each treatment arm and the associated cycle probability and relative risk.

Any serious treatment related adverse events post progression is assumed to be included in the per cycle monitoring cost for the progressed disease state.

Table 19. Costs of treating therapy related serious adverse events

Treatment	RR relative to dacarba-zine (NMA)	Per cycle probability of a serious adverse event	Expected cost per model cycle (NOK)
Dabrafenib	1.03	0.0167	348
Dabrafenib + trametinib	1.03	0.0167	348
Dacarbazine	1	0.0164	341
Ipilimumab	0.87	0.0141	294
Ipilimumab + Dacarbazine	1.51	0.0244	508
Nivolumab	0.61	0.0099	207
Nivolumab + Ipilimumab	1.28	0.0207	431
Pembrolizumab	0.49	0.0080	166
Trametinib	1.03	0.0167	348
Vemurafenib	1.02	0.0166	345
Vemurafenib + cobimetinib	1.1	0.0178	371

* We had no data to serious AEs for Trametinib. It was assumed that the RR for trametinib would be the same as for dabrafenib.

Monitoring costs

In the progression free health state patients are followed up during and after treatment stop in order to assess the course of the disease. While at treatment, the intensity and content of this follow-up schedule varies across interventions, and includes outpatient visits to specialists (oncologists and/or dermathologists), blood analyses and diagnostic imaging (CT, ultrasound, bone scintigraphy, PET and/or MR). The resulting cost estimates are shown in Table 20.

Table 20. Monitoring costs per model cycle in the progression-free health state

Treatment	Monitoring costs (NOK/model cycle)
Dacarbazine	2,858
Ipilimumab, ipilimumab + dacarbazine and pembrolizumab	3,033
Nivolumab, nivolumab + ipilimumab	3,938
Dabrafenib, dabrafenib + trametinib, vemurafenib, vemurafenib + cobimetinib, trametinib and cobimetinib	3,820

In the progressed health state the costs consists of a mix of surgery, radiotherapy and palliative treatment at a hospital center and/or through day care. Although we assume that some patients may be treated with PD-1 immunotherapy post progression (Table 15), we consider a mix of best supportive care (BSC) to best reflect the per cycle costs in the progressed health state.

Table 21. Monitoring costs per model cycle when treatment is discontinued

Treatment	Monitoring costs (NOK/model cycle)
All	11,747

See appendix 12 for more details regarding our monitoring costs estimates.

Health related quality of Life

We conducted a separate search in the literature for health related quality of life data measured with generic multi-attribute instruments or other instruments that provides values valid for use in economic evaluations. See Appendix 13 for more information.

We used EQ-5D values from Grob 2015 (47) for vemurafenib in monotherapy and dabrafenib and trametinib in combination thereapy to inform the progressive free survival and progressed disease health states for those interventions. We transferred the vemurafenib monotherapy values to dabrafenib monotherapy and the dabrafenib and trametinib values to the combination vemurafenib and cobimetinib.

Grob 2015 (47) indicated a slight decrease in health related quality of life following progression for vemurafenib in monotherapy, but an increase for the BRAF and MEK combination therapy. We chose not to include this increase in the analysis for the combination therapies, instead fixing the health related quality of life at the same level as in the progressive free health state.

The EQ-5D values for the interventions involving immunotherapies are from table 9 in a recently published single technology assessment of pembrolizumab compared to ipilimumab (81). To our knowledge all the EQ-5D values used the UK-tariff.

Table 22 shows the EQ-5D values we used in the model analysis for progression-free survival and progressed disease. The immunotherapies have a slightly higher health related quality of life in the progressive free survival health states than the BRAF and MEK mono- and combination therapies, but the BRAF and MEK combination therapies have a slightly higher health related quality of life in the progressed disease state.

Serious adverse events does not influence on HRQoL in our model because of the short duration, but the cost per cycle due to such events is included, as explained above for costs.

We used the BRAF or MEK monotherapies health related quality of life values for the common comparator dacarbazine.

Table 22. Health-related quality of life before and after progression.

Source	Generic MAU instrument	QALY-weights	
		Progression-free survival	Progressed disease
Values that applies to the BRAF or MEK targeted monotherapies: vemurafenib dabrafenib trametinib	EQ-5D	0.715	0.665
Values that applies to the BRAF+MEK targeted combination therapies: dabrafenib+trametinib vemurafenib+cobimetinib	EQ-5D	0.751	0.751
Values that applies to the immunotherapies: ipilimumab ipilimumab+dacarbazine ipilimumab+nivolimab nivolumab pembrolizumab	EQ-5D	0.80	0.70

Economic evaluation - Results

General

We will present the results as incremental cost-effectiveness ratios (ICER) for both quality adjusted life years (QALY) and life years gained (LYG). Our suggestions about cost-effectiveness will reflect a range of potential willingness-to-pay (WTP) values per gained QALY. Separate scenario analysis will investigate the importance of drug pricing, the choice of time horizon and health related quality of life weights. In the end of the chapter we will present a budget impact analysis.

We will first present the cost-effectiveness frontier curve in the the cost-effectivenes plane which gives a quick overview of how the interventions compare to each other. Then the point estimate results will be presented in table format for the incremental analysis.

The Monte Carlo results will be presented as scatterplots , cost-effectiveness acceptability curves (CEAC) and expected value of partial perfect information (EVPPI). (EVPPI). The results will be presented for willingness to pay values to a maximum of NOK 2.000.000 per QALY gained. We used 10.000 iterations in the Monte Carlo analyses.

Table 23 shows the interventions we included in the three incremental analyses. In Norway, all advanced malignant melanoma patients are tested for the BRAF gene mutation before deciding on treatment.

- *Results for the whole target population, including all drugs. The* first analysis includes all the interventions included in the systematic review and network meta-analysis, which included all advanced malignant melanoma patients irrespective of BRAF gene mutation status. However, in clinical practice, all patients are tested for the BRAF gene mutation status, so this analysis reflects a situation where both immunotherapies

and BRAF/MEK therapies are considered relevant treatment options for BRAF gene mutation positive patients.

- *Results for the BRAF gene mutation positive population including only the BRAF inhibitors and the MEK inhibitors*. The second analysis covers only the BRAF/MEK inhibitors to reflect a situation where immunotheraphy are not an option for BRAF gene mutation positive patients.
- *Results regardless of BRAF status, including only the immunotherapies*. This analysis reflects a situation where immunotherapies are considered relevant, regardless of the BRAF gene mutation status.

We did not conduct any subgroup analysis of the treatment effects, so analysis one and three rests on the assumption that the treatment effects of the immunotherapies are the same regardless of BRAF status. For the BRAF/MEK inhibitors in analysis two we assume that previous treatment with immunotherapy do not influence the treatment effects.

It can be discussed whether or not dacarbazine is a relevant intervention to include in the incremental analysis when immunotheraphies or BRAF/MEK inhibitors are available as treatment options. We will therefore present some of the results both with and without dacarbazine.

In the results of the incremental analyses reported in table format, we may refer to the "undominated" strategies. These are the interventions that have not been ruled out in the incremental analysis due to dominance. In the incremental analysis all interventions are ranked according to costs (from lowest to highest), and some interventions are ruled out due to dominance, i.e having a higher cost and a lower effectiveness than the less costly alternative. Others are ruled out because of "extended" dominance, i.e. showing a higher incremental cost-effectiveness ratio than the less costly non-dominated alternative.

The incremental analyses are based on the point estimates from the Monte Carlo simulations. Consequently, if some interventions have very similar costs and effectiveness, one intervention may coincidentally be highlighted in the incremental analysis in the results tables, but in practice it is very difficult to separate this intervention from the others when parameter uncertainty is accounted for. A first indication of this will be given by the cost-effectiveness graph, where some interventions may cluster together.

The results of the expected value of partial perfect information analysis are only presented for the first incremental analysis.

Table 23 Complete list of interventions included in each analysis

	1: Patients with advanced malignant melanoma, including all drugs	2: Patients with advanced malignant melanoma and BRAF gene mutation positive, when immunotherapy is not an option	3: Patients with advanced malignant melanoma, regardless of BRAF gene mutation status
	Incremental analyses reported both with and without dacarbazine		
Interventions included in analysis	Dabrafenib	Dabrafenib	Ipilimumab
	Dabrafenib +Trametinib	Dabrafenib +Trametinib	Ipilimumab +Dacarbazine
	Ipilimumab	Trametinib	Nivolumab
	Ipilimumab +Dacarbazine	Vemurafenib	Nivolumab+Ipilimumab
	Nivolumab	Vemurafenib +Cobimetinib	Pembrolizumab
	Nivolumab+Ipilimumab		
	Pembrolizumab		
	Trametinib		
	Vemurafenib		
	Vemurafenib +Cobimetinib		

Cost-effectiveness results and sensitivity analyses

1 Results when all interventions are included in the incremental analysis

Figure 7 shows the cost-effectiveness plane when all interventions are included in the analysis. The cost effectivenss frontier (blue curve) highlights nivolumab and vemurafenib in combination with cobimetinib as the undominated strategies. The new immunotherapies, pembrolizumab, nivolumab and the combination nivolumab ipilimumab clusters together in the cost-effectiveness plane, indicating that it would be difficult to separate any of these interventions with respect to cost-effectiveness when parameter uncertainty are accounted for.

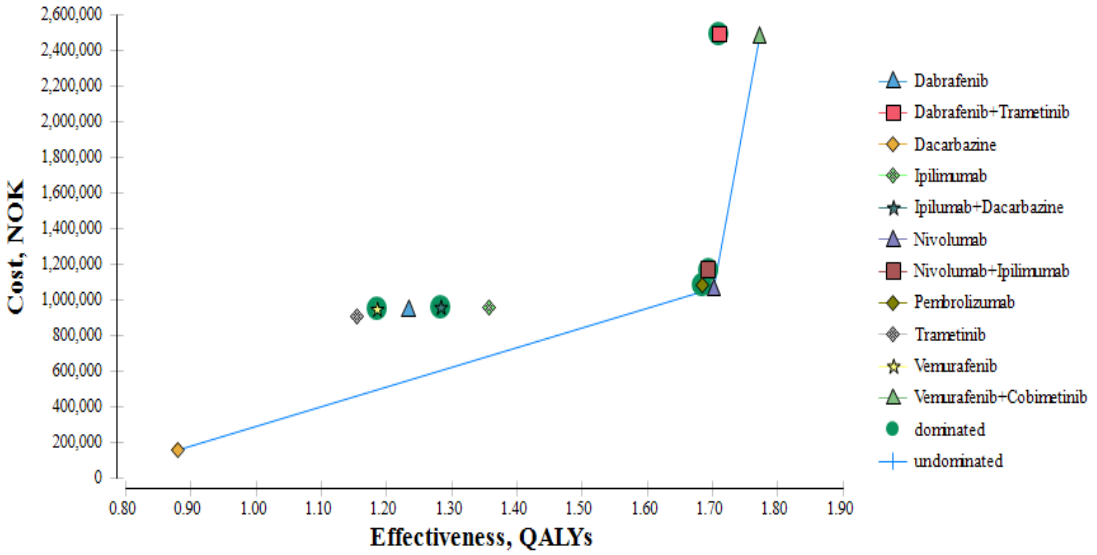

Figure 7 Cost-effectiveness graph when all interventions are included

Table 24 shows the results of the incremental analysis when effectiveness is measured in quality adjusted life years. Nivolumab has an incremental effect of 0.82 quality adjusted life years and an incremental cost-effectiveness ratio against dacarbazine of about 1.1 million NOK per quality adjusted life year gained. The combination vemurafenib in combination with cobimetinib has an incremental cost-effectiveness ratio against nivolumab of about 19.8 million NOK per quality adjusted life year gained.

