Antigen-specific active immunotherapy for ovarian cancer

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[Intervention Review]

Antigen-specific active immunotherapy for ovarian cancer

Sterre T Paijens[1], Ninke Leffers[1], Toos Daemen[2], Wijnand Helfrich[3], H Marike Boezen[4], Ben J Cohlen[5], Cornelis JM Melief[6], Marco de Bruyn[1], Hans W Nijman[2]

[1]Obstetrics & Gynaecology, University Medical Center Groningen (UMCG), Groningen, Netherlands. [2]University Medical Center Groningen (UMCG), Groningen, Netherlands. [3]Department of Surgery. Translational Surgical Oncology, University Medical Center Groningen (UMCG), Groningen, Netherlands. [4]Unit Chronic Airway Diseases, Department of Epidemiology, University Medical Center Groningen (UMCG), Groningen, Netherlands. [5]Department of Obstetrics & Gynaecology, Isala Clinics, Location Sophia, Zwolle, Netherlands. [6]Department of Immunohaematology and Blood Transfusion, Leiden University Medical Center, Leiden, Netherlands

Contact address: Sterre T Paijens, Obstetrics & Gynaecology, University Medical Center Groningen (UMCG), Groningen, 9713 GZ, Netherlands. s.t.paijens@umcg.nl.

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ABSTRACT

Background

This is the second update of the review first published in the Cochrane Library (2010, Issue 2) and later updated (2014, Issue 9).

Despite advances in chemotherapy, the prognosis of ovarian cancer remains poor. Antigen-specific active immunotherapy aims to induce tumour antigen-specific anti-tumour immune responses as an alternative treatment for ovarian cancer.

Objectives

Primary objective

• To assess the clinical efficacy of antigen-specific active immunotherapy for the treatment of ovarian cancer as evaluated by tumour response measured by Response Evaluation Criteria In Solid Tumors (RECIST) and/or cancer antigen (CA)-125 levels, response to post-immunotherapy treatment, and survival differences

◦ In addition, we recorded the numbers of observed antigen-specific humoral and cellular responses

Secondary objective

• To establish which combinations of immunotherapeutic strategies with tumour antigens provide the best immunological and clinical results

Search methods

For the previous version of this review, we performed a systematic search of the Cochrane Central Register of Controlled Trials (CENTRAL; 2009, Issue 3), in the Cochrane Library, the Cochrane Gynaecological Cancer Group Specialised Register, MEDLINE and Embase databases, and clinicaltrials.gov (1966 to July 2009). We also conducted handsearches of the proceedings of relevant annual meetings (1996 to July 2009).

For the first update of this review, we extended the searches to October 2013, and for this update, we extended the searches to July 2017.

Selection criteria

We searched for randomised controlled trials (RCTs), as well as non-randomised studies (NRSs), that included participants with epithelial ovarian cancer, irrespective of disease stage, who were treated with antigen-specific active immunotherapy, irrespective of type of vaccine, antigen used, adjuvant used, route of vaccination, treatment schedule, and reported clinical or immunological outcomes.

Data collection and analysis

Two reviews authors independently extracted the data. We evaluated the risk of bias for RCTs according to standard methodological procedures expected by Cochrane, and for NRSs by using a selection of quality domains deemed best applicable to the NRS.

Main results

We included 67 studies (representing 3632 women with epithelial ovarian cancer). The most striking observations of this review address the lack of uniformity in conduct and reporting of early-phase immunotherapy studies. Response definitions show substantial variation between trials, which makes comparison of trial results unreliable. Information on adverse events is frequently limited. Furthermore, reports of both RCTs and NRSs frequently lack the relevant information necessary for risk of bias assessment. Therefore, we cannot rule out serious biases in most of the included trials. However, selection, attrition, and selective reporting biases are likely to have affected the studies included in this review. GRADE ratings were high only for survival; for other primary outcomes, GRADE ratings were very low.

The largest body of evidence is currently available for CA-125-targeted antibody therapy (17 studies, 2347 participants; very low-certainty evidence). Non-randomised studies of CA-125-targeted antibody therapy suggest improved survival among humoral and/or cellular responders, with only moderate adverse events. However, four large randomised placebo-controlled trials did not show any clinical benefit, despite induction of immune responses in approximately 60% of participants. Time to relapse with CA-125 monoclonal antibody versus placebo, respectively, ranged from 10.3 to 18.9 months versus 10.3 to 13 months (six RCTs, 1882 participants; high-certainty evidence). Only one RCT provided data on overall survival, reporting rates of 80% in both treatment and placebo groups (three RCTs, 1062 participants; high-certainty evidence). Other small studies targeting many different tumour antigens have presented promising immunological results. As these strategies have not yet been tested in RCTs, no reliable inferences about clinical efficacy can be made. Given the promising immunological results and the limited side effects and toxicity reported, exploration of clinical efficacy in large well-designed RCTs may be worthwhile.

Authors' conclusions

We conclude that despite promising immunological responses, no clinically effective antigen-specific active immunotherapy is yet available for ovarian cancer. Results should be interpreted cautiously, as review authors found a significant dearth of relevant information for assessment of risk of bias in both RCTs and NRSs.

PLAIN LANGUAGE SUMMARY

Antigen-specific active immunotherapy for ovarian cancer

Background

Ovarian cancer is the leading cause of death from gynaecological cancers. Standard therapy consists of surgery and chemotherapy. Responses to chemotherapy are generally good; however, most women experience relapse, for which no curative treatment is available. The presence of certain immune cells in tumours is associated with longer survival. This suggests that stimulation of anti-tumour immune responses (i.e. immunotherapy) might be a useful approach for improving outcomes among women with ovarian cancer.

Review question

This review evaluated the feasibility of antigen-specific active immunotherapy. Antigen-specific active immunotherapy aims to induce anti-tumour immune responses through administration of a tumour antigen - a molecule that is expressed by tumour cells and is hardly expressed by healthy cells. Reviewers collected information on clinical outcomes, immunological responses, and side effects.

Main findings

We identified 67 studies, which included 3632 women with ovarian cancer and were published between 1966 and 2017. The most frequently described strategy was administration of antibodies targeting the tumour antigen CA-125 (2347 participants in 17 studies).

Most of these studies primarily evaluated safety and immunological responses. Severe flu-like and gastrointestinal symptoms occurred in 7% to 30% of participants. Researchers frequently detected antibodies and immune cells recognising the tumour antigen CA-125, albeit response rates varied between studies. Despite these promising immunological responses, four large studies reported no survival advantage for participants treated with CA-125-directed antibody over those given placebo.

For strategies not relying on antibody administration, similar conclusions cannot yet be drawn. Overall, study authors report that treatment was well tolerated and inflammatory side effects at the injection site were most frequently observed. Researchers observed responses of the immune system for most strategies studied, but the clinical benefit of these strategies remains to be evaluated in large trials.

Certainty of the evidence and conclusions

Because no high-certainty evidence of clinical benefit is currently available, antibody therapy targeting CA-125 should not be incorporated into standard treatment in its current form.

Based on lack of uniformity in included studies, we strongly advocate universal adoption of response definitions, guidelines for adverse events reporting, and directives for trial conduct and reporting. Furthermore, results from ongoing randomised controlled trials (RCTs) are awaited, and further RCTs should be conducted.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antigen-specific immunotherapy for ovarian carcinoma

Patient or population: ovarian carcinoma
Setting: primary and recurrent ovarian carcinoma
Intervention: antigen-specific immunotherapy

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Tumour response assessed with: RECIST	In total, 2 participants (0.01%) were defined as having a complete response, 9 (0.03%) had a partial response, and 50 (14%) had stable disease. Twelve participants (0.03%) showed no evidence of disease. Finally, 218 (61%) participants had progressive disease. The remaining 64 (18%) participants were not mentioned	355 (17 observational studies)	⊕◯◯◯ Very low[a,b,c,d]
Tumour response assessed with: CA-125 according to GCIG criteria	In total, 8 participants (13%) were reported to have an increase in CA-125. In 22 patients, CA-125 was stable or decreasing (34%). The remaining 34 participants (53%) were considered not evaluable or were not mentioned	64 (6 observational studies)	⊕◯◯◯ Very low[a,b,c,d,e]
Post-immunotherapy treatment response assessed with: survival	Two studies suggested that antigen-specific immunotherapy may lead to improved responses to future therapy. Two studies revealed no evidence of a difference	88 (4 observational studies)	⊕◯◯◯ Very low[a,f]
Survival assessed with: overall survival	None of the 3 RCTs estimating overall survival found a significant difference in overall survival. Two studies of CA-125 monoclonal antibody vs placebo evaluated overall survival, respectively, at 57.5 vs 48.6 months (95% CI 041 to 1.25) and 80%	1062 (3 RCTs)	⊕⊕⊕⊕ High

	survival for both groups		
Survival assessed with: progression-free survival/ time to relapse	None of the 6 RCTs found statistically significant differences in progression-free survival/time to relapse, including 4 RCTs evaluating CA-125 monoclonal antibody vs placebo; time to relapse ranged from 10. 3 to 18.9 months vs 10.3 to 13 months, respectively	1882 (6 RCTs)	⊕⊕⊕⊕ High
Antigen-specific immunogenicity (humoral response) assessed with: ELISA/Luminex assay	Nine studies evaluated anti-idiotopic (Ab2) humoral response, with responses ranging from 3% to 100%. Ten studies evaluated anti-anti-idiotropic (Ab3) humoral response, with responses ranging from 0% to 100%. Two studies observed no humoral response to other antigen-specific immunotherapy, and the 9 remaining studies noted large differences in percentages of participants with measurable antigen-specific antibodies (IgG: 8% to 96%)	1521 (25 observational studies)	⊕◯◯◯ Very low[a,d,g]
Antigen-specific immunogenicity (cellular response) assessed with: e.g. IFN-γ ELISPOT/proliferation assay/IFN-γ secretion assay	A total of 39 studies showed an induced cellular immune response in at least 1 cohort and to at least 1 target antigen; range of positive response varied broadly between 18% and 100%. One study retrospectively compared cellular immune response after CA-125 monoclonal antibody treatment vs placebo but showed no significant differences (31.8% intervention vs 26.3% control)	966 (40 observational studies)	⊕◯◯◯ Very low[a,d,g,h]

Ab2: anti-idiotopic; Ab3: anti-anti-idiotopic; CA: cancer antigen; CI: confidence interval; ELISA: enzyme-linked immunosorbent assay; GCIG: Gynecologic Cancer Intergroup; IFN: interferon; RCTs: randomised controlled trials; RECIST: Response Evaluation Criteria In Solid Tumors

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Most studies were uncontrolled phase I/II trials.
[b] A large percentage of the included participants were not mentioned or were not evaluable for the analysis.
[c] Explicit descriptions of tumour responses per participant and the time points at which evaluations took place frequently were not available.
[d] Disease status at start of treatment differed among studies. Therefore the likelihood of clinical and immune responses to immunotherapy, especially in uncontrolled studies, which frequently include participants with recurrent disease and previous exposure to different types of therapy, is likely to be affected.
[e] CA-125 is a biomarker that serves as an indication for response; however CA-125 does not directly reflect tumour size.
[f] Although in one study participants with a complete response had strong humoral responses, similar or stronger antibody responses were observed for participants with stable or progressive disease.
[g] Between studies, there were broad differences in (1) response definition, (2) number of treatment cycles after which immune responses were measured, and (3) targeted antigens.
[h] Explicit descriptions of immune responses per participant and the time points at which evaluations took place, types of evaluations, and when an evaluation was considered positive often were not available.

BACKGROUND

Description of the condition

Ovarian cancer is the sixth most common cancer and the seventh most common cause of death from cancer among women worldwide (Torre 2012). It is the second most common gynaecological cancer and the leading cause of death from gynaecological cancers in the Western world. As most ovarian malignancies (80% to 90%) arise from the epithelium, all statements about ovarian cancer presented in the remainder of this review apply to epithelial ovarian cancer only. Worldwide age-standardised incidence rates range from 5 per 100,000 in less developed areas to 9.1 per 100,000 in developed areas (Torre 2012).

Stage of disease at presentation is the most important prognostic factor. Owing to the asymptomatic course of the disease, most participants have extensive disease at presentation (stage III to IV, according to the International Federation of Gynecology and Obstetrics (FIGO) classification (Prat 2015)). Despite standard treatment, which consists of cytoreductive surgery and platinum-based chemotherapy, almost all women with advanced-stage disease at presentation will experience relapse, with median progression-free survival of only 18 months. When residual or recurrent disease manifests itself, resistance to chemotherapy often prohibits further curative therapy, resulting in disease-specific five-year survival for women with advanced-stage ovarian disease of only 10% to 20% (Agarwal 2006; Thigpen 2000).

Description of the intervention

The immune system seems to play a role in ovarian cancer. This is reflected in the observation that in more than half of women with ovarian cancer, T-cells are present within tumour islets (Raspollini 2005; Zhang 2003). Women with advanced ovarian cancer, whose tumour is infiltrated by these T-cells, have better clinical outcomes than women without these tumour-infiltrating T-cells (Dong 2006; Raspollini 2005; Zhang 2003). More specifically, higher numbers of cytotoxic T-cells, which can directly recognise and kill tumour cells, and increased ratios between cytotoxic T-cells (CD8+) and helper T-cells (CD4+) within the tumour epithelium are associated with improved survival (Gooden 2011; Sato 2005). Immunotherapy is one of the novel therapeutic strategies under investigation for ovarian cancer. It aims to induce or enhance active immune responses directed towards the tumour and to consolidate anti-tumour effects of standard therapy, delaying and possibly preventing disease progression. Antigen-specific active immunotherapy aims to activate the adaptive immune system directed towards a specific target antigen through administration of a molecularly defined antigen-specific vaccine to the patient.

How the intervention might work

An antigen is a molecule - usually a protein or a polysaccharide - that can stimulate an immune response. Tumour antigens can be subdivided into different categories such as mutated self-proteins, products of oncogenes (e.g. Her-2/Neu), mutated tumour suppressor genes (e.g. *p53*), and aberrantly expressed self-proteins (e.g. sperm protein 17, MAGE-1). Numerous tumour-associated antigens are known in ovarian cancer. To obtain a tumour-specific immune response, immunotherapy exploits the differential expression of antigens between normal and tumour cells. A major challenge related to the safety of immunotherapy lies in the prevention of autoimmunity (i.e. induction of immune cells that preferentially recognise and kill tumour cells while avoiding destruction of normal body cells). From a theoretical point of view, other possible side effects include allergic reactions to components of the vaccine and inflammatory reactions at the site of injection.

Why it is important to do this review

Researchers are now employing several immunotherapeutic strategies by using different tumour antigens. However, this research generally has not yet evolved past phase I/II studies. To our knowledge, no systematic review of antigen-specific active immunotherapy in ovarian cancer has been carried out so far.

This review evaluates the immunogenicity and clinical efficacy of antigen-specific active immunotherapy in ovarian cancer. A systematic review about this topic should prove useful for ascertaining the effectiveness of this treatment modality for ovarian cancer.

OBJECTIVES

Primary objective

- To assess the clinical efficacy of antigen-specific active immunotherapy for the treatment of ovarian cancer as evaluated by tumour response measured by Response Evaluation Criteria In Solid Tumors (RECIST) and/or cancer antigen (CA)-125 levels, response to post-immunotherapy treatment, and survival differences
    - In addition, we recorded the numbers of observed antigen-specific humoral and cellular responses

Secondary objective

- To establish which combinations of immunotherapeutic strategies with tumour antigens provide the best immunological and clinical results

METHODS

Criteria for considering studies for this review

Types of studies

We had anticipated that we would identify limited randomised controlled trials (RCTs) on this topic. Therefore, we included phase I and phase II non-randomised studies (NRSs) and phase III RCTs. We realise that results from NRSs cannot readily be extrapolated to the general population, but given the lack of RCTs, inclusion of these studies in the review was justifiable.

Types of participants

We included women with a diagnosis of epithelial ovarian cancer, irrespective of stage of disease. However, as patient populations may differ substantially between different types of studies to be included in this review, we documented what type of participant was included in each study (e.g. women with end-stage disease, women with residual disease).

Because we anticipated that we would find few studies that included women with ovarian cancer only, we also included immunotherapeutic studies in people with cancer that included at least two women with ovarian cancer, with the additional requirement that the results for these individual women were separately identifiable from those of the study publication or could be obtained by communication with the study author, and we extracted only data on these women for inclusion in the review. We are fully aware of the vigilance necessary when conclusions are based on studies with such small numbers, but we believe that given the anticipated lack of large RCTs, inclusion of these studies in this review is justifiable.

Types of interventions

Antigen-specific active immunotherapy is defined as therapy that aims to induce an adaptive immune response directed towards the tumour through administration of a specific well-defined tumour antigen. We compared interventions against each other based on the above-mentioned characteristics.

We included all interventions that aimed to provide antigen-specific active immunotherapy, irrespective of type of vaccine, antigen, or adjuvant used; route of vaccination; and vaccination schedule.

Types of outcome measures

Primary outcomes

Clinical efficacy

To assess clinical efficacy, we evaluated the following.

- Tumour responses to immunotherapy (complete/partial response, stable/progressive disease), as measured by:
  - cancer antigen (CA)-125 levels according to or transposable to Gynecologic Cancer Intergroup (GCIG) criteria (Rustin 2004); or
  - tumour response according to World Health Organization (WHO) criteria - WHO 1979 - or Response Evaluation Criteria in Solid Tumors (RECIST) criteria - Therasse 2000.
- We evaluated responses to post-immunotherapy treatment, as evidence suggests that people with small cell lung cancer treated with chemotherapy after immunotherapy have improved survival as opposed to people who do not receive immunotherapy (Antonia 2006).
- We assessed:
  - survival differences, including time to relapse or progression-free survival, based on treatment with immunotherapy.

Antigen-specific immunogenicity

We recorded the numbers of observed antigen-specific humoral and cellular responses. When possible, we separately reported responses of cytotoxic (CD8+) T-lymphocytes and/or helper (CD4+) T-lymphocytes.

Secondary outcomes

Carrier-specific immunogenicity

Given that certain immunotherapeutic strategies rely on the use of carriers that may be the target of an immune response besides the intended antigen-specific immune response, we recorded information on the induction of carrier-specific immune responses when appropriate.

Adverse events

To obtain information on the toxicity of antigen-specific immunotherapy, we extracted data on adverse events observed and reported in the different studies. We categorised adverse events as local adverse events at the site of immunisation and systemic adverse events (all other reported adverse events). We subdivided systemic adverse events into autoimmunity, allergic reactions, and other adverse events occurring after immunisation. If sufficient information was available, we classified adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (CTCAE 2009).

Search methods for identification of studies

Electronic searches

For the original review (Leffers 2010), we searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2013, Issue 9), in the Cochrane Library (Appendix 1), along with the Cochrane Gynaecological Cancer Group Specialised Register, in October 2013. We also searched MEDLINE (1966 to July 2009) and Embase (1974 to July 2009) according to the search strategies listed (Appendix 2; Appendix 3, respectively).

For the first update of the review, we extended the searches to October 2013, and for this update, we extended the searches to July 2017:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 6), in The Cochrane Library;
- MEDLINE via OVID (October 2013 to June week 4 2017);
- Embase via OVID (October 2013 to 2017 week 27).

Searching other resources

We also searched the prospective trial register at www.clinicaltrials.gov.

We undertook handsearching of abstracts in the proceedings of annual meetings of the Society of Gynecologic Oncologists, the American Association for Cancer Research, and the International Society for Biological Therapy of Cancer (1996 to July 2009). The International Society for Biological Therapy of Cancer has been renamed the Society for Immunotherapy of Cancer (SITC), thus we also searched the proceedings of the annual meeting of SITC. We checked the bibliography of each primary reference and of recent reviews on immunotherapy for ovarian cancer for additional study publications. In addition, we wrote to specialists involved in research regarding immunotherapy for ovarian cancer to ask for information about the results of unpublished and ongoing studies. We included relevant data in this review.

Data collection and analysis

Selection of studies

We downloaded to Reference Manager all titles and abstracts retrieved by electronic searching. We applied no language restrictions other than those inherent to the databases surveyed. We removed duplicates, and two review authors (HWN and NL) independently examined the remaining references. We excluded studies that clearly did not meet the review inclusion criteria and obtained copies of the full text of potentially relevant references. Two review authors (HWN and NL) independently assessed the eligibility of retrieved papers. We resolved differences by discussion or by appeal to a third review author (TD), if necessary. We documented reasons for exclusion. The second update included all titles and abstracts from October 2013 until July 2017 retrieved by electronic searches of MEDLINE, Embase, and CENTRAL. Two review authors (STP and MB) selected and independently assessed studies using the same procedure that was used in the primary review and the first update. We resolved differences by discussion or by appeal to a third review author (HWN), if necessary.

Data extraction and management

Two review authors (HWN and NL) independently extracted data on characteristics of participants and interventions, study quality, and endpoints for included studies, and entered them onto a data extraction form specially developed for this review (Appendix 4). Two review authors (STP and MB) followed the same procedure for the second update.

When data on clinical efficacy and antigen-specific immunogenicity were missing from reports, we attempted to contact study authors to obtain the missing information. A third review author (WH or TD; or HWN during the second update) checked the results.

Assessment of risk of bias in included studies

We assessed the risk of bias in RCTs using the Cochrane 'Risk of bias' tool.

No standard tools are available to evaluate validity for non-RCTs. For these studies, we evaluated the risk of bias using the following four domains (Table 1).

- Sample definition and selection.
  - Clear definition of inclusion/exclusion criteria.
  - Representative selection.
  - Adequate description of baseline characteristics.
- Interventions.
  - Clear specification.
  - Concurrent/concomitant treatment.
- Outcomes.
  - Specifications of outcome measures.
  - Relevance of outcome measures.
  - Reporting of outcome measures.
- Statistical analysis.
  - Adequate rationale for numbers of participants included.
  - Adequate description of withdrawals/exclusions during the study.
  - Adequate presentation of results.

We selected these domains as representative for, and applicable to, non-randomised non-controlled studies from a list of 12 quality domains and items deemed to be pivotal to the assessment of non-RCTs (Deeks 2003).

Two review authors (HWN and NL) carried out the 'Risk of bias' assessment. We resolved discrepancies by discussion; if necessary,

we consulted a third review author (WH or TD). For the second update, two review authors (STP and MB) carried out the 'Risk of bias' assessment. We resolved discrepancies by discussion; if necessary, we consulted a third review author (HWN).

Data synthesis

This review provides a narrative analysis because the included studies are highly heterogeneous in terms of intervention and outcome measures. Furthermore, publications often presented data with insufficient details (e.g. lack of standard deviations (SDs), presentation of only some of the multiple outcomes), and it was difficult for review authors to obtain additional information from report authors. Therefore we agreed that quantitative meta-analysis and calculation of effect size estimates would be neither meaningful nor appropriate for this review. We limited analysis to a structured summary and discussion of available studies and findings.

Certainty of the evidence

We assessed the certainty of the evidence for main outcomes using GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria (Guyatt 2008), and we presented the main findings along with our judgements in a 'Summary of findings' table.

We will present the overall certainty of the evidence for each outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt 2008), which takes into account issues related not only to internal validity (risk of bias, inconsistency, imprecision, publication bias for quantitative studies) but also to external validity (directness of results). We downgraded the evidence from 'high' certainty by one level for serious (or by two for very serious) concerns for each limitation.

