M-VAX™ – a treatment for patients with advanced stage III melanoma

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Assessment report

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The Medical Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which medical services should attract funding under Medicare.

This report was prepared by the Medical Services Advisory Committee with the assistance of Dr Adèle Weston, Mr Lachlan Standfield and Ms Alison Hillman from M-TAG Pty Ltd. The report was endorsed by the Commonwealth Minister for Health and Ageing on 8 October 2002.

Publication approval number: **3185**

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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The procedure

M-VAX™ is a vaccine composed of autologous melanoma cells modified with the hapten dinitrophenyl (DNP). The vaccine induces a cell-mediated immunity, which results in a delayed inflammatory response. The vaccine is manufactured with tumour cells obtained from the patient at the time of lymph node resection. Typically, a tumour of at least 3 cm in diameter is required to harvest sufficient cells to produce the patient-specific vaccine.

Vaccination commences after recovery from surgery and involves seven intradermal doses within six months. An intravenous bolus dose of cyclophosphamide is given six days after a 'skin test' using M-VAX™ without bacille Calmette-Guérin (BCG). The vaccine is administered together with BCG to maximise immunogenicity.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. Medical Technology Assessment Group (M-TAG Pty Ltd) was contracted to conduct a systematic review of literature regarding the use of the autologous vaccine M-VAX™ for the treatment of advanced stage III melanoma. A supporting committee with appropriate expertise then evaluated this evidence and provided advice to MSAC.

MSAC's assessment of M-VAX™

Clinical need

Melanoma is a cancer that develops in the pigment-producing cells of the skin. There is a strong association between sun exposure and melanoma development, particularly, but not exclusively, in individuals with a fair complexion.

In 1998, a total of 7891 people were diagnosed with melanoma in Australia (4398 men, 3493 women), an annual incidence of 32 per 100,000.[1] This equates to a lifetime risk of the disease of 1 in 30. The incidence is higher in Queensland and Western Australia than in other Australian states.

[1]Standardised to World Standard Population.

If melanoma cells penetrate into the dermis, they are likely to spread elsewhere. Initially, the melanoma will spread to the nearby lymph nodes, at which point it is classified as stage III disease. Lymph node resection is strongly recommended for local control of the disease and as a potentially curative procedure. After tumour resection, there are two broad adjuvant treatment options currently available to Australian stage III melanoma patients: observation or interferon α-2b. Interferon α-2b is currently used to treat a small minority of these patients. Therefore, observation is the comparator treatment for the purposes of this assessment.

Despite adjuvant treatment of stage III melanoma, progression to distant metastatic disease often occurs. The prognosis for these patients is currently poor. Approximately 1000 people die from melanoma in Australia each year, equating to approximately one in every eight people diagnosed with the disease.

It is estimated that approximately 250 patients undergo resection of lymph tissue for the treatment of melanoma in Australia each year. Of these, it is estimated fewer than 105 would be suitable for treatment with M-VAX™.

Safety

Mild nausea and vomiting occur in the majority of patients receiving M-VAX™, probably secondary to the use of cyclophosphamide. Injection site reactions are also common. Other adverse reactions are poorly reported. In the US, there have been several reports of contaminated vaccine being administered to patients.

After reviewing the available evidence, it was concluded that it is not possible to make a reliable comparison of the relative safety of M-VAX™ and observation. This is because only uncontrolled and poorly reported data are currently available for M-VAX™.

Effectiveness

At present, the highest level of evidence available to describe the efficacy of M-VAX™ as an adjuvant treatment for stage IIIB and IIIC melanoma, is level IV evidence. The primary evidence was data collected in four prospective, phase II, uncontrolled clinical trials. Furthermore, the dose regimens vary across the four trials, none of which are consistent with the dose regimen for which reimbursement is being sought.

On the basis of the available data, it is not possible to make a comparison of the relative efficacy of M-VAX™ and observation without the introduction of considerable bias.

Cost-effectiveness

There are insufficient data available to make a valid comparison of the relative efficacy of M-VAX™ and observation alone. Therefore, it is not possible to estimate the cost-effectiveness of M-VAX™ relative to observation. However, M-VAX™ is considerably more costly than observation (~$39,000 per patient).

Recommendation

MSAC recommended that on the strength of evidence pertaining to M-VAX™, a treatment for patients with advanced stage III melanoma, public funding should not be supported for this procedure.

The Minister for Health and Ageing accepted this recommendation on 8 October 2002.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of M-VAX™, which is a treatment for AJCC[2] stage IIIB and IIIC melanoma. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at **Appendix A**. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine, general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for M-VAX™ as a post-surgical adjuvant treatment of stage IIIB and IIIC melanoma.

[2]American Joint Committee on Cancer staging system (Balch *et al* 2001a).

Background

M-VAX™

The procedure

M-VAX™ is a vaccine composed of autologous melanoma cells modified with the hapten dinitrophenyl (DNP). The vaccine induces a cell-mediated immunity, which results in a delayed inflammatory response.

For the purposes of the current assessment, the indication[3] is:

> "for the post-surgical adjuvant treatment of patients with histologically confirmed stage IIIB[4] and IIIC melanoma who have a lymph node tumour of approximately 3 cm diameter or larger".

The vaccine is manufactured with tumour cells obtained from the patient at the time of lymph node resection. A minimum of 50 million cells are required to produce the patient-specific vaccine, which typically translates to a tumour of at least 3 cm in diameter. The resected tumour must be transported in sterile, refrigerated conditions and reach the company's central processing laboratory in Sydney within 48 hours. The tumour material is processed aseptically and cryopreserved in aliquots. The preparation of the vaccine itself only commences when the clinician notifies the company that the patient is ready for vaccination, as each batch of vaccine remains viable for only 18 hours. Therefore, the vaccine preparation process must be repeated for each of the eight doses occurring over a six-month period. This manufacturing process is currently under review, to allow for an improved shelf life and more comprehensive sterility testing.

Vaccination commences after recovery from surgery. After the initial skin test, doses are administered 9, 16, 23, 30, 37 and 44 days later and again after 6 months. An intravenous bolus dose of cyclophosphamide (300 mg/m^2) is given 6 days after the skin test. The vaccine is administered together with bacille Calmette-Guérin (BCG) to maximise immunogenicity. Paradoxically, the cyclophosphamide given on day 6 of the vaccine regimen also augments the immune response.

The vaccine is administered intradermally within 18 hours of production. For the majority of patients, the preferred injection site is the upper dorsal arm. However, for patients who have undergone bilateral axillary node dissection, the upper lateral thigh is recommended.

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[3]As M-VAX is an autologous vaccine, it is exempt from Part 3 of the Therapeutic Goods Administration Act 1989. As a result, there is no TGA-approved indication in Australia. The indication referred to in this assessment report is that for which reimbursement listing on the Medicare Benefits Schedule is sought.

[4]Also included within stage IIIB are patients a) with up to three clinically occult nodes but an ulcerated primary melanoma and b) with satellite or in-transit metastases but no evidence of nodal or distant metastases. However, M-VAX is not indicated for use in these patients.

Intended purpose

M-VAX™ is indicated as a therapeutic intervention for advanced melanoma. Specifically, this assessment focuses on the use of M-VAX™ as a post-surgical adjuvant treatment of histologically confirmed melanoma with large (> 3 cm) nodal metastases. This group of patients falls within stage IIIB or IIIC of the American Joint Committee on Cancer (AJCC) pathological staging classification.[5]

Clinical need / burden of disease

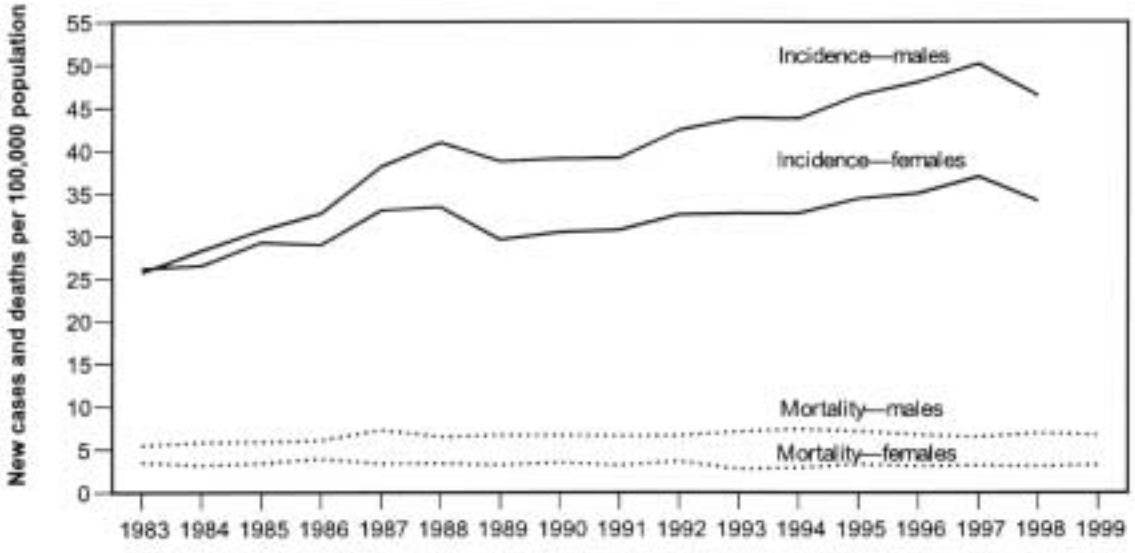
Melanoma is a cancer that develops in the pigment producing cells of the skin (melanocytes). Sun exposure is strongly associated with melanoma development, particularly, but not exclusively, in individuals with fair complexion. The lesion may be of either the superficial spreading or nodular type. The extent of invasion of the lesion at diagnosis is an important prognostic determinant. If the melanoma cells penetrate into the dermis, they are likely to spread elsewhere. Initially, the melanoma is most likely to spread to the nearby lymph nodes, but ultimately distant metastases may occur in the liver, lungs, bone or elsewhere. The prognosis for patients with distant melanoma metastases is poor.

Incidence of melanoma

The Australian Institute of Health and Welfare (AIHW), in conjunction with the Australasian Association of Cancer Registries, routinely compiles national cancer statistics based on data collected by state cancer registries. Data are available on the incidence and mortality of all cancers other than non-melanoma skin cancer. The most recently available data are from 1998 (AIHW and AACR 2001).

The incidence for melanoma (ICD–9 diagnosis code 172) has increased over the past 15 years (**Figure 1**). Early increases within this period may to some extent have been due to improved registration of data (AIHW and AACR 2001). A decrease was observed in the most recent year for which data are available, 1998. While the pattern of change is similar in males and females, the incidence and the rate of increase are more pronounced in males. Typically, the incidence of melanoma in men is approximately 1.5 times that of women.

[5]Also included within stage IIIB are patients a) with up to three clinically occult nodes but an ulcerated primary melanoma and b) with satellite or in-transit metastases but no evidence of nodal or distant metastases. However, M-VAX is not indicated for use in these patients.



Reproduced with permission from: Australian Institute of Health and Welfare & Australasian Association of Cancer Registries. 2001. Cancer in Australia 1998. AIHW cat. no. CAN 12. Canberra: AIHW (Cancer Series no. 17).

Figure 1 Incidence and mortality of melanoma in Australia

In 1998, a total of 7891 people were diagnosed with melanoma in Australia (4398 men, 3493 women). The crude incidence for melanoma in Australia in 1998 was 42.1 per 100,000 (95% CI 41.2–43.1). When age standardised to the world standard population, this decreases to 31.7 per 100,000 (95% CI 31.0–32.4). This equates to a lifetime (0–74 years) risk of the disease of 1 in 30. The incidence is higher in Queensland and Western Australia than in other Australian states.

Mortality due to melanoma

In 1998, a total of 979 people died from melanoma in Australia (635 men, 344 women). This represents a crude mortality of 5.2 (95% CI 4.9–5.6) per 100,000 population, or a world age-standardised mortality of 3.5 (95% CI 3.3–3.7) per 100,000. For every eight patients diagnosed with melanoma, it is estimated that one dies of the disease.[6] The lifetime risk of dying from melanoma is currently 1 in 254 for the entire Australian population.