Table 24 Results of the incremental analysis, excluding dominated strategies

Intervention	Costs (NOK)	Incremental Cost	Effectiveness (QALYs)	Incremental Effect	ICER
Dacarbazine	161,107		0.88		
Nivolumab	1,063,549	902,442	1.70	0.82	1,098,111
Vemurafenib+Cobimetinib	2,475,101	1,411,552	1.77	0.07	19,796,728

In Table 25, the effectiveness is measured in life years gained. For the combination nivolumab and ipilimumab, the life years gained over dacarbazine is about 12 months and the incremental cost-effectiveness ratio about 0,9 million NOK per QALY gained.

Table 25 Results of the incremental analysis, excluding dominated strategies. (LYG)

Intervention	Costs (NOK)	Incremental Cost	Effectiveness (LYG)	Incremental Effect	ICER
Dacarbazine	159,909		1.30		
Nivolumab	1,060,945	901,036	2.31	1.01	887,860
Vemurafenib+Cobimetinib	2,474,581	1,413,636	2.36	0.05	26,474,264

Table 26 shows the results when all the interventions refer to dacarbazine, when effectiveness are measured in quality adjusted life years. Table 27 shows the same results for effects measured in life years gained.

Table 26 Results when all incremental cost-effectiveness ratios refer to dacarbazine (QALYs)

Intervention	Costs (NOK)	Incremental Cost	Effectiveness (QALYs)	Incremental Effect	ICER
Dacarbazine	161,107		0.88		
Trametinib	901,641	740,534	1.16	0.28	2,689,950
Dabrafenib	943,009	781,902	1.23	0.35	2,208,510
Vemurafenib	943,589	782,482	1.19	0.31	2,545,205
Ipilimumab	956,069	794,962	1.36	0.48	1,662,160
Ipilumab+Dacarbazine	958,610	797,503	1.28	0.40	1,980,440
Nivolumab	1,063,549	902,442	1.70	0.82	1,098,111
Pembrolizumab	1,086,220	925,113	1.68	0.80	1,150,701
Nivolumab+Ipilimumab	1,168,791	1,007,684	1.69	0.81	1,239,204
Vemurafenib+Cobimetinib	2,475,101	2,313,994	1.77	0.89	2,590,925
Dabrafenib+Trametinib	2,485,786	2,324,679	1.71	0.83	2,816,246

Table 27 Results when all incremental cost-effectiveness ratios refer to dacarbazine (LYG)

Intervention	Costs (NOK)	Incremental Cost	Effetiveness (LYG)	Incremental Effect	ICER
Dacarbazine	159,909		1.30		
Trametinib	897,897	737,988	1.66	0.37	2,017,429
Dabrafenib	939,259	779,350	1.77	0.48	1,634,798
Vemurafenib	944,205	784,296	1.70	0.41	1,927,978
Ipilimumab	954,682	794,773	1.86	0.56	1,410,525
Ipilumab+Dacarbazine	957,470	797,561	1.75	0.46	1,738,840
Nivolumab	1,060,945	901,036	2.31	1.01	887,860
Pembrolizumab	1,083,656	923,747	2.28	0.98	940,212
Nivolumab+Ipilimumab	1,166,102	1,006,193	2.25	0.95	1,053,825
Vemurafenib+Cobimetinib	2,474,581	2,314,672	2.36	1.07	2,166,816
Dabrafenib+Trametinib	2,486,290	2,326,381	2.27	0.98	2,377,352

Figure 8 shows the scatterplot for 10.000 Monte Carlo simulations. The interventions are difficult to separate from each other. The combinations dabrafenib in combination with trametinib and vemurafenib in combination with trametinib cobimetinib can be found in the upper right scatter with the highest costs. The scatter in the centre consists of the BRAF inhibitors dabrafenib, vemurafenib and the MEK

inhibitor trametinib, the immunotherapies ipilimumab, nivolumab, pembrolizumab and the combination nivolumab and ipilimumab respectively.

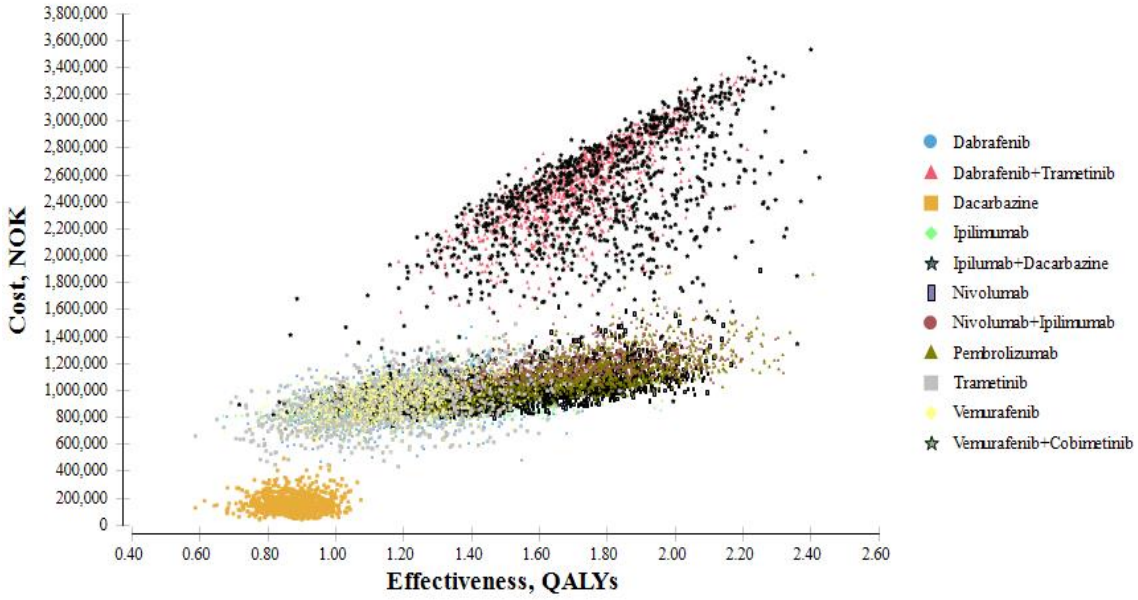

Figure 8 Scatterplot

The cost-effectiveness acceptability curves are presented both with (Figure 9) and without dacarbazine (Figure 10). For increasing willingness to pay values, the new immunotherapies in monotherapy, nivolumab and pembrolizumab have quite similar levels of iterations being cost effective, closely followed by the combination nivolumab and ipilimumab.

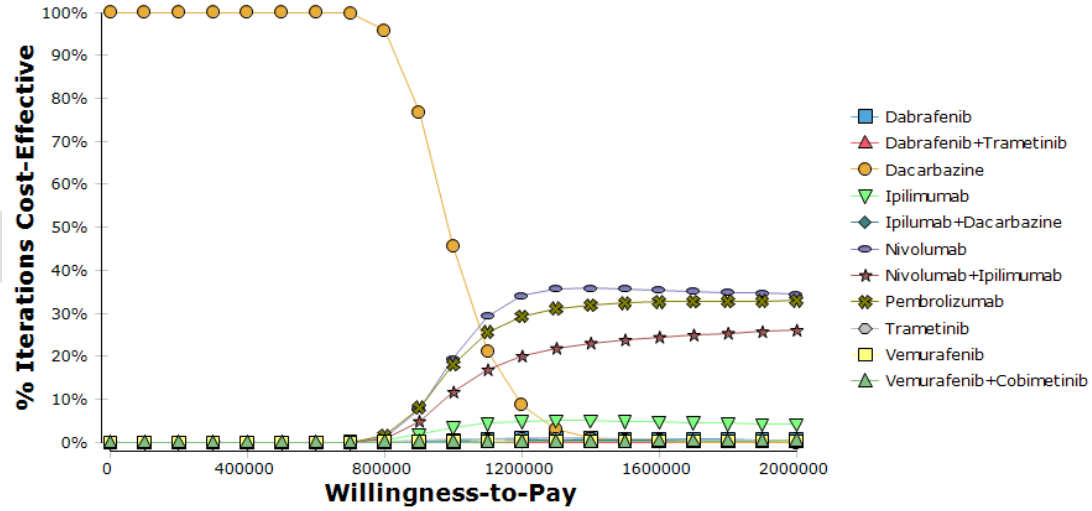

Figure 9 Cost-effectiveness acceptability curve with dacarbazine

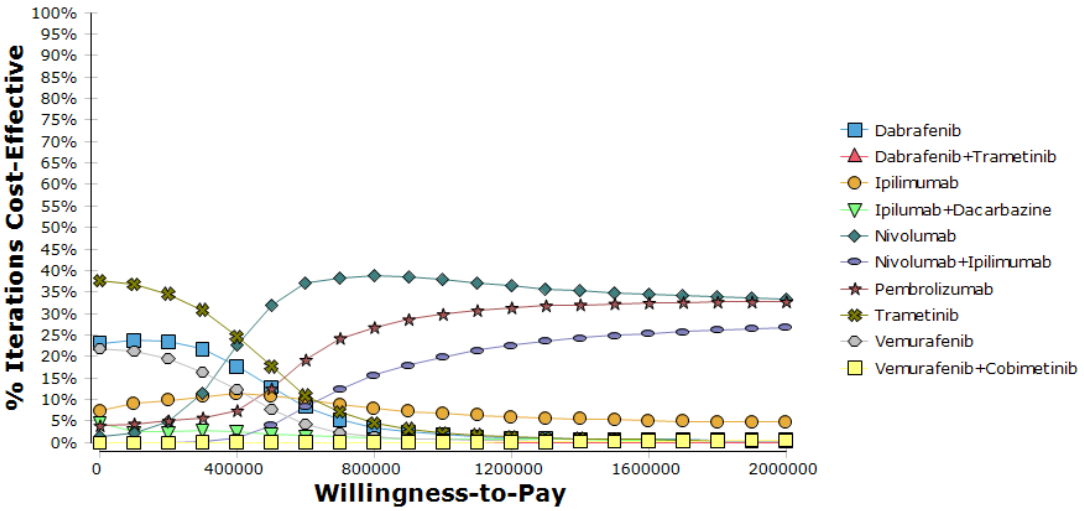

Figure 10 Cost-effectiveness acceptability curve without dacarbazine

The decision model includes many uncertain input parameters. In the expected value of partial perfect information analysis, the uncertain parameters are grouped according to type and the analysis shows which group of parameters that are the most influental on the results. New research should be aimed on the most influental groups of parameters, because the potential to reduce the decision uncertainty is the largest for those parameteres.