- High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate-certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low-certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low-certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

For qualitative studies, we would upgrade for large consistent effect, dose response, and confounders that only reduced the effect size.

RESULTS

Description of studies

Results of the search

Initial version of the review

Leffers 2010

Upon completing electronic searches of MEDLINE and Embase, we selected 56 out of 311 abstracts as potentially compliant with the selection criteria of this review and retrieved the full texts. Evaluation of the retrieved full texts resulted in the exclusion of 26 papers (see Excluded studies). In addition to the 30 selected full texts, we identified another 14 abstracts by handsearching the proceedings of the periodic meetings specified in the Methods section. We contacted study authors for manuscripts but obtained no full texts for these abstracts. Together, the 44 selected full texts and meeting abstracts described a total of 35 studies. A search of the prospective trial register www.clinicaltrials.gov resulted in identification of an additional 26 studies. We could retrieve a full text or meeting abstract for only four of these and found that only one study complied with our inclusion criteria (Sabbatini 2007). The remaining studies were either ongoing (n = 15) or completed but not yet published (n = 6). A search of CENTRAL (2009, Issue 3) yielded no additional studies. Thus, we included a total of 36 studies in this review. Generally, we selected the most recent peer-reviewed publication as the primary reference.

First update of the review

Leffers 2014

For the first update of this review, electronic searches of MEDLINE and Embase yielded 158 records, which resulted in an additional 23 included papers and 10 excluded papers (Characteristics of excluded studies). For five studies in the previous version of this review, a full-text publication, update, or additional paper was now available. A search of CENTRAL (2013, Issue 3) did not yield additional studies. A search of clinicaltrials.gov resulted in two additional published studies. Furthermore, we identified 26 relevant studies without available results (Characteristics of ongoing studies). Twelve studies are currently recruiting participants, four studies are ongoing but not recruiting, nine studies are classified as completed, and for two studies status is unknown. Overall, we included an additional 19 studies in the update of this review, resulting in a total of 55 included studies involving 3051 women (Characteristics of included studies).

Second update of the review

For the second update of the review, an electronic search of CENTRAL, MEDLINE, and Embase yielded 266 records, which resulted in an additional nine included papers and nine excluded

papers (Characteristics of excluded studies). For two studies identified in the previous version of this review, a full-text publication, update, or additional paper was now available.

A search of ongoing studies identified from the last update in clinicaltrials.gov revealed four additional published studies, three of which are included in this update. In addition, five studies were completed for which no results were published, four studies are still recruiting, and for one study status remains unknown. We removed four studies from the Ongoing studies section because the study had been terminated, or because studies did not include women with epithelial ovarian cancer. Furthermore, we identified 22 relevant new ongoing studies without available results (Characteristics of ongoing studies).

Overall, we included an additional 12 studies in the update of this review, resulting in a total number of 67 included studies involving 3632 women (Characteristics of included studies).

Included studies

The 67 studies included in this updated review were all published in English (Characteristics of included studies; Table 2).

Design

As we expected, most studies were uncontrolled phase I or II studies (52/67). Only four studies were randomised placebo-controlled studies (Berek 2001; Berek 2004; Berek 2009; Sabbatini 2013). Eleven studies randomly allocated participants to different regimens (Baumann 2011; Braly 2009; Chu 2012; Freedman 1998; Goh 2013; Gray 2016; Heiss 2010; Lennerz 2014; Method 2002; Sabbatini 2006; Sabbatini 2017). Five studies retrospectively studied the immunogenicity of a previously applied immunoscintigraphic agent (Buzzonetti 2014; Möbus 2003; Noujaim 2001; Schultes 1998; Wagner 1993).

Sample sizes

The median number of women with epithelial ovarian cancer treated per study was 20 (range 2 to 888). Twenty-one studies included fewer than 10 participants. Twenty studies also included participants with other types of cancer (Antonilli 2016; Berinstein 2012; Brossart 2000; Dhodapkar 2012; Gribben 2005; Gulley 2008; Heiss 2010; Kaumaya 2009; Le 2012; Lennerz 2014; Letsch 2011; Mohebtash 2011; Morse 2011; Odunsi 2012; Ohno 2009; Peethambaram 2009; Sandmaier 1999; Ströhlein 2009; Takeoka 2017; Tsuda 2004). Only 13 studies provided a sample size calculation or rationale (Baumann 2011; Berek 2004; Berek 2009; Braly 2009; Gribben 2005; Heiss 2010; Leffers 2009a; Rahma 2012; Sabbatini 2006; Sabbatini 2007; Sabbatini 2012; Sabbatini 2013; Vermeij 2012).

Participants

As was expected, disease status at study entry varied largely between studies (Table 2). Participants with evidence of residual or recurrent disease after treatment were most frequently included (30/67) (Baumann 2011; Brossart 2000; Dijkgraaf 2015; Ehlen 2005; Galanis 2010; Gordon 2004; Gribben 2005; Gulley 2008; Heiss 2010; Kaumaya 2009; Kawano 2014; Le 2012; Leffers 2009a; MacLean 1992; MacLean 1996; Möbus 2003; Mohebtash 2011; Nicholson 2004; Noujaim 2001; Odunsi 2014; Peethambaram 2009; Ströhlein 2009; van Zanten-Przybysz 2002; Vermeij 2012). Eight studies included participants with and without evidence of disease after prior therapy (Antonilli 2016; Berinstein 2012; Braly 2009; Chianese-Bullock 2008; Lennerz 2014; Odunsi 2007; Sabbatini 2006; Tsuda 2004). Seventeen studies included participants with complete response to therapy for primary or recurrent disease (Berek 2001; Berek 2004; Berek 2009; Buzzonetti 2014; Chu 2012; Diefenbach 2008; Goh 2013; Gray 2016; Imhof 2013; Morse 2011; Odunsi 2012; Rahma 2012; Sabbatini 2000; Sabbatini 2007; Sabbatini 2012; Sabbatini 2013; Sabbatini 2017). One study administered treatment together with adjuvant chemotherapy after primary cytoreductive surgery (Braly 2009). The remaining 18 studies did not report disease status at study entry (Berinstein 2013; Dhodapkar 2012; Freedman 1998; Kobayashi 2014; Letsch 2011; Ma 2002; Method 2002; Nishikawa 2006; O'Cearbhaill 2016; Ohno 2009; Pfisterer 2006; Reinartz 2004; Sandmaier 1999; Schultes 1998; Suzuki 2016; Takeoka 2017; Takeuchi 2013; Wagner 1993).

Interventions

Most studies described antibody therapy (22/55), usually targeting cancer antigen (CA)-125 (17/22 (2347 women)). Most studies included only one target antigen in the vaccine, but 15 studies simultaneously targeted multiple antigens (Antonilli 2016; Berinstein 2012; Chianese-Bullock 2008; Chu 2012; Gulley 2008; Imhof 2013; Kawano 2014; Kobayashi 2014; Mohebtash 2011; Morse 2011; O'Cearbhaill 2016; Sabbatini 2007; Sabbatini 2017; Takeuchi 2013; Tsuda 2004). Antibodies were usually administered intravenously (12/22). For other vaccine types, subcutaneous injections were most common (29/43).

Fifteen out of 55 studies did not allow concurrent treatment with immunomodulatory drugs. In an additional 20 studies, concomitant immunomodulatory agents were not part of the studied intervention but study authors made no explicit statements in the protocol about prohibition of such drugs. For 27 studies, immunomodulatory drugs were part of the protocol (i.e. carboplatin-paclitaxel, gemcitabine, doxorubicin and decitabine, cyclophosphamide, interleukin (IL)-2 ± granulocyte-macrophage colony-stimulating factor (GM-CSF), OK-432, OPT-821, PegIntron, toll-like receptor agonist poly-ICLC or resiquimod, or diphenhydramine) and one of these allowed interruption of immunotherapy by chemotherapy for progressive disease (Reinartz 2004). Fur-

thermore, two retrospective studies explicitly mentioned that concurrent chemotherapy was allowed at the discretion of the treating clinician (Möbus 2003; Wagner 1993).

Outcomes

Information on immunological responses, clinical responses, survival, and adverse events was available for 63, 43, 44, and 54 studies, respectively.

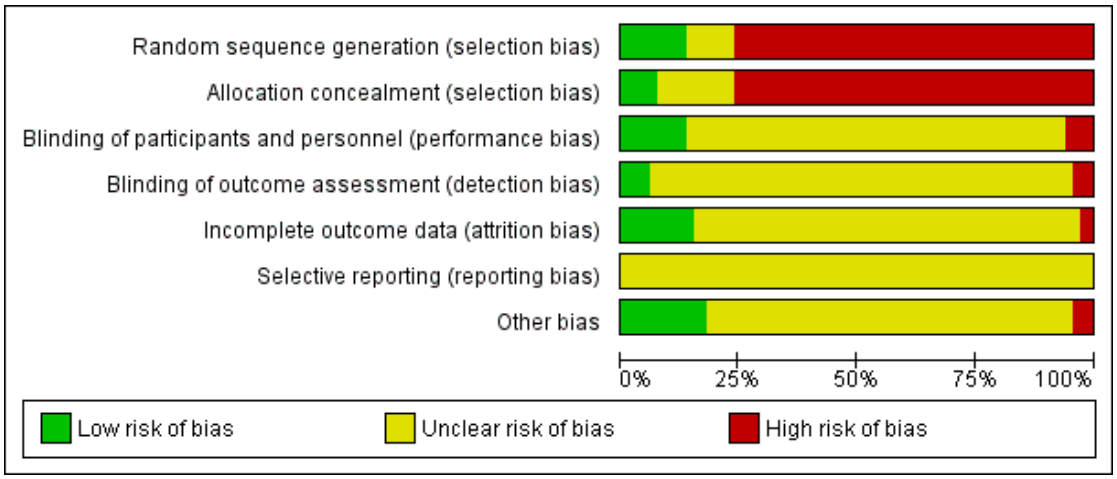
Excluded studies

A summary of the excluded studies is given in the Characteristics of excluded studies table. Frequent reasons for exclusion were inclusion of too few participants with ovarian cancer, use of antigen non-specific immunotherapy, and the impossibility of distinguishing results for women with ovarian cancer from results for other study participants.

Risk of bias in included studies

We included GRADE ratings for all primary outcomes. We rated survival as high but all other primary outcomes as very low, as is displayed in Summary of findings for the main comparison.
We evaluated risk of bias using the Cochrane 'Risk of bias' tool (Higgins 2011). Results of individual studies (both RCTs and NRSs) are available in the Characteristics of included studies table. The fact that for four of 16 RCTs only meeting abstracts were available hindered assessment of risk of bias. The 14 trials for which we could retrieve full texts also did not report on some of the items in the 'Risk of bias' tool. This substantial lack of information means it is highly likely that included studies are subject to biases, and it is therefore difficult to make any statements about the validity of the included RCTs (Figure 1).

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. The high risk of selection bias in the majority of included studies is a reflection of the large number of uncontrolled studies included in this review. The risk of remaining biases could not be adequately judged for the included uncontrolled studies, thus explaining the large percentage of missing risk assessments.



In addition to using the 'Risk of bias' tool, we evaluated non-RCTs using the checklist provided in Table 1. An overview of these results is provided in Table 3. Important observations from this table include lack of clearly defined inclusion/exclusion criteria in 13 out of 51 studies and serious under-reporting of baseline characteristics in 31 out of 51 studies; this combination makes it impossible to evaluate whether the study populations were representative of the true population. Although most studies carefully described the investigational interventions (47 out of 51), information on allowance or application of concomitant immunomodulatory treatment was frequently absent (24 out of 51). Albeit a clear description of outcome measures was available for 35 studies, adequate calculation of sample size based on a clearly defined

primary outcome measure was available for only five studies. Furthermore, the applied checklist shows that justification for withdrawals and exclusions during the study, as well as presentation of study results, requires serious attention in the reports of these non-randomised studies.

Based on the above, the risk of bias of studies included in this systematic review cannot be neglected. Especially selection bias (selection of a treatment population not comparable to the control group or the true population), attrition bias (inadequate reporting of withdrawal and exclusions during the study, resulting in possible overestimation or underestimation of effects), and selective reporting bias are likely to affect the studies included in this review. The effects of interventions described below must therefore be interpreted with prudence.

Allocation

As can be deduced from the Characteristics of included studies table, we were unable to identify the methods of randomisation and allocation used for several randomised studies, which means that we cannot rule out a selection bias for these studies. For the remaining RCTs, selection bias does not seem likely.

However most included studies were early-phase non-randomised studies including only a single study arm. Selection bias in these studies may have occurred in two ways: (1) by selective inclusion of participants with no other treatment options owing to end-stage disease, at which point function of the immune system may also be seriously impaired, thus resulting in an underestimation of immunogenicity and possible clinical benefit of a given vaccine, or (2) via selective recruitment of fairly immunocompetent patients with no evidence of disease, resulting in a possible overestimation of immunogenicity and possible clinical benefit of a given vaccine.

Blinding

Inherent to the study design, no non-RCTs blinded participants or treating (study) physicians. All participants may have derived benefit from the additional attention awarded to them as participants in a study, and thus performance bias may have influenced the results of these studies. Furthermore, it is unclear whether for these studies, outcome assessors were aware of the clinical condition of patients; thus detection bias may have occurred in these studies.

Only five RCTs described blinding of patients, caregivers, and/or outcome assessors; all compared antibody therapy versus placebo (Berek 2001; Berek 2004; Berek 2009; Sabbatini 2013; Sabbatini 2017). The other RCTs compared dosage levels (Baumann 2011; Freedman 1998; Lennerz 2014), administration route (Sabbatini 2006), number of gifts of a given drug (Method 2002), timing of the intervention in relation to standard chemotherapy (Braly 2009), addition of an immunomodulatory drug (Chu 2012), or immunotherapeutic intervention compared with standard of care (Goh 2013; Gray 2016; Heiss 2010). Given these study designs, we believe that for most of these studies, risk of performance bias is low. Information on blinding of outcome assessors is frequently missing, and risk of detection bias cannot be reliably judged.

Incomplete outcome data

We deemed that only one RCT had high risk of attrition bias based on differences in withdrawals between groups (Heiss 2010). Risk of attrition bias was unclear for nine other RCTs (Berek 2001; Buzzonetti 2014; Freedman 1998; Goh 2013; Gray 2016; Lennerz 2014; Method 2002; Sabbatini 2006; Sabbatini 2017), and risk was low for the remaining RCTs (Baumann 2011; Berek 2004; Berek 2009; Braly 2009; Chu 2012; Sabbatini 2013).

Selective reporting

None of the included studies had a publicly available registered study protocol. It is therefore unclear whether studies selectively reported outcomes.

Other potential sources of bias

Given the elapsed time since publication of the meeting abstract, a publication bias is likely to exist for two out of three RCTs for which only a meeting abstract was available (Berek 2001; Freedman 1998).

Effects of interventions

See: **Summary of findings for the main comparison** Antigen-specific immunotherapy for ovarian carcinoma

Primary outcomes

Clinical efficacy

Tumour responses

Forty-three studies evaluated clinical responses to therapy (Table 4). No RCTs evaluated tumour response (Berek 2001; Berek 2004; Berek 2009; Gray 2016; Sabbatini 2013; Sabbatini 2017). In reports on these studies, criteria for evaluation and/or explicit descriptions of tumour responses per patient as well as the time point at which the evaluation took place were frequently not available. For studies that did mention evaluation of tumour responses, response outcomes were based on CA-125 levels combined with tumour imaging (Baumann 2011; Chianese-Bullock 2008; Chu 2012; Diefenbach 2008; Dijkgraaf 2015; Ehlen 2005; Galanis 2010; Gordon 2004; Gulley 2008; Leffers 2009a; Ohno 2009; Rahma 2012; Sabbatini 2006; Ströhlein 2009; Tsuda 2004; van Zanten-Przybysz 2002; Vermeij 2012), CA-125 alone (Nicholson 2004; Wagner 1993), or imaging alone (Le 2012; Odunsi 2007;

Peethambaram 2009; Reinartz 2004; Sabbatini 2012; Takeuchi 2013). Eighteen studies explicitly mentioned evaluation of imaging according to the internationally accepted WHO or RECIST criteria (Baumann 2011; Dijkgraaf 2015; Galanis 2010; Kawano 2014; Kobayashi 2014; Leffers 2009a; Lennerz 2014; Odunsi 2014; Ohno 2009; Rahma 2012; Reinartz 2004; Sabbatini 2012; Suzuki 2016; Takeoka 2017; Takeuchi 2013; Tsuda 2004; Vermeij 2012), and only six studies evaluated CA-125 levels according to GCIG criteria or described CA-125 levels in such a way that evaluation according to these criteria was possible for at least some participants (Baumann 2011; Dijkgraaf 2015; Galanis 2010; Leffers 2009a; van Zanten-Przybysz 2002; Vermeij 2012). It is striking that eight studies stated that study authors evaluated tumour responses but did not provide these results in their publications (Dhodapkar 2012; Diefenbach 2008; Gulley 2008; Imhof 2013; Method 2002; Odunsi 2007; Reinartz 2004; Wagner 1993). Only seven studies reported complete or partial tumour responses in a small fraction of patients with evidence of disease at study entry (Baumann 2011; Dijkgraaf 2015; Gordon 2004; Kaumaya 2009; Kawano 2014; Odunsi 2007; Takeuchi 2013). These results must be interpreted with caution, as two of these studies did not define criteria for response evaluation (Gordon 2004; Odunsi 2007).

Post-immunotherapy treatment response

Although studies generally report a period of follow-up to obtain information on survival, most studies provide no report on subsequent treatment with and response to secondary chemotherapy. Nine studies mention that participants were treated with chemotherapy after immunotherapy (Berek 2004; Gordon 2004; Gribben 2005; Leffers 2009a; Möbus 2003; Odunsi 2007; Reinartz 2004; Ströhlein 2009; van Zanten-Przybysz 2002), but only four non-comparative phase I/II studies report response to secondary chemotherapy in relation to immunological responses to immunotherapy (Gordon 2004; Gribben 2005; Leffers 2009a; Reinartz 2004).

Reinartz 2004 provided a preliminary report on clinical responses of 28 out of 42 participants treated with chemotherapy for clinically relevant progression during or after antibody therapy in conjunction with the induction of human-anti-mouse and anti-anti-idiotype antibodies. Although both types of participants with a complete response had strong humoral responses, researchers observed similar or stronger antibody responses for participants with stable or progressive disease. In another study, shortly after monotherapy with a monoclonal antibody, 13 out of 20 participants received chemotherapy combined with the monoclonal antibody. Researchers in this study observed clinical responses to chemo-immunotherapy only in patients with cellular responses to CA-125 and/or autologous tumour (Gordon 2004). A study of synthetic long peptides targeting *p53* showed no improvement in survival or tumour responses to secondary chemotherapy (Leffers 2009a). Finally, the authors of a study investigating plasmid DNA vaccination targeting CYP1B1 suggest that treatment has led to improved responses to third-line therapy but included no control group, nor do we find this observation convincing when only patients with ovarian cancer are considered (Gribben 2005).

Survival and time to relapse

Definitions of survival used in the different studies varied greatly (Table 5 and Table 6). Furthermore, reliable statements about survival (dis)advantages can be made only on the basis of RCT findings. Only six studies were designed to primarily evaluate survival; however, investigators found no statistically significant differences in time to relapse and/or overall survival between patients treated with a monoclonal antibody and those given placebo (Berek 2001; Berek 2004; Berek 2009; Sabbatini 2013). Another study compared antigen-specific immunotherapy versus a non-specific immunotherapy and noted no significant differences in progression-free survival (Sabbatini 2017). Another study compared MUC1 dendritic cell therapy versus standard of care and reported no significant differences in progression-free survival and overall survival. However, when patients were divided into two subgroups (first and second clinical remission), a significant difference in overall survival and progression-free survival was evident among those with a second clinical remission. Researchers included a small number of participants in the trial and median overall survival of the treated group has not yet been reached; therefore these results must be interpreted with caution (Gray 2016). Many non-RCTs also evaluated survival, frequently by comparing survival of patients with robust immunological responses versus that of patients with no or weak immunological responses to treatment (Table 5 and Table 6). These results should be interpreted with great caution, as shorter survival among non-responders could merely be a reflection of the general condition of these patients and might reflect well-known clinical and pathological prognostic parameters. Patient numbers in the non-comparative groups were often too low to permit a reliable conclusion.

Antigen-specific immunogenicity

Humoral responses

Monoclonal antibodies may induce anti-idiotype antibodies (Ab2), directed primarily against the administered monoclonal antibody, as well as anti-anti-idiotype antibodies (Ab3), directed towards the target antigen. Anti-idiotype and anti-anti-idiotype antibodies were evaluated in 10 out of 22 studies and 9 out of 22 studies, respectively (Table 7 and Table 8). Response percentages varied greatly (Ab2: 3% to 100%, Ab3: 0% to 100%).

Twenty-one studies of other vaccine types evaluated the induction of antigen-specific antibodies as shown by enzyme-linked immunosorbent assay (ELISA) or luminex assay; however only 11 of

these studies clearly defined when an antibody titre or concentration was considered positive (Table 9) (Diefenbach 2008; Galanis 2010; Kaumaya 2009; Kawano 2014; O'Cearbhaill 2016; Odunsi 2014; Sabbatini 2007; Sabbatini 2012; Sabbatini 2017; Sandmaier 1999; Takeoka 2017). In addition, the study combining an NY-ESO-1 vaccine with chemotherapy and an anti-methylation agent tested humoral response with ELISA to 22 recombinant proteins that were not included in the vaccine and showed de novo serum reactivity to at least one of those proteins in all analysed participants (n = 3), suggesting that combination regimens may lead to a broadened profile of anti-tumour immune response in vivo (Odunsi 2014). Results show large differences in percentages of patients with measurable antigen-specific antibodies (IgG: 0% to 96%). Possible explanations for these broad ranges include differences in (1) response definition, (2) number of treatment cycles after which humoral responses were measured, and (3) targeted antigens.

Cellular responses

Thirteen out of 20 monoclonal antibody studies investigated induction of T-cells against the target antigen (Table 10). Investigators evaluated the presence of antigen-specific T-cells using commonly applied tests, such as interferon-gamma (IFN-γ) ELISPOT (Ehlen 2005; Gordon 2004; Method 2002; Sabbatini 2006), proliferation assay (Ma 2002; Noujaim 2001; van Zanten-Przybysz 2002), cytokine profiling (Noujaim 2001; Pfisterer 2006), IFN-γ secretion assay (Ströhlein 2009), and IFN-γ intracellular staining assay (Buzzonetti 2014). One study used the leucocyte migration inhibition assay, which nowadays is rarely used (Wagner 1993). As described above for humoral responses, response definitions were frequently lacking or inadequate. Nevertheless, results showed cellular immunity against CA-125 for 21% to 80% of participants. One study retrospectively compared cellular immune response after CA-125 monoclonal antibody treatment versus placebo but noted no significant differences (31.8% intervention vs 26.3% control) (Buzzonetti 2014). Antibody treatment targeting the membrane folate receptor did not however induce cellular responses (van Zanten-Przybysz 2002). Only two studies reported recognition of autologous tumour cells by induced T-cells, describing positive responses in five out of eight and one out of two patients, respectively (Gordon 2004; Ströhlein 2009).