Morbidity associated with melanoma

Malignant melanoma can metastasise to any of the body's lymphatic basins (Chan *et al* 2000). When the disease has progressed to the lymph nodes it is classified as stage III disease. Lymph node resection is strongly recommended for local control of the disease and as a potentially curative procedure (NHMRC 1999b).

[6]This calculation is based on the incidence and mortality in 1998. In reality, some of those diagnosed in 1998 may die of melanoma later, and some of those dying in 1998 may have been diagnosed in preceding years. However this approach is a valid estimate if one assumes minimal impact of longitudinal trends in incidence or mortality.

Morbidity associated with clinically apparent, stage IIIB and IIIC melanoma arises primarily from the surgical removal of the affected lymph nodes rather than the disease *per se*. However, some patients may experience pain from the diseased lymph nodes prior to surgical removal. The most frequent short-term complications from lymph node dissection at all sites are: seroma, temporary nerve dysfunction, pain and wound infections. The removal of ilioinguinal nodal metastases is frequently associated with leg oedema whilst the removal of axillary node metastases may result in arm oedema and functional deficit (Urist *et al* 1986). Cervical node metastases may be removed by radical or modified neck dissection. Radical neck dissection is associated with loss of shoulder function, shoulder drop and poor cosmetic results. In a modified neck dissection, the spinal accessory nerve and the sternomastoid muscle are spared. However, approximately 30 per cent of patients do not retain full spinal accessory nerve function (Schuller *et al* 1983).

Unfortunately, many patients will eventually have relapses of disease after surgical removal of nodal metastases, mainly in distant sites. Malignant melanoma can metastasise to almost any organ of the body. Common distant sites of metastatic melanoma include: skin, lymph nodes, lungs, liver, brain, bone, gastrointestinal tract, heart, pancreas, adrenal glands, kidneys, and thyroid. Many of these metastases cause pain, bleeding, muscle wasting and serious dysfunction. In general, the prognosis for patients who progress to stage IV melanoma is poor.

Patients who are suitable for M-VAX™ treatment

Annual incidence statistics are not recorded by melanoma stage. As the rate of progression to stage III and beyond is highly variable between patients, it is not possible to estimate the annual incidence of stage III melanoma accurately from cancer registry data. An alternative approach is to estimate the annual number of melanoma patients having a lymphadenectomy, as this is the procedure required immediately prior to treatment with M-VAX™.

In 1999–2000, a total of 284 patients had an excision procedure on a neck, axilla, groin or other lymph gland[7] for the treatment of melanoma. As this would have included a) patients who had a prophylactic lymph node resection and b) patients in whom disease failed to be histologically confirmed, this may be an overestimate of the incidence of stage III. Expert opinion estimates the annual number of patients with positive lymph nodes who undergo lymph node resection to be closer to 250. Nevertheless, in the absence of stage III incidence statistics, this is considered the best estimate of the annual number of patients with new stage III disease.

Of these patients, it is estimated that 42 per cent have clinically palpable tumours (stage IIIB) (Balch *et al* 2001b); however, many of these will be < 3 cm in diameter. Therefore, it is estimated that considerably fewer than 105 patients would be suitable for treatment with M-VAX™ in Australia each year.

[7]ICD-10-AM procedure codes 806, 808, 809, 811

In the future, it is possible that the number of patients with large nodal tumours will decrease. It is current practice at some, but not all, Australian melanoma treatment centres for patients to receive sentinel lymph node biopsies. Therefore, it is conceivable that at least some nodal tumours will be detected at a smaller size than would have been the case in the past. If this occurs, the incidence of patients with tumours suitable for M-VAX™ treatment will reduce over time.

Existing procedures

After tumour resection, there are two broad adjuvant treatment options[8] currently available to stage IIIB and IIIC melanoma patients. These are:

1. observation
2. interferon α-2b

Clinical practice guidelines have been produced by the Australian Cancer Network (NHMRC 1999b), on the basis of a systematic review of the evidence and expert opinion. With respect to existing adjuvant treatments (including interferon α-2b), these guidelines state that "there is no conclusive evidence that adjuvant therapy is beneficial" for melanoma patients, recommending instead that patients are offered inclusion in clinical trials for new therapies. Nevertheless, interferon α-2b is reimbursed under Section 100[9] of the publicly funded Pharmaceutical Benefits Scheme (PBS) for the "adjuvant therapy of malignant melanoma following surgery in patients with nodal involvement". Typically, the clinician explains the efficacy and toxicity associated with the use of interferon α-2b, after which the patient decides whether or not to proceed.

Insufficient national statistical information is available to measure the precise proportion of Australian stage IIIB and IIIC melanoma patients who currently elect to receive treatment with interferon α-2b. However, expert opinion estimates the proportion to be approximately 15 per cent. The applicant provided the findings of a telephone survey of 40 specialists treating a total of 430 stage III melanoma patients. The results showed that 77 per cent of patients received no intervention, and only 10 per cent of patients were treated with interferon α-2b. The remaining 13 per cent received other treatments or took part in clinical trials of emerging therapies. Three-quarters of all specialists interviewed indicated that they did not treat *any* patients with interferon α-2b.

Total interferon α-2b use can be estimated from PBS statistics. However, the relevant Section 100 PBS item numbers are also indicated for treatment of myelogenous leukaemia, hepatitis B and hepatitis C. As authority approval is required for private hospital use, it is possible to determine the relative use of interferon α-2b in private

[8]In Australia, a large proportion of melanoma patients take part in clinical trials for new therapies. It is beyond the scope of this assessment to consider therapies not yet approved for general use.

[9]Section 100 of the National Health Act, 1953 provides for the reimbursement of highly specialised drugs supplied through public and private hospitals having access to specialist facilities.

hospitals for each indication[10]. When extrapolated to all public and private use, it is estimated that 62 patients received interferon α-2b treatment for melanoma in 2001.

Comparator

The comparator is considered to be the adjuvant treatment most likely to be replaced in practice by M-VAX™. According to this definition, it is clear that the comparator is observation alone (**Table 1**).

Table 1 M-VAX™ comparator treatment

Indication	Primary comparator
Stage IIIB and IIIC melanoma – post-surgical resection of lymph node tumour(s)	Observation alone

Marketing status of the technology

As an autologous vaccine, M-VAX™ is exempt from Part 3 of the Australian Therapeutic Goods Act (1989). Therefore, the safety and efficacy of M-VAX™ has not been evaluated by the Therapeutic Goods Administration (TGA). For this reason, it does not have a TGA-listing or specific indication. However, M-VAX™ manufacturing facilities must comply with Part 4 of the Act with respect to Good Manufacturing Practice (GMP). The TGA has issued the Australian manufacturing facility with a licence for the preparation of autologous vaccines (licence no. 21529).

M-VAX™ is not currently approved by the Food and Drug Administration (FDA) in the USA. The FDA had previously issued interim approval for clinical trial use only under the Investigational New Drug program (IND), but this approval was inactivated in March 2001 after concerns relating to manufacturing practice. Modifications have subsequently been made to the manufacturing processes that allow additional quality assurance testing on each vaccine batch prior to dispensing. New IND applications, incorporating these changes, will be sought for further clinical trials.

M-VAX™ is exempt from marketing authorisation in both the Netherlands and Germany. However, authorisation of manufacturing procedures is required in both countries, and additional approval of the irradiation procedure is required in Germany. At the time of this assessment, no other European jurisdiction had been formally approached.

[10]Personal communication, Health Insurance Commission, Canberra, Australia

Current reimbursement arrangement

There is no current reimbursement arrangement for M-VAX™ in Australia. Interferon α-2b is reimbursed by Section 100 (highly specialised drugs program) of the PBS for the post-surgical treatment of melanoma with nodal involvement. At present, no other non-surgical interventions are publicly funded for the treatment of melanoma in Australia.

Approach to assessment

Review of literature

The medical literature was searched to identify relevant studies and systematic reviews for the period between 1980 and May 2002. Searches were not extended to cover the period before 1980 because the development timeline of M-VAX™ was known, making earlier searching unnecessary.

Searches were conducted via the following primary databases:

- Medline 1966 to current
- Embase 1980 to current
- Premedline
- Cancerlit 1975 to current
- Econlit 1969 to current
- HealthSTAR 1975 to current

For completeness, searches of the following secondary databases/sites were also performed:

- British Columbia Office of Health Technology Assessment
- Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
- Centre for Health Program Evaluation (Monash University, Australia)
- Centre for Reviews and Dissemination (University of York, UK)
- Cochrane Library
- Health Economics Research Group (Brunel University, UK)
- Health Information Research Unit (HIRU) internal database
- International Network of Agencies for Health Technology Assessment (INAHTA)
- International Society of Technology Assessment in Health Care (Montreal, Canada)
- National Health and Medical Research Council of Australia publication list

- National Health Service (UK)
- National Information Center on Health Services Research and Health Care Technology (HSTAT database)
- Swedish Council on Technology Assessment in Health Care (SBU)
- US Office of Technology Assessment 1974-1995 (closed), then,
- US Health Care Financing Administration (HCFA)

Search strategies are presented in **Appendix D**. After the removal of duplicate citations, 250 unique citations were obtained.

Inclusion criteria

- Original publication reporting the results of one or more clinical trials (ie, non-systematic reviews, editorials, opinion pieces and letters will be excluded).
- Human patients (*in vivo* application).
- M-VAX™ intervention.
- Stage III melanoma patients.
- 20 patients or more (those trials with < 20 patients will be assessed for relevant safety data).
- Reporting of relevant clinical outcomes (overall or relapse-free survival, disease progression).

After application of the above criteria, a total of 2 publications were included in the review. A flow chart indicating the reasons for exclusion is presented in **Figure 2,** and a full list of excluded publications appears in **Appendix E**.

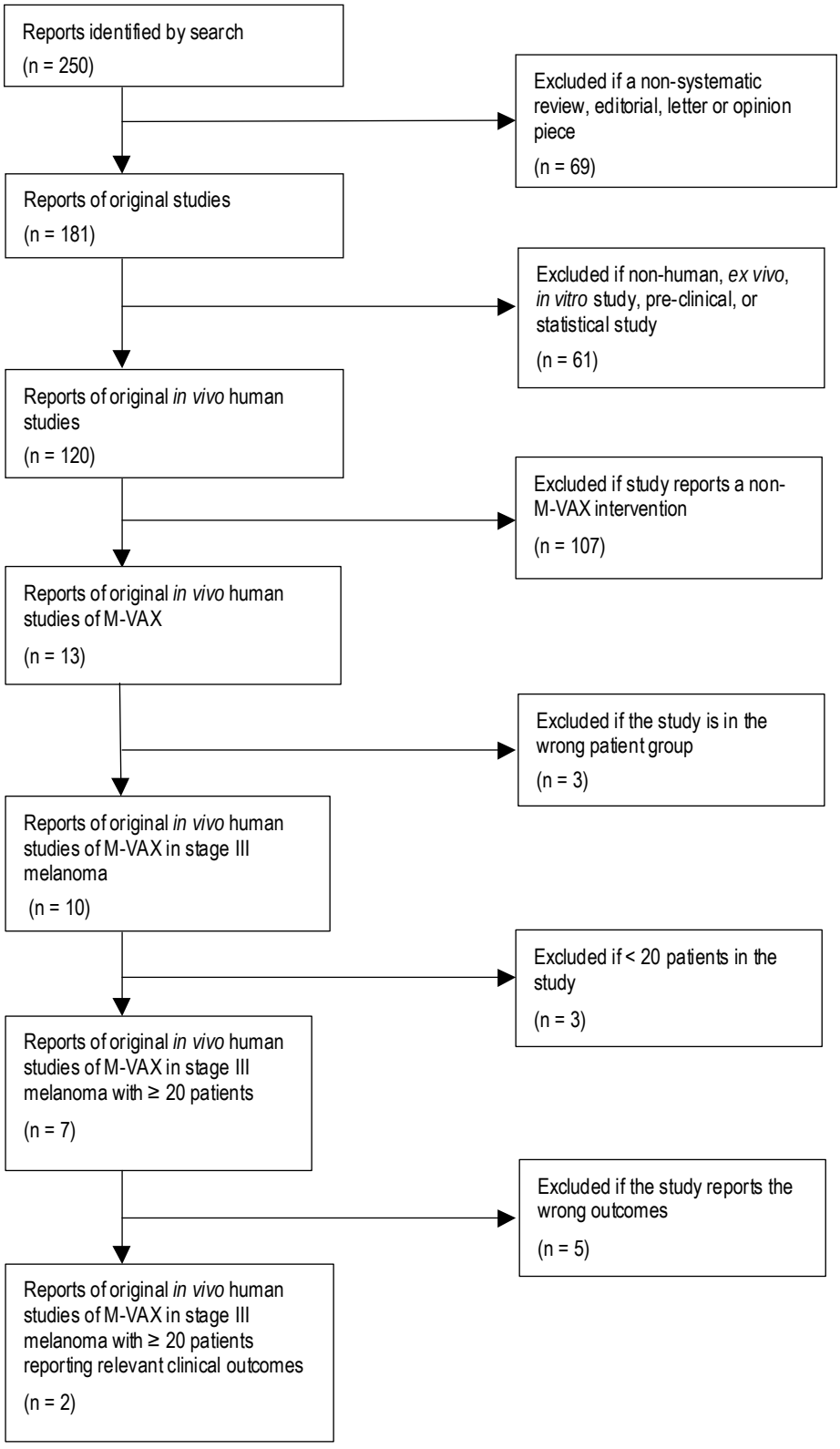


Figure 2 M-VAX™ effectiveness literature search – reasons for exclusion

Publications that duplicate all or some of the patients in other included trials were included in the first instance. These were subsequently reviewed and excluded if necessary. Similarly, publications that failed to report outcome measures adequately were subsequently excluded. All publications initially included, but subsequently excluded, are individually referred to in the body of this review.