Figure 11 shows the results of the expected value of partial perfect information analysis per patient for 50 outer x 500 inner loop Monte Carlo iterations, on the efficacy parameters, the serious adverse events parameters, costs and health related quality of life. The results indicates that the treatment efficacy data is the most influental source of uncertainty, followed by the health related quality of life data, costs and serious advers events data (hazard ratio for serious advers event). At a willingness to pay level of about NOK 1 million, the expected value of partial perfect information per patient have a value of about NOK 99,000 the treatment efficacy data (hazard ratios on overall survival and progression free survival), 46,000 for health related quality of life data, 3,700 for costs and 170 for the serious adverse events data.

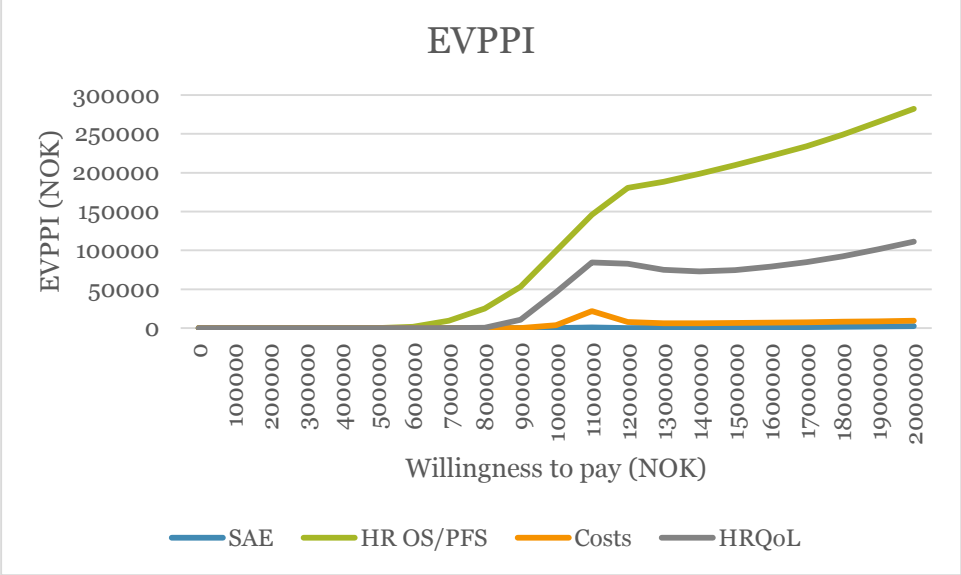

Figure 11 Results of the expected value of partial perfect information analysis

2. Results for the BRAF and MEK mono- and combination therapies

Figure 12 shows the cost-effectiveness graph. Dabrafenib and vemurafenib in combination with cobimetinib are the two undominated strategies. The monotherapies clusters together at a lower level of costs and effectiveness compared to the combination therapies.

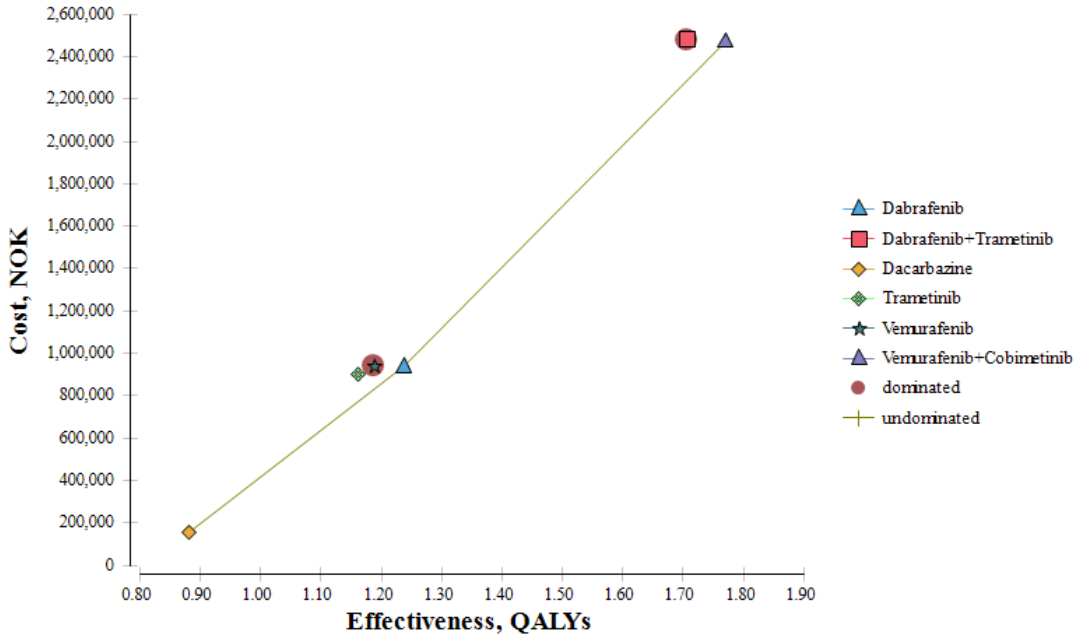

Figure 12 Cost-effectiveness graph

Dabrafenib has an incremental effect of 0.36 quality adjusted life years and a cost-effectiveness ratio compared to dacarbazine of approximately NOK 2.2 million per quality adjusted life year gained (Table 28). The combination vemurafenib in combination with cobimetinib have an incremental effect of 0.53 quality adjusted life years and incremental cost-effectiveness ratio compared to dabrafenib of about NOK 2.9

million per quality adjusted life year gained. The ranking of the interventions is unchanged when effectiveness is measured in life years gained and the associated incremental cost-effectiveness ratios are as expected a bit lower due to the slightly larger incremental effectiveness when gained life years are unweighted (Table 29).

Table 28 Results of the incremental analysis, excluding dominated strategies (QALY)

Intervention	Costs (NOK)	Incremental Cost	Effectiveness (QALY)	Incremental Effect	ICER
Dacarbazine	159,801		0.88		
Dabrafenib	940,235	780,434	1.24	0.36	2,191,383
Vemurafenib+Cobimetinib	2,471,755	1,531,520	1.77	0.53	2,876,095

Table 29 Results of the incremental analysis, excluding dominated strategies (LYG)

Intervention	Costs (NOK)	Incremental Cost	Effectiveness (LYG)	Incremental Effect	ICER
Dacarbazine	159,905		1.30		
Dabrafenib	941,617	781,712	1.78	0.48	1,626,422
Vemurafenib+Cobimetinib	2,479,862	1,538,245	2.37	0.59	2,604,396

The cost-effectiveness acceptability curves are shown both with (Figure 13) and without dacarbazine (Figure 14). The x-axis was extended to a willingness to pay level of NOK 3.0 million in order to improve readability. When dacarbazine is included, the curves shows that dacarbazine is more likely to be cost effective than the alternatives for willingness to pay values up to about 2.0 million NOK. The monotherapies shows a decreasing trend for further increasing willingness to pay values, contrary to the combination strategies. When dacarbazine is excluded, this picture is repeated, with the BRAF and MEK inhibitors in monotherapy having the highest probability of being cost-effective for the lowest willingness to pay values and the combination strategies showing an increasing trend for very high willingness to pay values.

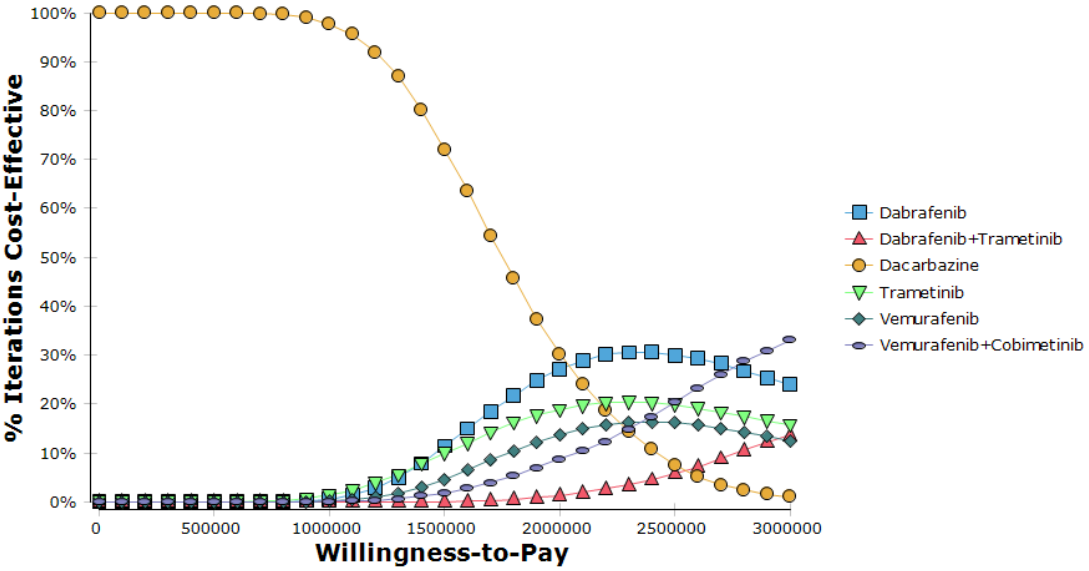

Figure 13 Cost-effectiveness acceptability curve with dacarbazine

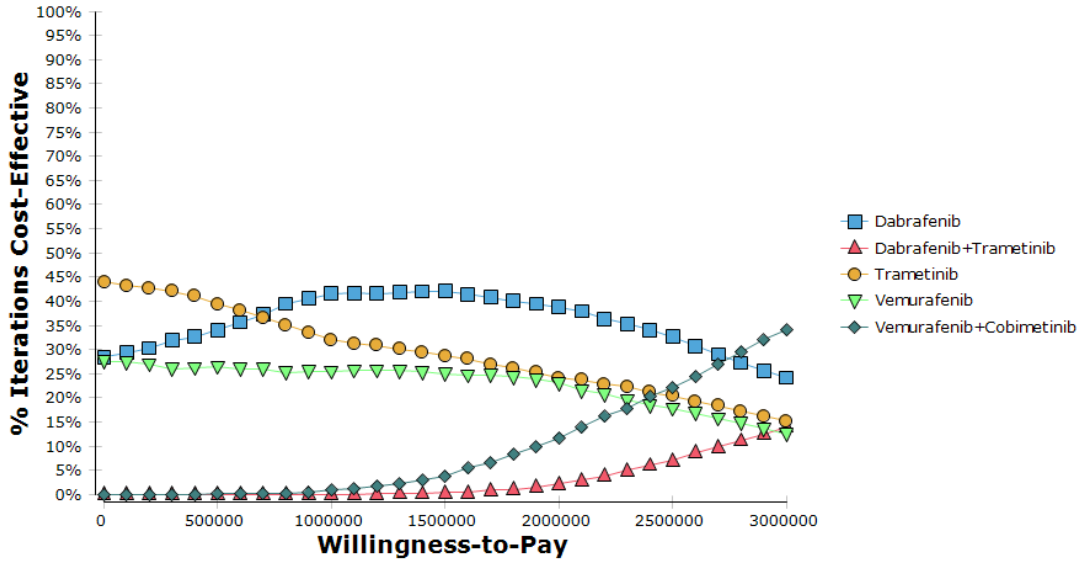

Figure 14 Cost-effectiveness acceptability curve without dacarbazine

The scatterplot in Figure 15 there ia a clear pattern with two separate clouds of scatter, one with the monotherapies vemurafenib, trametinib and dabrafeinb and the second with more expensive but more effective combination therapies.