A total of 35 out of 44 studies evaluated antigen-specific cellular immune responses with the use of other vaccine types (Table 11). The most frequently used assay was the IFN-γ ELISPOT assay, which sometimes was used to separately analyse CD4+ and/or CD8+ cells. Again, response definitions for positive and/or vaccine-induced responses were frequently absent or unclear (15 out of 44). Six of eight studies targeting NY-ESO-1 induced antigen-specific T-cells, with percentages of patients with NY-ESO-1-specific CD8+ ranging from 33% to 92% (Dhodapkar 2012; Diefenbach 2008; Nishikawa 2006; Odunsi 2007; Odunsi 2012; Odunsi 2014; Sabbatini 2012), and one study did not report the results for ovarian cancer participants separately (Dhodapkar 2012). Another study showed a positive NY-ESO-1-specific CD8+ T-cell induction by IFN-γ catch assay (1% to 5% positive CD8+ T-cells) (Takeoka 2017). After treatment with vaccines targeting *p53*, investigators observed *p53*-specific T-cells in 64% to 100% of patients, irrespective of the type of vaccine (Leffers 2009a; Rahma 2012; Vermeij 2012). One study compared *p53*-specific T-cell responses between treatment with a *p53*-targeting vaccine plus chemotherapy and PegIntron versus chemotherapy and PegIntron versus chemotherapy alone. Immune response rates were 100%, 22%, and 0%, respectively (Dijkgraaf 2015), indicating that applying chemotherapy and PegIntron at the same time as antigen-targeted immunotherapy may induce a stronger immune response. Studies targeting multiple antigens demonstrated antigen-specific cellular immunity with varying immunogenicity of the different antigens targeted (Antonilli 2016; Berinstein 2012; Brossart 2000; Chianese-Bullock 2008; Chu 2012; Gray 2016; Kaumaya 2009; Kawano 2014; Lennerz 2014; Mohebtash 2011; Morse 2011; Suzuki 2016; Tsuda 2004). Finally, a study testing dendritic cell-based immunotherapy showed no induction of IFN-γ-specific CD4+ and CD8+ cells by flow cytometry, although tetramer staining of WT1-specific cytotoxic T-lymphocytes did show an increase in 12 out of 17 patients (70.6%) (Kobayashi 2014).

Secondary outcomes

Carrier-specific immunogenicity

Most studies using a monoclonal antibody (18/22) used a murine antibody, two studies used a trifunctional rat-mouse hybrid (Baumann 2011; Heiss 2010), and one study used a chimeric antibody construct (van Zanten-Przybysz 2002). Next to antigen-specific immunity, 16 studies assessed the induction of human-anti-mouse antibodies (HAMAs) using HAMA-specific ELISA assays (Table 12). HAMAs were present in 4% to 97% of participants immunised (Baumann 2011; Berek 2004; Braly 2009; Ehlen 2005; Gordon 2004; Method 2002; Möbus 2003; Pfisterer 2006; Reinartz 2004; Sabbatini 2006; Schultes 1998). It seems that this large variation between studies cannot be attributed to differences in dosage but is best ascribed to different definitions of a HAMA response (i.e. some studies report only robust responses, whereas others report all responses above a certain threshold). Furthermore, the point in time at which HAMA titres were measured is of importance, as responses increase in frequency and strength with repeated administration of the antibody (Baumann 2011; Gordon 2004; Method 2002; Möbus 2003).

Although eight studies investigated synthetic carbohydrate antigens conjugated to the keyhole limpet haemocyanin (KLH) carrier protein (Freedman 1998; MacLean 1992; MacLean 1996;

O'Cearbhaill 2016; Sabbatini 2000; Sabbatini 2007; Sabbatini 2017; Sandmaier 1999), only one study reported on KLH-specific immunity (Sandmaier 1999). In this study, proliferative responses to stimulation with KLH and the KLH-antigen complex were substantially stronger than responses to the synthetic carbohydrate itself in all women with ovarian cancer tested, similar to what has previously been reported for viral vectors.

Five studies reported use of recombinant viruses or bacteria as vectors (Galanis 2010; Gulley 2008; Le 2012; Mohebtash 2011; Odunsi 2012). Three of these studies reported that they investigated anti-vector immune responses. One study used a recombinant pox-virus induced anti-vector immunity for all participants with ovarian cancer (Gulley 2008). Another study used a recombinant measles virus and did not show any differences in anti-measles-antibody titres, although inclusion criteria required that included participants must be immune to measles virus (Galanis 2010). In the third study, use of live-attenuated listeria did result in virus-specific T-cells in some cancer patients; however, too few patients with ovarian cancer were tested to permit any conclusions regarding this specific disease entity (Le 2012).

Adverse events

For this review, we defined adverse events as any adverse changes in health or side effects that occurred in a clinical study participant receiving treatment, irrespective of whether the event could be attributed to the treatment received.

Although 56 studies mentioned adverse events; sufficiently detailed information on adverse events that occurred during the study was available for 43 out of 67 studies. Thirty-four studies explicitly mentioned local adverse events, all of which involved local administration of the vaccine (i.e. intradermal, intramuscular, or subcutaneous injection). When local adverse events were further specified, these were best summarised as pain at the injection site and local inflammatory responses (erythema, induration, pruritis). Researchers observed ulceration and/or abscesses at the injection site in nine of 89 participants with varying types of cancer participating in four studies (Berinstein 2012; Berinstein 2013; Freedman 1998; Gribben 2005). One study described a patient with a grade III infection presenting with lower-limb lymphoedema at the injection site, which was attributed to the vaccine. This patient underwent a pelvic lymphadenectomy during the primary debulking surgery, suggesting in this case that women who have undergone pelvic lymphadenectomy might be less suitable for vaccination of the lower limbs (Kawano 2014).

Systemic adverse events occurred in 42 studies, and four studies explicitly reported that systemic adverse events did not occur. Two studies explicitly reported autoimmunity. In one study, a patient with strong immunological responses to the vaccine developed symptomatic hypothyroidism necessitating replacement therapy (Diefenbach 2008). Study authors described minor induction of anti-nuclear antibodies (grade I according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (Trotti 2003)) for two patients receiving a multi-peptide vaccine (Chianese-Bullock 2008). Allergic reactions occurred in a total of 14 participants (Berek 2009; Braly 2009; Ehlen 2005; MacLean 1992; Möbus 2003; Pfisterer 2006; Ströhlein 2009). Allergic reactions (e.g. hypersensitivity, allergic exanthema, urticaria) were mild and were easily managed. Continuation of study treatment did not result in renewed allergic reactions (Braly 2009; Ehlen 2005; Möbus 2003; Pfisterer 2006). Treatment with chemotherapy, an anti-methylation agent, and an NY-ESO-1-targeting vaccine resulted in clinically manageable adverse events (Odunsi 2014).

Other reported systemic adverse events, irrespective of whether attributable to the investigated drug, included haematological changes (e.g. anaemia, leucopenia), flu-like symptoms (including fatigue, myalgia, arthralgia, headache, fever, and chills), and gastrointestinal events (e.g. nausea, vomiting, diarrhoea, abdominal pain), most of which were classified as grade I or II events. Thirty-three studies reported serious (CTCAE grade III or IV) adverse events that varied from recurrent or progressive disease to local ulceration at the injection site, and from abdominal pain, neutropenia, and fever to elevated liver enzymes. One study compared standard of care versus MUC1 dendritic cell therapy. Respectively, 8% versus 27% of participants suffered an adverse event grade III or IV (Gray 2016). Another study combining vaccination with chemotherapy reported 10 high-grade adverse events, nine of which were attributed to the chemotherapy (Kawano 2014). In addition, one study comparing chemotherapy alone versus chemotherapy and PegIntron versus chemotherapy, PegIntron, and *p53* vaccination reported grade III or IV adverse events in 50% of participants, with no significant differences between treatment groups (Dijkgraaf 2015). A study combining chemotherapy, an anti-methylation agent, and an NY-ESO-1-targeting vaccine described three serious adverse events, which study authors did not attribute to any of the investigated drugs (Odunsi 2014). Twenty studies reported no serious adverse events. Ten studies did not mention lack or presence of serious adverse events (Berek 2001; Imhof 2013; Ma 2002; MacLean 1996; Möbus 2003; Nishikawa 2006; Noujaim 2001; Sandmaier 1999; Schultes 1998; Wagner 1993).

DISCUSSION

Summary of main results

The aim of this review was to evaluate the clinical and immunological efficacy of antigen-specific active immunotherapy in ovarian cancer, whilst also obtaining an impression of the safety and tolerability of this treatment modality. The antigen-specific active immunotherapy described in this review can largely be divided into two strategies: (1) administration of antibodies targeting a

specific tumour antigen and (2) administration of, or parts of, a specific tumour antigen itself. As expected, most studies were non-randomised controlled trials (NRSs).

Data suggest that almost all strategies are capable of inducing an immunological response to some extent. Furthermore, only two studies evaluated recognition of autologous tumour cells in vitro, and no studies evaluated immune responses at the tumour site. Although obtaining autologous tumour material may be burdensome, such assays would be extremely valuable, as they comprise true interactions between induced immunity and tumour cells and as such could provide important information on how immunotherapeutic strategies can continue to be improved to reach clinical effectiveness. Even though comparison between studies is difficult, it seems that most antigen-specific therapies, independent of the target, are able to induce at least a minimal immune response.

Clinical responses to immunotherapy (i.e. tumour responses, responses to post-immunotherapy treatment, and survival benefits) were observed only incidentally, and their occurrence cannot be used to draw a reliable conclusion. The indication for immunotherapeutic treatment in the adjuvant setting is supported by the observation of enhanced antigen-specific responses to immunotherapy when combined with chemotherapeutic agents currently or previously used in the primary treatment of ovarian cancer (i.e. docetaxel or cyclophosphamide) (Garnett 2008; Laheru 2008). However, four large randomised controlled trials (RCTs) using a monoclonal cancer antigen (CA)-125 antibody in the adjuvant setting after successful primary therapy did not demonstrate any differences in time to relapse and/or overall survival between treatment and placebo arms (Berek 2001; Berek 2004; Berek 2009; Sabbatini 2013), which indicates that despite immunogenicity, CA-125-targeted monoclonal antibody therapy is clinically ineffective. For studies of other vaccine types, no such conclusions can be made at this time, as large RCTs and more studies in the adjuvant rather than recurrent setting have yet to be performed to examine the different strategies.

Eighty per cent of studies reported adverse events in sufficient detail for interpretation. Study authors made a distinction between local and systemic events and further subdivided the latter into autoimmunity, allergy, and other adverse events. We did not evaluate whether adverse events could be or were considered attributable to the treatment studied, although for local adverse events, this is indisputably the case. Studies using intradermal, subcutaneous, or intramuscular application have frequently reported inflammatory reactions and pain at the injection site, with ulceration at the most severe side of the spectrum. Severe or life-threatening systemic adverse events occurred in approximately 50% of studies. Thirty per cent of studies explicitly described the lack of severe adverse events. For monoclonal antibody studies, researchers could identify no pattern suggestive of an underlying treatment-associated process and often considered events to be associated with ovarian cancer progression.

In summary, this review describes 67 immunotherapy studies including 3632 women with ovarian cancer. It seems that although all strategies described are capable of inducing immunological responses, be it humoral or cellular, clinical effectiveness thus far has not been convincingly demonstrated. The largest body of evidence is available for CA-125-directed antibody therapy, which has been studied in 2347 people participating in 17 studies. As only one study reported complete or partial clinical responses and four large RCTs did not demonstrate any clinical benefit of antibody treatment, we believe it is unlikely that the clinical effectiveness of CA-125-directed antibody therapy for ovarian cancer will ever be obtained. It is possible that inducing an immunological response alone is not enough to derive clinical benefit owing to immune suppressive characteristics of the tumour. To overcome this suppression, combining antigen-specific immunotherapy with other forms of immunotherapy (e.g. checkpoint inhibitors, chemotherapy, poly ADP ribose polymerase (PARP) inhibitors, anti-methylation agents) might be necessary to achieve clinical response. However, in view of the immunological responses and the usually mild side effects reported, we believe that further investigation of other antigen-specific active immunotherapy strategies in ovarian cancer is worthwhile.

Overall completeness and applicability of evidence

The most striking observations of this review unfortunately do not concern the aim of the review but address lack of uniformity in the conduct and reporting of early-phase immunotherapy studies. According to the GRADE rating, only certainty for the primary outcome survival is assessed as 'high', whereas that for all other outcomes is assessed as 'very low' (Summary of findings for the main comparison). Of note, most of the RCTs that were analysed for survival were investigating a CA-125 monoclonal antibody. Their results may not be applicable in a similar way for other strategies using antigen-specific immune therapy for ovarian carcinoma.

Reliability of the results for clinical response to immunotherapy was questionable because clear response definitions were lacking, and because concomitant immunotherapy or administration of additional treatment after immunotherapy often was not described. Furthermore, for studies that used a monoclonal antibody targeting CA-125, use of CA-125 as a marker for clinical response is questionable. An additional important comment regarding the likelihood of clinical response to immunotherapy, especially in uncontrolled studies, which frequently include patients with recurrent disease, is the fact that this likelihood may be affected by disease status at the start of treatment (Leffers 2009).

In addition, antigen-specific humoral and/or cellular immunogenicity of different interventions showed great variation for both monoclonal antibody studies and studies examining other strategies. This variation may be attributed at least in part to variation in the immunological response definitions used by different study

authors. Therefore it is not possible to reliably compare studies and infer which intervention and/or immunisation strategy is most promising for the induction of strong anti-tumour immunity.

A disturbing observation regarding adverse events is the lack of uniformity in adverse event reporting. Reporting of safety and tolerability of new treatment strategies should have high priority in all studies of investigational drugs, especially in uncontrolled phase I and II studies. To promote uniformity in adverse event evaluation and reporting, as well as comparability of adverse events between studies, in addition to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (Trotti 2003), the Brighton Collaboration has committed itself to developing standardised, widely disseminated, and globally accepted case definitions for an exhaustive number of adverse events following immunisation, as well as guidelines for data collection, analysis, and presentation (Brighton Collaboration 2009). These case definitions and guidelines are freely available, and we strongly recommend that, when applicable, they be used for all immunotherapeutic studies.

This review emphasises an aspect of immunotherapeutic studies that warrants serious attention in the immunotherapeutic scientific community, that is, lack of consensus on (1) what assays should be used to establish immunogenicity of an intervention (Britten 2008), (2) what cutoffs should be used to define true immunological responses, and (3) what response definitions should be used to determine clinical efficacy. Given these large inconsistencies, it is evident that elucidation of which type of immunological response is necessary for and/or is a surrogate marker of clinical activity of an immunotherapeutic intervention is burdensome.

Quality of the evidence

We assessed the included studies for risks of bias, using the Cochrane 'Risk of bias' tool. Risk of bias items, especially selection, attrition, and selective reporting bias, are likely to affect the studies included in this review.

It is interesting to note that for 10 studies described in this review, review authors collected study information only from a meeting abstract that was several years old. The lack of full-text manuscripts, even after contact was made with abstract authors, strongly suggests the existence of a publication bias. To avoid the disappearance of negative studies, registration of trials in a prospective trial register is widely recommended and is supported by the International Committee of Medical Journal Editors (ICMJE). However, at first, in 2005, registration was requested only for RCTs. Since July 1, 2008, all trials prospectively assigning human participants to one or more health-related interventions for evaluation of their effects on health outcomes are required to be registered in a clinical trial register approved by the World Health Organization (WHO). From the ongoing studies section, it is apparent that despite registration in a prospective trial register, studies may suffer from publication bias, as several relatively small studies that began more than five years ago have not yet been published to date nor closed according to the trial register. In addition to registration in trial registers, the uniform requirements for manuscripts submitted to biomedical journals drafted by the ICMJE encourage uniformity in reporting of clinical trials by stating ethical principles for the conduct and reporting of research and by providing recommendations related to specific elements of editing and writing. As is obvious from this review, the scientific community might benefit substantially if early-phase uncontrolled clinical trials would also strive for uniformity in trial conduct and reporting.

Potential biases in the review process

We minimised potential biases in the review process by searching the literature from a variety of sources with no restrictions on date of publication. At least two review authors independently extracted and assessed data.

To minimise the chances of error and bias, review authors adhered to Cochrane guidelines for selection of studies, extraction of data, and assessment of the certainty of evidence and potential risks of different types of biases in all included studies.

Agreements and disagreements with other studies or reviews

Our findings are in broad agreement with those presented by most systematic reviews on antigen-specific active immunotherapy for ovarian cancer (Drerup 2015; Hardwick 2016; Odunsi 2017). However, the focus of current publications leans more towards immunotherapy in general (e.g. whole tumour lysate-targeting immunotherapy, immune checkpoint blockade, cytokine induction, adoptive cell transfer) and not towards antigen-specific immunotherapy alone. The general consensus is that antigen-specific immunotherapy is sufficient for eliciting an immune response, but clinical response to monotherapy is only modest (Drerup 2015; Odunsi 2017). Combining antigen-specific immunotherapy with other types of immunotherapy, especially immune checkpoint blockade, is a promising approach to be examined by future researchers (Hardwick 2016; Odunsi 2017).

AUTHORS' CONCLUSIONS

Implications for practice

At this point, review authors have found no evidence of effective immunotherapy for ovarian cancer. Although promising immunological responses have been observed for most strategies evaluated, they do not coincide with clinical benefits for women with ovarian cancer. Furthermore, no immunological surrogate markers currently correlate with clinical outcomes. Therefore, until evidence

of true clinical effectiveness is available, immunotherapy should not be offered as an alternative to standard therapy for primary or recurrent ovarian cancer.

Implications for research

Our primary recommendation relates to the need for uniformity in trial conduct and reporting. Not until universally accepted immunological and clinical response definitions and guidelines for adverse events reporting are adopted for immunotherapeutic studies will it be possible to make any inferences about the effectiveness of immunotherapy as a treatment for ovarian cancer. Furthermore, expanding evaluation of immunogenicity to include recognition of autologous tumour is advisable. Given the usually mild side effects and the immunological responses witnessed in most studies, we believe that further investigation of antigen-specific active immunotherapy other than cancer antigen (CA)-125-targeted antibody therapy for ovarian cancer in randomised controlled trials is worthwhile. In addition, research combining antigen-targeted immunotherapy with other forms of immunotherapy to optimise response, and perhaps induce clinical response, is of interest.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Antonilli 2016

Methods	Uncontrolled phase I/II
Participants	14 high-risk, disease-free ovarian cancer (n = 7) or breast carcinoma participants + 3 recurrent OC patients vaccinated for compassionate use
Interventions	Triple peptide (MUC1, ErbB2, and CEA) with Montanide vaccine
Outcomes	Safety Immune response Clinical response
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not explicitly stipulated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not explicitly stipulated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Selective reporting (reporting bias)	Unclear risk	Study protocol not publicly available
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Baumann 2011

Methods	Randomised controlled phase II trial
Participants	45 ovarian cancer patients with evidence of disease after first- or second-line chemotherapy
Interventions	Intraperitoneal trifunctional bispecific antibody (catumaxomab - EpCAM): low dose (10-10-10-10 μg) vs high dose (10-20-50-100 μg)
Outcomes	Tumour responses Survival (progression-free survival/overall survival) Immune responses: humoral (HAMA) Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	Not explicitly stipulated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Data insufficient to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Study protocol not publicly available
Other bias	Low risk	No other sources of bias detected

Berek 2001

Methods	Randomised placebo-controlled trial
Participants	252 stage III/IV ovarian cancer patients after successful primary surgery and chemotherapy
Interventions	Intravenous monoclonal antibody (oregovomab - CA-125) vs placebo

Berek 2001 (*Continued*)

Outcomes	Survival (time to relapse) Immune responses: humoral (Ab2, HAMA)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Other bias	High risk	Publication bias possible

Berek 2004

Methods	Randomised placebo-controlled phase II trial
Participants	145 stage III/IV ovarian cancer patients with complete clinical response to primary therapy
Interventions	Intravenous monoclonal antibody (oregovomab) vs placebo
Outcomes	Survival (time to relapse/overall survival) Immune responses: humoral (Ab2, HAMA) Adverse events
Notes	

Berek 2004 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Low risk	No other sources of bias detected

Berek 2009

Methods	Randomised placebo-controlled phase III trial
Participants	371 stage III/IV ovarian cancer patients with complete clinical response to primary therapy
Interventions	Intravenous monoclonal antibody (oregovomab) vs placebo
Outcomes	Survival (time to relapse) Immune responses Adverse events
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Berek 2009 (*Continued*)

Random sequence generation (selection bias)	Low risk	Centralised randomisation procedure
Allocation concealment (selection bias)	Low risk	Centralised randomisation procedure
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded to treatment assignment, post-randomisation immune responses, and CA-125 measurements
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded to treatment assignment, post-randomisation immune responses, and CA-125 measurements
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Low risk	No other sources of bias detected

Berinstein 2012

Methods	Uncontrolled phase I study
Participants	23 late-stage cancer HLA-A2+ participants with complete or partial response to primary therapy (ovarian cancer n = 6)
Interventions	Subcutaneous 7 short peptides (topoisomerase IIα, integrin β8 subunit precursor, ABI-binding protein C3, TACE/ADAM17, junction plakglobin, EDDR1, BAP31) Adjuvant: DepoVax
Outcomes	Survival (time to progression) Tumour response Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Berinstein 2012 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants with OC included in analysis
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Low risk	No other sources of bias detected

Berinstein 2013

Methods	Uncontrolled phase I study
Participants	19 women with ovarian cancer with unknown disease status
Interventions	Subcutaneous peptides (survivin) Adjuvant: DepoVax
Outcomes	Immune responses (cellular) Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Berinstein 2013 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Braly 2009

Methods	Randomised controlled phase II trial
Participants	40 stage III/IV ovarian cancer patients after primary debulking surgery with or without residual disease
Interventions	Intravenous monoclonal antibody (oregovomab - CA-125): concurrent (SIM) or delayed (OWD) with standard carboplatin/paclitaxel primary chemotherapy
Outcomes	Survival (progression-free survival) Clinical responses Immune responses Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups

Braly 2009 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Low risk	No other sources of bias detected

Brossart 2000

Methods	Uncontrolled phase I/II study	
Participants	10 participants with measurable residual or recurrent breast or ovarian cancer (3 women with ovarian cancer)	
Interventions	Subcutaneous peptide pulsed dendritic cells (n = 1 Her-2/Neu; n = 2 MUC1)	
Outcomes	Tumour responses Immune response Adverse events	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Buzzonetti 2014

Methods	Randomised double-blind placebo-controlled trial
Participants	129 participants (n = 91 treatment arm; n = 38 placebo arm) with ovarian cancer in complete clinical remission after primary treatment
Interventions	Subcutaneous monoclonal antibody (abagovomab - CA-125)
Outcomes	Immune response Survival
Notes	Substudy of MIMOSA trial (NCT00418574)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Centralised randomisation
Allocation concealment (selection bias)	Low risk	Centralised randomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear whether samples used were coded for key study personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	Unknown why and which samples are missing
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Low risk	No other sources of bias detected