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 1999a).

These dimensions (**Table 2**) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

Table 2 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level*	The study design used, as an indicator of the degree to which bias has been eliminated by design
Quality	The methods used by investigators to minimise bias within a study design
Statistical precision	The *p* value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

*See Table 3.

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in **Table 3**.

Table 3 Designations of levels of evidence*

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

*Modified from NHMRC (2000).

As no controlled clinical trial evidence was available at the time of this assessment, it was not possible to make a direct comparison of M-VAX™ against observation, or to use a common comparator approach (eg, with interferon as the common comparator). For this

reason, it was necessary to conduct an additional systematic review of the efficacy and safety evidence for the comparator treatment, and then attempt to make an indirect comparison. As the aim of the comparator systematic review was to determine the efficacy and safety of the comparator as it is currently occurs, the search was restricted to 1996 onwards (Premedline, Medline and Embase). (Details of the search strategy for the comparator intervention are provided in **Appendix F**). Furthermore, as evidence from high quality, large, randomised, controlled, phase III clinical trials was known to exist, only studies constituting NHMRC level I or II evidence were included (ie, data from the observation arm of one or more randomised controlled clinical trials). After the removal of duplicate citations, 346 unique citations were obtained. The inclusion criteria for the systematic review of the comparator were as follows.

- Original publication reporting the results of one or more randomised, controlled, phase III clinical trial (ie, non-RCTs, non-systematic reviews, editorials, opinion pieces and letters were excluded).
- Human patients (*in vivo* application).
- One arm of the clinical trial was observation alone or a placebo intervention (ie, no intervention subsequent to lymphadenectomy).
- Stage III melanoma patients.
- 20 patients or more (those trials with < 20 patients will be assessed for relevant safety data).
- Reporting of relevant clinical outcomes (overall or relapse-free survival, disease progression).
- Median follow-up of at least five years

After application of the above criteria, a total of 8 publications were included in the systematic review of the comparator. A flow chart indicating the reasons for exclusion is presented in **Figure 3**. Excluded studies, with the reason for exclusion indicated, are listed in **Appendix G**.

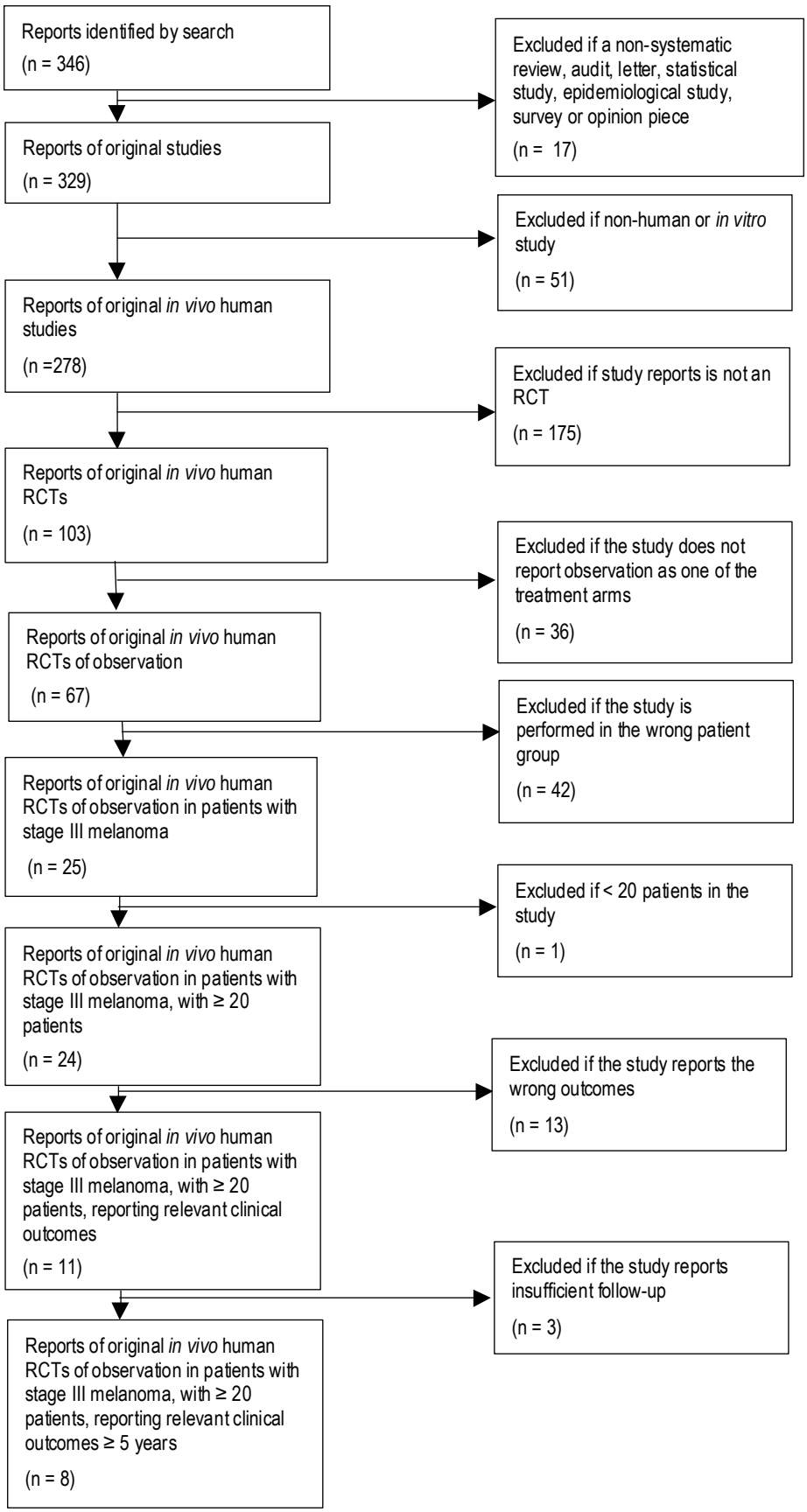


Figure 3 Comparator effectiveness literature search – reasons for exclusion

Indirect comparisons are generally considered inadequate for the assessment of relative efficacy and safety for reimbursement purposes. The extent of introduced bias was considered to determine whether it was appropriate to make relative efficacy and safety conclusions on the basis of an indirect comparison. Conducting an evaluation of the economic considerations of M-VAX™ was contingent on the ability to conduct an adequate assessment of relative efficacy and safety.

Expert advice

A supporting committee with expertise in medical oncology, general practice, general surgery, dermatopathology, epidemiology and health economics was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the supporting committee is provided at **Appendix B**.

Results of assessment

At present, the highest level of evidence available to describe the safety and efficacy of M-VAX™ as an adjuvant treatment for stage IIIB and IIIC melanoma, is level IV evidence. The primary evidence (Berd (2001), with an associated study report) is data collected in four prospective, phase II, uncontrolled clinical trials.

It is important to note that the dose and administration regimen varies across the four phase II trials, with none representing the currently recommended regimen (**Table 7**). In addition, the manufacturing process has been modified subsequent to these trials, and the effect of this upon safety and efficacy is unknown.

Is it safe?

Traditionally, the authority to regulate biological products used for medicinal use did not extend to organs or tissues obtained from the same patient, even when significant modification had occurred (Ward 2000). As a result, it is still common for autologous products to be exempt from registration and/or listing on national therapeutic goods registers, as is the case in Australia. In practice, this means that there is no requirement to demonstrate safety and efficacy of the product with rigorous evidence from preclinical and clinical trials. Technological advances have led to a dramatic increase in autologous therapies, and therefore an increase in the number of therapeutic products that fall beyond the boundaries of current legislation and are not subject to regulation.

The FDA has recently recognised the need to extend its authority to include autologous products, and has begun a process toward the regulation of cellular and tissue-based products[11]. Similarly, the European Medicines Evaluation Agency is initiating a regulatory requirement for these products. Currently, autologous products remain exempt from TGA safety and efficacy evaluation in Australia.

Therefore, in contrast to the majority of products assessed by MSAC for reimbursement purposes, M-VAX™ has had no prior evaluation of safety and efficacy by an Australian regulatory authority, other than licensing of the manufacturing facility. For this reason, it is necessary to consider all theoretical and reported safety issues.

Although M-VAX™ is produced from a patient's own tumour cells, considerable processing and modification takes place *ex vivo*. Initially, the tumour cells are transported to a central processing laboratory. Courier transportation must occur within 48 hours of resection. A tumour collection kit (TCK) is provided for this purpose, comprising:

- temperature bricks to maintain the temperature at 2–8º C and reduce the risk of tumour freezing or spoiling
- sterile containers for the tumour, to minimise the risk of infection
- sterile Hanks' solution to cover the tumour

[11]Tissue Action Plan, 1998.

- tumour registration form for completion by the surgical staff.

After processing of the tumour (commercial in confidence), vials are frozen and stored in liquid nitrogen. On the day of vaccination, cells are thawed and irradiated at 2500 cGy. This radiation dose is generally accepted as sufficient to prevent cell proliferation and therefore tumour growth after re-injection. Cells are then haptenised with dinitrophenyl (DNP), washed and resuspended in Hanks' solution buffered with human serum albumin (HSA). The vaccine is transported on ice to the clinic/hospital in a vaccine transport container.

Despite efforts to maintain sterility, the *ex vivo* storage and processing of biological material provides an opportunity for contamination. It is normal practice for injected pharmaceuticals and biologicals to undergo testing to confirm the absence of contaminants. In the case of the production of M-VAX™ in Australia, the vaccine is currently manufactured and shipped to the clinician within 24 hours, but complete results of sterility testing are not available until up to 14 days post-manufacture. Preliminary results are available after three days. Therefore, it is possible that a contaminated vaccine could be injected into a patient.

In October 2001, the FDA issued a warning letter relating to the use of M-VAX™ as an investigational new drug product in the USA, citing several occasions when patients were injected with contaminated vaccine. Furthermore, additional doses of the vaccine continued to be produced from the same tumour source material, even though the initial dose had already proved to be contaminated. The FDA were particularly concerned that treating clinicians were not always notified of vaccine contamination. All of the incidents referred to by the FDA relate to the USA manufacturing facility in Philadelphia, not to the Australian facility.

The manufacturer has since modified the processing in the USA to allow vaccine preparation (including irradiation and haptenisation) to occur before cryopreservation. A sample of this final product is obtained for sterility testing prior to cryopreservation. The results of the sterility assays are therefore available before distribution of the manufactured vaccine to the treating clinician. In addition, the shelf-life of the vaccine is extended to four days. While not current practice in Australia, the applicant states that these modifications to manufacturing processes will be adopted in the near future. Nevertheless, contamination remains a potential risk.