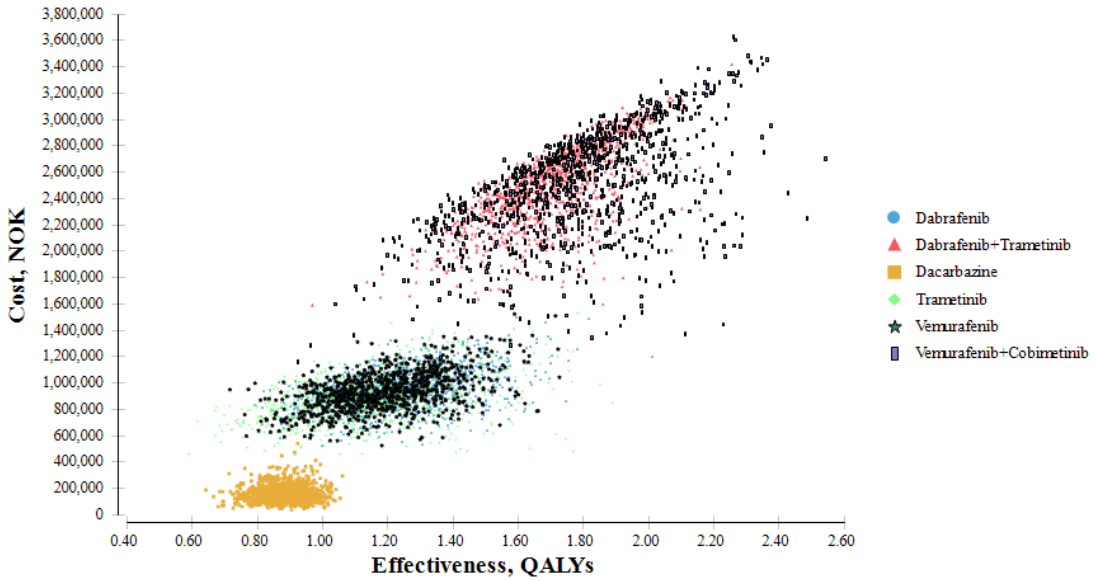

Figure 15 Scatterplot for the BRAF and MEK inhibitors

3. Results for the immunotherapies

Figure 16 reconfirms the same pattern that was shown in Figure 7. The new immunotherapies nivolumab, pembrolizumab and the combination nivolumab in combination with ipilimumab are very close with respect to costs and effectiveness.

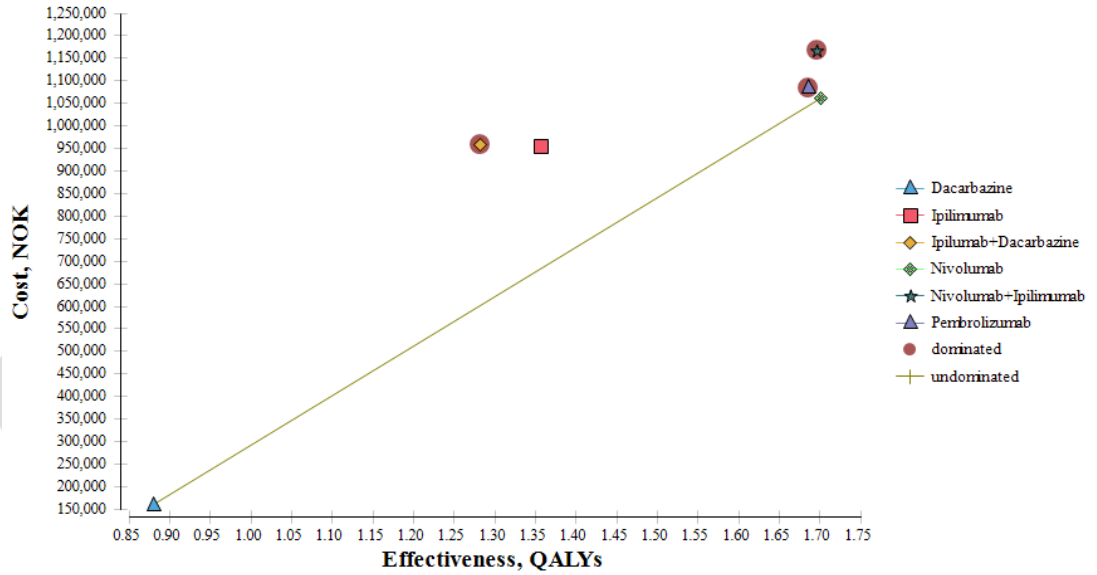

Figure 16 Cost-effectiveness graph for the immunotherapies

Table 30 and Table 31 shows the results of the incremental analysis in quality adjusted life years gained and life years gained. Nivolumab have an incremental effect of 0.82 quality adjusted life years and an incremental cost-effectiveness ratio of about 1.1 million NOK per quality adjusted life gained, the same as was described for table Table 24 and Table 25.

Table 30 Results of the incremental analysis, excluding dominated strategies (QALYs)

Intervention	Costs (NOK)	Incremental Cost	Effects (QALYs)	Incremental Effect	ICER
Dacarbazine	160,031		0.88		
Nivolumab	1,061,180	901,149	1.70	0.82	1,098,198

Table 31 Results of the incremental analysis, excluding dominated strategies (LYG)

Intervention	Costs (NOK)	Incremental Cost	Effects (QALYs)	Incremental Effect	ICER
Dacarbazine	160,827		1.30		
Nivolumab	1,063,492	902,664	2.32	1.02	885,048

Table 32 shows the incremental analysis when dacarbazine is excluded from the comparison. Please note that we used the maximum pharmacy retail prices, due to the fact that any negotiated discounts are hidden from the general public, as per contract between the Drug Procurement Cooperation system (LIS) and the manufacturers. Hence, our incremental analysis of nivolumab, pembrolizumab and the combination nivolumab and ipilimumab versus the established immunotherapy ipilimumab, have to be interpreted with caution.

The new immunotherapies, nivolumab, pembrolizumab and the combination nivolumab and ipilimumab have very similar costs and effectiveness. The combination therapy costs are only slightly higher than nivolumab and pembrolizumab in monotherapy, and this can be explained by a number of factors. Firstly, the dose reductions both for ipilimumab and nivolumab in combination therapy are substantial. Secondly, overall survival for the combination therapy is lower (0.48 versus 0.46 for pembrolizumab and 0.45 for nivolumab) which reduces the treatment costs slightly relative to the alternatives. The combination therapy also have a better effectiveness on progression free survival (0.35 versus 0.47 for pembrolizumab and 0.50 for nivolumab), which is advantegous both with respect to costs and effectiveness in the model.

Table 32 Results when all incremental cost-effectiveness ratios refer to ipilimumab (QALYs)

Intervention	Costs (NOK)	Incremental Cost	Effects (QALYs)	Incremental Effect	ICER
Ipilimumab	953,079		1.36		
Ipilumab+Dacarbazine	956,708	3,629	1.28	-0.07	-48,765
Nivolumab	1,059,893	106,814	1.70	0.35	307,651
Pembrolizumab	1,082,137	129,058	1.68	0.33	393,406
Nivolumab+Ipilimumab	1,165,460	212,381	1.69	0.34	633,271

Figure 17 shows the cost-effectiveness acceptability curves with dacarbazine, and Figure 18 without dacarbazine. When dacarbazine is included as a comparator, the

analysis shows that nivolumab and pembrolizumab and the combination nivolumab in combination with ipilimumab are more likely to be cost effective than the alternatives for willingness to pay values exceeding about NOK 1.0 million. When dacarbazine is exluded from the analysis, the differences between the new immunotherapies become more pronounced. Ipilimumab in monotherapy is more likely to be cost effective than the alternatives for willingness to pay values below NOK 0.3 million, whereafter nivolumab and pembrolizumab are more likely to be cost effective than the alternatives for increasing willingness to pay values.

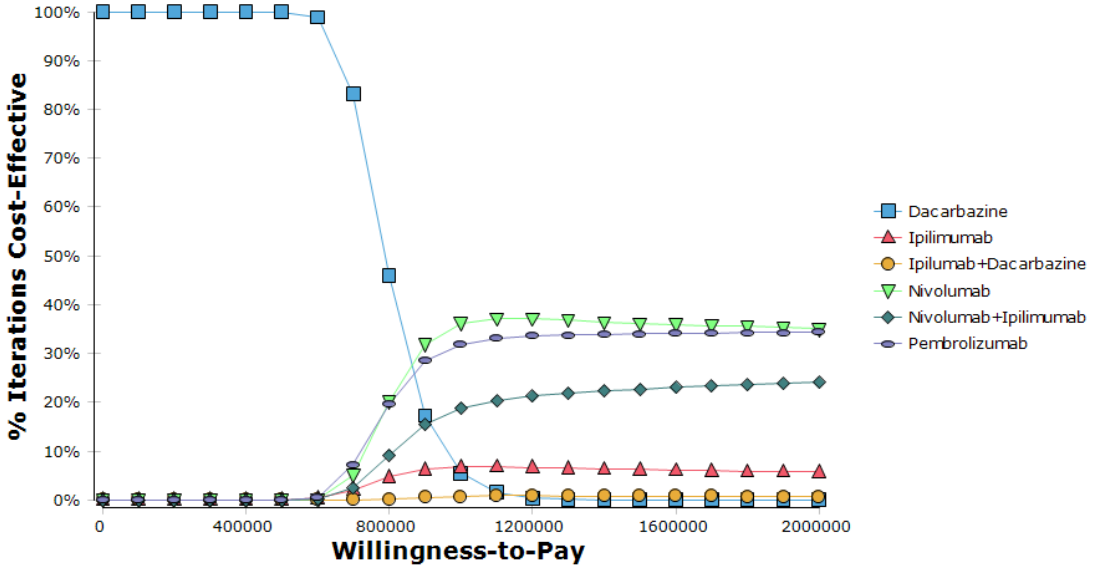

Figure 17 Cost-effectiveness acceptability curves with dacarbazine

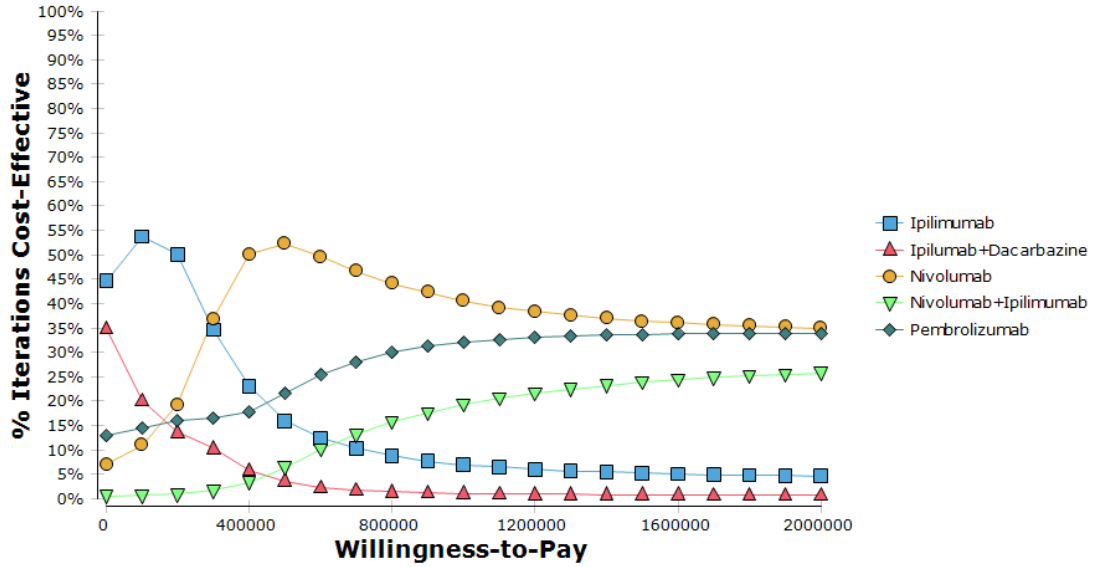

Figure 18 Cost-effectiveness acceptability curves without dacarbazine

The scatterplot in Figure 19 follows the same pattern as in Figure 8. The scatter for the new immunotherapies in monotherapy or combination therapy clusters at a higher level of effectiveness and costs than ipilimumab in monontherapy or in combination with dacarbazine.