Chianese-Bullock 2008

Methods	Uncontrolled phase I study
Participants	9 women with ovarian cancer with or without residual or recurrent disease after primary therapy
Interventions	Subcutaneous and intradermal multi-peptide vaccine (FBP, Her-2/Neu, MAGE-A1) Adjuvant: Montanide ISA-51, GM-CSF

Chianese-Bullock 2008 (*Continued*)

Outcomes	Tumour responses Immune response Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Chu 2012

Methods	Randomised controlled phase I/II study
Participants	14 ovarian cancer patients with complete clinical response to primary therapy (10 received treatment so far)
Interventions	Intradermal peptide pulsed dendritic cells (Her-2/Neu, hTERT, PADRE): vaccine alone vs single dose of cyclophosphamide before first vaccination
Outcomes	Tumour responses Immune response Adverse events
Notes	

Chu 2012 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding or incomplete blinding, but review authors judge that the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	High risk	Early termination due to financial limitations

Dhodapkar 2012

Methods	Uncontrolled phase I study
Participants	45 participants with advanced malignancies; exact disease status unknown (ovarian cancer n = 6)
Interventions	Fusion protein of full-length tumour antigen and human monoclonal antibody specific for DEC-205 Adjuvants: TLR agonist resiquimod and/or poly-ICLC
Outcomes	Immune responses (cellular and humoral) Adverse events
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Dhodapkar 2012 (*Continued*)

Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Diefenbach 2008

Methods	Uncontrolled phase I study
Participants	9 participants with ovarian cancer with complete clinical response to primary therapy
Interventions	Subcutaneous short peptide (NY-ESO-1) Adjuvant: Montanide ISA-51
Outcomes	Survival (time to progression) Tumour responses Immune responses: cellular and humoral Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Diefenbach 2008 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Dijkgraaf 2015

Methods	Controlled phase I/II trial
Participants	15 participants with platinum-resistant ovarian cancers expressing 'mutant' p53
Interventions	C1: 6 cycles of gemcitabine (n = 3) C2: 6 cycles of gemcitabine and interferon alpha-2b 7 days before and 22 days after first cycle of gemcitabine (n = 6) C3: 6 cycles of gemcitabine and interferon alpha-2b with p53 SLP vaccine 7 days before and 22 days after first cycle of gemcitabine (n = 6)
Outcomes	Immune response Safety Clinical response
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Not randomised to treatment groups
Allocation concealment (selection bias)	High risk	Sequencial allocation to treatment groups
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Dijkgraaf 2015 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Low risk	No other sources of bias detected

Ehlen 2005

Methods	Uncontrolled phase II study
Participants	13 women with ovarian cancer with measurable recurrent disease
Interventions	Intravenous monoclonal antibody (oregovomab - CA-125)
Outcomes	Survival (time to progression/survival) Tumour responses Immune responses: humoral (Ab2, Ab3, HAMA), cellular Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Ehlen 2005 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Freedman 1998

Methods	Randomised controlled phase II study
Participants	30 ovarian cancer patients previously treated with platinum-based chemotherapy (disease status at study entry not described)
Interventions	Subcutaneous KLH conjugate (Sialyl-Tn) at 2 different dosages Adjuvant: Detox B
Outcomes	Survival (progression-free interval/survival) Tumour responses Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reporting of attrition/exclusions insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available

Freedman 1998 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Other bias	High risk	Publication bias possible

Galanis 2010

Methods	Uncontrolled phase I study
Participants	21 ovarian cancer patients with persistent, recurrent, or progressive disease after primary therapy
Interventions	Intraperitoneal recombinant measles virus (CEA)
Outcomes	Tumour responses Immune responses (humoral) Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial and sequential allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Goh 2013

Methods	Randomised controlled phase IIb trial	
Participants	63 patients in complete remission after primary therapy	
Interventions	Protein-pulsed dendritic cells (MUC1) vs standard of care	
Outcomes	Survival Immune responses (cellular) Adverse events	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reporting of attrition/exclusions insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available; study recently completed

Gordon 2004

Methods	Uncontrolled phase II study
Participants	20 ovarian cancer patients with recurrent disease
Interventions	Intravenous monoclonal antibody (oregovomab - CA-125)
Outcomes	Survival (time to progression/survival) Tumour responses Immune responses: humoral (Ab2, Ab3, HAMA), cellular Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Gray 2016

Methods	Randomized controlled phase II
Participants	56 participants with epithelial ovarian cancer
Interventions	Mucin 1 targeted dendritic cell vs standard of care

Gray 2016 (*Continued*)

Outcomes	Progression-free survival Overall survival Immune response
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised trial
Allocation concealment (selection bias)	Low risk	Randomised trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Gribben 2005

Methods	Uncontrolled phase I study
Participants	17 participants with advanced cancer with progressive disease (ovarian cancer n = 6)
Interventions	Intramuscular plasmid DNA vaccine (CYP1B1)
Outcomes	Tumour responses Immune responses (cellular) Adverse events
Notes	

Risk of bias

Gribben 2005 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Gulley 2008

Methods	Uncontrolled phase I/II study
Participants	25 participants with CEA or MUC1 overexpressing metastatic cancer with progressive disease following standard chemotherapy (ovarian cancer n = 3)
Interventions	Subcutaneous recombinant pox virus (CEA, MUC1): 1× vaccinia, ≥ 4 fowlpox Adjuvant: local GM-CSF
Outcomes	Survival (progression-free survival/overall survival) Immune responses: cellular, humoral Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial

Gulley 2008 (*Continued*)

Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Heiss 2010

Methods	Randomised controlled open-label phase II/III trial
Participants	258 patients with malignant ascites due to epithelial cancer (ovarian cancer n = 129)
Interventions	Intraperitoneal trifunctional antibody (EpCAM) + paracentesis vs paracentesis
Outcomes	Survival (puncture-free survival/overall survival) Immune responses (HAMA) Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of

Heiss 2010 (*Continued*)

		blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	High risk	Reason for missing outcome data likely to be related to true outcome, with imbalance in numbers or reasons for missing data across intervention groups
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Low risk	No other sources of bias detected

Imhof 2013

Methods	Uncontrolled phase I study
Participants	15 participants with complete remission after primary therapy
Interventions	Intradermal dendritic cells pulsed with mRNA (TERT) and short peptide (survivin)
Outcomes	Immune responses (cellular) Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Imhof 2013 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Kaumaya 2009

Methods	Uncontrolled phase I study
Participants	24 participants with metastatic and/or recurrent solid tumours (ovarian cancer n = 5)
Interventions	Intramuscular synthetic long peptides (Her2) Adjuvant: Montanide ISA720
Outcomes	Tumour responses Immune responses (humoral) Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Kawano 2014

Methods	Uncontrolled phase II study
Participants	42 participants with platinum-sensitive (n = 17) and platinum-resistant (n = 25) recurrent ovarian cancer
Interventions	Personalised peptide vaccine (PPV); max of 4 peptides out of 31 different vaccine candidates + Montanide ± chemotherapy
Outcomes	Safety Immune response Clinical response
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Kobayashi 2014

Methods	Uncontrolled phase I/II or retrospective?
Participants	56 participants who received chemotherapy for recurrent ovarian carcinoma
Interventions	Peptide pulsed DC vaccine (WT-1 ± MUC1 ± CA-12) + OK-432

Kobayashi 2014 (*Continued*)

Outcomes	Safety Immune response Clinical response
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Le 2012

Methods	Uncontrolled phase I study
Participants	17 participants with advanced cancers after prior therapy (ovarian cancer n = 2)
Interventions	Intravenous recombinant listeria (mesothelin)
Outcomes	Immune responses (cellular) Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Le 2012 (*Continued*)

Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Leffers 2009a

Methods	Uncontrolled phase II study
Participants	20 women with epithelial ovarian cancer with (biochemical) recurrence not (yet) eligible for renewed chemotherapy
Interventions	Subcutaneous synthetic long peptides (p53) Adjuvant: Montanide ISA51
Outcomes	Survival (disease-specific survival) Tumour responses Immune responses: humoral, cellular Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Leffers 2009a (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	IInformation insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Lennerz 2014

Methods	Randomized phase I
Participants	49 participants with survivin expressing solid tumours (ovarian cancer n = 7)
Interventions	Three dosage groups of EMD640744 vaccine (5 HLA class I-binding survivin peptides in Montanide ISA 62 VG)
Outcomes	Immune response Safety Clinical response
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised between 3 dosage groups
Allocation concealment (selection bias)	Unclear risk	Randomised trial
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study

Lennerz 2014 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Low risk	No other forms of bias detected

Letsch 2011

Methods	Uncontrolled study
Participants	18 participants with WT1-expressing solid tumours (disease status unreported) (ovarian cancer n = 8)
Interventions	Short peptide (WT1) Adjuvant: KLH, GM-CSF
Outcomes	Tumour responses Immune responses (cellular) Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Letsch 2011 (*Continued*)

Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Ma 2002

Methods	Uncontrolled study	
Participants	4 women with ovarian cancer (disease status at study entry not described)	
Interventions	Monoclonal antibody (MJ01 - CA-125)	
Outcomes	Immune response: cellular	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

MacLean 1992

Methods	Uncontrolled phase I study
Participants	10 women with ovarian cancer and residual or recurrent disease
Interventions	Subcutaneous KLH conjugate (Thomsen Friedenreich) Adjuvant: Detox B
Outcomes	Tumour responses Immune responses: humoral Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

MacLean 1996

Methods	Uncontrolled phase II study
Participants	34 women with ovarian cancer and evaluable residual or recurrent disease
Interventions	Subcutaneous KLH conjugate (Sialyl-Tn) Adjuvant: Detox B

MacLean 1996 (*Continued*)

Outcomes	Survival (trial entry to death) Immune response: humoral
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Method 2002

Methods	Randomised controlled study
Participants	102 women with ovarian cancer after primary therapy (disease status at study entry not described)
Interventions	Intravenous monoclonal antibody (oregovomab - CA-125): 2 gifts vs 3 gifts vs 6 gifts
Outcomes	Tumour responses Immune response: humoral (Ab2, HAMA), cellular Adverse events
Notes	

Risk of bias

Method 2002 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding or incomplete blinding, but review authors judge that the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reporting of attrition/exclusions insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'; only abstract available

Mohebtash 2011

Methods	Uncontrolled study
Participants	31 metastatic ovarian and breast cancer patients (ovarian cancer n = 14)
Interventions	Subcutaneous recombinant pox virus (MUC1 and CEA) Adjuvant: local GM-CSF
Outcomes	Survival: median time to progression 2 months (range 1 to 36) Immune responses (cellular) Adverse events: no severe adverse events, mostly locoregional grade 1 or 2 reactions
Notes	Max 3 patients overlap with Gulley 2008

Risk of bias

Bias	Authors' judgement	Support for judgement

Mohebtash 2011 (*Continued*)

Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Morse 2011

Methods	Uncontrolled phase I study
Participants	15 ovarian and breast cancer patients with no evidence of disease after prior therapy (ovarian cancer n = 8)
Interventions	Intradermal and subcutaneous short peptides in 2 groups (group 1: APC, HHR6A, BAP31, replication protein A, Abl-binding protein 3c, cyclin I; group 2: topoisomerase IIα/β, integrin β 8 subunit precursor, CDC2, TACE, g-catenin, EEDDR1) Adjuvant: Montanide ISA-51, GM-CSF
Outcomes	Survival Immune responses: cellular Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Morse 2011 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Möbus 2003

Methods	Retrospective uncontrolled study
Participants	44 ovarian cancer patients with clinical recurrence after primary therapy
Interventions	Intravenous monoclonal antibody (oregovomab - CA-125)
Outcomes	Survival (time from first dose to death/overall survival) Immune response: humoral (Ab2, Ab3, HAMA) Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Möbus 2003 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Nicholson 2004

Methods	Uncontrolled phase I study
Participants	26 epithelial ovarian cancer patients with residual disease (n = 19), microscopic disease (n = 3) after chemotherapy, or second complete remission (n = 4)
Interventions	Monoclonal antibody (HMFG1 - MUC1); first gift intraperitoneal (n = 16) or intravenous (n = 10), then ID boosts Adjuvant: aluminium hydroxide
Outcomes	Tumour responses Immune response: humoral (Ab2) Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Nicholson 2004 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Nishikawa 2006

Methods	Uncontrolled phase II study
Participants	4 epithelial ovarian cancer patients after primary debulking surgery (disease status at study entry not described)
Interventions	Short peptide (NY-ESO-1) Adjuvant: incomplete Freund's adjuvant
Outcomes	Immune responses: cellular
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'&&

Noujaim 2001

Methods	Retrospective uncontrolled study
Participants	184 ovarian cancer patients with clinically or radiologically suspected recurrence
Interventions	Intravenous monoclonal antibody (oregovomab - CA-125)
Outcomes	Survival (overall survival) Immune responses: humoral (Ab3), cellular
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

O'Cearbhaill 2016

Methods	Uncontrolled phase I
Participants	24 participants with advanced-stage, first-remission ovarian cancer
Interventions	Dose escalation - 25, 50, 100 mcg - unimolecular pentavalent carbohydrate vaccine (Globo-H, GM2, sTn, TF and Tn in QS-21)
Outcomes	Safety Immune response

O'Cearbhaill 2016 (*Continued*)

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Odunsi 2007

Methods	Uncontrolled phase I study
Participants	18 ovarian cancer patients after chemotherapy for primary or recurrent disease with or without residual disease
Interventions	Subcutaneous short peptide (NY-ESO-1) Adjuvant: incomplete Freund's adjuvant
Outcomes	Survival: median time to progression: 19.0 months Tumour responses: 1× CR, 17× unknown Immune responses: humoral, cellular Adverse events: well tolerated, no further description
Notes	

Risk of bias

Odunsi 2007 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Odunsi 2012

Methods	Uncontrolled phase I/II study
Participants	22 women with ovarian cancer without evidence of disease after primary therapy
Interventions	intradermal recombinant virus (NY-ESO-1); 1× vaccinia virus, 6× fowlpox boost
Outcomes	Survival (disease-free survival) Immune responses: humoral, cellular Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Odunsi 2012 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Odunsi 2014

Methods	Uncontrolled phase I/II dose escalation trial
Participants	12 participants with recurrent epithelial ovarian cancer
Interventions	C1: day 1 decitabine (45 mg/m²), day 8 doxorubicin (40 mg/m²), day 15 NY-ESO-I vaccine C2: day 1 decitabine (90 mg/m²), day 8 doxorubicin (40 mg/m²), day 15 NY-ESO-I vaccine C3: days 1 to 5 decitabine (10 mg/m²), day 8 doxorubicin (40 mg/m²), day 15 NY-ESO-I vaccine
Outcomes	Immune response Clinical response
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

Odunsi 2014 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Ohno 2009

Methods	Uncontrolled phase II study
Participants	12 patients with gynaecological malignancies resistant to standard therapy (ovarian cancer n = 6)
Interventions	Intradermal short peptide (WT1) Adjuvant: Montanide ISA-51
Outcomes	Tumour responses
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Ohno 2009 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Peethambaram 2009

Methods	Uncontrolled phase I study
Participants	18 patients with refractory metastatic tumours (ovarian cancer n = 4)
Interventions	Intravenous recombinant fusion antigen pulsed antigen-presenting cells (Her-2/Neu) Adjuvant: GM-CSF (included in the recombinant fusion product)
Outcomes	Survival (time to progression) Tumour responses Immune responses: cellular Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Pfisterer 2006

Methods	Uncontrolled phase I study
Participants	36 stage I-IV ovarian cancer patients within 6 weeks after completion of chemotherapy for recurrent disease (disease status at study entry not described)
Interventions	Subcutaneous monoclonal antibody (abagovomab - CA-125)
Outcomes	Immune responses: humoral (Ab3, HAMA), cellular Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Rahma 2012

Methods	Uncontrolled phase II study
Participants	21 ovarian cancer patients without evidence of disease after prior therapy
Interventions	Subcutaneous short peptide (p53) vs intravenous peptide-pulsed dendritic cells (p53) Adjuvant: Montanide ISA-51 and GM-CSF (only in cohort treated with peptide)

Rahma 2012 (*Continued*)

Outcomes	Survival (progression-free survival, overall survival) Tumour responses Immune responses: cellular Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Reinartz 2004

Methods	Uncontrolled multi-centre phase Ib/II study
Participants	119 patients with ovarian cancer after at least primary treatment (disease status at entry not described)
Interventions	Intramuscular monoclonal antibody (ACA125 - CA-125)
Outcomes	Survival (time from first dose to death) Tumour responses Adverse events
Notes	

Reinartz 2004 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Sabbatini 2000

Methods	Uncontrolled phase I study	
Participants	25 ovarian cancer patients with complete clinical response to chemotherapy after residual or recurrent disease following primary therapy	
Interventions	Subcutaneous KLH conjugate (Lewis Y pentasaccharide - MUC1) Adjuvant: QS-21	
Outcomes	Survival (time to progression) Immune responses: humoral Adverse events	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Sabbatini 2000 (*Continued*)

Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Sabbatini 2006

Methods	Randomised open-label multi-centre phase I study
Participants	42 stage II-IV ovarian cancer patients after chemotherapy for recurrence of disease with complete clinical response or measurable disease (< 2 cm)
Interventions	Intramuscular (IM) or subcutaneous (SC) monoclonal antibody (abagovomab - CA-125): 4 cohorts (2× IM; 2× SC; 0.2 mg or 2 mg)
Outcomes	Survival (time to progression) Tumour responses Immune response: humoral (Ab3, HAMA), cellular Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Standard 2 × 2 factorial design

Sabbatini 2006 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding or incomplete blinding, but review authors judge that the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reporting of attrition/exclusions insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Low risk	No other sources of bias detected

Sabbatini 2007

Methods	Uncontrolled phase I/II study
Participants	11 epithelial ovarian cancer patients with complete clinical remission after primary therapy or chemotherapy for recurrent disease
Interventions	Subcutaneous heptavalent KLH conjugate (GM2, Globo-H, Lewis Y, Tn-MUC1, Tn (c), sTN(c), TF(c))
Outcomes	Survival (time to treatment failure) Immune responses: humoral
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Sabbatini 2007 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Sabbatini 2012

Methods	Uncontrolled phase I study
Participants	28 ovarian cancer patients in second or third remission
Interventions	Subcutaneous overlapping long peptides (NY-ESO-1) Adjuvant: cohort 1 - no (n = 4); cohort 2: Montanide ISA-51 (n = 13); cohort 3: poly-ICLC in Montanide ISA-51 (n = 11)
Outcomes	Survival (time to progression) Tumour responses Immune responses: cellular and humoral Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Sabbatini 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Sabbatini 2013

Methods	Randomised placebo-controlled trial
Participants	888 ovarian cancer patients in complete clinical remission after primary therapy
Interventions	Subcutaneous monoclonal antibody (abagovomab - CA-125)
Outcomes	Survival (recurrence-free survival, overall survival) Immune responses: humoral (Ab3, HAMA), cellular (to be reported in separate paper) Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Centralised randomisation
Allocation concealment (selection bias)	Low risk	Centralised randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured; unlikely that the blinding could have been broken
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment ensured; unlikely that the blinding could have been broken
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Sabbatini 2013 (*Continued*)

Other bias	Low risk	No other forms of bias detected

Sabbatini 2017

Methods	Randomised trial
Participants	171 participants with epithelial ovarian cancer in second or third clinical remission
Interventions	OPT-821 (n = 86) + polyvalent vaccine conjugate (Globo-H-GM2, MUC1-TN,TF) vs OPT-821 alone (n = 85)
Outcomes	
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised trial
Allocation concealment (selection bias)	Low risk	Randomised allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinding of participant and investigator
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinding of participant and investigator
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed for primary endpoint
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Low risk	No other forms of bias detected

Sandmaier 1999

Methods	Uncontrolled phase II study
Participants	40 breast or ovarian cancer (n = 7) patients who underwent high-dose chemotherapy and autologous or syngeneic stem cell rescue (disease status at study entry unknown)

Sandmaier 1999 (*Continued*)

Interventions	Subcutaneous KLH conjugate (Sialyl-Tn) Adjuvant: Detox B	
Outcomes	Immune responses: humoral, cellular	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Schultes 1998

Methods	Retrospective uncontrolled study
Participants	75 stage I-IV ovarian cancer patients (disease status at study entry not described)
Interventions	Intravenous monoclonal antibody (oregovomab - CA-125)
Outcomes	Survival (overall survival) Immune responses: humoral (Ab2, Ab3, HAMA)
Notes	

Risk of bias

Schultes 1998 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Ströhlein 2009

Methods	Uncontrolled phase I study
Participants	9 patients with progressive peritoneal carcinomatosis (ovarian cancer n = 2)
Interventions	Intraperitoneal trifunctional antibody targeting EpCAM (n = 1) or Her-2/Neu (n = 1)
Outcomes	Survival: not reported separately for ovarian cancer patients Tumour responses Immune responses: cellular, humoral (HAMA) Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Ströhlein 2009 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Suzuki 2016

Methods	Uncontrolled phase II
Participants	32 women with clear cell ovarian carcinoma
Interventions	Antigen glypican-3 (GPC3) vaccine
Outcomes	Immune response Clinical response Safety
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Suzuki 2016 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Takeoka 2017

Methods	Uncontrolled phase I
Participants	15 participants with advanced cancer expressing NY-ESO-1 (N = 2 ovarian cancer cohort 3)
Interventions	Cohort 1: NY-ESO-1 protein Cohort 2a: NY-ESO-1 protein + OK-432 Cohort 2b: NY-ESO-1 protein + poly-ICLC Cohort 3: NY-ESO-1 protein + OK-432 + poly-ICLC with Montanide ISA-51
Outcomes	Safety Immune response Clinical response
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All OC patients analysed

Takeoka 2017 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Takeuchi 2013

Methods	Uncontrolled phase I/II study
Participants	38 ovarian cancer patients with advanced/recurrent disease
Interventions	Subcutaneous peptide cocktail (HLA-A24 - n = 23: FOXM1, MELK, HJURP, VEGFR1, VEGFR2; HLA-A02 - n = 13: HIG2, VEGFR1, VEGFR2) Adjuvant: Montanide ISA-51
Outcomes	Survival Tumour responses Immune responses (not adequately reported) Adverse events (not adequately reported)
Notes	Meeting abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Takeuchi 2013 (*Continued*)

Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Tsuda 2004

Methods	Uncontrolled phase I/II study	
Participants	14 patients with gynaecological cancer after primary therapy (ovarian cancer n = 5; NED n = 2)	
Interventions	Subcutaneous individualised short peptide cocktail Adjuvant: Montanide ISA-51	
Outcomes	Tumour responses Immune responses: humoral, cellular Adverse events: not separately described for ovarian cancer patients	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

van Zanten-Przybysz 2002

Methods	Uncontrolled phase I/II study
Participants	5 patients with residual or recurrent ovarian cancer after primary debulking surgery and at least 1 course of chemotherapy
Interventions	Intravenous monoclonal antibody (c-MOv18 - membrane folate receptor)
Outcomes	Survival: median time from first dose to death: 22.0 months Tumour responses: 3× PD, 2× SD Immune responses: cellular Adverse events: max grade I events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Vermeij 2012

Methods	Uncontrolled phase II study
Participants	12 women with epithelial ovarian cancer with (biochemical) recurrence not (yet) eligible for renewed chemotherapy

Vermeij 2012 (*Continued*)

Interventions	Subcutaneous synthetic long peptides (p53) Adjuvant: Montanide ISA51 Immunomodulation: cyclophosphamide 2 days before each vaccination
Outcomes	Tumour responses Immunological responses: cellular Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Wagner 1993

Methods	Retrospective uncontrolled study
Participants	58 patients with advanced-stage ovarian cancer after primary treatment with high pre-operative CA-125 levels (disease status at study entry not described)
Interventions	Intravenous monoclonal antibody fragments ($F(Ab)_2$-fragments of MAb OC125 - CA-125)

Wagner 1993 (*Continued*)

Outcomes	Survival Tumour responses Immune responses: humoral (Ab2), cellular	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Information insufficient to permit judgement of 'low risk' or 'high risk'

Ab2: anti-idiotype antibody.
Ab3: anti-anti-idiotype antibody.
CA-125: cancer antigen-125.
CEA: carcinoembryonic antigen.
EpCAM: epithelial cell adhesion molecule.
ErbB2: human Epidermal growth factor Receptor 2.
FBP: folate binding protein.
GM-CSF: granulocyte-macrophage colony-stimulating factor.
GPC3: antigen glypican-3.
HAMA: human-anti-mouse antibody.
HLA: human leucocyte antigen.
hTERT: telomerase reverse transcriptase.
KLH: keyhole limpet haemocyanin.
MAb: monoclonal antibody.
MAGE-A1: melanoma-associated antigen A1.