There are only limited adverse event data available for the 214 patients who took part in the phase II studies (**Table 4**) and these are generally poorly reported. For trials 4.2–8.2, adverse reactions were not recorded if: a) they were expected outcomes of treatment or b) they were judged by the investigator not to be related to the vaccine.

Table 4 Adverse event data

	Patients reporting adverse reaction (%)[a]	
	Trials 4.2–8.2	**Trial 9.2**
Injection site adverse reactions	Not adequately reported	81/87 (93%)
Adverse reactions attributed to cyclophosphamide	Not adequately reported	62/87 (71%)
Other adverse reactions	3/127 (2.4%)	0/87 (0%)

[a]Many patients reported multiple reactions as a result of the multiple vaccine doses; therefore, the number of patients tabulated here does not equate to the number of reactions.

Almost all patients in trial 9.2 were found to develop a local reaction at the injection site, consisting of a draining, tender pustule that healed in 2–3 months. The investigators attributed this to BCG mixed with the vaccine, as these effects are common in response to BCG. However, the effect of multiple BCG doses in close succession may increase the reaction. Indeed, the authors report an increasing intensity of the reaction as the patients developed sensitivity to BCG over the course of the trial. Furthermore, as the BCG and vaccine are administered together, it is difficult to conclusively assign the injection site reactions to the BCG alone.

The publication summarising the results of the patients investigated in these four phase II trials states that "low-dose cyclophosphamide causes nausea and vomiting (generally grade 1) in approximately 25 per cent of patients" (Berd 2001). However, this statement is misleading. The authors appear to have used the total evaluable population from all trials as a denominator (n = 214), when these adverse events were adequately reported only in trial 9.2 (n = 87). The true incidence of nausea and vomiting attributable to cyclophosphamide is likely to be similar to that reported in trial 9.2 (ie, 71%). Furthermore, the study report indicates that while nausea was predominantly grade 1, grade 2 vomiting was actually more common than grade 1 vomiting.

Three patients experienced other adverse reactions thought to be attributable to the vaccine. Details are not available, but reactions included erythema, oedema, rash, fever, chills, malaise and myalgia. There is no information provided regarding the severity of these reactions; however, administration of the vaccine was stopped in one patient.

Safety of the comparator intervention, observation alone, was not reviewed. It was assumed that observation caused no treatment-related adverse reactions.

Summary of M-VAX™ safety relative to comparator

After reviewing the available evidence, it was concluded that it is not possible to make a reliable comparison of the relative safety of M-VAX™ and observation. This is because only uncontrolled and poorly reported data are currently available for M-VAX™.

Is it effective?

Table 5 provides a summary of the published clinical evidence meeting the inclusion criteria for review. A level of evidence was assigned to each publication according to the NHMRC definitions.

Table 5 Summary of clinical evidence of M-VAX™ in the treatment of stage IIIB and IIIC melanoma

Level of evidence	Publication and study design	Patient characteristics	Included in efficacy review
I	None available		
II	None available		
III-1	None available		
III-2	None available		
III-3	None available		
IV	Berd *et al* (1997) (trials 4.2, 6.2) Combination of two uncontrolled phase II clinical trials with variable dose regimens not consistent with current recommended use	n = 62 Patients included in Berd (2001) and accompanying study report	No[a]
	Berd (2001) (trials 4.2, 6.2, 8.2 and 9.2) (applicant has provided study report) Combination of four uncontrolled phase II clinical trials with variable dose regimens not consistent with current recommended use	n = 214 Minimal patient data, methodology and results presented in publication AJCC staging not reported	Yes

Abbreviation: AJCC, American Joint Committee on Cancer staging system
[a]Outcomes reported in Berd (2001).

At present, only level IV evidence exists to describe the efficacy and safety of M-VAX™ as an adjuvant treatment of stage IIIB and IIIC melanoma. As yet, no phase III, controlled clinical trial evidence is available.

The primary evidence (Berd (2001), and the associated study report) is data collected in four prospective, phase II, uncontrolled clinical trials (trials 4.2, 6.2, 8.2 and 9.2). Patients in these trials were recruited between October 1989 and September 1995 at a single centre (Thomas Jefferson University, Philadelphia, USA). **Table 6** presents the inclusion and exclusion criteria.

Table 6 Inclusion and exclusion criteria for M-VAX™ trials 4.2, 6.2, 8.2 and 9.2

Inclusion criteria	Exclusion criteria
Clinically evident metastatic disease in lymph nodes that can be completely resected	Insufficient quantity of tumour cells for vaccine and skin testing (< 100 x 10^6 cells)
	Estimated survival less than 6 months
	Karnofsky performance status < 80
	Administration of cytotoxic drugs within preceding 4 weeks[a] (8 weeks for nitrosourea drugs)
	Major field radiation therapy within preceding 8 weeks[b]
	Current administration of corticosteroids
	Haematocrit < 25% or WBC < 3000/l
	Age < 18 years
	Active, serious infections
	Concurrent active malignancy other than squamous cell carcinoma of skin or *in situ* carcinoma of the cervix, or early stage (A or B1) prostate cancer
	Evidence of infection with hepatitis B virus (circulating antigen) or with HIV (circulating antibody)
	Inability to give informed consent
	Metastatic melanoma indicated by postoperative clinical or laboratory evaluation

Abbreviations: WBC, white blood cell; HIV, human immunodeficiency virus
[a]For trial 9.2 only: administration of cytotoxic drugs within preceding 6 weeks.
[b]For trial 9.2 only: major field radiation therapy within preceding 6 months.

Furthermore, the dose regimens vary across the four trials. A summary of the dose regimens used in the four trials and that requested by the applicant for reimbursement are presented in **Table 7**. None of the regimens are identical to the currently recommended dose regimen that is the subject of this application for reimbursement. Furthermore, the manufacturing process has recently been modified in the USA and will be modified in Australia in the near future. The effect of these changes on the efficacy of the treatment has not yet been reported.

Table 7 M-VAX™ treatment regimens in the phase II clinical trials and the regimen recommended in current application

	Cyclo-phosphamide	DNFB sensitisation	Vaccine regimen[a]	Vaccine mixed with BCG?
Trial 4.2	Days –17, 0, 28	Days –14, –13	Days 3, 31, 59, 87, 115, 143, 171, 199 Dose: 5–20 x 10^6 cells	All doses mixed with BCG
Trial 6.2	Days –17, 0, 70	Days –14, –13	Days 3, 10, 17, 73, 80, 87 (DNP-modified) Days 24, 31, 38, 94, 101, 108 (not DNP-modified) Dose: 5–20 x 10^6 cells	Only doses on days 3, 24, 73, and 94 were mixed with BCG
Trial 8.2	Days –17, 0, 70	Days –14, –13	Days 3, 10, 17, 24, 31, 38, 73, 80, 87, 94, 101, 108 Dose: 5–20 x 10^6 cells	All doses given with BCG
Trial 9.2	Day 0	None	Days 3, 10, 17, 24, 31, 38, then 6 and 12 months Dose: 2.5–7.5 x 10^6 cells	All doses given with BCG
Current[b]	Day 0	None	Days 3, 10, 17, 24, 31, 38 then 6 months Dose: 2.5–7.5 x 10^6 cells	All doses given with BCG

Abbreviations: DNFB, dinitrofluorobenzene; DNP, dinitrophenyl; BCG, bacille Calmette-Guérin.
[a]All vaccine doses DNP-modified unless otherwise indicated.
[b]The currently recommended dose regimen for which the applicant is seeking reimbursement.

The dose regimens investigated in trials 4.2, 6.2 and 8.2 are quite different from the recommended dose regimen. The dose regimen used in trial 9.2 differs from the current recommendation only because it has an additional vaccine dose 12 months after surgery. For this reason, wherever possible, this assessment report will present data a) for trial 9.2 alone and b) pooled across all four trials, separately.

The demographic characteristics were consistent across the four trials. The median age of patients was 52 years (range 16–83 years), of whom 57 per cent were male. The majority of patients had a primary melanoma of the trunk (46%) or extremity (34%). All patients had at least one macroscopic nodal tumour, but a considerable proportion had more than one positive node (**Table 8)**. No other patient characteristics (eg, AJCC staging) are reported in either the publication or study report.

Table 8 M-VAX™ disease characteristics

Number of positive nodes	Combined total for trials 4.2, 6.2, 8.2 and 9.2 n (%)	Trial 9.2 n (%)
One nodal basin		
1	64 (29.9)	24 (27.6)
2–3	41 (19.2)	16 (18.4)
4 or more	46 (21.5)	20 (23.0)
Unknown	3 (1.4)	3 (3.4)
2 nodal basins	40 (18.7)	16 (18.4)
In-transit metastases	20 (9.3)	8 (9.2)
Total	**214 (100)**	**87 (100)**

The primary outcome measure for the purposes of this assessment was overall survival after 5 years. The secondary outcome was relapse-free survival. All patients in trials 4.2, 6.2 and 8.2 had been followed up for longer than 5 years. At the time of this assessment, 41 patients in trial 9.2 had been followed for 5 years. **Table 9** present the 5-year overall and relapse-free survival results.

Table 9 Overall and relapse-free survival at 5 years

	Trial 4.2	Trial 6.2	Trial 8.2	Trial 9.2[a]
Overall survival	25/47 (53%)	13/30 (43%)	17/50 (34%)	19/41 (46%) (95% CI: 28.2–65.5)
Relapse-free survival	20/47 (43%)	8/30 (27%)	10/50 (20%)	14/41 (34%) (95% CI: 18.5–54.2)

[a]Patient follow-up is incomplete in trial 9.2. Results presented here are as at 20 June 2002.

There was considerable heterogeneity among the dose regimens and vaccine preparations administered to patients in each of the four trials. Furthermore, the demographic and disease characteristics of the included patients is poorly reported in the publication and study report. Therefore, the inconsistency in treatment regimens and the uncertainty surrounding the patient populations included in the trials mean that it is inappropriate to pool the results of the phase II trials.

Hence, the best available evidence indicates that the 5-year overall survival of stage III melanoma patients receiving treatment with an M-VAX™ regimen very close to that currently recommended is approximately 46 per cent (trial 9.2).

A systematic review of the evidence describing the efficacy of the comparator (observation alone) was undertaken for this assessment report. The review indicated that good quality evidence from randomised controlled clinical trials was available. In addition, a systematic review of the observation arm of randomised controlled trials has recently presented in abstract form only (Wheatley *et al* 2001). Only studies with data for stage III melanoma patients were included. A summary of level I and II evidence is presented in **Table 10.** As high quality level I and II evidence was available, level III evidence was not sourced or reviewed for the comparator.