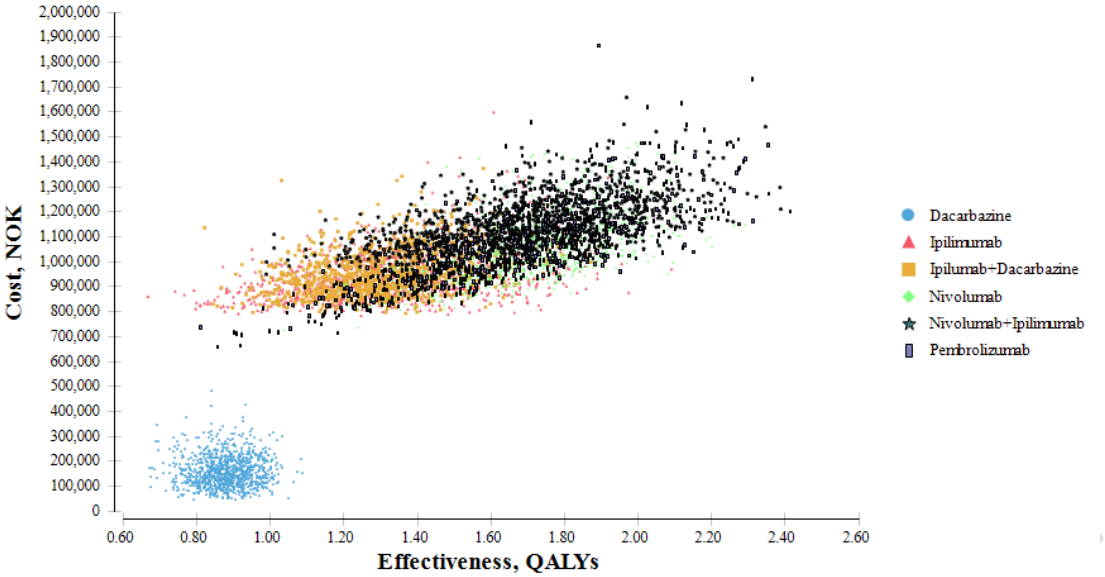

Figure 19 Scatterplot of the parenteral based immunotherapies

Scenario-analyses

Alternative drug prices:
All the prices for the new drug interventions in our analysis are maximum pharmacy retail prices.

In this scenario we will highlight the extent of price reductions that would be necessary in order for the interventions to match the intervention with the lowest incremental cost-effectiveness ratio against dacarbazine (nivolumab) as well as an incremental cost-effectiveness ratio against dacarbazine of NOK 500,000 per quality adjusted life year gained.

In

Table 33, the per-cycle drug costs (not including administration costs) were determined from a series of 1-way sensitivity analyses, changing the per-cycle drug cost of the intervention and choosing the cost that resulted in an incremental cost-effectiveness ratio compared to dacarbazine that were similar to the incremental cost-effectiveness ratio of nivolumab compared with dacarbazine.

The maximum pharmacy retail price for dabrafenib, dabrafenib in combination with trametinib, trametinib, vemurafenib, vemurafenib in combination with cobimetinib, ipilimumab, and pembrolizumab would need to be reduced by 56%, 64%, 65%, 62%, 63%, 40% and 9% respectively in order to match the incremental cost-effectiveness of nivolumab versus dacarbazine. For the combination ipilimumab+dacarbazine the drug cost of ipilimumab would need to be reduced by approximately 51%. For nivolumab in combination with ipilimumab, assuming price reduction of one drug while the other is fixed, the per cycle cost of nivolumab would have to be reduced with 65% or ipilimumab by 24%.

Table 34 shows the results for an incremental cost-effectiveness ratio of NOK 500.000 against dacarbazine. The maximum pharmacy retail price would have to be reduced by approximately 79% for dabrafenib, 83 % for trametinib, 84% for dabrafenib in combination with trametinib, 81% for vemurafenib, 84% for vemurafenib in combination with cobimetinib, 75% for ipilimumab, 63% for nivolumab and 64% for pembrolizumab. For the combination ipilimumab+dacarbazine the drug cost of ipilimumab would need to be reduced by approximately 82%. For the combination nivolumab in combination with ipilimumab, the ipilimumab price would have to be reduced by 91% if the nivolumab price was fixed. A price reduction in nivolumab alone would not be enough to bring the incremental cost-effectiveness ratio relative to dacarbazine down to 500,000 NOK per quality adjusted life year gained.

Table 33 Results of drug price scenario when the interventions refer to the incremental cost-effectiveness ratio of nivolumab to dacarbazine.

Active ingredient	Approximate drug cost per month for same ICER versus dacarbazine as trametinib	Drug cost per month in model	Difference	Percentage reduction
Dabrafenib	36,000	80,932	-44,932	56%
Dabrafenib +Trametinib	61,000	169,949	-108,949	64%
Trametinib	31,000	88,987	-57,987	65%
Vemurafenib	32,000	83,538	-51,538	62%
Vemurafenib +Cobimetinib	64,000	172,525	-108,525	63%
Ipilimumab	443,000	740,863	-297,863	40%
Ipilimumab*	364,000	740,863	-376,863	51%

+dacarbazine				
Nivolumab +ipilimumab**	Nivolumab: 10,000 Ipilimumab: 518,000	Nivolumab: 28,817 Ipilimumab: 677,360	Nivolumab: -18,817 Ipilimumab: -159,360	Nivolumab: 65% Ipilimumab: 24%
Pembrolizumab	84,600	92,902	-8,302	9%

*Reduction applies to ipilimumab only. Ipilimumab cost is not per month, but the full treatment drug cost that applies for the first month in the model.

**Reductions applies to each therapy alone keeping the other drug cost fixed.

Table 34 Results of drug price scenario when the interventions refer to a incremental cost-effectiveness ratio of NOK 500.000 per QALY gained relative to dacarbazine.

Active ingredient	Approximate drug cost per month for same ICER of 500,000 ver-sus dacarba-zine	Drug cost per month in model	Difference	Percentage reducion
Dabrafenib	17,000	80,932	-63,932	79%
Trametinib	15,000	88,987	-73,987	83%
Dabrafenib +Trametinib	28,000	169,949	-141,949	84%
Vemurafenib	16,000	83,538	-67,538	81%
Vemurafenib +Cobimetinib	28,000	172,525	-144,525	84%
Ipilimumab	182,000	740,863	-558,863	75%
Ipilimumab* +dacarbazine	136,000	740,863	-604,360	82%
Nivolumab	32,000	86,452	-54,452	63%
Nivolumab+ipilimumab*	61,000	677,360	-616,360	91%
Pembrolizumab	33,000	92,902	-59,902	64%

*Reductions applies to ipilimumab only. Ipilimumab cost is not per month, but the full treatment drug cost that applies for the first month in the model.

Treatment until progression also for the PD-1 immunotherapies and different assumptions about treatment extension

In this scenario we changed the structural assmumption regarding treatment with the new PD-1 immunotherapies, from treatment independent of progression status and gradual reduction in the proportion being treated of those alive over time, to treatment in the progression free health state only, for two years. We also extended the treatment duration from 24 months to 36 months in two scenarios, assuming further treatment for 50% and 100% of those in the progression free health state at two years following treatment. The changes were only applied to the cost side of the model.

Table 35 shows the results for our base case and the three scenarios. We believe treatment costs are likely to be underestimated for nivolumab and pembrolizumab in monotherapy when the treatment duration is limited to 24 months and to the progression free health state only. The scenario that assumes that 100% of those in progression free survival at 24 months, will be treated for another 12 months, is the closest to our base case scenario, with the exception of nivolumab in combination with ipilimumab where the treatment costs exceeds our base case for that combination. This can be explained by the effectiveness on progression free survival (hazard ratio of 0.35 compared to 0.50 for nivolumab and 0.47 for pembrolizumab). Our base case cost estimates for the immunotherapies are are independent of the transition probability from progressive free survival to progressed disease.

Table 35 Results of the scenario analyses.

Intervention	Base case model	24 months PFS only	24 months PFS only +50%	24 months PFS only +100%
Nivolumab	1,059,893	956,444	971,676	1,008,276
Pembrolizumab	1,082,137	1,002,658	1,052,403	1,099,255
Nivolumab+Ipilimumab	1,165,460	1,210,312	1,239,601	1,263,824

Time-horizon (5 years vs 10 years)

The time-horizon influences both costs and effects, but the ranking of the interventions in the incremental analysis is unchanged when we change the time time-horizon to 5 years instead of 10 years as in the base case. All other assumptions are the same as in the base case.

Table 36 Results with 5 years time horizon, first incremental analysis

Intervention	Costs (NOK)	Incremental Cost	Effectiveness (QALYs)	Incremental Effect	ICER
Dacarbazine	144,693		0.80		
Nivolumab	1,021,777	877,084	1.48	0.68	1,294,410
Vemurafenib+Cobimetinib	2,441,256	1,419,479	1.53	0.05	27,945,644

Table 37 Results with 5 years time horizon, second incremental analysis

Intervention	Costs (NOK)	Incremental Cost	Effectiveness (QALYs)	Incremental Effect	ICER
Dacarbazine	144,656		0.80		
Dabrafenib	915,999	771,343	1.09	0.29	2,649,025
Vemurafenib+Cobimetinib	2,441,364	1,525,365	1.53	0.43	3,510,567

Table 38 Results with 5 years time horizon, third incremental analysis

Intervention	Costs (NOK)	Incremental Cost	Effectiveness (QALYs)	Incremental Effect	ICER
Dacarbazine	144,597		0.80		
Nivolumab	1,021,823	877,226	1.48	0.68	1,294,205

Quality of life weights:

In this scenario we used the standard gamble weights from Beusterien (82) for all interventions, which were 0.80 for progression free survival and 0.52 in progressed disease. The tables below summarizes the results for the three incremental analyses. In the first incremental analysis, the incremental effect of nivolumab compared to dacarbazine is reduced compared to the base case analysis, resulting in a higher incremental cost-effectiveness ratio. This can be explained by the immunotherapy no longer having an advantage in health related quality of life in the progression free and progressed health state in this scenario. Although some changes in the results can be observed, the choice of health related quality of life weights and assumptions about different quality of life weights across the interventions does not seem to be decisive for the results of our cost-effectiveness analysis.