MUC1: Mucin-1.
NED: no evidence of disease.
OC: ovarian carcinoma.
OWD: 1-week delayed
PADRE: DR-restricted Th helper epitope.
poly-ICLC: polyinosinic-polycytidylic acid complexed with poly-L-lysine and carboxymethylcellulose.
SIM: simultaneous infusion.
SLP: synthetic long peptide.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anderson 2000	Only 1 woman with epithelial ovarian cancer; no ASAI
Baek 2015	No ASAI
Bapsy 2014	No ASAI
Bender 2007	Only 1 woman with epithelial ovarian cancer
Bernal 2012	Only 1 woman with epithelial ovarian cancer; no ASAI
Carbone 2005	Only 1 woman with epithelial ovarian cancer
Chiang 2013	No ASAI
Coosemans 2013	Only 1 woman with epithelial ovarian cancer
Dhodapkar 2014	Impossible to distinguish between other and women with ovarian cancer
Disis 1999	Impossible to distinguish between other and women with ovarian cancer
Disis 2000	Impossible to distinguish between other and women with ovarian cancer
Disis 2002	Impossible to distinguish between other and women with ovarian cancer
Disis 2002a	Only 1 woman with epithelial ovarian cancer
Disis 2004	Impossible to distinguish between other and women with ovarian cancer
Disis 2004a	Only 1 woman with epithelial ovarian cancer
Galanis 2013	No ASAI
Haakenstad 2012	Impossible to distinguish between other and women with ovarian cancer

(*Continued*)

Hasumi 2011	No ASAI
Hernando 2002	Autologous tumour lysate vaccine
Hernando 2007	Only 1 woman with epithelial ovarian cancer
Holmberg 2000	Impossible to distinguish between women with breast cancer and women with ovarian cancer
Hui 1997	No ASAI
Jackson 2017	Impossible to distinguish between other and women with ovarian cancer
Jager 2006	Only 1 woman with epithelial ovarian cancer
Kandalaft 2010	Autologous tumour lysate vaccine
Karbach 2010	Only 1 woman with epithelial ovarian cancer
Kato 2010	Impossible to distinguish between other and women with ovarian cancer
Khranovska 2011	Autologous tumour lysate vaccine
Knutson 2001	Only 1 woman with epithelial ovarian cancer
Knutson 2002	Women with epithelial ovarian cancer withdrew before evaluation of immune responses
Letsch 2008	Impossible to distinguish between other and women with ovarian cancer
Loveland 2006	Only 1 woman with epithelial ovarian cancer
Manjunath 2012	Only 1 woman with epithelial ovarian cancer
Marshall 2005	Only 1 woman with ovarian cancer
Matsuzaki 2014	Additional results to Odunsi 2007; irrelevant for review
Miotti 1999	Autologous T-cell vaccine
Morera 2017	Only 1 woman with epithelial ovarian cancer
Morse 1999	Impossible to distinguish between other and women with ovarian cancer
Morse 2003	Uncertain if and how many women with ovarian cancer were included
Morse 2011a	Impossible to distinguish between other and women with ovarian cancer; unclear number of women with ovarian cancer

(*Continued*)

Murray 2002	Only 1 woman with epithelial ovarian cancer
Oh 2016	No ASAI
Parkhurst 2004	No women with epithelial ovarian cancer
Reddish 1996	Impossible to distinguish between other and women with ovarian cancer
Salazar 2006	Impossible to distinguish between other and women with ovarian cancer
Schiffman 2002	No immunisations carried out
Tsuji 2013	Additional results to Sabbatini 2013; irrelevant for review
Yacyshyn 1995	Additional results to MacLean 1992; irrelevant for review
Zaks 1998	Impossible to distinguish between other and women with ovarian cancer

ASAI: antigen-specific active immunotherapy.

Characteristics of ongoing studies *[ordered by study ID]*

NCT00003002

Trial name or title	Her-2/Neu vaccine plus GM-CSF in treating participants with stage III or stage IV breast, ovarian, or non-small cell lung cancer
Methods	Uncontrolled phase I
Participants	Participants with stage III or IV Her-2/Neu-expressing breast, ovarian, or non-small cell lung cancer
Interventions	Intradermal vaccinations of Her-2/Neu-derived peptides with sargramostim (GM-CSF)
Outcomes	Immune responses Adverse events
Starting date	April 1996
Contact information	
Notes	Completed January 2004; no publication available

NCT00004604

Trial name or title	Biological therapy in treating patients with metastatic cancer
Methods	Uncontrolled phase I
Participants	24 participants with histologically confirmed metastatic adenocarcinoma expressing carcinoembryonic antigen (CEA) who has failed conventional therapy
Interventions	Intravenous CEA RNA-pulsed autologous dendritic cells
Outcomes	Adverse events Immune responses Clinical and biochemical responses
Starting date	February 1998
Contact information	
Notes	Completed July 2002; no publication available

NCT00006041

Trial name or title	Vaccine therapy in treating patients with ovarian, fallopian tube, or peritoneal cancer
Methods	Uncontrolled phase I
Participants	18 patients with histologically confirmed ovarian, fallopian tube, or peritoneal epithelial cancer (any stage at diagnosis); refractory or recurrent after cytoreductive surgery and at least 1 prior regimen of platinum-based chemotherapy
Interventions	Glycosylated MUC1-KLH vaccine plus QS21
Outcomes	Adverse events Immune responses
Starting date	February 2000
Contact information	
Notes	Completed February 2002; no publication available

NCT00381173

Trial name or title	A phase I open-label study of the safety and feasibility of ZYC300 administration with cyclophosphamide pre-dosing
Methods	Phase I

NCT00381173 (*Continued*)

Participants	22 advanced-stage malignancies with evidence of disease and no therapeutic options
Interventions	IM ZYC300 (a plasmid DNA formulated within biodegradable microencapsulated particles) with IV cyclophosphamide
Outcomes	Safety Immune responses Tumour responses
Starting date	November 2006
Contact information	
Notes	Study completion January 2009; no published records available

NCT00803569

Trial name or title	Phase I study of ALVAC(2)-NY-ESO-1(M)/TRICOM in patients with epithelial ovarian, fallopian tube, or primary peritoneal carcinoma whose tumours express NY-ESO-1 or LAGE-1 antigen
Methods	Phase I
Participants	12 stage II-IV women with ovarian cancer with complete response to primary or secondary (chemo)therapy
Interventions	SC ALVAC(2)-NY-ESO-1(M)/TRICOM vaccine plus SC GM-CSF
Outcomes	Safety Tumour responses Immune responses
Starting date	November 2008
Contact information	
Notes	Completed 2011; no publication available

NCT01223235

Trial name or title	Polyvalent vaccine-KLH conjugate + Opt-821 given in combination with bevacizumab
Methods	Uncontrolled phase I
Participants	22 participants who have recently completed chemotherapy and/or surgery for recurrent epithelial carcinoma arising from the ovary, fallopian tube, or peritoneum
Interventions	Bevacizumab and polyvalent vaccine KLH-conjugate + OPT-821

NCT01223235 (*Continued*)

Outcomes	Adverse events Immune responses Survival
Starting date	October 2010
Contact information	
Notes	Completed September 2017; no publication available

NCT01322802

Trial name or title	Vaccine therapy in treating patients with stage III-IV or recurrent ovarian cancer
Methods	Uncontrolled phase I
Participants	22 participants with advanced-stage or recurrent ovarian cancer treated to complete remission with standard therapies
Interventions	pUMVC3-hIGFBP-2 multi-epitope plasmid DNA vaccine
Outcomes	Adverse events Immune responses Survival
Starting date	March 2012
Contact information	
Notes	Active April 2017; not recruiting

NCT01376505

Trial name or title	Vaccine therapy in treating patients with metastatic solid tumors
Methods	Uncontrolled phase I trial
Participants	36 participants with malignant solid tumour, breast cancer, malignant tumour of colon, GIST, or ovarian cancer
Interventions	HER-2 vaccine
Outcomes	Immune response Clinical response Adverse events
Starting date	June 2011

NCT01376505 (*Continued*)

Contact information	
Notes	Recruiting, April 2018

NCT01522820

Trial name or title	Vaccine therapy with or without sirolimus in treating patients with NY-ESO-1-expressing solid tumours
Methods	Uncontrolled phase I
Participants	30 participants with solid NY-ESO-1- or LAGE-1-expressing tumours at high risk of recurrence or with minimal residual disease
Interventions	Intranodal injections with DEC-205-NY-ESO-1 fusion protein vaccine with or without oral sirolimus
Outcomes	Adverse events Immune responses Survival
Starting date	March 2012
Contact information	
Notes	Completed October 2016; no publication available

NCT01536054

Trial name or title	Sirolimus and vaccine therapy in treating patients with stage II-IV ovarian epithelial, fallopian tube, or primary peritoneal cavity cancer
Methods	Uncontrolled phase I
Participants	12 women with completed therapy for primary or recurrent disease with asymptomatic residual disease or complete remission
Interventions	Subcutaneous injections with ALVAC(2)-NY-ESO-1 (M)/TRICOM vaccine, subcutaneous GM-CSF, and oral sirolimus
Outcomes	Adverse events Immune responses Survival
Starting date	August 2012
Contact information	
Notes	Active not recruiting, March 2017

NCT01556841

Trial name or title	A phase II study to assess the activity of TroVax® (MVA-5T4) versus placebo in patients with relapsed asymptomatic epithelial ovarian, fallopian tube, or primary peritoneal cancer
Methods	Randomised phase II
Participants	97 participants with CA-125-relapsed asymptomatic ovarian cancer
Interventions	Vaccine targeting 5T4 (TroVax) vs placebo
Outcomes	Clinical response Immune response Survival
Starting date	November 2013
Contact information	
Notes	Active, not recruiting, December 2017

NCT01584115

Trial name or title	Clinical trial of therapeutic vaccine with NY-ESO-1 in combination with the adjuvant monophosphoryl lipid A (MPLA)
Methods	Uncontrolled phase I/II
Participants	15 participants with a NY-ESO-1-expressing malignancy after standard treatment
Interventions	Intramuscular injection with NY-ESO-1 combined with MPLA vaccine
Outcomes	Adverse events Immune responses
Starting date	July 2012
Contact information	
Notes	Status unknown

NCT01606241

Trial name or title	Cyclophosphamide and vaccine therapy in treating patients with stage II-III breast, ovarian, primary peritoneal, or fallopian tube cancer
Methods	Uncontrolled phase I
Participants	24 women in complete remission after systemic treatment of breast, ovarian, primary peritoneal, or fallopian tube cancer

NCT01606241 (*Continued*)

Interventions	Oral cyclophosphamide and intradermal multi-epitope folate receptor alpha peptide vaccine
Outcomes	Adverse events Immune responses
Starting date	July 2012
Contact information	
Notes	Manuscript submitted January 2018

NCT01616303

Trial name or title	A controlled study of effectiveness of oregovomab (antibody) plus chemotherapy in advanced ovarian cancer
Methods	Randomised open-label phase II
Participants	80 women with newly diagnosed ovarian, tubal, or peritoneal cancer after optimal cytoreductive surgery about to start first-line chemotherapy
Interventions	Carboplatin + paclitaxel vs carboplatin + paclitaxel + oregovomab
Outcomes	Adverse events Immune responses Survival Clinical responses
Starting date	June 2012
Contact information	
Notes	Active not recruiting, September 2017

NCT01621542

Trial name or title	Clinical study of WT2725 in patients with advanced solid malignancies
Methods	Uncontrolled phase I
Participants	80 participants with measurable WT1-expressing advanced-stage malignancies
Interventions	WT2725 injection
Outcomes	Adverse events Immune responses

NCT01621542 (*Continued*)

Starting date	July 2012
Contact information	
Notes	Completed June 2017; no publication available

NCT01673217

Trial name or title	Decitabine, vaccine therapy, and pegylated liposomal doxorubicin hydrochloride in treating patients with recurrent ovarian epithelial cancer, fallopian tube cancer, or peritoneal cancer
Methods	Uncontrolled phase I
Participants	18 women with relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer who are to receive liposomal doxorubicin as salvage therapy for recurrent disease
Interventions	Intravenous decitabine, intravenous liposomal doxorubicin, subcutaneous NY-ESO-1 peptide vaccine in Montanide ISA-51, subcutaneous GM-CSF
Outcomes	Adverse events Immune responses Survival
Starting date	April 2009
Contact information	
Notes	Study completed June 2013; no publication available

NCT02111941

Trial name or title	A pilot study of the safety and immunogenicity of folate receptor alpha peptide-loaded dendritic cell vaccination in patients with advanced stage epithelial ovarian cancer
Methods	Uncontrolled phase I
Participants	19 women with stage IIIC-IV ovarian epithelial, fallopian tube, or primary peritoneal cavity cancer following surgery and chemotherapy
Interventions	Multi-epitope folate receptor alpha-loaded dendritic cell vaccine
Outcomes	Adverse events Survival Immune response
Starting date	April 2014

NCT02111941 (*Continued*)

Contact information	
Notes	Active not recruiting, October 2017

NCT02132988

Trial name or title	An open labeled phase II trial of active immunotherapy with Globo H-KLH (OPT-822/821) in women who have non-progressive epithelial ovarian, fallopian tube, or primary peritoneal cancer
Methods	Phase II
Participants	110 participants with non-progressive epithelial ovarian, fallopian tube, or primary peritoneal cancer after cytoreductive surgery and platinum-based chemotherapy as initial treatment for primary disease or as salvage treatment for first relapse
Interventions	Globo H-KLH vaccine (OPT-822/OPT-821)
Outcomes	Progression-free survival Disease recurrence rate
Starting date	November 2013
Contact information	
Notes	Recruiting, May 2014

NCT02146313

Trial name or title	A phase I, open-label, dose-escalation study of the safety, tolerability, and pharmacokinetics of DMUC4064A administered intravenously to patients with platinum-resistant ovarian cancer or unresectable pancreatic cancer
Methods	Non-randomised phase I
Participants	30 participants with platinum-resistant ovarian cancer or unresectable pancreatic cancer
Interventions	Intravenous DMUC4064A
Outcomes	DLT Adverse events Immune response Clinical response
Starting date	May 2014
Contact information	

NCT02146313 (*Continued*)

Notes	Active not recruiting, March 2018

NCT02166905

Trial name or title	A phase I/IIb study of DEC205mAb-NY-ESO-1 fusion protein (CDX-1401) given with adjuvant poly-ICLC in combination with INCB024360 for patients in remission with epithelial ovarian, fallopian tube, or primary peritoneal carcinoma whose tumors express NY-ESO-1 or LAGE-1 antigen
Methods	Phase II and randomised phase IIb
Participants	62 participants with epithelial ovarian, fallopian tube, or primary peritoneal carcinoma whose tumours express NY-ESO-1 or LAGE-1 antigen
Interventions	Phase I: DEC-205/NY-ESO-1 fusion protein CDX-1401, poly ICLC, and IDO1 inhibitor INCB024360 Phase IIb cohort I: DEC-205/NY-ESO-1 fusion protein CDX-1401 and poly ICLC Phase IIB cohort II: DEC-205/NY-ESO-1 fusion protein CDX-1401, poly ICLC, and IDO1 inhibitor INCB024360
Outcomes	Adverse events Immune response
Starting date	August 2014
Contact information	
Notes	Recruiting, May 2018

NCT02275039

Trial name or title	A phase I study of a p53MVA vaccine in combination with gemcitabine in ovarian cancer
Methods	Uncontrolled phase I
Participants	9 participants with recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma
Interventions	Vaccinia virus ankara vaccine expressing p53 and gemcitabine hydrochloride
Outcomes	Dosage determination Immune response
Starting date	October 2014
Contact information	
Notes	Completed, April 2018

NCT02387125

Trial name or title	A phase Ib study evaluating the safety, tolerability and immunogenicity of CMB305 (sequentially administered LV305 and G305) in patients with locally advanced, relapsed, or metastatic cancer expressing NY-ESO-1
Methods	Non-randomised open-label multi-centre phase Ib
Participants	69 participants with melanoma, sarcoma, ovarian cancer, or non-small cell lung cancer that expresses NY-ESO-1
Interventions	CMB305 (sequentially administered LV305 (a dendritic cell-targeting viral vector expressing the NY-ESO-1 gene) and G305 (NY-ESO-1 recombinant protein plus GLA-SE))
Outcomes	Adverse events Clinical response Survival Immune response
Starting date	March 2015
Contact information	
Notes	Recruiting, January 2018

NCT02498665

Trial name or title	A phase I clinical study of DSP-7888 dosing emulsion in adult patients with advanced malignancies
Methods	Non-randomised phase I
Participants	96 participants with advanced malignancies
Interventions	WT1 protein-derived peptide vaccine (DSP-7888)
Outcomes	DLT Survival Immune response
Starting date	November 2015
Contact information	
Notes	Recruiting, April 2018

NCT02575807

Trial name or title	A phase I/II open-label safety and efficacy evaluation of CRS-207 in combination with epacadostat in adults with platinum-resistant ovarian, fallopian, or peritoneal cancer
Methods	Randomised phase I/II
Participants	126 participants with platinum-resistant ovarian, fallopian, or peritoneal cancer
Interventions	Phase I cohort I: CRS-207/epacadostat Phase I cohort II: CRS-207 Phase 2 cohort I: CRS-207, pembrolizumab Phase II cohort II: CRS-207, pembrolizumab, epacadostat
Outcomes	DLT Adverse events Clinical response Survival
Starting date	October 2015
Contact information	
Notes	Active not recruiting, February 2018

NCT02737787

Trial name or title	A phase I study of concomitant WT1 analog peptide vaccine with Montanide and GM-CSF in combination with nivolumab in patients with recurrent ovarian cancer who are in second or greater remission
Methods	Uncontrolled phase I
Participants	10 participants with ovarian, fallopian tube, or primary peritoneal cancer
Interventions	WT1 vaccine and nivolumab
Outcomes	Dose-limiting toxicity
Starting date	April 2016
Contact information	
Notes	Active not recruiting, March 2018

NCT02764333

Trial name or title	A phase II trial of TPIV200/huFR-1 (a multi-epitope anti-folate receptor vaccine) plus anti-PD-L1 MEDI4736 (durvalumab) in patients with platinum-resistant ovarian cancer
Methods	Uncontrolled phase II
Participants	40 participants with epithelial ovarian, fallopian tube, or primary peritoneal carcinoma
Interventions	Intradermal TPIV200 (vaccine targeting folate receptor alpha mixed with GM-CSF) and intravenous durvalumab
Outcomes	Clinical response
Starting date	May 2016
Contact information	
Notes	Active not recruiting, March 2018

NCT02785250

Trial name or title	A phase Ib study of an immunotherapeutic vaccine, DPX-Survivac with low dose cyclophosphamide and epacadostat (INCB024360), in patients with recurrent ovarian cancer
Methods	Uncontrolled phase I
Participants	40 participants with recurrent epithelial ovarian, fallopian tube, or peritoneal cancer
Interventions	Survivin vaccine DPX-Survivac, low-dose oral cyclophosphamide, and IDO1 inhibitor epacadostat
Outcomes	Adverse events Immune response Clinical response Survival
Starting date	May 2016
Contact information	
Notes	Recruiting, June 2017

NCT02833506

Trial name or title	A phase I clinical trial of mTOR inhibition with sirolimus for enhancing NY-ESO-1 protein with MIS416 vaccine induced anti-tumor immunity in ovarian, fallopian tube, and primary peritoneal cancer
Methods	Non-randomised phase I

NCT02833506 (*Continued*)

Participants	12 participants with stage II-IV ovarian, fallopian tube, or primary peritoneal cancer
Interventions	Cohort 1: NY-ESO-1 protein with MIS416 Cohort 2: sirolimus and NY-ESO-1 protein with MIS416
Outcomes	Adverse events Immune response Clinical response
Starting date	December 2017
Contact information	
Notes	

NCT02933073

Trial name or title	A phase I study of OncoImmunome for the treatment of stage III/IV ovarian carcinoma
Methods	Uncontrolled phase I
Participants	15 participants
Interventions	Personalised vaccine containing a mixture of 7 to 10 peptides, each containing 17 or 18 amino acids (OncoImmunome)
Outcomes	Adverse events Immune response Survival
Starting date	November 2016
Contact information	
Notes	Recruiting, July 2017

NCT02978222

Trial name or title	A randomized multicenter phase II trial to evaluate the safety, efficacy and immunogenicity of vaccination with folate receptor alpha peptides with GM-CSF versus GM-CSF alone in patients with platinum sensitive ovarian cancer and a response or stable disease to platinum therapy
Methods	Multi-centre double-blind controlled randomised phase II study
Participants	120 participants with platinum-sensitive ovarian cancer
Interventions	FRα peptide vaccine with GM-CSF or GM-CSF alone

NCT02978222 (*Continued*)

Outcomes	Survival Clinical response
Starting date	November 2016
Contact information	
Notes	Recruting, April 2018

NCT03029403

Trial name or title	A phase II study of pembrolizumab (MK-3475), DPX-Survivac vaccine and low dose of cyclophosphamide combination in patients with advanced ovarian, primary peritoneal or fallopian tube cancer
Methods	Non-randomised phase II
Participants	42 participants with advanced ovarian, primary peritoneal, or fallopian tube cancer
Interventions	Intravenous pembrolizumab, subcutaneous DPX-Survivac vaccine, and oral low-dose cyclophosphamide
Outcomes	Overall response rate Survival Adverse events
Starting date	January 2017
Contact information	
Notes	Recruiting, May 2018