Table 10 Summary of clinical evidence for efficacy of the comparator treatment for stage III melanoma[a]

Level of evidence	Publication, study design and location	Relevant treatment arm	Characteristics of patients in the observation arm	Included in efficacy review?
I	Wheatley et al (2001)[b] Systematic review and meta-analysis of 10 randomised, controlled clinical trials International	Observation	Currently only limited data available in abstract form	No
II	Kikwood et al (1996) (ECOG 1684) Multicentre, randomised, controlled clinical trial USA	Observation	n = 137; 58% male CS1, PS1: 11% of trial population CS1, PS2: 10% CS2, PS2: 15% CS2R: 64% ECOG performance status 0: 90% ECOG performance status 1: 10% Ulceration: 17% No ulceration: 77% Ulceration unknown: 6%	Yes
II	Kirkwood et al (1997) (ECOG 1684) Multicentre, randomised, controlled clinical trial USA	As above	As above	No Duplicates data of Kirkwood (1996)
II	Kirkwood (2000) (ECOG 1690) Multicentre, randomised, controlled clinical trial USA	Observation	AJCC stage IIB and III Stage IIB: 26% Clinically-occult node positive (~stage IIIA): 14% Clinically-apparent (~stage IIIB): 10% Recurrent lymph node positive: 49% ECOG performance status 0: 84% ECOG performance status 1: 16% Ulceration: 38% No ulceration: 58% Ulceration unknown: 4% No positive nodes: 26% 1 positive node: 33% 2–3 positive nodes: 21% > 4 positive nodes: 20%	Yes
II	Rao et al (2002) Multicentre, randomised, controlled clinical trial USA	As above	As above	No Duplicates data of Kirkwood (2000)

(continued overleaf)

Table 10 (*continued*) Summary of clinical evidence for efficacy of the comparator treatment for stage III melanoma[a]

Level of evidence	Publication, study design and location	Relevant treatment arm	Characteristics of patients in the observation arm	Included in efficacy review?
II	Cascinelli et al (2001) Multicentre, randomised, controlled clinical trial WHO Melanoma Programme, Europe	Observation	n = 219 52% male AJCC stage III, histologically confirmed ECOG performance status 0: 99% ECOG performance status unknown: 1% Ulceration: 37% No ulceration: 35% Ulceration unknown: 28% Clinically detectable nodes: 98% 1 positive node: 38% >1 positive nodes: 62%[these last two figs add to 100%, so where did you put the 2% with **no** clinically detectable nodes?	Yes
II	Cameron et al (2001) Multicentre, randomised, controlled clinical trial Scotland	Observation	n = 48 AJCC stage IIB and III, histologically confirmed Patients with undefined 'poor' performance status were excluded. Ulceration status not reported	Yes 5-year overall survival data obtained directly from author
II	Wallack et al (1998) Multicentre randomised, placebo-controlled clinical trial USA	Placebo vaccine	n = 113; 66% male AJCC stage III, histologically confirmed 1 positive node: 51% of trial population 2–3 positive nodes: 32% 4–5 positive nodes: 6% >5 positive nodes: 11% Karnofsky performance status > 70 Ulceration: 33% No ulceration: 67%	Yes
II	Hersey et al (2002) Multicentre, randomised, controlled clinical trial Australia	Observation	n = 347; 71% male AJCC stage IIB and III, histologically confirmed ECOG performance status 0 or 1 Ulceration: 48% No ulceration: 28% Ulceration unknown: 24% No positive nodes: 23% (of all patients) 1 positive node: 46% (of all patients) >1 positive node: 31% (of all patients)	Yes

Abbreviations: ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer Staging System; WHO, World Health Organisation

[a]Several large, multicentre, randomised controlled clinical trials with an observation arm currently have patient follow-up extending to four years (EORTC 18991 and UKCCCR AIM High).

[b]Abstract only available (ASCO 2001).

The overall survival results of the studies are indicated in **Table 11**. Where possible, data specific to AJCC stages IIIB and IIIC are presented. Where the outcomes of interest were not adequately reported for these sub-stages, this is noted.

Table 11 Summary of patient characteristics and outcomes reported in comparator studies

Level of evidence	Publication	Patient sub-stage reported here	n	Primary outcome: 5-year overall survival	Secondary outcome: 5-year disease-free survival
				% (95% CI)[e]	% (95% CI)[e]
II	Kikwood et al (1996) (ECOG 1684)	All patients:	137	37[a] (30–46)	26 (19–34)
		CS1, PS1: (~IIB)	15	nr	67
		CS1, PS2: (~IIIA)	14	nr	28
		CS2, PS2: (~IIIB)	21	nr	5
		CS2R: (~IIIB)	87	nr	24
II	Kirkwood (2000)[a] (ECOG 1690)	All patients:	212	54 (45–62)	35 (27–44)
		IIB:	56	nr	nr
		IIIA:	29	nr	nr
		IIIB:	22	nr	nr
		IIIC:	104	nr	nr
II	Cascinelli et al (2001)	All patients:	219	37[b] (31–44)	28 (23–35)
		IIIA:	nr	nr	nr
		IIIB:	nr	nr	nr
		IIIC:	nr	nr	nr
II	Cameron et al (2001)	All patients:	48	29[d] (16–48)	33[d] (19–52)
		IIB:	nr	nr	nr
		III:	nr	23	24
II	Wallack et al (1998)	All patients:	113	48 (36–60)	40 (30–53)
		IIIA:	nr	nr	nr
		IIIB:	nr	nr	nr
		IIIC:	nr	nr	nr
II	Hersey et al (2002)[a]	All patients:	347	55 (46–62)	46 (39–53)
		Strata 1 (~IIB):	80	59 (44–72)	47 (33–60)
		Strata 2	37	64 (44–81)	53 (34–73)
		Strata 3:	21	15 (4–42)	13 (4–42)
		Strata 2 and 3 (~IIIA)	58	46 (31–63)	39 (24–55)
		Strata 4:	120	67 (56–77)	61 (49–72)
		Strata 5:	89	40 (28–54)	31 (20–44)
		Strata 4 and 5 (~IIIB):	209	56 (47–65)	48 (40–57)

Abbreviations: ECOG, Eastern Cooperative Oncology Group

[a]Intention-to-treat.

[a]Evaluable.

[a]Denominator not specified.

[d]The explanation for the higher relapse free survival than overall survival is not apparent from the publication.

[e]Survival results have been rounded to nearest whole percentage. If not reported in publication, 95% confidence intervals were calculated using the Wilson method.

It is clear from the systematic review of the comparator that prognostic factors such as AJCC stage critically influence the survival outcomes. This is most clearly demonstrated in the analysis of prognostic factors conducted by the AJCC in order to finalise the staging guidelines (Balch *et al* 2001a). Specifically, the prognosis of patients with AJCC stage III is significantly influenced by: a) the number of metastatic nodes; b) the extent of the tumour burden (micrometastases versus macrometastases); c) ulceration of the primary melanoma; and d) the presence of satellite or in-transit metastases.

The diversity in the natural history of stage III melanoma is graphically demonstrated by five-fold differences in 5-year survival rates for the substages. Balch *et al* (2001b) report a survival of 69 per cent for patients with non-ulcerated melanoma who have a single, clinically occult nodal metastasis, compared with just 13 per cent for patients with an ulcerated melanoma with four or more clinically apparent nodal metastases. This is reinforced by the variability of the survival results obtained in the observation of the randomised controlled clinical trials reviewed here (**Table 11**).

It is clear that randomised controlled trials need to be well-balanced with respect to prognostic factors. Furthermore, indirect comparison with historical controls is fraught with potential bias. This is particularly the case when patient characteristics and results are poorly reported, or not reported by sub-stage.

The results of Hersey *et al* (2002) provide the only indication of the survival of stage III melanoma patients specific to the current Australian clinical context, and therefore are considered the best evidence of the efficacy of observation in this context. The patients of strata 4 and 5 best represent those likely to be treated with M-VAX™, although the size of the nodal tumour is not specified. The 5-year overall survival rate of this group was 55.8 per cent while the relapse-free survival rate was 48.2 per cent. If the somewhat poorer results of strata 2 and 3 were to be included, these estimates would fall to 53.7 per cent and 46.1 per cent, respectively.

Summary of M-VAX™ efficacy relative to comparator

There are insufficient data available to make a comparison between M-VAX™ and observation alone, without the introduction of considerable bias. It is recommended that future assessments of the relative effectiveness of M-VAX™ and observation be based on data from randomised, controlled phase III clinical trials.

What are the economic considerations?

It is a requirement of the MSAC terms of reference that the economic implications of the new health technology are considered. This is particularly important when a new technology offers health benefits at an additional cost, as is so often the case. An economic evaluation helps to determine whether the additional cost represents value for money. To assess the value for money of a new health intervention, it is necessary to express the incremental cost associated with the new treatment relative to the incremental health benefit gained. When this information is available, an incremental cost-effectiveness ratio (ICER) can be calculated

$$\text{ICER} = \frac{\text{Cost}_{\text{new technology}} - \text{Cost}_{\text{comparator}}}{\text{Effectiveness}_{\text{new technology}} - \text{Effectiveness}_{\text{comparator}}}$$

In cases where a new technology offers inferior or equal health benefits at a higher cost, it clearly does not provide value for money.

When determining the incremental cost of the new technology, several factors should be considered: the costs of the treatment itself; the costs of any downstream management; treatment costs for any adverse reactions; and also any cost savings achieved. With respect to incremental effectiveness, there are several possible ways of expressing the effectiveness of the treatment. In this case an estimate of the incremental survival between the two treatments would be most appropriate (eg, additional patients alive, life-years gained or quality-adjusted life-years gained). In order to conduct an economic evaluation, it is essential that an accurate measure of incremental effectiveness is available from high quality evidence with minimal potential for bias.

It is concluded that there is currently insufficient data to estimate the relative effectiveness of M-VAX™ and observation alone without the introduction of considerable bias. Conducting an economic evaluation on the basis of an indirect comparison between M-VAX™ data (derived from uncontrolled phase II clinical trials) and observation data (derived from high quality phase III clinical trials) may be misleading. This is particularly the case when prognostic factors and patient inclusion/exclusion criteria are not consistent.

Conclusions

At present, only low-level evidence is available to describe the safety and efficacy of M-VAX™ as an adjuvant treatment for stage IIIB and IIIC melanoma. The primary evidence comes from data collected in four prospective, phase II, uncontrolled clinical trials. Furthermore, the manufacturing process, dose and administration regimens vary across the four trials, with none equating exactly to the currently recommended procedure.

Safety

Mild nausea and vomiting occur in the majority of patients receiving M-VAX™, probably secondary to the use of cyclophosphamide. Injection site reactions are also common. In the USA, there have been several reports of contaminated vaccine being administered to patients.

After reviewing the available evidence, it was concluded that it is not possible to make a reliable comparison of the relative safety of M-VAX™ and observation. This is because only uncontrolled and poorly reported data are currently available for M-VAX™.

Effectiveness

There are insufficient data available to make a comparison of the relative efficacy of M-VAX™ and observation, without the introduction of considerable bias.

Cost-effectiveness

Conducting an economic evaluation on the basis of an indirect comparison between M-VAX™ data (derived from uncontrolled phase II clinical trials) and observation data (derived from high quality phase III clinical trials) may be misleading. Therefore it is concluded that there is currently insufficient data to estimate the cost effectiveness of M-VAX™ relative to observation.

Recommendation

MSAC recommended that on the strength of evidence pertaining to M-VAX™, a treatment for patients with advanced stage III melanoma, public funding should not be supported for this procedure.

The Minister for Health and Ageing accepted this recommendation on 8 October 2002.

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	**Expertise or affiliation**
Mr Stephen Blamey (Chair)	General surgery
Professor Bruce Barraclough	General surgery
Professor Syd Bell	Pathology
Dr Paul Craft	Clinical epidemiology and oncology
Professor Ian Fraser	Reproductive medicine
Professor Jane Hall	Health economics
Dr Terri Jackson	Health economics
Ms Rebecca James	Consumer health issues
Professor Brendon Kearney	Health administration and planning
Mr Alan Keith	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Ageing
Associate Professor Richard King	Internal medicine
Dr Ray Kirk	Health research
Dr Michael Kitchener	Nuclear medicine
Mr Lou McCallum	Consumer health issues
Dr Ewa Piejko	General practice
Professor John Simes	Clinical epidemiology and clinical trials

Professor Richard Smallwood	Chief Medical Officer, Commonwealth Department of Health and Ageing
Dr Robert Stable	Representing Australian Health Ministers' Advisory Council
Professor Bryant Stokes	Neurological surgery
Professor Ken Thomson	Radiology
Dr Douglas Travis	Urology

Appendix B Supporting committee

Supporting committee for MSAC application 1049 M-VAX™ as a treatment for advanced melanoma

Dr Paul Craft (Chair) MB BS, MPH, FRACP Director Medical Oncology Unit Canberra Hospital	Member of MSAC
Professor Bruce Barraclough MB BS, FRACS, FACS, DDU Professor of Cancer Services University of Sydney and Northern Sydney Health	Member of MSAC
Dr Philip Clarke MB BS, FRACGP, DipFamMed Dip Dermatological Sciences Dermatologist Clinical Lecturer, Dermatology University of Tasmania Medical School VMO consultant in dermatology Launceston General Hospital Tasmania	Nominated by Royal Australian College of General Practitioners
Mr Clive Deverall Hon DLitt Consumer representative	Consumer Health Forum
Professor Jane Hall BA, PhD Director of the Centre for Health Economic Research and Evaluation, University of Technology Sydney	Member of MSAC