Table 39 Results with health related quality of life weights from Beusterien. Results for the first incremental analysis.

Intervention	Costs (NOK)	Incremental Cost	Effects (QALYs)	Incremental Effect	ICER
Dacarbazine	160,557		0.78		
Nivolumab	1,061,238	900,681	1.43	0.66	1,373,795
Nivolumab+Ipilimumab	1,167,382	106,144	1.50	0.07	1,526,256
Vemurafenib+Cobimetinib	2,468,363	1,300,980	1.69	0.19	6,892,259

Table 40 Results with health related quality of life weights from Beusterien. Results for the second incremental analysis.

Intervention	Costs (NOK)	Incremental Cost	Effects (QALYs)	Incremental Effect	ICER
Dacarbazine	159,949		0.78		
Dabrafenib	941,252	781,303	1.24	0.46	1,712,097
Vemurafenib+Cobimetinib	2,484,230	1,542,978	1.69	0.46	3,367,645

Table 41 Results with health related quality of life weights from Beusterien. Results for the third incremental analysis.

Intervention	Costs (NOK)	Incremental Cost	Effects (QALYs)	Incremental Effect	ICER

Dacarbazine	159,482		0.78		
Nivolumab	1,059,938	900,456	1.43	0.65	1,375,990
Nivolumab+Ipilimumab	1,167,536	107,598	1.51	0.07	1,517,905

The price of the combination vemurafenib and cobimetinib:

At the time of writing we did not have a maximum pharmacy retail price for cobimetinib. In the base case of the model we chose to assume that cobimetinib has the same price as trametinib and that the combination cost was the sum of the monthly cost of vemurafenib in monotherapy plus trametinib, resulting in a combined monthly drug cost of NOK 172,525 per month.

We did however receive a montly treatment drug price from Roche of €12,294 per month (price to wholesaler, GIP) for the combination vemurafenib and cobimetinib (Espen Movik, Health Economics Manager, Roche Norway). Multiplying with a grossist margin of 1,85% and an exchange rate of 1€=8.78 NOK we get a a pharmacy purchase price (AIP) of about NOK 109,938, and a maximum pharmacy retail (AUP) of NOK 141,586[3]. If we assume a relative dose intensity of 88% as for the other peroral drugs, the monthly drug cost in the model, if we had used the information from Roche, would be approximately NOK 124,596.

If all other drug costs remains unchanged, it is not suprising to see improvement both in terms of the incremental cost and the incremental cost-effectiveness ratio relative to the alternatives, as is shown in the tables below. In the first incremental analysis, the incremental cost-effectiveness ratio relative to nivolumab is almost cut in half. In the second incremental analysis, the combination will be the only undominated intervention among the BRAF and MEK inhibitors, but still with a very high incremental cost-effectiveness ratio over NOK 1.8 million per quality adjusted life year gained.

Table 42 Incremental analysis with all interventions when the price of vemurafenib+cobimentinib have changed

Intervention	Costs (NOK)	Incremental Cost	Effects (QALYs)	Incremental Effect	ICER
Dacarbazine	160,513		0.88		
Nivolumab	1,060,579	900,066	1.70	0.82	1,097,293
Vemurafenib+Cobimetinib	1,844,505	783,926	1.78	0.07	10,622,019

[3] Using the calculator available on the Norwegian medicines agencies webpages: http://www.legemiddelverket.no/Blaa_resept_og_pris/pris-paa-legemidler/apotekavanse/Sider/default.aspx

Table 43 Incremental analysis of the BRAF and MEK inhibitors when the price of vemurafenib+cobimentinib have changed

Intervention	Costs (NOK)	Incremental Cost	Effects (QALYs)	Incremental Effect	ICER
Dacarbazine	160,493		0.88		
Vemurafenib+Cobimetinib	1,843,128	1,682,635	1.78	0.90	1,876,632

Budget impact

Table 44 gives an overview of the input to our budgetary impact analysis. We separated the drugs into two categories, the peroral BRAF/MEK inhibitors and the parenteral based immunotherapies.

For the BRAF and MEK inhibitors, the present value of the cumulative drug cost per patient reflects what our decision model predicts for the given dosages and treatment duration (2 years). The differences in costs between the interventions are large and the treatment durations, which are dependent on time in the progression free survival health state, explain some of the observed variation (see

Table 46). The administration costs are very low for the peroral therapies.

The parenteral based immunotherapies have more similar drug costs per patient, with ipilimumab demonstrating the lowest expected cumulative drug cost. The combination ipilimumab+nivolumab have only slightly higher expected costs per patient than nivolumab in monotherapy. The administration costs are higher than for the peroral drugs, but still low relative to the drug cost. The drug costs for ipilimumab as well as the new PD-1 immunotherapies are independent of time in the progressive free survival health state in our model. As for the BRAF/MEK inhibitors, the treatment duration is limited to two years.

Table 46 shows the median treatment time and median survival as predicted in the model. The peroral combination therapies have longer treatment duration than the monotherapies, but also longer expected survival.

Table 44 Overview of the input to the budget impact calculations for maximum pharmacy retail price (PRP).

Intervention	Present value of cumulative drug cost per patient (2 yrs) (NOK)	Present value of cumulative administration/dispensing cost per patient (NOK)	Total costs
Peroral, BRAF/MEK inhibitors			
Dabrafenib	768,710	3,937	772,647
Dabrafenib + trametinib	2,288,728	5,584	2,294,312

Trametinib	716,010	1,668	717,678
Vemurafenib	781,219	3,878	785,097
Vemurafenib + cobimetinib	2,234,637	5,371	2,240,008
Parenteral based immunotherapies			
Ipilimumab	740,863	4,592	745,455
Ipilimumab + dacarbazine	745,876	11,236	757,111
Ipilimumab + nivolumab	916,761	32,112	948,873
Nivolumab	783,983	31,028	815,011
Pembrolizumab	830,750	20,685	851,436

Table 45 Overview of the input to the budget impact calculations when the prices have been reduced accordring to the price scenarios in table 36.

Intervention	Present value of cumulative drug cost per patient (2 yrs) (NOK)	Present value of cumulative administration/dis-pensing cost per patient (NOK)	Total costs
Peroral, BRAF/MEK inhibitors			
Dabrafenib	768,710	3,937	772,647
Dabrafenib + trametinib	2,288,728	5,584	2,294,312
Trametinib	282,608	1,668	284,276
Vemurafenib	781,219	3,878	785,097
Vemurafenib + cobimetinib	2,234,637	5,371	2,240,008
Parenteral based immunotherapies			
Ipilimumab	602,119	4,592	606,711
Ipilimumab + dacarbazine	607,132	11,236	618,367
Ipilimumab + nivolumab	851,489	32,112	883,601
Nivolumab	816,611	31,028	847,639
Pembrolizumab	865,336	20,685	886,022

Table 46 Overview of median treatment time and median survival in the model.

Intervention	Median treat-ment duration (months)	Median survival (months)	Median survival/ median treatment duration
Peroral, BRAF/MEK inhibitors			
Dabrafenib	6.5	11.5	1.8
Dabrafenib + trametinib	13.5	17.5	1.3

Trametinib	5.5	11.0	2.0
Vemurafenib	6.5	11.5	1.8
Vemurafenib + cobimetinib	12.0	17.5	1.5
Parenteral based immunotherapies			
Ipilimumab	3.0*	12.5	4.2
Ipilimumab + dacarbazine	3.0*	12.5	4.2
Ipilimumab + nivolumab	10.5**	18.5	1.8
Nivolumab	12.5***	20.5	1.6
Pembrolizumab	12.5***	19.5	1.6

*Not predicted in model, but it is the normal treatment length if the patient gets all four doses over a 3 month period.

**Applies to nivolumab in combination therapy.

*** By assumption, the median treatment duration for nivolumab and pembrolizumab in monotherapy are the same in the model.

The budgetary impacts for the next 5 years are difficult to predict. The impacts will for instance be dependent on any change in clinical practice from current practice, the number of patients eligible for the different treatment options in any given calendar year, the treatment durations and the drug prices. Also, the price paid by the regional health authorities consists of the maximum pharmacy retail price, adjusted for any discount negotiated through the Drug Procurement Cooperation system (LIS). The discounts are not publicly available for the interventions in this analysis, and because we can't use the actual LIS prices, we don't have a correct baseline for the budget impact estimation.

We will therefore present the budgetary impacts in the form of potential savings to the budget in a case where LIS may have achieved substantial discounts in the region 63-91% of the maximum pharmacy retail prices across the new interventions, using the results of the price scenarios in Table 34 where drug prices were adjusted according to an incremental cost-effectiveness ratio against dacarbazine of 500,000 NOK per quality adjusted life year gained.

We assume that the new immunotherapies, nivolumab, pembrolizumab, and the combination nivolumab+ipilimumab have equal market shares of 33.3%, throughout a 5 year period, assuming 200 patients each year. For the BRAF/MEK inhibitors, we assume that the combination therapies each have 33.3% market share with the remaining 33.3% divided between the monotherapies, assuming 100 patients each year.

Table 47 shows the results. The potential annual savings from the immunotherapies are about NOK 109 million per year and for the BRAF/MEK inhibitors NOK 140 million per year. The combined savings accumulates over a 5 year period to about NOK 1,248 million.

Table 47 The results of the budget impact analysis, when comparing the maximum pharmacy retail price with the discounted price that results in an incremental cost-effectiveness ratio against dacarbazine of 500,000 NOK per quality adjusted life year gained.

Budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
Immunotherapies					
Max pharmacy retail price	174,180,282	174,180,282	174,180,282	174,180,282	174,180,282
With discount	64,823,945	64,823,945	64,823,945	64,823,945	64,823,945
Savings	109,356,337	109,356,337	109,356,337	109,356,337	109,356,337
BRAF/MEK inhibitors					
Max pharmacy retail price	176,250,027	176,250,027	176,250,027	176,250,027	176,250,027
With discount	35,957,700	35,957,700	35,957,700	35,957,700	35,957,700
Savings	140,292,327	140,292,327	140,292,327	140,292,327	140,292,327
Total accumulated savings	249,648,664	499,297,328	748,945,992	998,594,656	1,248,243,319

Discussion

In this health technology assessment we have compared the effectiveness and cost-effectiveness of seven new drugs used for inoperable or metastatic malignant melanoma patients. Six of these drugs, dabrafenib, ipilimumab, nivolumab, trametinib and vemurafenib have received marketing authorization in Norway at the time of writing this health technology assessment; and cobimetinib has not. For the effectiveness analyses we have systematically reviewed and summarized 17 randomized controlled trials, published in a total of 24 articles and 16 abstracts/posters between 2010 and 2015. We have focused on the clinical important endpoints such as overall survival, progression free survival, health related quality of life, and serious adverse events.

Summary of results

Clinical effectiveness

We performed both pairwise analyses and network meta-analysis for each endpoint individually.

For pairwise comparisons we had 15 possible comparisons. For overall survival, progression free survival and serious adverse events there were only two head to head comparison of two monotherapies: pembrolizumab versus ipilimumab (9); and nivolumab versus ipilimumab (39). In both cases a difference in favour of the intervention group (pembrolizumab and nivolumab respectively) could be established for all the three endpoints. There was no head to head comparisons of two monotherapis for health related quality of life.

Further, five comparison directly compared a combination therapy versus a monotherapy. The comparison dabrafenib in combination with trametinib versus vemurafenib was the only one that included all our endpoints, and for all these endpoints we could established a difference in favour of the combination group.
None of the included trials compared a BRAF inhibitor (dabrafenib or vemurafenib) head to head with a drug acting on the immune system.

More information about the pairwise comparisons can be seen in Appendix 6.

Our aim are to assess the effectiveness and cost-effectiveness of the new drugs used for inoperable or metastatic malignant melanoma patients relative to each other. However, due to paucity in data for direct comparisons the best available comparisons are the indirect evidences via dacarbazine as a common comparator.

Hence, our conclusions for the relative comparisons of the included drugs or combinations of drugs are based on the network meta-analyses. Further, we indicate a ranking of the different drugs for each endpoint in terms of their probability of leading to the best results by help of SUCRA (the surface under the cumulative ranking curve) and by grading the evidence from the network analyses (using the GRADE approach for network meta-analyses). For overall survival, progression free survival and serious adverse events all the interventions/treatment strategies were included in the network, hence they could all be compared relative to dacarbazine. Due to insufficient data we could not performed a network meta-analysis for health related quality of life.

Based on the results of the network meta-analyses (ranking as measured by the SUCRA) as well as the quality of the evidence (GRADEing of the network analyses):

Comparisons of the efficacy for the BRAF/MEK inhibitors versus the immunotherapies

Nivolumab, pembrolizumab, nivolumab in combination with ipilimumab, vemurafenib in combination with cobimetinib, and dabrafenib in combination with trametinib seem to have a higher probability of good performance for overall survival than monotherapies with a BRAF inhibitor or a MEK inhibitor. Dabrafenib in combination with trametinib, and vemurafenib in combination with cobimetinib seem to have a higher probability of good performance for progression free survival than the immunotherapies, as well as the monotherapies of BRAF- and MEK inhibitors. Ipilimumab has poorer progression free survival than monotherapies of the BRAF inhibitors, as well as the BRAF inhibitors in combination with a MEK inhibitor. Pembrolizumab og nivolumab seem to have a higher probability of fewer serious adverse events than monotherapies of the BRAF inhibitors, as well as the BRAF inhibitors in combination with a MEK inhibitor. We have no results from network meta-analyses for health related quality of life.

- *Comparisons of the efficacy for the BRAF/MEK inhibitors*

The combination treatments with a BFRA inhibitor and a MEK inhibitor seem to have higher probability of good performance for overall survival and progression free survival than the monotherapies. For serious adverse events we could not establish any differences between the combination treatments and the monotherapies. For health related quality of life, we have only results from a pairwise comparison (dabrafenib in combination with tramentinib versus vemurafenib), which reported better health related quality of life in the combination group.

- *Comparisons of the efficacy for the immunotherapies*

Nivolumab and pembrolizumab seem to have higher probability of good performance for overall survival, progression free survival and serious adverse events than ipilimumab in monotherapy. Nivolumab in combination with ipilimumab seem to have higher probability of good performance for overall survival and progression free survival than ipilimumab in monotherapy. For serious adverse events we could not establish any differences between the combination treatment and ipilimumab in monotherapy. We have no results from network meta-analyses for health related quality of life.

Of the endpoints studied in this health technology assessment, we consider overall survival to be of higher importance than progression free survival, since progression free survival is a surrogate endpoint. However, health related quality of life and serious adverse events are also of great importance for these patients. From the included trials we were not able to find data usable for our analyses for health related quality of life, and the quality of the evidence for serious adverse events were mostly low and very low.

In this health technology assessment we also included the two MEK inhibitors cobimetinib and trametinib, the first without marketing approval in Norway at time of writing. According to the literature, the MEK inhibitors may have the potential to reduce the resistance seen to BRAF inhibitors (15, 45). Our results show that the combination of a BRAF inhibitor and a MEK inhibitor comes out better than the same drugs used as monotherapy, both for overall survival and progression free survival, while the monotherapies of the BRAF inhibitors may have a similar number of serious adverse events as compared to the combination treatment.

Economic evaluation

The economic model predicts a median survival of about 12.5 months for ipilimumab and about 19 months for the new immunotherapies. The immunotherapies have quite similar expected drug costs per patient, with ipilimumab demonstrating the lowest expected cumulative drug cost. The combination ipilimumab in combination with nivolumab have only slightly higher expected costs per patient than nivolumab in monotherapy. The administration costs for parenteral based drugs are higher than for the peroral drugs, but still low relative to the drug cost.

The median survival for the BRAF/MEK monotherapies are about 11 months and for the combination therapies, 17.5 months. The differences in costs between the BRAF/MEK interventions are more pronounced when compared to the immunotheraphies. The administration costs are very low for the peroral based therapies.

Generally, all the interventions have very high incremental cost-effectiveness ratios. We are not allowed to refer to any discounts from the maximum pharmacy retail price that may already have been achieved through the Drug Procurement Cooperation system (LIS). We therefore used the maximum pharmacy retail price in this

analysis and the ranking of the interventions as well as the budget impacts may change as a result of price changes.

The first incremental analysis includes all the interventions included in the network meta-analysis. The new immunotherapies nivolumab, pembrolizumab and the combination nivolumab in combination with ipilimumab clusters together in the cost-effectiveness plane, for similar levels of costs and effectiveness, but at a noticeably higher effectiveness than ipilimumab in monotheraphy or any of the BRAF/MEK inhibitors. The BRAF/MEK combination therapies have about the same effectiveness, but higher costs compared with the new immunotherapies. Nivolumab and the combination vemurafenib and cobimetinib are the two undominated strategies in the incremental analysis. Nivolumab has an incremental effect of 0.82 quality adjusted life years and an incremental cost-effectiveness ratio against dacarbazine of about 1.1 million NOK per quality adjusted life year gained. The combination vemurafenib and cobimetinib has an incremental effectiveness of 0.07 quality adjusted life years and an incremental cost-effectiveness ratio of about 19.8 million NOK per quality adjusted life year gained against nivolumab. In the cost-effectiveness acceptability curves, nivolumab and pembrolizumab have quite similar levels of iterations being cost effective, closely followed by the combination nivolumab and ipilimumab.

When we restrict the incremental analysis to the BRAF/MEK inhibitors, dabrafenib and the combination vemurafenib and cobimetinib are the two undominated strategies. Dabrafenib has an incremental effect of 0.36 quality adjusted life years and an incremental cost-effectiveness ratio compared to dacarbazine of approximately NOK 2.2 million per quality adjusted life year gained. The combination vemurafenib and cobimetinib has an incremental effect of 0.53 quality adjusted life years and incremental cost-effectiveness ratio compared to dabrafenib of about NOK 2.9 million per quality adjusted life year gained. In the cost-effectiveness acceptability curves, the BRAF/MEK monotheraphies have a higher probability of being cost-effective for the lowest willingness to pay values, and the combination strategies show an increasing trend for very high willingness to pay values. The BRAF and MEK inhibitor monotherapies (dabrafenib, vemurafenib, trametinib) all have very similar costs and effectiveness. The same applies to the BRAF/MEK combinations (dabrafenib and trametinib or vemurafenib and cobimetinib), but at a higher level of costs and effectiveness.

When the incremental analysis is limited to the immunotherapies, nivolumab is still the only undominated intervention. Nivolumab, pembrolizumab and the combination nivolumab and ipilimumab all have very similar incremental effectiveness and costs, and we cannot conclude that any one of these interventions are more cost effective than the alternatives. In the cost-effectiveness acceptabilility curves, the new PD-1 immunotherapies in monotherapy however have a slight advantage over the combination nivolumab and ipilimumab.

The scatterplots indicates much uncertaintly in the results, particularly for effectiveness. The expected value of partial perfect information analysis identified the efficacy data used in the model as the dominating source of parameter uncertainty, followed by health related quality of life data, costs and serious advers events.

The choice of time horizon (5 yrs versus 10 yrs) or quality-of-life weights (SG versus EQ-5D) does not seem to influence the ranking of the alternatives in this analysis.

The structural uncertainty surrounding how to model the treatment with nivolumab and pembrolizumab was investigated in a scenario analysis. Our base case cost estimates for the immunotherapies are independent of the transition probability from progressive free survival to progressed disease, and is closest to a scenario that assumes that 100% of those in progression free survival at 24 months, will be treated for another 12 months.

The maximum pharmacy retail price would have to be reduced by approximately 63-91%, depending on drug, in order to obtain incremental cost-effectiveness ratios relative to dacarbazine of 500,000 NOK per quality adjusted life year gained. For such price reductions, the annual budgetary savings could be about NOK 249 million and the accumulated budgetary savings over a 5 year period NOK 1,248 million.

Overall summary of results

None of the interventions included in the systematic review and economic evaluation are cost effective at the maximum pharmacy retail prices. The budgetary impact and incremental cost-effectiveness ratios can however be reduced through price reductions. Drug price reductions from the maximum pharmacy retail prices in the region of 63-91%, are necessary in order for the new interventions to represent more cost-effective use of resources in the Norwegian health sector.

The results from the network meta-analyses indicates that in addition to nivolumab and pembrolizumab, the combination treatments for nivolumab and ipilimumab, vemurafenib and cobimetinib; and dabrafenib in combination with trametinib seems to have a higher probability of good performance than the other available treatment strategies for overall survival. For progression free survival dabrafenib in combination with trametinib, and vemurafenib in combination with cobimetinib seems to have a higher probability of good performance than the other available treatment strategies.

In Norway, health care decisions are not necessarlily linked to a defined threshold value. All the estimated incremental cost-effectiveness ratios in this analysis are very high, and represents a challenge for any decision maker that aims to prioritise within a fixed health care budget. Allocating resources to these interventions without price reductions may potentially inflict on other interventions or treatment areas in the health sector and lead to a net health loss.

Quality of the clinical evidence

We assessed the quality of the evidence for overall survival, progression free survival and serious adverse events for all the comparisons with direct evidence. By doing so we have also assessed the quality for the loops the indirect evidence consist of. The quality of the indirect evidence was equal to the lowest quality of the comparisons in that loop. The quality of the combined evidence from the network meta-analyses are based upon the highest quality obtained from the respective direct and indirect assessments. We did these assessments by using the GRADE approach for network meta-analyses.

For overall survival and progression free survival we assessed the quality of the evidence to be moderate or high for the majority of our assessments. For serious adverse events we assessed the quality to be low or very low in most of our assessments. Due to insufficient data we were not able to use the GRADE method for the endpoint health related quality of life.

The main reasons for downgrading were weaknesses associated with the study design and imprecise results. We downgraded for study design for the seven trials that allowed the participants randomized to the control group to cross over to the intervention group after progression. This had implicationfor overall survival and serious adverse events. The downgradings for imprecision were because the 95% confidential interval was wide and included null effect and/or few events. As shown in the Summary of Findings Tables in Appendix 8, the downgrading for imprecision were used for all the endpoints, but has most impact for serious adverse events.

Strengths and weaknesses of this report

Clinical effectiveness

Strengths

We only included randomized controlled trials to assess clinical effectiveness. We identified trials from our systematic literature search, and we also asked the manufactures to provide relevant literature that we had not identified. We received an additional five full text articles and nine abstracts/posters. Some of this additional literature was not present in the databases at the time of our search for literature.

All the interventions could be included in our network meta-analyses.

Our clinical endpoints were all well-defined and harmonized in their definitions. A few trials did not define some of the endpoints, or they may differ slightly, but the trials that reported an explicit definition of the endpoint, did it in the same way. Overall survival was defined specifically as the time from randomization to death

from any cause. Progression free survival was defined as the time from randomization to the earliest date disease progression or death due to any cause. Progression free survival was assessed by the investigator (14 of 15 trials), and confirmed by an independent review committee in eight of the trials (in one study progression was only assessed by the independent review committee). Health related quality of life was measured by the same instrument (EORTC-QLQ-C30) in all the nine trials reporting this outcome. Serious adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.for the majority of the trials. As a consequence, the trials reported the adverse events in the same way, by splitting the adverse events in the same way using grade groups from 1 to 4 (or in a few cases four or higher, i.e. including group 5). We have included serious adverse events reported as grade 3 and 4 (and 5 if reported).

Overall survival was measured with up to 3 years follow-up for two comparisons: dabrafenib versus dacarbazine (56) and dabrafenibin combination with trametinib versus dabrafenib (52, 63), and up to five years for the comparison ipilimumab in combination with dacarbazine versus dacarbazine (50). The results from these analyses did not differ substantially from earlier reports measuring OS up to two years.

For overall survival and progression free survival the results of the pairwise estimates performed in RevMan and network meta-analyses are consistent. That is, the results from network meta-analyses and pairwise comparisons are similar in magnitude and direction. For serious adverse events the results from the pairwise estimates performed in RevMan and network meta-analyses are consistent when it comes to the ability to conclude, but the estimated direction of the difference relative to dacarbazine seems to differ between the pairwise comparisons and the network-meta-analysis for vemurafenib and dabrafenib (for neither of the treaments, neither the pairwise comparisons nor the network meta-analysis could establish a difference relative to dacarbazine).

Weaknesses
Due to insufficient data we could not perform network meta-analysis for health related quality of life, hence we were not able to draw any conclusions for the relative efficacy of the interventions for this endpoint.

However, four trials reported better health related quality of life in the intervention group as compared to the control group (dabrafenib versus dacarbazine, trametinib versus dacarbazine/paclitaxel, pembrolizumab versus investigator choice of chemoterapy and dabrafenib in combination with trametinib versus vemurafenib respectively).

Seven of the trials allowed patients in the control group to cross over to the intervention group after progression. The statistical analyses of the endpoint overall survival was based on the intention to treat population in all seven trials, i.e. the analyses

were done without taking the crossover into account. By doing this, the assumption underlying the statistical analysis is that crossover does not alter mortality patterns. In one of the publications, this was pointed out as a weakness (11). However, we decided to include these data since the results for the intervention will not be favoured. One of the trials that allowed cross over of patients from the control group to the intervention group did, however, present results from both analyses where participants who crossed over were censored at the time of cross-over, and analyses without censoring (61). In our network meta-analyses we only included the data without censoring at time of cross over, since this was what we had for all the other trials.

Economic evaluation

Strengths
We based the economic evaluation on a thorough systematic review of the literature and network meta-analysis to inform the treatment effects and serious adverse events in the model.

We included a wide spectrum of relevant costs from the health care perspective with close assistance of experts in the field.

We have used a well-known three-health state probabilistic Markov model design used by many other economic evaluations within the cancer field, which utilizes the most important clinical endpoint, the effect on overall survival. The output from the probabilistic model provides information relevant for the decision uncertainty and on what parameters more research should be directed.

Weaknesses
We did not have individual-level state history data to inform our transition probabilities, and the randomized controlled trial data we used were not from a Norwegian patient population. The analysis is dependent on the validity of the baseline overall survival and progression-free-survival functions, and the estimation of transition probabilities from aggregate data may have introduced errors.

There is uncertainty with regards to the correct treatment duration in the model, both both for the new immunotherapies and the BRAF/MEK inhibitors. For the latter the treatment duration is sensitive to time in the progression free health state. Treatment. See

Table 46 for an overview of median treatment durations in the model.

We are extrapolating the effectiveness data beyond the clinical trial follow-up period for nivolumab, nivolumab in combination with ipilimumab, pembrolizumab and vemurafenib in combination with cobimetinib. Use of the hazard ratio in our model assumes constant proportional hazards. Altough the assumption is assumed to hold for the study follow-up period in the pairwise comparisons and in the network meta-

analysis, the extrapolation increases the uncertainty regarding the validity of this assumption.

The results are dependent on strong assumptions regarding treatment efficacy across different subgroups. Analysis one and three rests on the assumption that the treatment effects of the immunotherapies are the same regardless of BRAF status. For the BRAF/MEK inhibitors in analysis two we assume that past treatment with immunotherapy not influence the treatment effects. We have however not found indications in our material that rejects these assumptions.

Differences between the drugs with respect to survival before and after progression are not captured in our model. The assumption of equal overall survival, before and after progression may generally overestimate the mortality before progression and underestimate the mortality after progression, for all interventions.

Important differences between the interventions regarding patients health related quality of life may not have been captured in our analysis, due to very limited evidence on health related quality of life of the alternative interventions.

The unit prices were generally drawn from official price tariffs or hospital diagnosis related groups with the assumption that the reimbursement covers 100% of the cost of the health care provision. We also assumed that all costs were gamma distributed with the point estimate as the mean and the standard error 0.5 times the mean. Both assumptions may lead to possible underestimation or overestimation of actual costs.

Our results compared to other findings/other reviews or results

To our knowledge a relative comparison for all the different new drugs used for inoperable or metastatic malignant melanoma patients has not been done by any others, neither for effectiveness nor for cost-effectiveness.

The Norwegian Medicines Agency (NMA), Canadian Agency for Drugs and Technologies in Health (CADTH), and National Institute for Health and Clinical Excellence (NICE), have performed single technology assessments on drugs used for metastatic melanoma. This has been done for dabrafenib versus dacarbazine (17)(NICE), dabrafenib in combination with trametinib versus dabrafenib (16)(CADTH), dabrafenib in combination with trametinib versus vemurafenib (16, 24)(CADTH), ipilimumab in combination with gp100 versus ipilimumab in previous treated patients (18-20)(NMA, CADTH, NICE), ipilimumab in previous untreated patients (indirect comparisons to dacarbazine, vemurafenib and dabrafenib (21)(NICE), trametinib versus dacarbazine (22)(CADTH) and vemurafenib versus dacarbazine (23, 24)(NICE, CADTH). In our health technology assessment we have included all the trials used in these assessments. None of these assessments has compared all the different new drugs for advanced metastatic malignant melanoma patients relatively

to each other. We have therefore conducted this health technology assessment including all the new drugs for these patients in a Norwegian setting to be able to identify which intervention is most cost-effective.

We have chosen not to explicitly compare our incremental cost-effectiveness results with the results of other single technology assessments. Any such comparison would be highly dependent on how data on clinical effectiveness was used in the model, structural assumptions in the decision model and differences in cost data.

Conclusion

Relative effectiveness for seven new drugs used for advanced malignant melanoma patients have been synthesized in a systematic review including 17 randomized controlled trials presented in 40 publications.

The drugs are: Cobimetinib, dabrafenib, ipilimumab, nivolumab, pembrolizumab, trametinib and vemurafenib. These are used as monotherapy or in combination with each other.

We have used both direct and indirect evidence and performed network meta-analyses for each clinical endpoint which allows a ranking of the different interventions relative to each other.

The cost-effectiveness analysis were based on the maximum pharmacy retail prices for the new interventions. We are not allowed to refer to any discounts from the maximum pharmacy retail price that may have been achieved through the Drug Procurement Cooperation system (LIS), because the contracts are not open to the public.

None of the interventions are cost-effective at the maximum pharmacy retail prices. The budgetary impact of accepting some or all of the new interventions in clinical practice can be substantial, potentially diverting resources away from other interventions or treatment areas with better cost-effectiveness. The budgetary impact and incremental cost-effectiveness ratios can however be reduced through price reductions. We believe that drug price reductions in the region of 63 to 91 percent, depending on drug, would be necessary for the interventions to represent cost-effective use of resources in the Norwegian setting.

We find it difficult to separate the new immunotherapies nivolumab and pembrolizumab, or the combination nivolumab and ipilimumab with respect to cost-effectiveness. If the new immunotheraphies are accepted in clinical practice, we expect increased effectiveness compared to ipilimumab in monotherapy, but at an increased cost. The potential budgetary savings with price reductions from the maximum pharmacy retail price may be as high as NOK 109 million per year.

Based on the cost-effectiveness results, we cannot argue that any of the BRAF or MEK inhibitor monotherapies (dabrafenib, vemurafenib, trametinib), should be preferred over another, or that any BRAF/MEK combination (dabrafenib and trametinib or vemurafenib and cobimetinib), should be preferred over another. However, the combination therapies are more likely to give the highest quality adjusted life year gains in the long run. For the BRAF/MEK inhibitors, the potential budgetary savings with price reductions may be as high as NOK 140 million per year.

All conclusions are given with respect to the current state of the evidence and with the reservation that new evidence from randomized controlled trials can change the ranking of the interventions both with regards to effectiveness and cost-effectiveness (one of the interventions still do not have marketing authorization).

Need for further research

The sensitivity analysis showed that the clinical effectiveness data is the most influental source of uncertainty, followed by health related quality of life data, costs and the relative risks for serious adverse events.

It is expensive to conduct or to co-finance randomized controlled trials. However, it is worthwile conducting more research if the value of added information reduces the decision uncertainty, and the expected returns exceeds the costs of the research.

It is a need for more research

- to confirm the studies available
- comparing the interventions directly
- on subgroups of the advanced malignant melanoma population
- on health related quality of life
- longer-term trials both for monotherapies and combination therapies for efficacy (to follow development of resistance for the BRAF inhibitors and safety)
- on optimal treatment time for the different drugs and combination of drugs
- on the optimal sequence of the alternative treatments
- combination of drugs with different mechanisms of actions

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