NCT03029611

Trial name or title	A phase II study of concurrent IGFBP-2 vaccination and neoadjuvant chemotherapy to increase the rate of pathologic complete response at the time of cytoreductive surgery
Methods	Uncontrolled phase II
Participants	38 participants with fallopian tube cancer, ovarian cancer, or primary peritoneal cancer
Interventions	Intravenous paclitaxel and carboplatin, intradermal IGFBP-2 vaccine
Outcomes	Clinical response Immune response
Starting date	April 2017

NCT03029611 (*Continued*)

Contact information	
Notes	Recruiting, May 2018

NCT03113487

Trial name or title	A phase II study of a P53MVA vaccine in combination with pembrolizumab in platinum resistant ovarian cancer
Methods	Uncontrolled phase II trial
Participants	28 participants with ovarian, primary peritoneal, or fallopian tube cancer
Interventions	Vaccinia virus ankara vaccine expressing p53 (p53MVA) and pembrolizumab
Outcomes	Clinical response Survival
Starting date	March 2017
Contact information	
Notes	Not yet recruiting, April 2018

NCT03127098

Trial name or title	Phase Ib/II study of ETBX-011 (Ad5 (E1-, E2b-)-CEA(6D)) vaccine in combination with ALT-803 (super-agonist IL-15) in subjects having CEA-expressing cancer
Methods	Phase Ib/II
Participants	3 participants with locally advanced or metastatic CEA-expressing cancers
Interventions	Subcutaneous ETBX-011 and subcutaneous ALT-803.
Outcomes	Adverse events Survival
Starting date	April 2017
Contact information	
Notes	Active not recruiting, June 2018

NCT03197584

Trial name or title	NANT ovarian cancer vaccine: combination immunotherapy in subjects with epithelial ovarian cancer who have progressed on or after standard-of-care (SoC) therapy
Methods	Uncontrolled phase Ib/II
Participants	67 participants with epithelial ovarian cancer
Interventions	Avelumab, bevacizumab, capecitabine, cyclophosphamide, 5-fluorouracil, fulvestrant, leucovorin, paclitaxel, omega-3-acid ethyl esters, oxaliplatin, stereotactic body radiation therapy, ALT-803, ETBX-021, ETBX-051, ETBX-061, GI-4000, GI-6301, and hank
Outcomes	Adverse events Response rate (RECIST) Immune response
Starting date	June 2017
Contact information	
Notes	Not yet recruiting, October 2017

NCT03206047

Trial name or title	A randomized phase II trial of atezolizumab (MPDL3280A), SGI-110 and CDX-1401 vaccine in recurrent ovarian cancer
Methods	Randomised phase I/IIb
Participants	78 participants
Interventions	Cohort 1: intravenous atezolizumab Cohort 2: intravenous atezolizumab and subcutaneous guadecitabine Cohort 3: intravenous atezolizumab, subcutaneous guadecitabine, and DEC-205/NY-ESO-1 fusion protein CDX-1401
Outcomes	Adverse events Survival Immune response Clinical response
Starting date	September 2017
Contact information	
Notes	Recruiting, June 2018

NCT03300843

Trial name or title	A phase II trial to evaluate the ability of a dendritic cell vaccine to immunize melanoma or epithelial cancer patients against defined mutated neoantigens expressed by the autologous cancer
Methods	Uncontrolled phase II
Participants	86 participants with evaluable metastatic melanoma or epithelial cancer refractory to standard treatment
Interventions	Personalised therapeutic dendritic cell vaccine
Outcomes	Clinical response Immune response Adverse events
Starting date	October 2017
Contact information	
Notes	Recruiting, May 2018

CA-125: cancer antigen-125.
CEA: carcinoembryonic antigen.
DLT: dose-limiting toxicity.
GIST: gastrointestinal stromal tumour.
GM-CSF: granulocyte-macrophage colony-stimulating factor.
KLH: keyhole limpet haemocyanin.
MPLA: monophosphoryl lipid A.
MUC1: Mucin-1.
RECIST: Response Evaluation Criteria In Solid Tumors.

ADDITIONAL TABLES

Table 1. Study report to assess quality of non-randomised, non-controlled studies

Item	Question	Evaluation
1. a. b. c.	**Sample definition and selection** Are inclusion and exclusion criteria clearly defined? Is the study population a representative selection of the true population? Are baseline characteristics adequately described?	Yes No ? Yes No ? Yes No ?
2 a. b.	**Interventions** Are the interventions clearly defined (type of vaccine, antigen, adjuvant, route of vaccination, and vaccination schedule)? Did patients receive concurrent/concomitant treatment	Yes No ? Yes No ?

Table 1. Study report to assess quality of non-randomised, non-controlled studies (*Continued*)

	with immunomodulatory effects?	
3 a. b. c.	**Outcomes** Are the selected outcome measures clearly specified? Are the outcome measures relevant? Are the outcome measures clearly reported?	Yes No ? Yes No ? Yes No ?
4. a. b. c.	**Statistical analysis** Is there an adequate rationale for the number of participants included? Is there an adequate description of withdrawal/exclusion of participants during the study? Is presentation of the results adequate?	Yes No ? Yes No ? Yes No ?

Table 2. Overview of included studies

Study	Design	N	Disease status	Target antigen	Type of intervention
Antonilli 2016	Uncontrolled phase I/II	10	No evidence of disease (n = 7) + recurrent disease (n = 3)	MUC1 ± ErbB2 ± CEA	Multi-peptide vaccine
Baumann 2011	RCT	45	Evidence of disease after first- and/or second-line chemotherapy	EpCAM	Antibody (low dose vs high dose)
Berek 2001	RCT	252	No evidence of disease after primary surgery and chemotherapy	CA-125	Antibody vs placebo
Berek 2004	RCT	145	No evidence of disease after primary surgery and chemotherapy	CA-125	Antibody vs placebo
Berek 2009	RCT	317	No evidence of disease after primary surgery and chemotherapy	CA-125	Antibody vs placebo
Berinstein 2012	Uncontrolled phase I	6	(No) evidence of disease after primary surgery	Topoisomerase IIα, integrin β8 subunit precursor, ABI-binding protein C3, TACE/ADAM17, junction plakglobin, EDDR1, BAP31	Short peptides
Berinstein 2013	Uncontrolled phase I	19	Unknown	Survivin	Short peptides

Table 2. Overview of included studies (*Continued*)

Braly 2009	RCT	40	(No) evidence of disease after primary surgery	CA-125	Antibody (concurrent or delayed with standard chemotherapy)
Brossart 2000	Uncontrolled phase I/II	3	Residual or recurrent disease	Her-2/Neu or MUC1	Peptide-pulsed dendritic cells
Buzzonetti 2014	RCT	129	No evidence of disease after primary treatment	CA-125	Antibody vs placebo
Chianese-Bullock 2008	Uncontrolled phase I	9	(No) evidence of disease or recurrence after primary therapy	FBP, Her-2/Neu, MAGE-A1	Multi-peptide vaccine
Chu 2012	RCT	11	No evidence of disease after primary therapy or surgery for first recurrence	Her-2/Neu, hTERT, PADRE	Peptide-pulsed dendritic cells (with vs without cyclophosphamide)
Dhodapkar 2012	Uncontrolled phase I	6	Unknown	NY-ESO-1	Fusion protein
Diefenbach 2008	Uncontrolled phase I	9	No evidence of disease after primary surgery and chemotherapy	NY-ESO-1	Short peptide
Dijkgraaf 2015	Uncontrolled phase I/II	15	Evidence of disease	P53	Synthetic long peptides
Ehlen 2005	Uncontrolled phase II	13	Measurable recurrent disease	CA-125	Antibody
Freedman 1998	RCT	30	Unknown	Sialyl-Tn	KLH conjugate (low dose vs high dose)
Galanis 2010	Uncontrolled phase I	21	Persistent, recurrent, or progressive disease after primary therapy	CEA	Recombinant virus
Goh 2013	RCT	63	No evidence of disease after first- or second-line therapy	MUC1	Protein-pulsed dendritic cells vs standard of care
Gordon 2004	Uncontrolled phase II	20	Recurrent disease	CA-125	Antibody
Gray 2016	Randomised phase II	56	First or second clinical remission	MUC1	Dendritic cell therapy

Table 2. Overview of included studies (*Continued*)

Gribben 2005	Uncontrolled phase I	6	Evidence of disease	CYP1B1	Plasmid DNA
Gulley 2008	Uncontrolled phase I/II	3	Progressive disease after standard chemotherapy	CEA, MUC1	Recombinant virus
Heiss 2010	RCT	129	Recurrent malignant ascites	EpCAM	Antibody + paracentesis vs paracentesis
Imhof 2013	Uncontrolled phase I	15	No evidence of disease after primary therapy	TERT, survivin	mRNA- and peptide-pulsed dendritic cells
Kaumaya 2009	Uncontrolled phase I	5	Evidence of disease after prior therapy	Her-2/Neu	Long peptides
Kawano 2014	Uncontrolled phase II	42	Recurrent and persistent disease	Personalised (max 4 out of 31 vaccine candidates)	Peptides
Kobayashi 2014	Uncontrolled trial	56	Recurrent disease	WT1 ± MUC1 ± CA-125	Peptide-pulsed DC vaccine
Le 2012	Uncontrolled phase I	2	Evidence of disease after prior therapy	Mesothelin	Recombinant bacteria
Leffers 2009a	Uncontrolled phase II	20	Recurrent disease	p53	Long peptides
Lennerz 2014	Uncontrolled randomised phase I	7	(No) evidence of disease	Survivin	Five short peptides
Letsch 2011	Uncontrolled	8	Unknown	WT1	Short peptide
Ma 2002	Uncontrolled	4	Unknown	CA-125	Antibody
MacLean 1992	Uncontrolled phase I	10	Residual or recurrent disease	Thomsen Friedenreich	KLH conjugate
MacLean 1996	Uncontrolled phase II	34	Residual or recurrent disease	Sialyl-Tn	KLH conjugate
Method 2002	RCT	102	Unknown	CA-125	Antibody (2 vs 3 vs 6 gifts)
Möbus 2003	Retrospective uncontrolled	44	Recurrent disease after primary therapy	CA-125	Antibody
Mohebtash 2011	Uncontrolled	14	Recurrent or residual disease after therapy	CEA, MUC1	Recombinant virus

Table 2. Overview of included studies (*Continued*)

Morse 2011	Uncontrolled phase I	8	No evidence of disease after first- or second-line chemotherapy	APC, HHR6A, BAP31, replication protein A, Abl-binding protein 3c, cyclin I, topoisomerase IIα/β, integrin β 8 subunit precursor, CDC2, TACE, g-catenin, EEDDR1	Short peptides
Nicholson 2004	Uncontrolled phase I	26	Residual disease after primary therapy or second complete remission	MUC1	Antibody
Nishikawa 2006	Uncontrolled phase II	4	Unknown	NY-ESO-1	Short peptide
Noujaim 2001	Retrospective uncontrolled	184	Recurrent disease	CA-125	Antibody
O'Cearbhaill 2016	Uncontrolled phase I	24	No evidence of disease	Globo-H, GM2, sTn, TF, and Tn	Unimolecular pentavalent vaccine
Odunsi 2007	Uncontrolled phase I	18	(No) evidence of disease after chemotherapy for primary or recurrent disease	NY-ESO-1	Short peptide
Odunsi 2012	Uncontrolled phase I/II	22	No evidence of disease after primary therapy	NY-ESO-1	Recombinant virus
Odunsi 2014	Uncontrolled phase I/II	12	Recurrent epithelial cancer	NY-ESO-1	Protein vaccine with Montanide
Ohno 2009	Uncontrolled phase II	6	Unknown	WT1	Short peptide
Peethambaram 2009	Uncontrolled phase II	4	Progressive disease after therapy	Her-2/Neu	Fusion protein pulsed antigen-presenting cells
Pfisterer 2006	Uncontrolled phase I	36	Unknown	CA-125	Antibody
Rahma 2012	Uncontrolled phase II	21	No evidence of disease	p53	Short peptide vs peptide-pulsed dendritic cells
Reinartz 2004	Uncontrolled phase Ib/II	119	Unknown	CA-125	Antibody

Table 2. Overview of included studies (*Continued*)

Sabbatini 2000	Uncontrolled phase I	25	No evidence of disease after chemotherapy for primary or recurrent disease	MUC1	KLH conjugate
Sabbatini 2006	RCT	42	(No) evidence of disease (< 2 cm) after chemotherapy for recurrent disease	CA-125	Antibody (intramuscular vs subcutaneous)
Sabbatini 2007	Uncontrolled phase I/II	11	No evidence of disease after chemotherapy for primary or recurrent disease	GM2, Globo-H, Lewis Y, Tn-MUC1, Tn(c), sTN (c), TF(c)	Heptavalent KLH conjugate
Sabbatini 2012	Uncontrolled phase I	28	No evidence of disease after second- or third-line therapy	NY-ESO-1	Long peptides
Sabbatini 2013	RCT	888	No evidence of disease after primary therapy	CA-125	Antibody vs placebo
Sabbatini 2017	RCT	171	No evidence of disease after second- or third-line therapy	Globo-H, GM2, MUC1-TN, TF	Polyvalent antigen-KLH vaccine
Sandmaier 1999	Uncontrolled phase II	7	Unknown	Sialyl-Tn	KLH conjugate
Schultes 1998	Retrospective uncontrolled	75	Unknown	CA-125	Antibody
Ströhlein 2009	Uncontrolled phase I	2	Progressive disease	EpCAM or Her-2/Neu	Trifunctional antibody
Suzuki 2016	Uncontrolled phase II	32	Unknown	Glypican-3 (GCP3)	Peptide vaccine
Takeoka 2017	Uncontrolled phase I	2	Advanced cancer	NY-ESO-1	Whole protein vaccine
Takeuchi 2013	Uncontrolled phase I/II	38	Unknown	HLA-A24: FOXM1, MELK, HJURP, VEGFR1, VEGFR2; HLA-A02: HIG2, VEGFR1, VEGFR2	Short peptides
Tsuda 2004	Uncontrolled phase I/II	7	(No) evidence of disease	Patient-tailored cocktail	Multi-peptide vaccine

Table 2. Overview of included studies (*Continued*)

van Zanten-Przybysz 2002	Uncontrolled phase I/II	5	Residual or recurrent disease after prior chemotherapy	Membrane folate receptor	Antibody
Vermeij 2012	Uncontrolled phase II	12	Recurrent disease	p53	Long peptides
Wagner 1993	Retrospective uncontrolled	58	Unknown	CA-125	Antibody

APC: Adenomatous polyposis coli.
CA-125: cancer antigen-125.
CDC2: Cell division control protein 2.
CEA: carcinoembryonic antigen.
ED: Evidence of disease.
EPCAM: epithelial cell adhesion molecule.
ERbB2: Human Epidermal growth factor Receptor 2.
FBP: Folate binding protein.
HLA: human leucocyte antigen.
hTERT: telomerase reverse transcriptase.
MAGE-A1: melanoma-associated antigen A1.
MUC1: Mucin-1.
NED: No evidence of disease.
NY-ESO-1: New York esophageal squamous cell carcinoma 1.
PADRE: DR-restricted Th helper epitope.
RCT: randomised controlled trial.
sTn: sialyl Tn.
TERT: Telomerase Reverse Transcriptase.
TF: Thompson Friedreich.

Table 3. Assessment of quality of non-randomised, (un)controlled studies

	N	Clear definition of inclusion/ exclusion criteria	Representative of true population	Baseline characteristics adequately described	Interventions clearly described	Concomitant/ concurrent immunomodulatory treatment	Outcome measures clearly specified	Outcome measures relevant	Outcome measures clearly reported	Adequate rationale for number of patients	Adequate description of exclusion / withdrawal	Adequate presentation of results
Antonilli 2016	10	yes	unknown	yes	yes	no	yes	yes	yes	no	no	yes

Table 3. Assessment of quality of non-randomised, (un)controlled studies (*Continued*)

Berinstein 2012	6	no	unknown	yes	yes	unknown	yes	yes	yes	no	no	yes
Berinstein 2013	19	yes[a]	unknown	no	yes[a]	yes	no	yes	no	no	no	no
Brossart 2000	3	yes	unknown	no	yes	unknown	yes	yes	yes	no	no	no
Chianese-Bullock 2008	9	yes	no	yes	yes	unknown	yes	yes	yes	no	yes	no
Dhodapkar 2012	6	no	unknown	no	no	unknown	no	yes	no	unknown	no	no
Diefenbach 2008	9	yes	no	yes	yes	no	yes	yes	yes	no	yes	yes
Dijkgraaf 2015	6	yes	no	yes	yes	yes	yes	yes	yes	no	yes	yes
Ehlen 2005	13	yes	yes	yes	yes	unknown	yes	yes	yes	no	yes	yes
Galanis 2010	21	yes	unknown	no	yes	no	yes	yes	yes	no	yes	yes
Goh 2013	63	yes[a]	unknown	no	no	no	no	yes	no	no	no	no
Gribben 2005	6	no	no	no	yes	unknown	no	yes	no	yes	yes	no
Gulley 2008	3	yes	unknown	no	yes	unknown	yes	yes	yes	no	yes	no
Imhof 2013	15	yes[a]	unknown	no	yes	no	no	yes	no	no	no	no
Kaumaya 2009	5	no	no	no	yes	no	yes	yes	yes	no	no	no

Table 3. Assessment of quality of non-randomised, (un)controlled studies (*Continued*)

Kawano 2014	42	yes	no	yes	yes	yes	yes	yes	yes	no	no	yes
Kobayash 2014	56	yes	un-known	yes	yes	no	no	yes	no	no	yes	no
Le 2012	2	yes	no	no	yes	no	yes	yes	yes	no	no	no
Leffers 2009a	20	yes	un-known	yes	yes	no	yes	yes	yes	yes	yes	yes
Letsch 2011	8	un-known	un-known	no	yes	un-known	un-known	un-known	un-known	un-known	un-known	un-known
Ma 2002	4	no	un-known	no	no	un-known	no	no	no	no	no	no
MacLean 1992	10	no	un-known	no	yes	yes	yes	yes	yes	no	no	yes
MacLean 1996	34	yes	un-known	no	yes	yes	no	yes	no	no	yes	no
Möbus 2003	44	yes	yes	yes	yes	yes	no	yes	yes	no	no	yes
Mo-hebtash 2011	14	yes	un-known	no	yes	no	yes	yes	yes	no	no	no
Morse 2011	8	yes	no	no	yes	un-known	yes	yes	no	no	yes	no
Nichol-son 2004	26	yes	un-known	no	yes	un-known	yes	yes	yes	no	yes	yes
Nishikaw 2006	4	no	un-known	no	no	un-known	yes	yes	yes	no	no	no
Nou-jaim 2001	184	yes	yes	yes	no	un-known	yes	yes	yes	no	no	yes
O'Cearbł 2016	24	yes	yes	yes	yes	no	no	yes	no	no	no	no

Table 3. Assessment of quality of non-randomised, (un)controlled studies (*Continued*)

Odunsi 2007	18	no	no	yes	yes	unknown	no	yes	yes	no	unknown	yes
Odunsi 2012	22	no	yes	yes	yes	no	yes	yes	yes	no	no	yes
Odunsi 2014	12	yes	unknown	no	yes	yes	yes	yes	yes	no	no	yes
Ohno 2009	6	no	unknown	no	yes	no	yes	yes	yes	no	yes	yes
Peethambaram 2009	4	yes	unknown	no	yes	no	yes	yes	no	no	no	no
Pfisterer 2006	36	yes	unknown	no	yes	unknown	yes	yes	yes	no	yes	yes
Rahma 2012	21	no	unknown	no	yes	yes	yes	no	no	yes	yes	no
Reinartz 2004	119	yes	unknown	no	yes	no	yes	yes	yes	no	no	yes
Sabbatini 2000	25	yes	yes	yes	yes	unknown	no	yes	yes	no	yes	yes
Sabbatini 2007	11	yes	unknown	yes	yes	unknown	yes	yes	yes	yes	yes	no
Sabbatini 2012	28	yes	no	yes	yes	no	yes	yes	yes	yes	yes	no
Sandmaier 1999	7	yes	unknown	no	yes	no	no	yes	yes	no	yes	yes
Schultes 1998	75	no	unknown	no	yes	unknown	no	yes	yes	no	no	yes
Ströhlein 2009	2	yes	no	no	yes	unknown	yes	yes	yes	no	yes	yes

Table 3. Assessment of quality of non-randomised, (un)controlled studies (*Continued*)

Suzuki 2016	32	yes	no	yes	yes	no	yes	yes	yes	no	yes	yes
Takeoka 2017	2	yes	unknown	no	yes	no	yes	yes	yes	no	yes	yes
Takeuchi 2013	38	yes	unknown	no	yes	no	no	yes	no	no	no	no
Tsuda 2004	5	yes	no	no	yes	no	yes	yes	no	no	yes	no
van Zanten-Przybysz 2002	5	yes	no	yes	yes	unknown	yes	yes	yes	no	yes	yes
Vermeij 2012	12	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	no
Wagner 1993	58	no	unknown	no	yes	unknown	no	yes	no	no	no	no

[a] Specified in clinical trial register, not in publication.