Professor Peter Hersey
MB BS, FRACP, DPhil(Oxon)

Senior Staff Specialist
Newcastle Mater Hospital

Research Director
Newcastle Melanoma Unit

Consultant Immunologist
Sydney Melanoma Unit

Conjoint Professor in Oncology
University of Newcastle

Co-opted

Professor Michael O'Rourke
MB BS, FRACS, FRCS, FACS, FRCS(Ed)

Director of Surgery
Mater Melanoma Research Unit, Queensland

Clinical Director
Queensland Institute of Medical Research
Melanoma Vaccine Group

Nominated by Royal Australasian College of Surgeons

Associate Professor Ruth Salom
MB BS, BMedSci, MD, FRCPA

Pathologist
Dorevitch Pathology

Pathologist
Monash University, Melbourne

Nominated by Royal Australasian College of Pathologists

Appendix C Studies included in the review

Table 12 Studies included in the review

Publication	Study design and patient characteristics	Comments	Outcomes
Berd *et al* (1997)	n = 62 Uncontrolled phase II clinical trials (trials 4.2 and 6.2) AJCC staging not reported	Combination of two uncontrolled phase II clinical trials with variable dose regimens not consistent with current recommended use	Overall survival and relapse-free survival
Berd (2001)	n = 214 Uncontrolled phase II clinical trials (trials 4.2, 6.2, 8.2 and 9.2) Minimal patient data and methodology presented in publication AJCC staging not reported (Applicant has provided associated study report)	Combination of four uncontrolled phase II clinical trials with variable dose regimens not consistent with current recommended use	Overall survival and relapse-free survival

Abbreviation: AJCC, American Joint Committee on Cancer Staging System

Appendix D M-VAX™ – literature search strategies

Medline search strategy

The search strategy used to identify relevant studies of M-VAX™ in Medline is presented in **Table 13**

Table 13 M-VAX™ Medline search strategy (1966 to April week 3 2002)

	Keyword/search history	Results
1	exp cancer vaccines/	1748
2	vaccines/	5581
3	or/1–2	7319
4	3 and autologous.ti,ab.	301
5	3 and exp haptens/	31
6	3 and dinitrofluorobenzene/	1
7	or/4–6	325
8	7 and exp melanoma/	97
9	7 and melanoma.ti,ab.	109
10	7 and *neoplasms/th	28
11	((m adj vax) or mvax).mp.	1
12	or/5–6,8–11	155

Embase search strategy

The search strategy used to identify relevant studies of M-VAX™ in Embase is presented in **Table 14**.

Table 14 M-VAX™ Embase search strategy (1980 to 2002 week 18)

	Keyword/search history	Results
1	melanoma vaccine/	249
2	cancer vaccine/	1574
3	tumor vaccine/	899
4	tumor cell vaccine/	153
5	or/1–4	2771
6	5 and autologous.ti,ab.	413
7	hapten/	2100
8	2,4 dinitrophenol/	2488
9	or/7–8	4513
10	9 and exp vaccine/	55
11	9 and intradermal drug administration/	24
12	or/10–11	77
13	6 and 12	7
14	5 and 12	17
15	or/6,12	483
16	15 and exp melanoma/	134
17	15 and melanoma.ti,ab.	143
18	((m adj vax) or mvax).mp.	3
19	or/14,16–18	163

Appendix E M-VAX™ – list of citations and reasons for exclusion

1. Anonymous (1981), Measles and mumps virus vaccine (M-M-Vax), *Medical Journal of Australia* 2: 40.
Reason for exclusion: Non M-VAX intervention.

2. Anonymous (1985), [From artificial antigens to artificial vaccines][Russian], *Zhurnal Mikrobiologii, Epidemiologii i Immunobiologii* 7: 106-111.
Reason for exclusion: Review.

3. Anonymous (2002), Cancer vaccine – antigenics, *Biodrugs* 16: 72-74.
Reason for exclusion: Non M-VAX intervention.

4. Abdel-Wahab Z, Weltz C, Hester D, Pickett N, Vervaert C, Barber JR, Jolly D, Seigler HF (1997), A phase I clinical trial of immunotherapy with interferon-gamma gene-modified autologous melanoma cells: monitoring the humoral immune response, *Cancer* 80: 401-412.
Reason for exclusion: Non M-VAX intervention.

5. Abdel-Wahab ZA, Osanto S, Darrow TL, Barber JR, Vervaert CE, Gangavalli R, McCallister TJ, Seigler HF (1994), Transduction of human melanoma cells with the gamma interferon gene enhances cellular immunity, *Cancer Gene Therapy* 1: 171-179.
Reason for exclusion: *In vitro* study.

6. Agarwala SS, Kirkwood JM (1998), Adjuvant therapy of melanoma, *Seminars in Surgical Oncology* 14: 302-310.
Reason for exclusion: Review.

7. Agarwala SS (2001), Chemotherapy Foundation Symposium XVIII: session on malignant melanoma, *Expert Opinion on Investigational Drugs* 10: 381-385.
Reason for exclusion: Review.

8. Ahn SS, Irie RF, Weisenburger TH, Jones PC, Juillard G, Roe DJ, Morton DL (1982), Humoral immune response to intralymphatic immunotherapy for disseminated melanoma: correlation with clinical response, *Surgery* 92: 362-367.
Reason for exclusion: Non M-VAX intervention.

9. Akiyoshi T (1997), Cancer vaccine therapy using peptides derived from tumor-rejection antigens, *Japanese Journal of Cancer & Chemotherapy* 24: 511-519.
Reason for exclusion: Non M-VAX intervention.

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Reason for exclusion: non-human study.

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Reason for exclusion: Wrong outcomes.

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Reason for exclusion: Non-human study.

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Reason for exclusion: Non M-VAX intervention.

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Reason for exclusion: Non M-VAX intervention.

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Reason for exclusion: Non M-VAX intervention.

213. Suranyi MG, Hogan PG, Falk MC, Axelsen RA, Rigby R, Hawley C, Petrie J (1998), Advanced donor origin melanoma in a renal transplant recipient: immunotherapy, cure, and retransplantation, *Transplantation* 66: 655-661.
Reason for exclusion: Non M-VAX intervention.

214. Suzue K, Young RA (1996), Heat shock proteins as immunological carriers and vaccines [Review], *EXS* 77: 451-465.
Reason for exclusion: Review.

215. Tagliaferri F, Sirovich I, Stipa F, Giovanna VM, Pupelis G, Tremiterra S (1994), Systemic specific active immunotherapy for solid tumors. An overview about cancer vaccine therapy, *Recenti Progressi in Medicina* 85: 591-596.
Reason for exclusion: Review.

216. Tanosaki R, Takaue Y (2001), Cell therapy against cancer, *Biotherapy* 15: 621-629.
Reason for exclusion: Review.

217. Thomas R, Padmanabha J, Chambers M, McFadyen S, Walpole E, Nielssen G, Smithers M (2001), Metastatic lesions in the joint associated with acute inflammatory arthritis after dendritic cell immunotherapy for metastatic melanoma, *Melanoma Research* 11: 167-173.
Reason for exclusion: Non M-VAX intervention.

218. Todryk S, Birchall L, Erlich R, Halanek N, Orleans-Lindsay JK, Dalgleish A (2001), Cytokine gene transfection for autologous and allogeneic melanoma vaccines, *Advances in Experimental Medicine & Biology* 495: 365-368.
Reason for exclusion: Non M-VAX intervention.

219. Todryk SM, Birchall LJ, Erlich R, Halanek N, Orleans-Lindsay JK, Dalgleish AG (2001), Efficacy of cytokine gene transfection may differ for autologous and allogeneic tumour cell vaccines, *Immunology* 102: 190-198.
Reason for exclusion: Non-human study.

220. Toungouz M, Libin M, Bulte F, Faid L, Lehmann F, Duriau D, Laporte M, Gangji D, Bruyns C, Lambermont M, Goldman M, Velu T (2001), Transient expansion of peptide-specific lymphocytes producing IFN-gamma after vaccination with dendritic cells pulsed with MAGE peptides in patients with mage-A1/A3-positive tumors, *Journal of Leukocyte Biology* 69: 937-943.
Reason for exclusion: Non M-VAX intervention.

221. Traversari C (1999), Tumor-antigens recognised by T lymphocytes, *Minerva Biotecnologica* 11: 243-253.
Reason for exclusion: Review.

222. Uchiyama A, Hoon DSB, Morisaki T, Kaneda Y, Yuzuki DH, Morton DL (1993), Transfection of interleukin 2 gene into human melanoma cells augments cellular immune response, *Cancer Research* 53: 949-952.
Reason for exclusion: Preclinical study.

223. Uchiyama A (1995), Active specific immunotherapy using interleukin-2 (IL-2) gene-transfected cancer cells, *Biotherapy* 9: 628-630.
Reason for exclusion: Non M-VAX intervention.

224. Uhlig H (1965), [The acid-soluble hapten from *Erysipelothrix insidiosa*] [German], *Archiv fur Experimentelle Veterinarmedizin* 19: 277-280.
Reason for exclusion: Non-human study.

225. Valmori D, Dutoit V, Lienard D, Rimoldi D, Pittet MJ, Champagne P, Ellefsen K, Sahin U, Speiser D, Lejeune F, Cerottini JC, Romero P (2000), Naturally occurring human lymphocyte antigen-A2 restricted CD8+ T-cell response to the cancer testis antigen NY-ESO-1 in melanoma patients, *Cancer Research* 60: 4499-4506.
Reason for exclusion: Non M-VAX intervention.

226. Valmori D, Scheibenbogen C, Dutoit V, Nagorsen D, Asemissen AM, Rubio-Godoy V, Rimoldi D (2002), Circulating tumor-reactive CD8 (+) T cells in melanoma patients contain a CD45RA (+) CCR7(–) effector subset exerting *ex vivo* tumor-specific cytolytic activity, *Cancer Research.* 62: 1743-1750.
Reason for exclusion: *In vitro* study.

227. Van den Eynde BJ (1999), T-cell defined tumor antigens: perspectives for cancer vaccine development, *Gann Monographs on Cancer Research* 48: 17-29.
Reason for exclusion: Review.

228. van Elsas A, Aarnoudse C, Van der Minne CE, Van der Spek CW, Brouwenstijn N, Osanto S, Schrier PI (1997), Transfection of IL-2 augments CTL response to human melanoma cells *in vitro*: immunological characterization of a melanoma vaccine, *Journal of Immunotherapy* 20: 343-353.
Reason for exclusion: *In vitro* study.

229. Veelken H, Mackensen A, Lahn M, Kohler G, Becker D, Franke B, Brennscheidt U, Kulmburg P, Rosenthal FM, Keller H, Hasse J, Schultze-Seemann W, Farthmann EH, Mertelsmann R, Lindemann A (1997), A phase-I clinical study of autologous tumor cells plus interleukin-2-gene-transfected allogeneic fibroblasts as a vaccine in patients with cancer, *International Journal of Cancer* 70: 269-277.
Reason for exclusion: Non M-VAX intervention.

230. Verdegaal EME, Ten Bokkel HD, Hoogstraten C, Marijnissen AK, Gorsira MB, Claas FHJ, Osanto S (1999), Isolation of broadly reactive, tumor-specific, HLA class-I restricted CTL from blood lymphocytes of a breast cancer patient, *Human Immunology* 60: 1195-1206.
Reason for exclusion: Non M-VAX intervention.

231. Wang R-F, Johnston SL, Southwood S, Sette A, Rosenberg SA (1998), Recognition of an antigenic peptide derived from tyrosinase-related protein-2 by CTL in the context of HLA-A31 and -A33, *Journal of*

Immunology 160: 890-897.
Reason for exclusion: *In vitro* study.

232. Wang RF (1997), Tumor antigens discovery: perspectives for cancer therapy [Review], *Molecular Medicine* 3: 716-731.
Reason for exclusion: Review.

233. Wang RF (1999), Human tumor antigens: implications for cancer vaccine development [Review], *Journal of Molecular Medicine* 77: 640-655.
Reason for exclusion: Review.