Table 4. Evaluation of clinical responses to immunotherapy

	N	Analysed	Method	CA-125		Tumour		Overall conclusion
				Response definition	*Results*	*Definition for tumour response*	*Results*	
Antonilli 2016	10	yes	tumour			unknown	Cohort 1 (baseline status; disease free): 1× PD and 6× NED Cohort 2 (baseline status; recurrent disease): 3× PD	6× NED 4× PD

Table 4. Evaluation of clinical responses to immunotherapy (*Continued*)

Baumann 2011	45	yes	both	Gynaecologic Cancer Intergroup Guidelines (evaluable patients: cohort 1: 7; cohort 2: 3)	Cohort 1: 7× , Cohort 2: 3×	RECIST	Cohort 1: 2× SD, 21× PD Cohort 2: 1× PR, 5× SD, 16× PD	Cohort 1: 2× SD, 21× PD Cohort 2: 1× PR, 5× SD, 16× PD
Braly 2009	18/22	yes	unknown			unknown		complete clinical remission 15×/18×
Brossart 2000	3	yes	unknown					2× SD, 1× PD
Chianese-Bullock 2008	9	yes	both	unknown		unknown		1× NED, 8× PD
Chu 2012	11	yes	both	unknown		unknown		3× PD, 7× NED
Dhodapkar 2012	6	yes	unknown					not reported
Diefenbach 2008	9	yes	both	unknown		unknown		not reported
Dijkgraaf 2015	6	yes	both	Gynaecologic Cancer Intergroup Guidelines	Cohort 3 (n = 6): 4× PD, 2× PR	RECIST	Cohort 3 (n = 6): 2× PR, 3× PD, 1× SD	Cohort 3: 2× PR, 3× PD, 1× SD
Ehlen 2005	13	yes	both	decrease > 15% (); < 15% change (=) stable; > 15% increase ()	4× , 1× =, 6×	unknown		3× SD, 10× PD
Freedman 1998	30	yes	unknown					18× SD, 10× PD
Galanis 2010	21	yes	both	Gynaecologic Cancer Intergroup Guidelines	2× , 3× =, 16× ^?	RECIST	14× SD, 7× PD	14× SD, 7× PD

Table 4. Evaluation of clinical responses to immunotherapy (*Continued*)

Gordon 2004	20	yes	both	unknown	6×	unknown		2× NED, 2× CR, 1× PR, 1× SD, 9× PD
Gribben 2005	6	yes	unknown					6× PD
Gulley 2008	3	yes	both	unknown		unknown		not reported
Imhof 2013	15	yes	unknown					not reported
Kaumaya 2009	5	yes	unknown					2× SD, 3× PD
Kawano 2014	42	yes	tumour			RECIST	1× CR, 3× SD, 21× PD	1× CR, 3× SD, 21× PD
Kobayashi 2014	56	yes	tumour			RECIST 3 months after first vaccination	2× PR, 14× SD, 32× PD Disease control rate: 29% Objective response rate: 3.6%	PR: 3.6%, SD: 25%, PD: 57%
Le 2012	2	yes	tumour			RECIST	2× PD	2× PD
Leffers 2009a	20	yes	both	Gynaecologic Cancer Intergroup Guidelines	not reported	RECIST	not reported	2× SD, 18× PD
Lennerz 2014	7	yes	tumour			RECIST	5× PD, 2× NE	5× PD
Letsch 2011	8	yes	unknown					4× SD, 4× PD
MacLean 1992	10	yes	unknown					3× SD, 7× PD
Method 2002	102	yes	unknown					not reported
Mohebtash 2011	14	yes	unknown					1× SD, 11× PD
Nicholson 2004	26	yes	CA-125	unknown				21× PD, 1× SD, 1× lost to follow-up, 3×

Table 4. Evaluation of clinical responses to immunotherapy (*Continued*)

								unknown
Odunsi 2007	18	yes	tumour			unknown		1× CR, 17× unknown
Odunsi 2014	12	yes	tumour			RECIST	1× PD, 5× SD	PD: 10%, SD: 50%
Ohno 2009	6	yes	both	unknown	not reported	RECIST	1× SD, 3× PD	1× SD, 4× PD, 1× withdrawal
Peetham-baram 2009	4	yes	tumour			unknown	2× SD, 2× PD	2× SD, 2× PD
Rahma 2012	21	yes	both	unknown	not reported	RECIST	Cohort 1: 2× NED, 11× PD Cohort 2: 2× NED, 5× PD	Cohort 1: 2× NED, 11× PD Cohort 2: 2× NED, 5× PD
Reinartz 2004	119	yes	tumour			WHO		not reported
Sabbatini 2006	42	yes	both	unknown		unknown		12× SD, 21× PD, 9× withdrawal (6× PD)
Sabbatini 2012	28	yes	tumour			RECIST	Cohort 1: 1× NED, 3× PD Cohort 2: 3× NED, 10× PD Cohort 3: 2× NED, 9× PD	Cohort 1: 1× NED, 3× PD Cohort 2: 3× NED, 10× PD Cohort 3: 2× NED, 9× PD
Ströhlein 2009	2	yes	both	unknown		unknown		1× PD, 1× PR or SD
Suzuki 2016	32	yes	tumour			RECIST	12 months: PR: 2/32, PD: 28/32	2× PR, 28× PD
Takeoka 2017	2	yes	tumour			RECIST	2× PD	2× PD
Takeuchi 2013	38	yes	tumour			RECIST	1× CR, 2× PR, 10× SD, 9× PD	1× CR, 2× PR, 10× SD, 9× PD

Table 4. Evaluation of clinical responses to immunotherapy (*Continued*)

Tsuda 2004	5	yes	both	unknown		WHO		4× PD, 1× SD
van Zanten-Przybysz 2002	5	yes	both	unknown	1× , 1× =, 1× , 2× unknown	unknown	1× NED, 1× SD, 2× PD, 1× unknown	3× PD, 2× SD
Vermeij 2012	12	yes	both	Gynaecologic Cancer Intergroup Guidelines	7× /=, 3×	RECIST	not reported	2× SD, 8× PD
Wagner 1993	58	yes	CA-125	unknown				not reported
Berek 2001	252	no						
Berek 2004	145	no						
Berek 2009	371	no						
Berinstein 2012	6	no						
Berinstein 2013	19	no						
Buzzonetti 2014	129	no						
Goh 2013	63	no						
Gray 2016	56	no						
Heiss 2010	129	no						
Ma 2002	4	no						
MacLean 1996	34	no						
Möbus 2003	44	no						
Morse 2011	8	no						
Nishikawa 2006	4	no						

Table 4. Evaluation of clinical responses to immunotherapy (*Continued*)

Noujaim 2001	184	no						
O'Cearbhaill 2016	24	no						
Odunsi 2012	22	no						
Pfisterer 2006	36	no						
Sabbatini 2000	25	no						
Sabbatini 2007	11	no						
Sabbatini 2013	888	no						
Sabbatini 2017	171	no						
Sandmaier 1999	7	no						
Schultes 1998	75	no						

C1: cohort 1.
C2: cohort 2.
C3: cohort 3.
CA-125: cancer antigen-125.
CR: complete response.
GCIG: Gynecologic Cancer Intergroup.
NED: no evidence of disease.
PD: progressive disease.
PR: partial response.
RECIST: Response Evaluation Criteria In Solid Tumors.
SD: stable disease.
WHO: World Health Organization.

Table 5. Definitions and results of survival and/or relapse analysis in antigen-specific antibody studies

Study	Analysed	Definition	Results
Baumann 2011	yes	progression-free survival/overall survival	median progression-free survival: low dose 70 days (95% CI 63 to 91), high dose 68 days (95% CI 58 to 77) median overall survival: low dose 137 days (95% CI 99 to 218), high dose 185 days (95% CI 134 to 472)
Berek 2001	yes	time to relapse	median time to relapse: placebo 11.3, robust HAMA 16.4, robust Ab2 18.9 months
Berek 2004	yes	time to relapse	all patients: time to relapse: oregovomab 13.3 vs placebo 10.3 months (P = 0.71) (HR 0.881, 95% CI 0.578 to 1.349) successful front-line therapy patients: time to relapse: oregovomab 24 vs placebo 10.8 months (P = 0.71) (HR 0.543, 95% CI 0.287 to 1.025)
Berek 2009	yes	time to relapse (randomisation to relapse)	median time to relapse: oregovomab 10.3 months (95% CI 9.7 to 13.0 months) vs placebo 12.9 months (95% CI 10.1 to 17.4 months) (P = .29)
Braly 2009	yes	progression-free survival	median progression-free survival: simultaneous administration 17.9 months vs delayed administration 16.1 months
Buzzonetti 2014	no		
Ehlen 2005	yes	time to progression/survival (first dose to death)	time to progression: median 8.4 weeks (range 2 to 61 weeks); survival 37 weeks (range 11 to 110)
Gordon 2004	yes	time to progression/survival (first dose to death)	time to progression: median 11 weeks (T-cell responders vs non-responders; P < 0.0001; HR 0.150, 95% CI 0.006 to 0.168); survival: median 70.4 weeks (T-cell responders vs non-responders; P < 0.002; HR 0.157, 95% CI 0.009 to 0.347)
Heiss 2010	yes	puncture-free survival (first dose to therapeutic puncture or death)/overall survival (first dose to death)	Median puncture-free survival: paclitaxel + catumaxomab 52 days (95% CI 38 to 62) vs catumaxomab 11 days (95% CI 9 to 20) Median overall survival: paclitaxel + catumaxomab 110 days (95% CI 70 to 164) vs catumaxomab 81 days (95% CI 68 to 134)

Table 5. Definitions and results of survival and/or relapse analysis in antigen-specific antibody studies (*Continued*)

Ma 2002	no		
Method 2002	no		
Möbus 2003	yes	survival (first dose to death)/overall survival (diagnosis to death)	survival: median 16.8 months (95% CI 10.3 to 22.6) (Ab3 responders vs non-responders 18.2 vs 13.1, P = 0.0896; HAMA responders vs non-responders 22.6 months vs 7.6 months, P = 0.0016); overall survival: median 34.4 months
Nicholson 2004	no		
Noujaim 2001	yes	survival (first dose to death)	median survival and 3-year survival: Ab3 responders vs non-responders 22.9 vs 13.5 months, P = 0.0089, 38% vs 8%; T-cell responders vs non-responders (n = 16) > 84 vs 13.2 months, P = 0.0202, 75% vs 0%
Pfisterer 2006	no		
Reinartz 2004	yes	survival (first dose to death)	median survival: 19.4 months, Ab3 responders vs non-responders: 23.4 vs 4.9 months, P < 0.0001
Sabbatini 2006	yes	time to progression	time to progression: 4 months (95% CI 3 to 5 months)
Sabbatini 2013	yes	recurrence-free survival (randomisation to recurrence)/overall survival (randomisation to death)	median recurrence-free survival: abagovomab 403 days (95% CI 323 to 414) vs placebo 402 days (95% CI 323 to 487) 2-year overall survival rate: abagovomab 80% (SE 1.71) vs placebo 80% (SE 2.43)
Schultes 1998	yes	overall survival (diagnosis to death)	median overall survival: robust Ab3 responders vs non-robust responders 49 vs 38 months, P = 0.0029; Ab2 robust vs non-robust responders 30.0 vs 44.0 months, P = 0.0475
Ströhlein 2009	yes	overall survival	not described separately for ovarian cancer patients
van Zanten-Przybysz 2002	yes	survival (first dose to death)	median survival: 22.0 months
Wagner 1993	yes	not described	survival: robust Ab2 vs non-robust Ab2 responders: NS

Ab2: anti-idiotype antibody.

Ab3: anti-anti-idiotype antibody.
CI: confidence interval.
HAMA: human-anti-mouse antibody.
HR: hazard ratio.
SE: standard error.

Table 6. Definitions and results of survival and/or relapse analysis in other antigen-specific immunotherapy studies

Study	Analysed	Definition	Results
Antonilli 2016	yes	recurrence rate	recurrence rate: n = 2
Berinstein 2012	yes	time to progression (study day 0 to relapse)	median time to progression > 8 months (range 4 to > 9)
Berinstein 2013	no		
Brossart 2000	no		
Chianese-Bullock 2008	no		
Chu 2012	yes	progression-free survival (first vaccination to relapse)/overall survival (first vaccination to death/last follow-up)	3-year progression-free survival: arm 1 vs arm 2, 40% vs 80% (P = 0.17) 3-year overall survival: arm 1 vs arm 2, 80% vs 100% (P = 1.00)
Diefenbach 2008	yes	time to progression (last chemo to relapse)	median time to progression 13.0 months (95% CI 11.2 to not reached)
Dijkgraaf 2015	yes	progression-free survival: time from start of therapy until progression in weeks overall survival: time from start of therapy until death in weeks	Progression-free survival cohort 3: 8 to 36 (median 13) Overall survival cohort 3: 12 to 48 (median 37)
Dhodapkar 2012	no		
Freedman 1998	yes	progression-free interval; survival	median progression-free interval: 4 months (95% CI 1.9 to 7.6) median survival: 13.3. months (95% CI 1.5 to 30.8)
Galanis 2010	yes	overall survival	median overall survival: 12.2 months (range 1.3 to 38.4)
Goh 2013	yes	progression-free survival; overall survival	median progression-free survival vaccine vs standard of care 365 days vs 321 days overall survival: not reported

Table 6. Definitions and results of survival and/or relapse analysis in other antigen-specific immunotherapy studies (*Continued*)

Gray 2016	yes	progression-free survival overall survival	progression-free survival: 13 months (Cvac) vs 9 months (standard of care) overall survival: median not reached at 43 months in both study arms
Gribben 2005	no		
Gulley 2008	yes	progression-free survival; overall survival	progression-free survival: 9, 18, 19+ months; OS: 6, 19+, 21 months
Imhof 2013	yes	time to progression (first vaccination to relapse)/overall survival (first vaccination to death)	not reported
Kaumaya 2009	no		
Kawano 2014	yes	median survival time	median survival time overall (n = 42): 19.1 months median survival time platinum-sensitive (n = 17): 39.3 months median survival time platinum-resistant (n = 25): 16.2 months
Kobayashi 2014	yes	median survival time from first vaccination	median survival time 14.5 months
Le 2012	no		
Leffers 2009a	yes	disease-specific survival (diagnosis to death of ovarian cancer)	median disease-specific survival participants vs historical controls: 44.0 months vs 47.4 months
Lennerz 2014	no		
Letsch 2011	no		
MacLean 1996	yes	survival (trial entry to death)	median survival: 12.7 months
MacLean 1992	no		
Mohebtash 2011	yes	progression-free survival/overall survival	median progression-free survival: 2 months (range 1 to 36) median overall survival: 15.5 months (range 1.5 to > 57.0)
Morse 2011	yes	overall survival	median overall survival: not reached (range 289 to 1115+ days)
Nishikawa 2006	no		

Table 6. Definitions and results of survival and/or relapse analysis in other antigen-specific immunotherapy studies (*Continued*)

O'Cearbhaill 2016	yes	progression-free survival: time from the end of adjuvant chemotherapy until disease progression	not adequately described
Odunsi 2007	yes	time to progression (first vaccination to relapse)	median time to progression: 19.0 months (95% CI 9.0 to not reached)
Odunsi 2012	yes	progression-free survival/overall survival	median progression-free survival: 21 months (95% CI 16 to 29 months) median overall survival: 48 months (95% CI not estimable)
Odunsi 2014	no		
Ohno 2009	no		
Peethambaram 2009	yes	time to progression	median time to progression: 14.0 (range 12.1 to 18.3)
Rahma 2012	yes	progression-free survival (date on study to date of progression) overall survival (date on study to date of death or last follow-up)	median progression-free survival: 4.2 vs 8.7 months median overall survival: 40.8 vs 29.6 months
Sabbatini 2000	yes	time to progression (trial entry to relapse)	median time to progression: 6 months (range 2 to 17)
Sabbatini 2007	yes	time to progression (first vaccination to relapse)	median time to progression: 4.2 months (95% CI 2.7 to 8.5)
Sabbatini 2012	yes	time to progression	no differences between cohorts (numbers not reported)
Sabbatini 2017	yes	progression-free survival: time from randomisation to first clinical, biochemical, or radiological evidence of progression overall survival: time from study untill death.	progression-free survival: 5.9 months vaccine + OPT-821 vs 6.5 months OPT-821 only overall survival: 46.5 months vaccine + OPT-821 vs 46.2 months OPT-821 only
Sandmaier 1999	no		
Suzuki 2016	yes	time to progression/overall survival	time of progression: not reported overall survival after 12 months of all patients: 20.6%
Takeoka 2017	no		
Takeuchi 2013	yes	overall survival	median overall survival: HLA-A24 5 months (range 30 to 623 days), HLA-A02 9 months

Table 6. Definitions and results of survival and/or relapse analysis in other antigen-specific immunotherapy studies (*Continued*)

			(range 54 to 921 days)
Tsuda 2004	no		
Vermeij 2012	no		

CI: confidence interval.

Table 7. Definitions and results of anti-idiotypic (Ab2) humoral responses in antigen-specific monoclonal antibody studies

Study	N	Dose	Target antigen	Analysed	Positive if:	% positive	Robust if:	% robust
Baumann 2011	45	C1: 10-10-10-10 μg C2: 10-20-50-100 g	EpCAM	no				
Berek 2001	252	2 mg	CA-125	yes	> 50 ng/mL	63%	> 100 ng/mL	
Berek 2004	145	2 mg	CA-125	yes			> 100 ng/mL	67%
Berek 2009	371	2 mg	CA-125	no				
Braly 2009	40	unknown	CA-125	yes			> 100 ng/mL	94% vs 74%
Buzzonetti 2014	129	2 mg	CA-125	no				
Ehlen 2005	13	2 mg	CA-125	yes	> 50 ng/mL	45%		
Gordon 2004	20	2 mg	CA-125	yes	> 50 ng/mL		> 100 ng/mL	79%
Heiss 2010	129	10-20-50-150 μg	EpCAM	no				
Ma 2002	4	unknown	CA-125	no				
Method 2002	102	2 mg	CA-125	yes			> 100 ng/mL	13% vs 31% vs 67%
Möbus 2003	44	2 mg	CA-125	yes			> 50 ng/mL	77%
Nicholson 2004	26	25 mg	MUC1	yes	unknown	100%		

Table 7. Definitions and results of anti-idiotypic (Ab2) humoral responses in antigen-specific monoclonal antibody studies (*Continued*)

Noujaim 2001	184	2 mg	CA-125	yes				
Pfisterer 2006	36	2 mg	CA-125	no				
Reinartz 2004	119	2 mg	CA-125	no				
Sabbatini 2006	42	2 mg/0.2 mg	CA-125	no				
Sabbatini 2013	888	2 mg	CA-125	no				
Schultes 1998	75	2 mg	CA-125	yes	> 50 ng/mL	64%	> 250 ng/mL	
Ströhlein 2009	2	10/20/40 μg 10/40/80 μg	EpCAM Her-2/Neu	no				
van Zanten-Przybysz 2002	5	50 mg	membrane folate receptor	no				
Wagner 1993	58	1 mg	CA-125	yes	> 0 μ/L	64%	> 10 μ/L	32%

Table 8. Definitions and results of anti-anti-idiotypic (Ab3) humoral responses in antigen-specific antibody studies

Study	N	Dose	Target antigen	Analysed	Positive if:	% positive	Robust if:	% robust
Baumann 2011	45	C1: 10-10-10-10 μg C2: 10-20-50-100 μg	EpCAM	no				
Berek 2001	252	2 mg	CA-125	no				
Berek 2004	145	2 mg	CA-125	no				
Berek 2009	371	2 mg	CA-125	no				
Braly 2009	40	unknown	CA-125	no				

Table 8. Definitions and results of anti-anti-idiotypic (Ab3) humoral responses in antigen-specific antibody studies (*Continued*)

Buzzonetti 2014	129	2 mg	CA-125	yes; reported in Sabbatini 2013				
Ehlen 2005	13	2 mg	CA-125	yes	> 100 ng/mL		> 3× baseline	0%
Gordon 2004	20	2 mg	CA-125	yes	> 100 ng/mL		> 3× baseline	10.5%
Heiss 2010	129	10-20-50-150 μg	EpCAM	no				
Ma 2002	4	unknown	CA-125	no				
Method 2002	102	2 mg	CA-125	no				
Möbus 2003	44	2 mg	CA-125	yes			> 3× baseline	28%
Nicholson 2004	26	25 mg	MUC1	yes	> 0.015 μg/mL	38%		
Noujaim 2001	184	2 mg	CA-125	yes			> 3× baseline	43%
Pfisterer 2006	36	2 mg	CA-125	yes	> 1000 ng/mL	L vs S: 100% vs 100%		
Reinartz 2004	119	2 mg	CA-125	yes	> 1000 μ/mL	68%		
Sabbatini 2006	42	2 mg/0.2 mg	CA-125	yes	> 1000 μ/mL	100%		
Sabbatini 2013	888	2 mg	CA-125	yes	unknown	placebo: stable abagovomab: increase		
Schultes 1998	75	2 mg	CA-125	yes	> 200 ng/mL	24%	> 3× baseline	
Ströhlein 2009	2	10/20/40 μg 10/40/80 μg	EpCAM Her-2/Neu	no				
van Zanten-Przybysz 2002	5	50 mg	membrane folate receptor	no				

Table 8. Definitions and results of anti-anti-idiotypic (Ab3) humoral responses in antigen-specific antibody studies (*Continued*)

Wagner 1993	58	1 mg	CA-125	no				

Table 9. Definitions and results of humoral response evaluation in other antigen-specific immunotherapy studies

Study	N	Target antigen(s)	Analysed	Assay	Positive if:	% positive
Antonilli 2016	10	MUC1 ± ErbB1 ± CEA	no			
Berinstein 2012	6	topoisomerase IIα, integrin β8 subunit precursor, ABI-binding protein C3, TACE/ADAM17, junction plakglobin, EDDR1, BAP31	no			
Berinstein 2013	19	survivin	no			
Brossart 2000	3	Her-2/Neu, MUC1	no			
Chianese-Bullock 2008	9	FBP, Her-2/Neu, MAGE-A1	no			
Chu 2012	11	Her-2/Neu, hTERT, PADRE	no			
Diefenbach 2008	6	NY-ESO-1	yes	unknown	unknown	not reported
Dijkgraaf 2015	6	p53	no			
Dhodapkar 2012	9	NY-ESO-1	yes	ELISA	> 100	0%
Freedman 1998	21	CEA	yes	ELISA	≥ 2× pretreatment and > mean + 2 SD of 10 normal sera	0%
Galanis 2010	63	MUC1	yes	unknown	unknown	0%
Goh 2013	6	CYP1B1	no			
Gray 2016	56	MUC1	yes	ELISA	unknown	No response measured

Table 9. Definitions and results of humoral response evaluation in other antigen-specific immunotherapy studies (*Continued*)

Gribben 2005	3	CEA, MUC1	no			
Gulley 2008	30	Sialyl-Tn	no			
Imhof 2013	15	TERT, survivin	no			
Kaumaya 2009	5	Her-2/Neu	yes	ELISA	high response: > 0.6 intermediate response: 0.2 to 0.6	60% high responses, 40% intermediate responses
Kawano 2014	42	personalised (max 4 out of 31 vacinne candidates)	yes	Luminex assay	1 out of 4 vaccine-specific IgG titers is 2-fold higher than pre-vaccination	6 vaccinations: 16/42 12 vaccinations: 29/30
Kobayashi 2014	56	WT1 ± MUC1 ± CA-125	no			
Le 2012	2	mesothelin	no			
Leffers 2009a	20	p53	yes	unknown	unknown	pre-imm: 40%, post-imm: 45%
Lennerz 2014	7	survivin	no			
Letsch 2011	8	WT1	no			
MacLean 1996	10	Thomsen Friedenreich	yes	ELISA	unknown	80% IgA, 90% IgM, 90% IgG, 0% IgE
MacLean 1992	34	Sialyl-Tn	yes	ELISA	unknown	96%
Mohebtash 2011	14	MUC1, CEA	no			
Morse 2011	8	APC, HHR6A, BAP31, replication protein A, Abl-binding protein 3c, cyclin I, toposiomerase IIα/β, integrin β 8 subunit precursor, CDC2, TACE, g-catenin, EEDDR1	no			
Nishikawa 2006	4	NY-ESO-1	no			
O'Cearbhaill 2016	24	GM2, Globo-H, Tn, TF, sTN	yes	ELISA	IgM titer > 1:80 or at least 4-fold increase from baseline	IgM: GM2 25%, Globo-H 8%, Tn 58%, TF 67%, sTn 92%

Table 9. Definitions and results of humoral response evaluation in other antigen-specific immunotherapy studies (*Continued*)

						IgG: GM2 17%, Globo-H 58%, Tn 83%, TF 25%, sTN 67% 20/24 responded to at least 3 antigens
Odunsi 2007	18	NY-ESO-1	yes	ELISA	unknown	22%
Odunsi 2012	22	NY-ESO-1	yes	ELISA	unknown	50%
Odunsi 2014	12	NY-ESO-1	yes	ELISA	reciprocal titer > 100	4 patients remained seropositive 5/6 became seropositive no differences between cohorts.
Ohno 2009	6	WT1	no			
Peethambaram 2009	4	Her-2/Neu	yes	ELISA	unknown	unknown
Rahma 2012	21	p53	no			
Sabbatini 2000	25	Lewis Y	yes	ELISA	unknown	67%
Sabbatini 2007	11	GM2, Globo-H, Lewis Y, Tn-MUC1, Tn(c), sTN(c), TF(c)	yes	ELISA	negative to ≥ 1:40 or 8-fold increase	89% ≥ 3 antigens; 22% GM2, 33% Globo-H, 11% Lewis Y, 100% Tn-MUC1, 44% Tn(c), 44% sTN(c), 78% TF(c)
Sabbatini 2012	28	NY-ESO-1	yes	ELISA	≥ 100	cohort 1: 25%, C2: 46%, C3: 91%
Sabbatini 2017	86	Globo-H, GM2, MUC1-TN, TF	yes	unknown	1:40 or 2-fold increase	IgG: GLOBO-H 7%, GM2 8%, MUC1-TN 32%, MUC1 45%, TF 13% IgM: GLOBO-H 21%, GM2 26%, MUC1-TN 40%, MUC1 49%, TF 22%
Sandmaier 1999	7	Sialyl-Tn	yes	ELISA	≥ 1:20	100% IgM, 80% IgG
Suzuki 2016	32	GPC3	no			

Table 9. Definitions and results of humoral response evaluation in other antigen-specific immunotherapy studies (*Continued*)

Takeoka 2017	2	NY-ESO-1	yes	ELISA	optical density cutoff value 0.47	> 2
Takeuchi 2013	38	HLA-A24: FOXM1, MELK, HJURP, VEGFR1, VEGFR2 HLA-A02: HIG2, VEGFR1, VEGFR2	no			
Tsuda 2004	5	patient-tailored cocktail	yes	ELISA	unknown	67%
Vermeij 2012	12	p53	no			

SD: standard deviation.