234. Weibel RE, Buynak EB, McLean AA, Hilleman MR (1978), Persistence of antibody after administration of monovalent and combined live attenuated measles, mumps, and rubella virus vaccines, *Pediatrics* 61: 5-11.
Reason for exclusion: Non M-VAX intervention.

235. Williams TW, Yanagimoto JM, Mazumder A, Wiseman CL (1992), Interleukin-2 increases the antibody response in patients receiving autologous intralymphatic tumor cell vaccine immunotherapy, *Molecular Biotherapy* 4: 66-69.
Reason for exclusion: Non M-VAX intervention.

236. Wise RA, Ranaldi R (1996), Cocaine vaccines revisited, *Nature Medicine* 2: 1073-1074.
Reason for exclusion: Letter.

237. Wiseman C, Rao VS, Bakke A (1986), Increased T-helper lymphocytes following active specific intralymphatic immunotherapy of cancer, *Journal of Biological Response Modifiers* 5: 490-497.
Reason for exclusion: Non M-VAX intervention.

238. Wiseman CL, Rao VS, Kennedy PS, Presant CA, Smith JD, McKenna RJ (1989), Clinical responses with active specific intralymphatic immunotherapy for cancer – a phase I-II trial, *Western Journal of Medicine* 151: 283-288.
Reason for exclusion: Non M-VAX intervention.

239. Wittig B, Marten A, Dorbic T, Weineck S, Min H, Niemitz S, Trojaneck B, Flieger D, Kruopis S, Albers A, Loffel J, Neubauer A, Albers P, Muller S, Sauerbruch T, Bieber T, Huhn D, Schmidt-Wolf IG (2001), Therapeutic vaccination against metastatic carcinoma by expression-modulated and immunomodified autologous tumor cells: a first clinical phase I/II trial, *Human Gene Therapy* 12: 267-278.
Reason for exclusion: Non M-VAX intervention.

240. Wiznerowicz M, Fong AZ, Mackiewicz A, Hawley RG (1997), Double-copy bicistronic retroviral vector platform for gene therapy and tissue engineering: application to melanoma vaccine development, *Gene Therapy* 4: 1061-1068.
Reason for exclusion: *In vitro* study.

241. Wolchok JD, Livingston PO (2001), Vaccines for melanoma: translating basic immunology into new therapies, *Lancet Oncology* 2: 205-211.
Reason for exclusion: Review.

242. Xiang R, Lode HN, Chao TH, Ruehlmann JM, Dolman CS, Rodriguez F, Whitton JL, Overwijk WW, Restifo NP, Reisfeld RA (2000), An autologous oral DNA vaccine protects against murine melanoma, *Proceedings of the National Academy of Sciences of the United States of America* 97: 5492-5497.
Reason for exclusion: Non M-VAX intervention.

243. Yamasaki S, Okino T, Chakraborty NG, Adkisson WO, Sampieri A, Padula SJ, Mauri F, Mukherji B (1995), Presentation of synthetic peptide antigen encoded by the MAGE-1 gene by granulocyte/macrophage-colony-stimulating-factor-cultured macrophages from HLA-A1 melanoma patients, *Cancer Immunology, Immunotherapy* 40: 268-271.
Reason for exclusion: Non M-VAX intervention.

244. Yang S, Darrow TL, Seigler HF (1997), Generation of primary tumor-specific cytotoxic T lymphocytes from autologous and human lymphocyte antigen class I-matched allogeneic peripheral blood lymphocytes

by B7 gene-modified melanoma cells, *Cancer Research* 57: 1561-1568.
Reason for exclusion: *In vitro* study.

245. Zarour HM, Kirkwood JM, Kierstead LS, Herr W, Brusic V, Slingluff CL, Jr, Sidney J, Sette A, Storkus WJ (2000), Melan-A/MART-1(51-73) represents an immunogenic HLA-DR4-restricted epitope recognized by melanoma-reactive CD4(+) T cells, *Proceedings of the National Academy of Sciences of the United States of America* 97: 400-405.
Reason for exclusion: *In vitro* study.

246. Zarour HM, Maillere B, Brusic V, Coval K, Williams E, Pouvelle-Moratille S, Castelli F, Land S, Bennouna J, Logan T, Kirkwood JM (2002), NY-ESO-1 119-143 is a promiscuous major histocompatibility complex class II T-helper epitope recognized by Th1- and Th2-type tumor-reactive CD4+ T cells, *Cancer Research* 62: 213-218.
Reason for exclusion: *In vitro* study.

247. Zhang J, Kovac P (1999), A highly efficient preparation of neoglycoconjugate vaccines using subcarriers that bear clustered carbohydrate antigens, *Bioorganic & Medicinal Chemistry Letters* 9: 487-490.
Reason for exclusion: *In vitro* study.

248. Zitvogel L, Couderc B, Mayordomo JI, Robbins PD, Lotze MT, Storkus WJ (1996), IL-12-engineered dendritic cells serve as effective tumor vaccine adjuvants *in vivo*, *Annals of the New York Academy of Sciences* 795: 284-293.
Reason for exclusion: *In vitro* study.

Appendix F Comparator – literature search strategies

Medline search strategy

The search strategy used to identify relevant studies of surgery and observation in Medline is presented in **Table 15**.

Table 15 Comparator Medline search strategy (1966 to June week 1 2002)

	Keyword/search history	Results
1	randomized controlled trial.pt.	162,132
2	controlled clinical trial.pt.	61,352
3	randomized controlled trials.sh.	23,582
4	random allocation.sh.	44,972
5	double-blind method.sh.	68,931
6	single-blind method.sh.	6486
7	clinical trial.pt.	331,047
8	exp clinical trials/	130,877
9	(clin$ adj25 trial$).ti,ab.	80,582
10	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	68,020
11	placebos.sh.	21,421
12	placebo$.ti,ab.	72,335
13	random$.ti,ab.	235,637
14	research design.sh.	30,882
15	volunteer$.ti,ab.	73,286
16	animal.sh.	3,282,741
17	human.sh.	7,622,484
18	16 not 17	2,564,158
19	or/1-15	633,527
20	19 not 18	587,035
25	observation.ti,ab.	101,332
26	placebo.ti,ab.	71,845
27	control.ti,ab.	742,388
28	no treatment.ti,ab.	1,235,000
29	25 or 26 or 27 or 28	1,933,289
30	exp Melanoma/mo,dt,su,th [Mortality, Drug Therapy, Surgery, Therapy]	14,135
31	20 and 30	1984
32	29 and 31	1128
33	limit 32 to yr=1992-2002	803
34	exp survival analysis/	142
35	exp Survival rate/	52,760
36	survival.ti,ab.	210,195
37	34 or 35 or 36	245,155
38	33 and 37	368
39	limit 38 to review	74

	Keyword/search history	Results
40	38 not 39	294
41	limit 40 to english	283
42	limit 41 to human	283
43	limit 42 to yr=1996-2002	201

Embase search strategy

The search strategy used to identify relevant studies of surgery and observation in Embase is presented in **Table 16**.

Table 16 Comparator Embase search strategy (1988 to 2002 week 24)

	Keyword/search history	Results
1	clinical article/	612,000
2	clinical study/	2247
3	clinical trial/	229,818
4	controlled study/	1,343,477
5	randomized controlled trial/	65,169
6	major clinical study/	588,358
7	double blind procedure/	39,414
8	multicenter study/	22,636
9	single blind procedure/	3668
10	phase 3 clinical study/	0
11	phase 4 clinical study/	0
12	crossover procedure/	12,287
13	placebo/	32,756
14	or/1-13	2,170,105
15	allocat$.ab,ti.	16,106
16	assign$.ab,ti.	53,115
17	blind$.ab,ti.	68,077
18	(clinic$ adj25 (study or trial)).ab,ti.	148,983
19	compar$.ab,ti.	970,721
20	control$.ab,ti.	709,769
21	cross?over.ab,ti.	13,740
22	factorial$.ab,ti.	3497
23	follow?up.ab,ti.	5611
24	placebo$.ab,ti.	55,194
25	prospectiv$.ab,ti.	117,171
26	random$.ab,ti.	177,938
27	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ab,ti.	49,100
28	trial.ab,ti.	87,714
29	(versus or vs).ab,ti.	221,186
30	or/15-29	1,720,706
31	14 or 30	2,850,093
32	human/	3,222,085
33	nonhuman/	1,664,688
34	animal/	6795
35	animal experiment/	565,983
36	33 or 34 or 35	1,675,523
37	36 not 32	1,445,903
38	31 not 37	2,008,901
39	exp Melanoma/	23,169
40	melanoma.ti,ab.	23,360

	Keyword/search history	Results
41	39 or 40	27,933
42	observation.ti,ab.	61,463
43	placebo.ti,ab.	54,941
44	38 and 41	14,403
45	42 or 43	115,357
46	44 and 45	350
47	limit 46 to yr=1996-2004	203
48	limit 47 to human	199
49	limit 48 to review	16
50	48 not 49	183
51	limit 50 to english language	175

Appendix G Comparator – list of citations and reasons for exclusion

1. Abeck D, Schmidt T, Fesq H, Strom K, Mempel M, Brockow K, Ring J (2000), Long-term efficacy of medium-dose UVA1 phototherapy in atopic dermatitis, *Journal of the American Academy of Dermatology* 42: 254-257.
Reason for exclusion: Not an RCT.

2. Agarwala SS, Ferri W, Gooding W, Kirkwood JM (1999), A phase III randomized trial of dacarbazine and carboplatin with and without tamoxifen in the treatment of patients with metastatic melanoma, *Cancer* 85: 1979-1984.
Reason for exclusion: Wrong intervention.

3. Agarwala SS, Glaspy J, O'Day SJ, Mitchell M, Gutheil J, Whitman E, Gonzalez R, Hersh E, Feun L, Belt R, Meyskens F, Hellstrand K, Wood D, Kirkwood JM, Gehlsen KR, Naredi P (2002), Results from a randomized phase III study comparing combined treatment with histamine dihydrochloride plus interleukin-2 versus interleukin-2 alone in patients with metastatic melanoma, *Journal of Clinical Oncology* 20: 125-133.
Reason for exclusion: Wrong intervention.

4. Alexander HR, Libutti SK, Bartlett DL, Puhlmann M, Fraker DL, Bachenheimer LC (2000), A phase I-II study of isolated hepatic perfusion using melphalan with or without tumor necrosis factor for patients with ocular melanoma metastatic to liver, *Clinical Cancer Research* 6: 3062-3070.
Reason for exclusion: Not an RCT.

5. Amirkhosravi A, Amaya M, Siddiqui F, Biggerstaff JP, Meyer TV, Francis JL (1999), Blockade of GpIIb/IIIa inhibits the release of vascular endothelial growth factor (VEGF) from tumor cell-activated platelets and experimental metastasis, *Platelets* 10: 285-292.
Reason for exclusion: Non human/*in vitro*.

6. Anastassiou G, Coupland SE, Stang A, Boeloeni R, Schilling H, Bornfeld N (2001), Expression of Fas and Fas ligand in uveal melanoma: Biological implication and prognostic value, *Journal of Pathology* 194: 466-472.
Reason for exclusion: Non human/*in vitro*.

7. Andres P, Le F, Stalder JF (1997), Computerized analysis of atypical and multiple nevi: more efficient than classical clinical comparison for the detection of modifications in surface area? *European Journal of Dermatology* 7: 577-580.
Reason for exclusion: Not an RCT.

8. Andres P, Cupissol D, Guillot B, Avril MF, Dreno B (1998), Subcutaneous interleukin-2 and interferon-alpha therapy associated with cisplatin monochemotherapy in the treatment of metastatic melanoma, *European Journal of Dermatology* 8: 235-239.
Reason for exclusion: Not an RCT.

9. Antoine EC, Benhammouda A, Bernard A, Youssef A, Mortier N, Gozy M, Nizri D, Auclerc G, Rocher MA, Soubrane CL, Weil M, Khayat D (1997), Salpetriere Hospital experience with biochemotherapy in metastatic melanoma, *Cancer Journal From Scientific American* 3 Suppl 1: S16-S21.
Reason for exclusion: Not an RCT.

10. Anuszewska EL, Gruber BM, Koziorowska JH (1997), Studies on adaptation to adriamycin in cells pretreated with hydrogen peroxide, *Biochemical Pharmacology* 54: 597-603.
Reason for exclusion: Non human/*in vitro*.

11. Aoyama T, Mastrangelo MJ, Berd D, Nathan FE, Shields CL, Shields JA, Rosato EL, Rosato FE, Sato T (2000), Protracted survival after resection of metastatic uveal melanoma, *Cancer* 89: 1561-1568.
Reason for exclusion: Not an RCT.

12. Arbiser JL, Kraeft SK, Van L, Hurwitz SJ, Selig M, Dickersin GR, Flint A, Byers HR, Lan B (1998), Clioquinol-zinc chelate: a candidate causative agent of subacute myelo-optic neuropathy, *Molecular Medicine* 4: 665-670.
Reason for exclusion: Non human/*in vitro*.

13. Ascierto PA, Palmieri G, Parasole R, Daponte A, Castello G (1999), 3-year treatment with recombinant interferon-alpha as adjuvant therapy of cutaneous malignant melanoma, *International Journal of Molecular Medicine* 3: 303-306.
Reason for exclusion: Not an RCT.

14. Ascierto PA, Daponte A, Giuseppe P (1999), Adjuvant treatment of melanoma using placebo or no therapies as control-arm: is it ethically correct? *Melanoma Research* 9: 528-529.
Reason for exclusion: Review.

15. Atkins MB, Kunkel L, Sznol M, Rosenberg SA (2000), High-dose recombinant interleukin-2 therapy in patients with metastatic melanoma: long-term survival update, *Cancer Journal From Scientific American* 6 Suppl 1: S11-S14.
Reason for exclusion: Wrong intervention.

16. Augsburger JJ, Correa ZM, Freire J, Brady LW (1998), Long-term survival in choroidal and ciliary body melanoma after enucleation versus plaque radiation therapy, *Ophthalmology* 105: 1670-1678.
Reason for exclusion: Wrong patient group.

17. Augsburger JJ, Schneider S, Freire J, Brady LW (1999), Survival following enucleation versus plaque radiotherapy in statistically matched subgroups of patients with choroidal melanomas: results in patients treated between 1980 and 1987, *Graefes Archive for Clinical & Experimental Ophthalmology* 237: 558-567.
Reason for exclusion: Not an RCT.

18. Baars A, Claessen AM, van den Eertwegh AJ, Gall HE, Stam AG, Meijer S, Giaccone G, Meijer CJ, Scheper RJ, Wagstaff J, Vermorken JB, Pinedo HM (2000), Skin tests predict survival after autologous tumor cell vaccination in metastatic melanoma: experience in 81 patients, *Annals of Oncology* 11: 965-970.
Reason for exclusion: Not an RCT.

19. Baekke J, Rytter C, Mouridsen H, Madsen EL, Moholt K, Bastholt L (2000), A phase II trial of recombinant interferon alpha-2b and cisplatin in metastatic melanoma, *Acta Oncologica* 39: 625-628.
Reason for exclusion: Not an RCT.

20. Bafaloukos D, Gogas H, Georgoulias V, Briassoulis E, Fountzilas G, Samantas E, Kalofonos C, Skarlos D, Karabelis A, Kosmidis P (2002), Temozolomide in combination with docetaxel in patients with advanced melanoma: a phase II study of the Hellenic Cooperative Oncology Group, *Journal of Clinical Oncology* 20: 420-425.
Reason for exclusion: Not an RCT.

21. Balch CM, Soong SJ, Bartolucci AA, Urist MM, Karakousis CP, Smith TJ, Temple WJ, Ross MI, Jewell WR, Mihm MC, Barnhill RL, Wanebo HJ (1996), Efficacy of an elective regional lymph node dissection of 1 to 4 mm thick melanomas for patients 60 years of age and younger, *Annals of Surgery* 224: 255-266.
Reason for exclusion: Wrong patient group.

22. Balch CM, Soong SJ, Ross MI, Urist MM, Karakousis CP, Temple WJ, Mihm MC, Barnhill RL, Jewell WR, Wanebo HJ, Harrison R (2000), Long-term results of a multi-institutional randomized trial comparing prognostic factors and surgical results for intermediate thickness melanomas (1.0 to 4.0 mm), *Annals of Surgical Oncology* 7: 87-97.
Reason for exclusion: Wrong patient group.

23. Balch CM, Soong SJ, Smith T, Ross MI, Urist MM, Karakousis CP, Temple WJ, Mihm MC, Barnhill RL, Jewell WR, Wanebo HJ, Desmond R, Investigators from the Intergroup Melanoma Surgical Trial (2001), Long-term results of a prospective surgical trial comparing 2 cm vs 4 cm excision margins for 740 patients

with 1-4 mm melanomas, *Annals of Surgical Oncology* 8: 101-108.
Reason for exclusion: Wrong patient group.

24. Batioglu F, Gunalp I (1998), Malignant melanomas of the iris, *Japanese Journal of Ophthalmology* 42: 281-285.
Reason for exclusion: Not an RCT.

25. Batliwalla FM, Bateman BA, Serrano D, Murray D, Macphail S, Maino VC, Ansel JC, Gregersen PK, Armstrong CA (1998), A 15-year follow-up of AJCC stage III malignant melanoma patients treated postsurgically with Newcastle disease virus (NDV) oncolysate and determination of alterations in the CD8 T cell repertoire, *Molecular Medicine* 4: 783-794.
Reason for exclusion: Not an RCT.

26. Bechrakis NE, Foerster MH, Bornfeld N (2002), Biopsy in indeterminate intraocular tumors, *Ophthalmology* 109: 235-242.
Reason for exclusion: Not an RCT.

27. Ben Izhak O, Levy R, Weill S, Groisman G, Cohen H, Stajerman S, Misselevich I, Nitecky S, Eidelman S, Kerner H (1997), Anorectal malignant melanoma: a clinicopathologic study, including immunohistochemistry and DNA flow cytometry, *Cancer* 79: 18-25.
Reason for exclusion: Not an RCT.

28. Berd D, Maguire HCJ, Schuchter LM, Hamilton R, Hauck WW, Sato T, Mastrangelo MJ (1997), Autologous hapten-modified melanoma vaccine as postsurgical adjuvant treatment after resection of nodal metastases, *Journal of Clinical Oncology* 15: 2359-2370.
Reason for exclusion: Not an RCT.

29. Berking C, Takemoto R, Binder RL, Hartman SM, Ruiter DJ, Gallagher PM, Lessin SR, Herlyn M (2002), Photocarcinogenesis in human adult skin grafts, *Carcinogenesis* 23: 181-187.
Reason for exclusion: Non human/*in vitro*.

30. Bernengo MG, Doveil GC, Bertero M, Quaglino P, Fierro MT, Savoia P, Appino A, Colonna S (1996), Low-dose integrated chemoimmuno-hormonotherapy with cisplatin, subcutaneous interleukin-2, alpha-interferon and tamoxifen for advanced metastatic melanoma – a pilot study, *Melanoma Research* 6: 257-265.
Reason for exclusion: Not an RCT.

31. Bieligk SC, Ghossein R, Bhattacharya S, Coit DG (1999), Detection of tyrosinase mRNA by reverse transcription-polymerase chain reaction in melanoma sentinel nodes, *Annals of Surgical Oncology* 6: 232-240.
Reason for exclusion: Not an RCT.

32. Blum A, Brand CU, Ellwanger U, Schlagenhauff B, Stroebel W, Rassner G, Garbe C (1999), Awareness and early detection of cutaneous melanoma: an analysis of factors related to delay in treatment, *British Journal of Dermatology* 141: 783-787.
Reason for exclusion: Not an RCT.

33. Bodey B, Bodey BBJ, Groger AM, Siegel SE, Kaiser HE (1997), Nm23/nucleoside diphosphate (NDP) kinase expression in human malignant melanomas: significance and implications in tumor biology, *Anticancer Research* 17: 505-511.
Reason for exclusion: Non human/*in vitro*.

34. Bonfrer JM, Korse CM (2001), Monitoring malignant melanoma with the S-100B tumour marker, *Recent Results in Cancer Research* 158: 149-157.
Reason for exclusion: Not an RCT.

35. Bowen GM, Chang AE, Lowe L, Hamilton T, Patel R, Johnson TM (2000), Solitary melanoma confined to the dermal and/or subcutaneous tissue: evidence for revisiting the staging classification, *Archives of Dermatology* 136: 1397-1399.
Reason for exclusion: Not an RCT.

36. Box NF, Duffy DL, Irving RE, Russell A, Chen W, Griffiths LR, Parsons PG, Green AC, Sturm RA (2001), Melanocortin-1 receptor genotype is a risk factor for basal and squamous cell carcinoma, *Journal of*

Investigative Dermatology 116: 224-229.
Reason for exclusion: Not an RCT.

37. Bremer M, Neuhofer C, Auberger T, Zimmermann FB, Kneschaurek P, Reuschel W, Molls M (1999), Palliative radiotherapy of malignant melanoma with reactor fission neutron therapy (RENT): a prospective study, *Radiation Oncology Investigations* 7: 118-124.
Reason for exclusion: Not an RCT.

38. Brenner B, Sulkes A, Rakowsky E, Feinmesser M, Yukelson A, Bar-Haim E, Katz A, Idelevich E, Neuman A, Barhana M, Fenig E (2001), Second neoplasms in patients with Merkel cell carcinoma, *Cancer* 91: 1358-1362.
Reason for exclusion: Not an RCT.

39. Brochez L, Verhaeghe E, Bleyen L, Naeyaert JM (2001), Time delays and related factors in the diagnosis of cutaneous melanoma, *European Journal of Cancer* 37: 843-848.
Reason for exclusion: Not an RCT.

40. Brocker EB, Bohndorf W, Kampgen E, Trcka J, Messer P, Tilgen W, Engenhart K, Flentje M (1996), Fotemustine given simultaneously with total brain irradiation in multiple brain metastases of malignant melanoma: report on a pilot study, *Melanoma Research* 6: 399-401.
Reason for exclusion: Not an RCT.

41. Brown AM, Christie D, Taylor R, Secombe MA, Coates MS (1997), The occurrence of cancer in a cohort of New South Wales coal miners, *Australian & New Zealand Journal of Public Health* 21: 29-32.
Reason for exclusion: Not an RCT.

42. Butow PN, Coates AS, Dunn SM (1999), Psychosocial predictors of survival in metastatic melanoma, *Journal of Clinical Oncology* 17: 2256-2263.
Reason for exclusion: Not an RCT.

43. Buzaid AC, Colome M, Bedikian A, Eton O, Legha SS, Papadopoulos N, Plager C, Ross M, Lee JE, Mansfield P, Rice J, Ring S, Lee JJ, Strom E, Benjamin R (1998), Phase II study of neoadjuvant concurrent biochemotherapy in melanoma patients with local-regional metastases, *Melanoma Research* 8: 549-556.
Reason for exclusion: Not an RCT.

44. Bystryn JC, Zeleniuch-Jacquotte A, Oratz R, Shapiro RL, Harris MN, Roses DF (2001), Double-blind trial of a polyvalent, shed-antigen, melanoma vaccine, *Clinical Cancer Research* 7: 1882-1887.
Reason for exclusion: Small sample size.

45. Capuron L, Gumnick JF, Musselman DL, Lawson DH, Reemsnyder A, Nemeroff CB, Miller AH (2002), Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions, *Neuropsychopharmacology* 26: 643-652.
Reason for exclusion: Wrong intervention.

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Abbreviations

AIHW	Australian Institute of Health and Welfare
AJCC	American Joint Committee on Cancer staging system
ASCO	American Society of Clinical Oncology
BCG	Bacille Calmette-Guérin
DNFB	Dinitrofluorobenzene
DNP	Dinitrophenyl
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
IND	Investigational New Drug program
MSAC	Medical Services Advisory Committee
M-TAG Pty Ltd	Medical Technology Assessment Group Pty Ltd
NHMRC	National Health and Medical Research Council
PBS	Pharmaceutical Benefits Scheme
TCK	Tumour collection kit
TGA	Therapeutic Goods Administration
UKCCCR	United Kingdom Coordinating Committee on Cancer Research

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