Table 10. Definitions and results of cellular responses in antigen-specific antibody studies

Study	N	Dose	Target antigen	Analysed	Assay	Positive if:	% positive
Baumann 2011	45	C1: 10-10-10-10 μg C2: 10-20-50-100 μg	EpCAM	no			
Berek 2001	252	2 mg	CA-125	no			
Berek 2004	145	2 mg	CA-125	no			
Berek 2009	371	2 mg	CA-125	no			
Braly 2009	40	unknown	CA-125	yes	ELISPOT	permutation test	44% vs 21%
Buzzonetti 2014	129	2 mg	CA-125	yes	flow cytometry	patients with a CA-125-CTL count above 0.410 × 10^6 (=90th percentile level of CA-125-specific CTL count in the placebo arm) for at least 1 of the time points throughout the study	31.8% (treatment arm) vs 26.3% (placebo arm)

Table 10. Definitions and results of cellular responses in antigen-specific antibody studies (*Continued*)

Ehlen 2005	13	2 mg	CA-125	yes	ELISPOT	permutation test	n = 4 CA-125: 75%; n = 3 oregovomab 67%
Gordon 2004	20	2 mg	CA-125	yes	ELISPOT	permutation test	n = 18 CA-125: 39%; n = 8 oregovomab 50%; n = 8 autologous tumour cells 63%
Heiss 2010	129	10-20-5-150 μg	EpCAM	no			
Ma 2002	4	unknown	CA-125	yes	proliferation assay	unknown	n = 4: 50%
Method 2002	102	2 mg	CA-125	yes	ELISPOT	not reported	not reported
Möbus 2003	44	2 mg	CA-125	no			
Nicholson 2004	26	25 mg	MUC1	no			
Noujaim 2001	184	2 mg	CA-125	yes	proliferation assay/ cytokine ELISA	proliferation assay: Wilcoxon signed rank test; cytokine ELISA: unknown	n = 17 CA-125 53%; Th1 cytokines 41%, Th2 cytokines 94%
Pfisterer 2006	36	2 mg	CA-125	yes	cytokine flow cytometry	> 2-fold increase in IFN-γ-expressing T-cells	L vs S: n = 12 vs 17, CD4: 58% vs 29%; CD8 75% vs 18%
Reinartz 2004	119	2 mg	CA-125	no			
Sabbatini 2006	42	2 mg/0.2 mg	CA-125	yes	ELISPOT	spots experimental wells - control wells > 20 and experimental wells/ control wells > 1.5×	n = 5: 80%
Sabbatini 2013	888	2 mg	CA-125	yes	not reported		not reported
Schultes 1998	75	2 mg	CA-125	no			

Table 10. Definitions and results of cellular responses in antigen-specific antibody studies (*Continued*)

Ströhlein 2009	2	10/20/40 μg 10/40/80 μg	EpCAM Her-2/Neu	yes	IFN-γ secretion assay	unknown	EpCAM n = 1 (100%) Her-2/Neu n = 1 (0%)
van Zanten-Przybysz 2002	5	50 mg	membrane folate receptor	yes	proliferation assay	unknown	0%
Wagner 1993	58	1 mg	CA-125	yes	leucocyte migration inhibition assay	unknown	21%

CTL: cytotoxic T-cell.

Table 11. Definitions and results of cellular responses in other antigen-specific immunotherapy studies

Study	N	Target antigen(s)	Analysed	Assay	Positive if:	% positive
Antonilli 2016	10	MUC1 ± ErbB1 ± CEA	yes	IFN-γ ELISPOT delayed hypersensitvity test	ELISPOT: 2-fold increase in IFN-γ production Delayed hypersensitvity test: unknown	ELISPOT: 6/7 + 0/3 Delayed hypersensitvity test: 3/7
Berinstein 2012	6	topoisomerase IIα, integrin β8 subunit precursor, ABI-binding protein C3, TACE/ADAM17, junction plakglobin, EDDR1, BAP31	yes	pentamer staining (CD8)	> 2× increase in pentamer-positive CD8- cells	83% against at least 1 peptide
Berinstein 2013	19	survivin	yes	ELISPOT tetramer staining intracellular cytokine staining	unknown	combined results cohort 2 + 3: 92% on ≥ 2 assays
Brossart 2000	3	Her-2/Neu, MUC1	yes	intracellular IFN-γ staining (CD8)	unknown	n = 1: Her-2/Neu 100%; n = 2: MUC1 50%
Chianese-Bullock 2008	9	FBP, Her-2/Neu, MAGE-A1	yes	ELISPOT (CD8)	unknown	n = 9: FBP 40%, Her-2/Neu 83%, MAGE-A1 83%

Table 11. Definitions and results of cellular responses in other antigen-specific immunotherapy studies (*Continued*)

Chu 2012	14	Her-2/Neu, hTERT, PADRE	yes	ELISPOT tetramer staining (CD8)	unknown	hTERT: cohort 1: 100%, cohort 2: 100% Her-2/Neu: cohort 1: 60%, cohort 2: 0% PADRE: cohort 1: 60%, cohort 2: 60%
Diefenbach 2008	6	NY-ESO-1	yes	ELISPOT intracellular cytokine staining	unknown	not reported
Dijkgraaf 2015	6	Cohort 3: gemcitabine, PegIntron, and p53 SLP vaccine	yes	IFN-γ ELISPOT	> 3-fold change compared to baseline	cohort 3: 6/6
Dhodapkar 2012	9	NY-ESO-1	yes	ELISPOT/Tetramer staining (CD8)	specific spots > 30 and > 3× spots irrelevant control > 0.1% tetramer-positive CD8-cells	both assays n = 9: 67%
Freedman 1998	30	Sialyl-Tn	no			
Galanis 2010	21	CEA	no			
Goh 2013	63	MUC1	yes	unknown		not reported
Gray 2016	56	MUC1	yes	intracellular cytokine staining (CD4/CD8)	unknown	inadequately reported
Gribben 2005	6	CYP1B1	yes	ELISPOT	spots minus negative control > 20/10^6 PBMC and > 2× baseline	n = 5: 20%
Gulley 2008	3	CEA, MUC1	yes	ELISPOT (CD8)/ IFN-γ ELISA (CD4)	ELISPOT: $\geq$ 2-fold increase in IFN-γ-secreting cells IFN-γ ELISA: unknown	n = 3: 100% CEA n = 3: 33% CEA
Imhof 2013	15	TERT, survivin	yes	intracellular cytokine staining	unknown	overall > 90%
Kaumaya 2009	5	Her-2/Neu	no			

Table 11. Definitions and results of cellular responses in other antigen-specific immunotherapy studies (*Continued*)

Kawano 2014	42	personalised (max 4 out of 31 vaccine candidates)	yes	ELISPOT	2-fold higher values post-vaccination than pre-vaccination	6 vaccinations: 18/42 12 vaccinations: 19/42
Kobayashi 2014	56	WT1 ± MUC1 ± CA-125	yes	Flow cytometry (CD4/CD8/NK) Tetramer staining (WT-1 CTLs)	unknown	flow cytometry: no chances in CD4+, CD8+, and NK cell frequency tetramer staining: 12/17 increased
Le 2012	2	mesothelin	yes	ELISPOT (CD8)	specific spots > 2× baseline and ≥ 1 per 10^5 PBMC	n = 1 evaluable, mesothelin-specific CD8 cells present
Leffers 2009a	20	p53	yes	ELISPOT proliferation assay intracellular cytokine staining (CD4/CD8)	specific spots ≥ 10/10^5 PBMC and ≥ 3× pre-immunisation cpm > 1000/min, SI ≥ 3, and ≥ 2× pre-immunisation ≥ 3 pre-immunisation	n = 18: 100% n = 17: 82% n = 5: CD8 0%, CD4 100%
Lennerz 2014	7	survivin	yes	ELISPOT/HLA-multimer staining	ELISPOT (CD8): spot number > 10 and 2-fold higher than background and 2-fold higher than standard deviation of all combined negative values HLA-multimer staining: detection of > 50 cells in the multimer gate, minimum percentage of 0.03% CD8+ cells	ex vivo ELISPOT: n = 0/7 in vivo ELISPOT: n = 1/2 ex vivo multimer: n = 2/5 in vivo multimer: n = 3/4
Letsch 2011	8	WT1	yes	tetramer staining	unknown	not reported
MacLean 1996	10	Sialyl-Tn	no			
MacLean 1992	34	Thomsen Friedenreich	no			
Mohebtash 2011	14	MUC1, CEA	yes	ELISPOT (CD8)	≥ 2× pre-immunisation	n = 2: 0%; MUC1-specific

Table 11. Definitions and results of cellular responses in other antigen-specific immunotherapy studies (*Continued*)

						CD8 cells 50%, CEA-specific CD8 cells
Morse 2011	8	APC, HHR6A, BAP31, replication protein A, Abl-binding protein 3c, cyclin I, toposiomerase IIα/β, integrin β 8 subunit precursor, CDC2, TACE, g-catenin, EEDDR1	yes	ELISPOT	> 40 spots/10^5 PBMC over pre-vaccination	n = 8: 63%
Nishikawa 2006	4	NY-ESO-1	yes	ELISPOT (CD4)	unknown	n = 4: 75%
O'Cearbhaill 2016	24	GM2, Globo-H, Tn, TF, sTN	no			
Odunsi 2007	18	NY-ESO-1	yes	ELISPOT (CD4/CD8)	mean ± 3 SD	n = 18; CD4: 83%, CD8: 33%
Odunsi 2012	22	NY-ESO-1	yes	ELISPOT (CD4/CD8) intracellular cytokine staining (CD8)	unknown	CD4: 91% CD8: 45%
Odunsi 2014	12	NY-ESO-1	yes	ELISPOT (CD4/CD8) tetramer staining	ELISPOT: spot numbers in the presence of target cells exceeded cutoff value (> 50 spots/50,000 cells) + at least 3 times more spots than unpulsed target cells tetramer: > 0.1% tetramer-positive cells are CD8+ T-cells and at least 3 times more than the percentage obtained with control tetramer	CD8: 5/11 (45%), of which 3 de novo inductions CD4: 7/10 (70%), of which 2 de novo responses tetramer staining: 2× NY-ESO-1 CD8 cell expansion
Ohno 2009	6	WT1	no			
Peethambaram 2009	4	Her-2/Neu	yes	proliferation assay ELISPOT assay	unknown	not reported separately for ovarian cancer patients

Table 11. Definitions and results of cellular responses in other antigen-specific immunotherapy studies (*Continued*)

Rahma 2012	21	p53	yes	ELISPOT tetramer staining	≥ 2× pre-immunisation	cohort 1: 64%, cohort 2: 83%
Sabbatini 2000	25	Lewis Y	no			
Sabbatini 2007	11	GM2, Globo-H, Lewis Y, Tn-MUC1, Tn(c), sTN(c), TF(c)	no			
Sabbatini 2012	28	NY-ESO-1	yes	ELISPOT (CD4/CD8)	> 50 spots/5 × 10^4 cells and > 3× unstimulated cells	CD4: 100% in cohort 1, 2, and 3 CD8: cohort 1: 0%, cohort 2: 62%, cohort 3: 92%
Sabbatini 2017	171	Globo-H, GM2, MUC1-TN, TF	no			
Sandmaier 1999	7	Sialyl-Tn	yes	proliferation assay[a]	> upper limit of normal (SI 2.35)	n = 4: 50%
Suzuki 2016	32	GPC3	yes	ELISPOT (CD8)	unknown	n = 15/24: 62.5%
Takeoka 2017	2	NY-ESO-I	yes	IFN-γ catch assay (CD4/CD8)	> 0.5%	CD4: n = 2; > 5% CD8: n = 2; 1% to 5%
Takeuchi 2013	38	HLA-A24: FOXM1, MELK, HJURP, VEGFR1, VEGFR2 HLA-A02: HIG2, VEGFR1, VEGFR2	yes	unknown	unknown	inadequately reported
Tsuda 2004	5	patient-tailored cocktail	yes	IFN-γ ELISA	unclear	n = 2 after 6 vacc 100%; n = 1 after 12 vacc 100%
Vermeij 2012	12	p53	yes	ELISPOT proliferation assay	specific spots ≥ 10/10^5 PBMC and ≥ 3× pre-immunisation cpm > 1000/min, SI ≥ 3, and ≥ 2× pre-immunisation	90% after 2 vacc, 87.5% after 4 vacc 80% after 2 vacc, 62.5% after 4 vacc

[a] as measured after at least three immunisations.
C1: cohort 1.
SD: standard deviation.

SI: stimulation index.

Table 12. Definitions and results of human-anti-mouse antibody (HAMA) evaluation in antigen-specific antibody studies

Study	N	Dose	Target antigen	Analysed	Positive if:	% positive	Robust if:	% robust
Baumann 2011	45	C1: 10-10-10-10 μg C2: 10-20-50-100 μg	EpCAM	yes	unknown	C1: 61%, C2: 100%		
Berek 2001	252	2 mg	CA-125	yes			> 5000 ng/mL	51%
Berek 2004	145	2 mg	CA-125	yes	> 200 ng/mL	unknown	> 5000 ng/mL	59%
Berek 2009	371	2 mg	CA-125	yes	unknown	n.r.		
Braly 2009	40	unknown	CA-125	yes	unknown	SIM vs OWD: 100% vs 80%	> 3000 ng/mL	SIM vs OWD: 88% vs 74%
Buzzonetti 2014	129	2 mg	CA-125	yes; reported in Sabbatini 2013				
Ehlen 2005	13	2 mg	CA-125	yes	> 200 ng/mL	100%	> 5000 ng/mL	58%
Gordon 2004	20	2 mg	CA-125	yes	> 200 ng/mL	unknown	> 5000 ng/mL	79%
Heiss 2010	129	10-20-50-150 μg	EpCAM	yes	unknown	not reported		
Ma 2002	4	unknown	CA-125	no				
Method 2002	102	2 mg	CA-125	yes	> 200 ng/mL	unknown	unknown	4% vs 36% vs 39%
Möbus 2003	44	2 mg	CA-125	yes			> 5000 ng/mL	68%
Nicholson 2004	26	25 mg	MUC1	no				
Noujaim 2001	184	2 mg	CA-125	no				

Table 12. Definitions and results of human-anti-mouse antibody (HAMA) evaluation in antigen-specific antibody studies (*Continued*)

Pfisterer 2006	36	2 mg	CA-125	yes	> 15 ng/mL	L vs S: 94% vs 100%		
Reinartz 2004	119	2 mg	CA-125	yes	> 100 ng/mL	78%		
Sabbatini 2006	42	2 mg/0.2 mg	CA-125	yes	> 100 ng/mL	90%		
Sabbatini 2013	888	2 mg	CA-125	yes	unknown	inadequately reported		
Schultes 1998	75	2 mg	CA-125	yes	> 200 ng/mL	90%		
Ströhlein 2009	2	10/20/40 μg 10/40/80 μg	EpCAM Her2/Neu	yes	unknown	100% (n = 1)		
van Zanten-Przybysz 2002	5	50 mg	membrane folate receptor	n.a.				
Wagner 1993	58	1 mg	CA-125	no				

n.r.: not reported.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Ovarian Neoplasms] explode all trees
#2 ovar* near/5 (cancer* or neoplas* or tumor* or tumour* or carcinoma* or adenocarcinoma* or malignan*)
#3 #1 or #2
#4 MeSH descriptor: [Immunotherapy, Active] explode all trees
#5 MeSH descriptor: [Cancer Vaccines] explode all trees
#6 immunotherapy or vaccination* or vaccine* or immunization or immunisation
#7 #4 or #5 or #6
#8 MeSH descriptor: [Antigens, Neoplasm] explode all trees
#9 antigen*
#10 #8 or #9
#11 MeSH descriptor: [T-Lymphocytes] explode all trees
#12 (T cell*) or T-cell* or (T lymphocyte*) or T-lymphocyte* or CD4* or CD8*
#13 #11 or #12

#14 #3 and #7 and #10 and #13

Appendix 2. MEDLINE search strategy

MEDLINE Ovid
1 exp Ovarian Neoplasms/
2 (ovar* adj5 (cancer* or neoplas* or tumor* or tumour* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3 1 or 2
4 exp Immunotherapy, Active/
5 Cancer Vaccines/
6 (immunotherapy or vaccination* or vaccine* or immunization or immunisation).mp.
7 4 or 5 or 6
8 exp Antigens, Neoplasm/
9 antigen*.mp.
10 8 or 9
11 exp T-Lymphocytes/
12 (T cell* or T-cell* or T lymphocyte* or T-lymphocyte* or CD4* or CD8*).mp.
13 11 or 12
14 3 and 7 and 10 and 13
key:
mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier

Appendix 3. Embase search strategy

Embase Ovid
1 exp ovary tumor/
2 (ovar* adj5 (cancer* or neoplas* or tumor* or tumour* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3 1 or 2
4 active immunization/
5 cancer vaccine/
6 (immunotherapy or vaccination* or vaccine* or immunization or immunisation).mp.
7 4 or 5 or 6
8 exp tumor antigen/
9 antigen*.mp.
10 8 or 9
11 exp T lymphocyte/
12 (T cell* or T-cell* or T lymphocyte* or T-lymphocyte* or CD4* or CD8*).mp.
13 11 or 12
14 3 and 7 and 10 and 13
key:
mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword

Appendix 4. Data extraction form

CRITICAL REVIEW & DATA EXTRACTION FORM
Review Title: Antigen-specific active immunotherapy for ovarian cancer
Date: …… Reviewer: ……
Study Title: …….

First Author	
Year of Publication	
Country of Publication	
Publication Type	Journal/Abstract/Other (specify)

Study Characteristics

	Study
Study inclusion criteria	
Study exclusion criteria	
Participants	· Total number of participants: …… · Number of patients with EOC: ……. · Age: o Median + range: …… o Mean + SD: …… · FIGO stage: …… · Histological tumour type: …… · Tumour grade: …… · Previous therapy: …… · Concurrent therapy: ……..
Trial intervention	· Type of vaccine: …… · Antigen used: …… · Adjuvant used: ……. · Route of vaccination: …… · Vaccination schedule: …….

Outcomes

Trial	N + reason
Patients excluded during trial	
Patients lost to follow-up	

Clinical responses	N
CA-125 levels according to GCIG definition	Decreasing: ……. Stable: …….. Progressing: …… Total: …….
Tumour response according to RECIST or WHO criteria	Complete remission: ……. Partial remission: …….. Stable disease: …….. Progressive disease: …….. Total: …….
Post-immunotherapy treatment	Administered: Yes ? No ? If yes: specify response to post-immunotherapy treatment: Complete remission: ……. Partial remission: …….. Stable disease: …….. Progressive disease: …….. Total: …….
Survival	Information on survival available: Yes ? No ? If yes, specify: …… ……

Immunogenicity	
1. *Antigen-specific immunogenicity*	
Humoral responses	Observed Total Assay(s) used: ……
Cellular responses	Observed Total Assay(s) used: ……

(*Continued*)

	Separate information on cytotoxic T-lymphocytes and T-helper lymphocytes available: Yes ? No ? If yes, specify: ……
Vaccine- or vector-specific immunogenicity: Applicable Yes ? No ?	
Humoral responses	Observed Total Assay(s) used: ……
Cellular responses	Observed Total Assay(s) used: ……

Adverse events	
Type of AEs	· Local events (injection site): Yes ? No ? If yes, specify: …… · Systemic: Yes ? No ? If yes: Autoimmunity: Yes ? No ? If yes, specify: …… Allergic reactions: Yes ? No ? If yes, specify: …… Other: Yes ? No ? If yes, specify: ……

Other

Contact with primary investigators	Clarify methods ? Clarify results ?
Notes	

WHAT'S NEW

Last assessed as up-to-date: 3 July 2017.

Date	Event	Description
13 March 2018	New citation required but conclusions have not changed	Review text updated to reflect additional studies, both included and excluded. Overall, conclusions unchanged
1 August 2017	New search has been performed	Searches re-run July 2017. New studies included and excluded

HISTORY

Protocol first published: Issue 3, 2008

Review first published: Issue 1, 2010

Date	Event	Description
8 September 2014	Amended	Author details amended
31 July 2014	New search has been performed	Searches re-run October 2013. New studies included and excluded
10 July 2014	New citation required but conclusions have not changed	Review text updated to reflect additional studies, both included and excluded. Overall, conclusions unchanged

CONTRIBUTIONS OF AUTHORS

NL selected relevant studies, assessed study quality, extracted data, and wrote the review. HWN selected relevant studies, assessed study quality, and extracted data. TD and WH checked all rejected titles and resolved disagreements on study selection and data extraction. HMB and BC provided statistical and methodological support. KM was supportive of writing the review as an expert in immunology. STP and MDB selected relevant studies, assessed study quality, extracted data, and wrote the second update of this review.

DECLARATIONS OF INTEREST

Ninke Leffers, Cornelis Melief, Toos Daemen, and Hans Nijman were investigators in two studies included in this review (Leffers 2009a; Vermeij 2012). No potential conflicts of interest are known for the other contributing review authors (WH, BJC, STP, MDB) .

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

TD was added to the team. For the update of this review, we used the Cochrane 'Risk of bias' tool to assess risk of bias in randomised controlled trials, whereas for the protocol and the previous version of this review, we used the Delphi list. We can report no further relevant differences between protocol and review. For the second update, STP and MB were added to the review author team.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal [adverse effects; therapeutic use]; CA-125 Antigen [immunology]; Clinical Trials, Phase I as Topic; Clinical Trials, Phase II as Topic; Immunotherapy, Active [adverse effects; *methods]; Molecular Targeted Therapy [methods]; Neoplasms, Glandular and Epithelial [immunology; *therapy]; Ovarian Neoplasms [immunology; *therapy]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans