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European Journal of Cancer xxx (xxxx) xxx

Available online at www.sciencedirect.com

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Review

Efficacy of cancer vaccines in selected gynaecological breast and ovarian cancers: A 20-year systematic review and meta-analysis

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Received 30 July 2020; received in revised form 29 September 2020; accepted 8 October 2020
Available online ■ ■ ■

KEYWORDS
Breast cancer;
Ovarian cancer;
Vaccine;
Meta-analysis;
Systematic review

Abstract ***Background:*** Therapeutic cancer vaccination is an area of interest, even though promising efficacy has not been demonstrated so far.
Design: A systematic review and meta-analysis was conducted to evaluate vaccines' efficacy on breast cancer (BC) and ovarian cancer (OC) patients. Our search was based on the PubMed electronic database, from 1st January 2000 to 4th February 2020.
Objective: response rate (ORR) was the primary end-point of interest, while progression-free survival (PFS), overall survival (OS) and toxicity were secondary end-points. Analysis was performed separately for BC and OC patients. Pooled ORRs were estimated by fixed or random effects models, depending on the detected degree of heterogeneity, for all studies with more than five patients. Subgroup analyses by vaccine type and treatment schema as well as sensitivity analyses, were implemented.
Results: Among 315 articles initially identified, 67 were eligible for our meta-analysis (BC: 46, 1698 patients; OC: 32, 426 patients; where both BC/OC in 11). Dendritic-cell and peptide vaccines were found in more studies, 6/10 BC and 10/13 OC studies, respectively.
In our primary BC analysis (21 studies; 428 patients), the pooled ORR estimate was 9% (95%CI[5%,13%]). The primary OC analysis (12 studies; 182 patients), yielded pooled ORR

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https://doi.org/10.1016/j.ejca.2020.10.014

estimate of 4% (95%CI[1%,7%]). Similar were the results derived in sensitivity analyses. No statistically significant differences were detected by vaccine type or treatment schema.

Median PFS was 2.6 months (95% confidence interval (CI)[1.9,2.9]) and 13.0 months (95% CI[8.5,16.3]) for BC and OC respectively, while corresponding median OS was 24.8 months (95%CI[15.0,46.0]) and 39.0 months (95%CI[31.0,49.0]). In almost all cases, the observed toxicity was only moderate.

Conclusion: Despite their modest results in terms of ORR, therapeutic vaccines in the last 20 years display relatively long survival rates and low toxicity. Since a plethora of different approaches have been tested, a better understanding of the underlying mechanisms is needed in order to further improve vaccine efficacy.

1. Introduction

Vaccines account for some of the greatest public health achievements in the last century in the treatment of infectious diseases, eradicating smallpox worldwide and significantly reducing the incidence of several major diseases such as polio and measles [1,2]. On the other hand, cancer vaccines have produced mixed results. Therapeutic cancer vaccines have a long history of efficacy shortcomings. The better understanding and detection of responsible factors for previous failures has allowed development of new strategies to address them. In this respect, in a previous meta-analysis performed in 2004 at the Surgery Branch of National Cancer Institute [NCI] working under the umbrella of US National Institutes of Health including cancer vaccine trials of 440 patients, the objective response rate (ORR) was low (2.6%) [3]. Vaccines, however, have few side-effects and invasive procedures, and therefore measures being implemented to improve their therapeutic efficacy are of interest.

Factors affecting the efficacy of vaccines may be grouped into three categories: the type of vaccine itself, the route of administration and the patient population being targeted for therapy. In the first category, different measures may be implemented in order to enhance the vaccine's efficacy. Thus, the selection of an antigen source is one of the main aspects of therapeutic vaccination; it is typically one or more tumour-associated antigen(s) (TAAs) that are added in the form of synthetic protein, peptides, RNA, DNA or whole tumour lysate. Additionally, the selected antigens can be delivered as bare molecules mixed with activating compounds, or rather administered to *ex vivo* isolated antigen-presenting cells (APCs) that are subsequently activated and infused back to the patient. The selected antigens to be used in vaccines can be either non-mutated self-antigens (the so-called "public" antigens) or mutated neo-antigens, which arise as a result of the large number of mutations occurring in tumour cells due to their inherent genetic instability. To date, most vaccines are targeted against identified non-mutated antigens, which could be a potential explanation for the observed decreased efficacy [4]. In contrast to public antigens, neo-antigens are able to induce a T-cell response similar to the one found in antiviral T cells [5]. Moreover, no autoimmune toxicity is predicted to be induced against healthy tissues, rendering neo-antigen vaccination a very attractive choice, recently introduced in the clinic [6].

Additionally, as vaccination efficacy was reportedly low in previous studies, a number of potential interventions have been suggested in order to improve it [3]. One challenge for cancer vaccines to be effective is their capacity to induce both long-term memory cells and activate antitumour T cells. Thus, it was recognised that active suppressor mechanisms from both the tumour and the immune system itself could inhibit antitumour reactions. For example, the CD4+CD25+ lymphocytes are regulatory T cells capable of suppressing both the proliferation and effector function of immune cells [7,8]. Therefore, for cancer vaccines to be effective, elimination of regulatory T cells may be required, as these cells have the ability to suppress both the proliferation and effector function of immune cells [9]. In this respect, cyclophosphamide is a chemotherapeutic agent which has been shown to selectively deplete Treg cells and restore T cell function [10,11]. For this reason, cyclophosphamide has been incorporated in some trials in combination with vaccines, aiming to improve their efficacy [12−14]. In addition, blocking of secreted immunosuppressive molecules such as transforming growth factor-beta (TGF-β), interleukin-10 (IL-10), interleukin (IL-13) or prostaglandins may be necessary as well as selective means of removing CD4+CD25+ regulatory cells, and different approaches have been tested to achieve dendritic cell (DC) activation [12,15]. Recently, inhibitors of the immune checkpoints (ICIs) have provided a paradigm shift in cancer therapy [16], enhancing T cell activation, and combinations with therapeutic vaccines suggest a promising synergistic effect [17].

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Another important factor that could impact vaccine efficacy is the delivery route [18]. Most vaccines are typically administered using subcutaneous (SC) or intramuscular (IM) route, and different approaches have been used in the studies compiled herein. Nevertheless, it is still not clear which is the most efficient way, and novel vaccine delivery devices and systems are currently in development to improve vaccine efficacy [18]. Importantly, each distribution pathway relies on the presence of DCs in the tissues that pick up the antigen, process it and present it in the draining lymphoid organs to T lymphocytes.

Over the years, different groups have used multiple approaches for therapeutic vaccination, with variable outcomes. Different approaches have variable delivery methods and strategies, which may have had an impact on vaccine efficacy [19]. In this meta-analysis, the main types of vaccines being used in the treatment of the selected cancer types are described in Table 1, and the specific approach used in each study is summarised in Table S1. In summary, the vaccines included in this study consisted of either carrier cells (such as DCs loaded *ex vivo* with a variety of antigenic sources, or *Listeria monocytogenes*), or specific tumour antigens that could be either a complex mixture (as in whole tumour extracts) or a purified antigen in different formats (DNA, RNA, protein, or peptides).

1.1. Cancer types

In this meta-analysis, we also aim to evaluate the efficacy of therapeutic vaccination in two different cancers affecting women, namely breast cancer (BC) and ovarian cancer (OC), depending on the kind of vaccine used, combining the results observed in studies performed during a 20-year period, from 2000 to 2019.

In clinical practice, most BC tumours are classified as Luminal A or B, human epidermal growth factor receptor 2 (HER2) positive, or triple negative (TN) based on pathological parameters in immunohistochemistry, such as hormone receptor status, HER2 status, grade, and proliferation index (Ki-67), that have been well defined [20], although they do not perfectly overlap with the molecular subtypes defined by Perou [21]. Except for some specific subtypes (TN and HER2 positive), BC is considered to be poorly immunogenic. Thus, in 2009 patients participating in the Breast International Group (BIG) 02–98 trial (a phase III study in early BC adjuvant setting), Loi et al. demonstrated that tumour-infiltrating lymphocytes (TILs) are a significant

Table 1
Types of vaccines used in the meta-analysis.

Type of vaccine	Antigen source	Characteristics
Dendritic cell (DC) vaccines	DCs can be loaded *ex vivo* with synthetic proteins, peptides, RNA, DNA, or whole tumour lysate	Generally safe and very low in toxicity, but they have shown only modest clinical benefit to date, with most indications only attaining around 15% of the objective clinical response [45]
Protein vaccines	Purified or recombinant proteinaceous antigens from tumours	Sipuleucel-T vaccine was developed using this approach and obtained FDA approval for the treatment of advanced prostate cancer patients in 2010 [10], one of the few therapeutic vaccines approved to date.
Peptide vaccines	Specific peptides from antigenic proteins	Based on the biological principle that T-cell response activation depends on T-cell receptor specificity to detect a presented oligopeptide epitope. However, the immunogenicity of synthetic peptide-based vaccines can be significantly affected by the delivery process, thus chemically defined synthetic vaccine development approaches are underway [46]
Whole tumour cell (WTC) vaccines	Whole tumour cell used as tumour antigen	Considered a very promising alternative in tumour immune protection and immunotherapy that can theoretically eliminate some important limitations in the development of vaccines, as all tumour cells express a wide range of tumour-associated antigens (TAAs) and can simultaneously induce CTLs and CD4+T helper cell activation. Clinically approved additives can be used to enhance immunogenicity in tumour cells by enhancing both the humoral and cellular response [47]
Carbohydrate (CH) vaccines	Carbohydrates coupled to carrier proteins to improve their immunogenicity [48]	Carbohydrates are considered to be promising targets for the development of vaccines against both infectious diseases and tumour cells, as oncogenic transformation of normal cells also results in aberrant glycosylation of the surface cells that form carbohydrate antigens associated with the tumour.
Virus vaccines	Natural and recombinant immunogenic viruses are widely used to express tumour antigen transgenes [49]	Recombinant viruses can be logistically produced, administered and regulated more easily compared to other immunotherapy approaches. There are strong benefits and drawbacks to each virus' intrinsic properties, which can define its applicability in each therapeutic environment.
Listeria monocytogenes strain vaccines	Antigens integrated inside the bacterial pathogen Listeria monocytogene	*Listeria monocytogenes* is a bacterial pathogen that generates a strong cellular immune response and therefore has the potential to be used as a vaccine vector [50]. This pathogen is replicated in the intracytoplasmic environment, which facilitates the delivery of the antigen to the endogenous processing and presentation pathway, with subsequent stimulation of the peptide-specific Major Histocompatibility Complex (MHC) class I-restricted CD8 + effector cells [51]

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prognostic biomarker, but only in TN patients [22]. The OS and DFS advantage was recently verified in a TNBC meta-analysis, where a gain of 15−20 percent in either recurrence or mortality was seen for every 10 percent rise in TILs [23]. In 12,439 BC patients it was then shown that the presence of CD8 + TILs in HER2 positive patients (regardless of ER positivity) is also correlated with good prognosis [24]. Yet TN and HER2 positive subtypes account for ∼30% of all BC patients, whereas ∼75% are hormone receptor-positive, i.e. non-immunogenic.

OC, on the other hand, is nowadays recognised as an immunogenic cancer. Early findings in OC patients showed a link between tumour infiltration of T-cells, improved clinical and therapeutic outcome, and improved survival [25]. This finding was later also validated by a meta-analysis of specimens of over 1800 OC patients [26], which suggested that the immune system played a major role in the outcomes of patients and endorsed immunotherapy in different forms for OC [27,28]. Surgical debulking followed by chemotherapy, using a platinum and taxane combination regimen, is the first-line of OC treatment, leading to an overall response rate in 80−90% of the patients. OC patients usually have repetitive episodes of relapse with gradually shorter duration, as progression free survival periods, due to increased resistance to chemotherapy treatments. Platinum treatment may be prescribed in the recurrent setting provided that there is a sufficient platinum-free interval and absence of allergic reactions. Patients experiencing tumour progression during first-line platinum chemotherapy or within 1 month from the last platinum administration, and those with short platinum-free interval (<6 months) -based regimen can be again relapsing within are considered 'refractory' or 'resistant' for subsequent platinum treatment. There are several chemotherapy options and bevacizumab available for platinum-resistant or refractory OC (PRROC) patients. These options exhibit only marginal benefits, therefore new treatment options are required for this population [28].

2. Methods

The current analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [29,29,29,29]. A statistical analysis plan, specifying all analysis methods and inclusion criteria, was developed prior to search initiation.

2.1. Eligibility criteria

In this meta-analysis we have taken into account data from studies, randomised or not, involving treatment with cancer vaccine on BC or OC patients. Cases of combination treatment with other therapies (e.g. chemotherapy) were also allowed. The selection criteria included: presence of efficacy measures of the vaccine treatment, including either tumour response according to standard oncology assessment criteria, progression-free survival (PFS) or overall survival (OS). Only studies from 2000 onwards were included, aiming to analyse results obtained in the field, starting from the previous meta-analysis performed in 2004 [3]. Case reports of single patients were excluded.

2.2. Information sources, search strategies & study selection

The PubMed electronic database was used for study identification with search date being the 4th February 2020. The Medical Subject Headings (MeSH) terms as well as the exact step-by-step strategy adopted for study selection are illustrated in Fig. 1.

Initially, the title and abstract of all identified articles were screened and studies clearly not satisfying the set criteria were excluded. In the second step, full text review was performed for the remaining articles in order to create the list of eligible studies. All publications referenced in each eligible study or relevant reviews identified in the initial search were further searched. This process was performed independently by two reviewers (SML, KV) and potential differentiations were resolved by discussion and consensus.

Specific checks, cross-checking authors' names, treatment groups, sample size, outcome and recruitment period, were additionally performed in order to identify studies published more than once or with overlapping cohorts. If a patient cohort was described in more than one manuscript, only data from the most recent publication was included in the meta-analysis. In addition, subcohorts violating the inclusion criteria were excluded as well.

Finally, the process involved consultation with specialists (GC, LK, KZ, AS) in the field of cancer vaccine therapy and BC/OC.

2.3. Data extraction and quality assessment

The collection of data (study/patient/treatment characteristics, outcome) from all eligible studies was based on a pre-defined standardised form. Details on the information extracted and the extraction process methodology, are provided in Tables S2 and S3 (similar to Dafni et al. [30]) respectively. Of note, in all cases that patient-level data were available, the relevant information was recorded. The quality of the studies was assessed according to ROBINS-I [31] and Cochrane's [32] tool for non-randomised and randomised trials, respectively, funnel plots and Egger's test [33]. Data extraction and quality assessment was performed independently by two reviewers (ZT, KV) and cross-checked by a third (UD).

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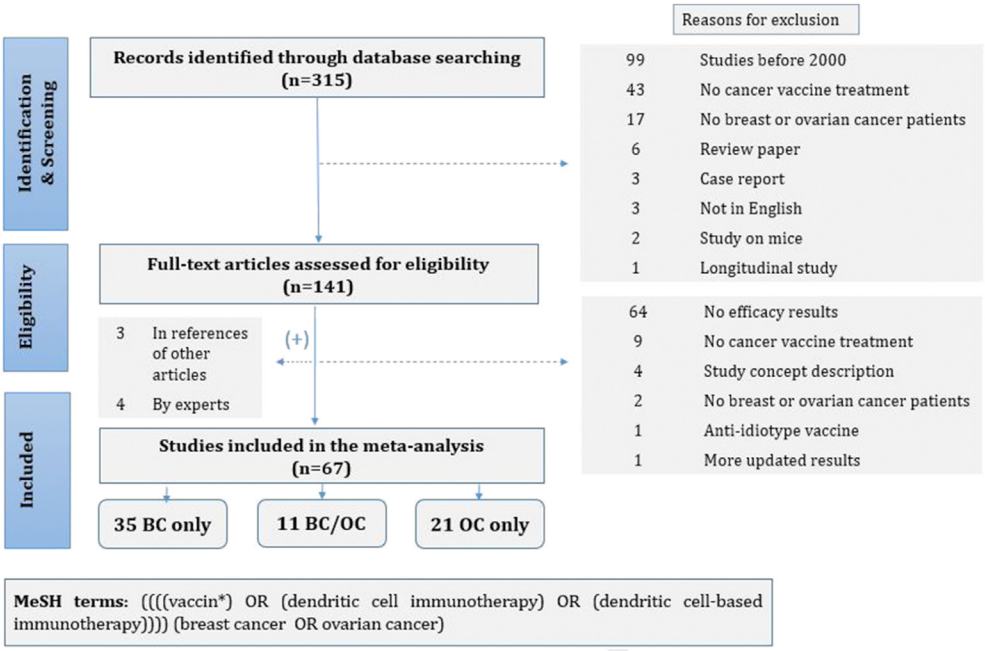

Fig. 1. Flowchart.

2.4. Statistical analysis

The primary end-point of the meta-analysis was objective response (OR) rate (ORR; including Complete and Partial Response- CR and PR), according to study-specific response criteria, and based on the patients with residual disease at study enrollment. The secondary end-points were PFS, OS and toxicity (according to Common Terminology Criteria for Adverse Events, version 5.0 [CTCAE v5.0]). All end-points were based on patients having received at least one vaccine dose. Breakdown of OR into complete response (CR) and partial response (PR) was not available in most manuscripts, and thus CR rate could not be presented and analysed.

In the primary analysis, ORR and 95% exact binomial confidence intervals (95%CI) are provided by study, while pooled estimates are based on fixed or random effects models (FEM, REM) [34,35].The choice between FEM or REM depends on the amount of heterogeneity, i.e., the variation of ORR between the studies included in the analysis, as assessed by the Cochran's Q test and the I^2measure [32,36]. In the cases of significant heterogeneity (Cochran's Q p-value$<$ 0.10), REM are adopted.

For the time-to-event end-points (PFS/OS), Kaplan−Meier curves with 95% confidence bands (95% CBs), median values and rates at specific time-points with 95%CIs, were estimated, whenever patient-level data were available.

Toxicity was evaluated based on the reported number of treated patients experiencing specific adverse events (AEs) in each study. Information was obtained either from frequency tables summarizing the respective data or from values reported in each manuscript.

All analyses were performed separately for BC and OC patients. In the primary analyses of ORR, PFS, OS only the studies with more than 5 BC/OC patients were included, while corresponding sensitivity analyses including also the small-size trials ($\leq$5 patients) were implemented.

Subgroup analyses of ORR by vaccine type and treatment schema (vaccine alone or in combination with other treatments) were also performed.

Statistical analysis was carried out with SAS-v4 (SAS Institute, Cary, NC) and R-v3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Studies included in the meta-analysis

Overall, 315 articles were initially identified in PubMed. The details of the selection process and exclusion reasons are illustrated in Fig. 1. One-hundred and forty-one studies were deemed eligible for full text review, leading to a total of 67 studies, satisfying all inclusion criteria and thus did qualify for our meta-analysis (Table S4). Forty-six studies provide information for BC and 32 for OC patients, with 11 studies among them including results for both BC and OC patients.

Study characteristics, including the phase of the trial, the disease stage of included patients, vaccine type as well as the type of available information on primary outcome are summarised in Table 2.

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Table 2
Study characteristics.

Study	Trial phase	Study cohort details	Stage	Vaccine type	No of patients	Median age (range) in yrs	Info on ORR	Info on PFS/OS
Breast Cancer								
Jiang-2000 [52]	II	*Breast cancer* with mastectomy	Advanced/ Metastatic	Multi-antigen	16[a]	50 (30−83)[b]	+	
Scholl-2000 [53]	I/II	Advanced inoperable *breast cancer*; Mucin 1+ (MUC1+)	Advanced/ Metastatic	Virus	9	51 (41−72)		+
Triozzi-2000 [54]	–	Metastatic dermal or subcutaneous tumours (melanoma, *breast*)	Advanced/ Metastatic	DC	3	49 (39−52)	+ (Standard response criteria)	
Gilewski-2001 [55]	I	Metastatic *breast cancer*	Advanced/ Metastatic	CH	12[c]	46 (35−63)[b]	+	
Pecher-2002 [56]	I/II	Mucin expressing metastatic *breast,* pancreatic or papillary cancer	Advanced/ Metastatic	DC	7	48 (38−66)	+	
Dols-2003 [57]	I	Metastatic *breast cancer*; HLA-A2+	Advanced/ Metastatic	WTC-allogeneic	30	53 (31−79)	+	+
Holmberg-2003 [58]	II/III	Advanced *breast* or ovarian cancer	Mixed	CH	53	–		+
Avigan-2004 [59]	I	Metastatic *breast* or renal cancer, with tumour lesions accessible to biopsy or resection without invasive surgery	Advanced/ Metastatic	DC	10	54[d]	+	
Dees-2004 [15]	I/II	Metastatic *breast cancer* with stable disease; human leukocyte antigen (HLA-A0201+)	Advanced/ Metastatic	DC	10	48 (33−63)	+ (WHO criteria)	
Svane-2004 [60]	I	Metastatic or locally advanced *breast cancer* with progressive disease; HLA-A2+	Advanced/ Metastatic	DC	6	50 (41−65)	+ (RECIST criteria)	+
Vonderheide-2004 [61]	I	Progressive metastatic *breast cancer* resistant to conventional cytotoxic therapy or progressive hormone-independent prostate cancer; HLA-A2+	Advanced/ Metastatic	DC	2	46 (40−52)	+ (Standard response criteria)	
Lasalvia-Prisco-2006 [62]	Prospective	Advanced metastatic *breast cancer*	Advanced/ Metastatic	Multi-antigen	54	59[e] (39−78)	+ (RECIST criteria)	+
Loveland-2006 [63]	I	Advanced adenocarcinoma (fallopian tube, colon, lung, oesophagus, renal cell, *breast,* ovary); MUC1+	Advanced/ Metastatic	DC	2	42 (33−51)	+	
Morita-2006 [64]	I	Refractory solid tumours (*breast*, glioblastoma, malignant, fibrous histiocytoma, neuroectodermal tumour, rectal)	Advanced/ Metastatic	Peptide	2	47.5 (47−48)	+ (RECIST criteria)	
Ciocca-2007 [65]	I	Advanced solid tumours (renal, *breast*, melanoma, astrocytoma, oligodendroglioma, meningioma, parotid carcinoma, rhabdomyosarcoma, colon) with progressive or recurrent disease	Advanced/ Metastatic	aTL	7	73 (46−75)	+	+
Gilewski-2007 [66]	–	High risk *breast* cancer without evidence of disease	Mixed	CH	27	(28−63)		+
Mayordomo-2007 [67]	–	Advanced cancer (melanoma, *breast*, renal, malignant Schwannoma, lung) not amendable to curative therapy	Advanced/ Metastatic	DC	1	51 (35−74)[b]	+ (Standard response criteria)	+
Morse-2007 [68]	I	High-risk *breast cancer* and disease-free after surgery and adjuvant therapy; human epidermal growth factor receptor 2 (HER2)+	Advanced/ Metastatic	DC	7	47 (38−58)		+
Park-2007 [69]	I	Metastatic *breast cancer*; HER2+	Advanced/ Metastatic	DC	18	50 (31−74)[b]	+ (RECIST criteria)	+
Svane-2007 [70]	II	Progressive metastatic *breast cancer*; human leukocyte antigen (HLA)-A2+	Advanced/ Metastatic	DC	26[e]	57 (33−74)[b]	+ (Response Evaluation Criteria in Solid Tumours [RECIST] criteria)	+
Gulley-2008 [71]	Pilot	CEA- or MUC-1-expressing metastatic cancers (gastric, *breast*, colon, pancreatic, appendiceal, lung, esophageal, rectal, ovarian) with progressive disease following standard chemotherapy; HLA-A2+	Advanced/ Metastatic	Virus	2	62 (57−67)		+

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Table 2 (*continued*)

Study	Trial phase	Study cohort details	Stage	Vaccine type	No of patients	Median age (range) in yrs	Info on ORR	Info on PFS/OS
Tsuruma-2008 [72]	I	Unresectable advanced or recurrent *breast cancer*; HLA[b]2402+	Advanced/ Metastatic	Peptide	14	50.5 (34 −71)[b]	+	
Disis-2009 [73]	I/II	Metastatic *breast cancer* in complete remission or stable disease on trastuzumab with documented HER2/neu overexpression; HLA-A2+	Advanced/ Metastatic	Peptide	21	49 (33 −76)[b]		+
Kaumaya-2009 [74]	I	Metastatic and/or recurrent solid tumours (colon, squamous cell, ovarian, endometrial, *breast*, adrenal, pancreas, rectal, colon, colorectal, gastrointestinal, cervical, lung)	Advanced/ Metastatic	Peptide	5	66 (37 −74)	+ (RECIST criteria)	
Peethambaram-2009 [75]	I	Advanced adenocarcinomas of the *breast*, ovary, endometrium, or gastrointestinal tract; HER-2/neu-positive	Advanced/ Metastatic	DC	11	56 (34 −76)[b]	+	+
Norell-2010 [76]	I	Advanced/Metastatic *breast cancer*	Advanced/ Metastatic	DNA	8	60.5 (44 −67)		+
Baek-2011 [77]	I/II	Advanced renal cell carcinoma or *breast cancer*	Mixed	DC	4	51 (29 −66)	+	
Miles-2011 [78]	III	Metastatic *breast cancer*	Advanced/ Metastatic	CH (STn-KLH)	501	53		+
				CH (KLH)	521	53		+
Morse-2011 [79]	Pilot	Resected *breast cancer* without evidence of clinical disease & ovarian (epithelial ovarian, tubal or peritoneal) after cytoreductive surgery and with complete clinical response to front-line or second-line chemotherapy; HLA-A2+	Mixed	Peptide	7	53 (41 −72)		+
Hamilton-2012 [80]	I	Metastatic, trastuzumab-refractory, HER2-overexpressing *breast cancer*	Advanced/ Metastatic	Protein	12	54 (45 −65)	+	+
Qi-2012 [81]	–	Double-negative (oestrogen receptor [ER]-/progestin receptor [PR]-) *breast cancer* with stable disease	Early	DC	31	56 (36 −74)		+
Rech-2012 [82]	Prospective	Metastatic refractory *breast cancer*; HLA-A2+	Advanced/ Metastatic	Peptide	11	50 (35 −61)	+ (RECIST criteria)	+
Senzer-2012 [83]	I	Advanced or metastatic non-curable solid tumour (gall bladder, melanoma, colorectal, lung, *breast,* colon, liposarcoma, synovial sarcoma, ovarian, adenoid cystic, hepatocellular, bile duct)	Advanced/ Metastatic	WTC	2	62 (26 −84)[b]	+ (RECIST criteria)	
Vassilaros-2013 [84]	III	*Breast cancer* (ER+ and with involvement of no more than four ipsilateral nodes) and no evidence of distant disease	Early	Protein	16	58.5 (52 −78)		+
Bapsy-2014 [85]	II	Refractory solid malignancies (head and neck, colon, sarcoma, cervix, lung, colon, *breast*, *ovary*, prostate, melanoma, renal cell)	Advanced/ Metastatic	DC	2	44.5 (38 −51)	+ (RECIST criteria)	+
Chen-2014 [86]	Feasibility	Metastatic *breast cancer*; HER2+	Advanced/ Metastatic	WTC-allogeneic	20	52 (34 −69)	+ (RECIST criteria)	+
Takashashi-2014 [87]	II	Metastatic recurrent *breast cancer*	Advanced/ Metastatic	Peptide	64	57 (30 −77)[b]	+ (RECIST criteria)	+
Tiriveedhi-2014 [88]	I	*Breast cancer* with stable metastatic disease; mammaglobin-A (MAM-A+)	Advanced/ Metastatic	DNA	14	48.6 (33 −70)		+
Heery-2015 [89]	II	Metastatic breast cancer	Advanced/ Metastatic	Virus	25	55 (33 −72)	+ (RECIST criteria)	+
Sakamoto-2015 [90]	II	Heavily treated cancer with solid tumours (lung, breast, pancreas, colon, prostate, stomach, liver, kidney, bladder, uterus, ovary)	Advanced/ Metastatic	Peptide	3	55 (55 −68)	+ (RECIST criteria)	+
Antonilli-2016 [91]	I/II	High-risk, disease-free ovarian and breast cancer	Mixed	Peptide	8[f]	45[g]	+	+
Curigliano-2016 [92]	I/II	Metastatic breast cancer; HER2+	Advanced/ Metastatic	Protein	40 (17 1st line, 23 2nd line)	66 for 1st line, 56 for 2nd line	+ (RECIST criteria)	+

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Table 2 (*continued*)

Study	Trial phase	Study cohort details	Stage	Vaccine type	No of patients	Median age (range) in yrs	Info on ORR	Info on PFS/OS
Higgins-2017 [93]	I	Stage II/III breast cancer, Wilms tumour 1 (WT1)+	Mixed	Protein	35	72 (54 −84)	+ (Miller/Payne criteria)	
Kalli-2018 [94]	I	*Breast cancer* after conventional treatment and with no evidence of disease or ovarian cancer (including primary peritoneal and fallopian tube) or	Mixed	Peptide	8	48 (39 −61)		+
Zhang-2018 [95]	I/II	Advanced cancer (*breast*, ovarian, gastric)	Mixed	DC	4	50.5 (37 −57)	+ (RECIST criteria)	+
Chung-2019 [96]	I	Advanced solid tumours (*breast*, pancreatic, hepatocellular, or head and neck cancer)	Advanced/ Metastatic	Virus	7	56 (41 −70)	+ (RECIST criteria)	+
Ovarian Cancer								
Hernando-2002 [97]	I	Progressive or recurrent *ovarian carcinoma* or uterine sarcoma with no possibility of further conventional treatment	Mixed	DC	6	45 (35 −46)	+ (WHO criteria)	+
Freedman-2003 [98]	Pilot	Abdominal cancers; specifically, Müllerian carcinoma (*epithelial ovarian or peritoneal carcinoma*), gastrointestinal cancers, or abdominal mesothelioma	Advanced/ Metastatic	Protein	8	55 (40 −68)[b]	+	
Tsuda-2004 [99]	–	Recurrent gynecologic cancer (cervical, *ovarian*, endometrial, uterine); HLA-A2+ or HLA-A24+	Mixed	Peptide	5	57 (49 −68)	+ (RECIST criteria)	+
Loveland-2006 [63]	I	Advanced adenocarcinoma (*fallopian tube*, colon, lung, oesophagus, renal cell, breast, *ovary*); MUC1+.	Advanced/ Metastatic	DC	2	61 (58 −64)	+	
Chianese-Bullock-2008 [100]	I	*Epithelial ovarian, fallopian tube, or primary peritoneal carcinoma*; HLA-A1+, HLA-A2+, or HLA-A3+	Advanced/ Metastatic	Peptide	2[h]	54 (38 −79)[b]	+	
Diefenbach-2008 [101]	I	High-risk *epithelial ovarian cancer* after first clinical remission; HLA-A[b]0201+	Advanced/ Metastatic	Peptide	9	54 (37 −66)		+
Gulley-2008 [71]	Pilot	carcinoembryonic antigen (CEA)- or MUC-1-expressing metastatic cancers (gastric, breast, colon, pancreatic, appendiceal, lung, oesophageal, rectal, *ovarian*) with progressive disease following standard chemotherapy; HLA-A2+	Advanced/ Metastatic	Virus	3	53 (42 −57)		+
Kaumaya-2009 [74]	I	Metastatic and/or recurrent solid tumours (colon, squamous cell, *ovarian*, endometrial, breast, adrenal, pancreas, rectal, colon, colorectal, gastrointestinal, cervical, lung).	Advanced/ Metastatic	Peptide	5	67 (65 −74)	+ (RECIST criteria)	
Peethambaram-2009 [75]	I	Advanced adenocarcinomas of the breast, *ovary*, endometrium, or gastrointestinal tract; HER-2/neu-positive	Advanced/ Metastatic	DC	4	56 (34 −76)[b]	+	+
Galanis-2010 [102]	I	Persistent, recurrent or progressive *ovarian cancer or primary peritoneal cancer* after prior treatment with platinum and Taxol compounds	Advanced/ Metastatic	Virus	21	57 (43 −82)	+ (RECIST criteria)	+
Morse-2011 [79]	Pilot	Ovarian (*epithelial ovarian, tubal or peritoneal*) after cytoreductive surgery and with complete clinical response to front-line or second-line chemotherapy & resected breast cancer without evidence of clinical disease; HLA-A2+	Mixed	Peptide	8	54 (43 −66)		+
Chu-2012 [12]	I/II	Advanced *epithelial ovarian or primary peritoneal cancer* in remission; HLA-A2+	Mixed	DC	11	51 (18 −62)		+
Le-2012 [103]	I	Treatment-refractory mesothelin-expressing cancers (pancreatic, colorectal, melanoma, mesothelioma, *ovarian*, lung)	Advanced/ Metastatic	LMS	2	58 (52 −64)	+ (RECIST criteria)	+
Leffers-2012 [104]	II	*Epithelial ovarian cancer*, any HLA type	Mixed	Peptide	15[i]	50.5 (43 −69)[b]	+ (RECIST criteria)	
Odunsi-2012 [105]	II	Advanced *epithelial ovarian cancer* at high risk for recurrence/progression	Advanced/ Metastatic	Virus	22			+
Rahma-2012 [106]	II	Stage III, IV, or recurrent *ovarian cancer* over-expressing the p53 protein with no evidence of disease	Advanced/ Metastatic	Peptide	20	56 (39 −71)		+

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Table 2 (*continued*)

Study	Trial phase	Study cohort details	Stage	Vaccine type	No of patients	Median age (range) in yrs	Info on ORR	Info on PFS/OS
Senzer-2012 [107]	I	Advanced or metastatic non-curable solid tumour (gall bladder, melanoma, colorectal, lung, breast, colon, liposarcoma, synovial sarcoma, ovarian, adenoid cystic, hepatocellular, bile duct)	Advanced/ Metastatic	WTC	5	62 (26 −48)[b]	+ (RECIST criteria)	
Vermeij-2012 [14]	II	*Epithelial ovarian cancer* with evidence of recurrent disease after prior cytoreductive surgery and chemotherapy	Advanced/ Metastatic	Peptide	9[j]	60 (46 −73)	+ (RECIST criteria)	
Chiang-2013 [108]	Pilot	Recurrent *ovarian cancer* after prior cytoreductive surgery and chemotherapy	Mixed	DC	5	49 (46 −63)	+ (RECIST criteria)	
Kandalaft-2013 [109]	Pilot	Recurrent *ovarian cancer* after prior cytoreductive surgery	Advanced/ Metastatic	DC	6	57 (48 −69)	+ (RECIST criteria)	
Bapsy-2014 [85]	II	Refractory solid malignancies (head and neck, colon, sarcoma, cervix, lung, colon, breast, *ovary*, prostate, melanoma, renal cell)	Advanced/ Metastatic	DC	7	54 (31 −66)	+ (RECIST criteria)	+
Kawano-2014 [110]	II	Recurrent *ovarian, fallopian tubal or primary peritoneal cancer*; positive status for HLA-A2, -A3, -A11, -A24, -A26, -A31, or -A33	Advanced/ Metastatic	Peptide	42[k]	57.5 (22 −80)	+ (RECIST criteria)	+
Kobayashi-2014 [111]	Retrospective	Recurrent *ovarian cancer*, any HLA type	Advanced/ Metastatic	DC	56	55 (23 −70)	+ (RECIST criteria)	+
Odunsi-2014 [112]	I	Relapsed *epithelial ovarian cancer (including fallopian tube and primary peritoneal cancer)*	Advanced/ Metastatic	Protein	12	59	+ (irRECIST criteria)	
Baek-2015 [113]	I/II	Primary or recurrent *ovarian cancer*	Mixed	DC	10[l]	44 (37 −60)	+	+
Dijkgraaf-2015 [114]	I/II	Platinum-resistant *ovarian cancer* with confirmed mutant p53-expression pattern	Advanced/ Metastatic	Peptide	6	58 (57 −69)	+ (RECIST criteria)	+
Sakamoto-2015 [90]	II	Heavily treated cancer with solid tumours (lung, breast, pancreas, colon, prostate, stomach, liver, kidney, bladder, uterus, *ovary*).	Advanced/ Metastatic	Peptide	1	65	+ (RECIST criteria)	+
Antonilli-2016 [91]	I/II	High-risk, disease-free *ovarian* and breast cancer	Mixed	Peptide	10[m]	53[n]	+	+
Hardwick-2018 [115]	I	Recurrent *epithelial ovarian, peritoneal or fallopian tube* cancer with tumoural p53 overexpression	Advanced/ Metastatic	Virus	11	59 (41 −76)	+ (irRECIST criteria)	
Kalli-2018 [94]	I	*Ovarian cancer (including primary peritoneal and fallopian tube)* or breast cancer after conventional treatment and with no evidence of disease	Mixed	Peptide	14	57 (35 −68)		+
Zhang-2018 [95]	I/II	Advanced cancer (breast, *ovarian*, gastric)	Advanced/ Metastatic	DC	3	50 (39 −59)	+ (RECIST criteria)	+
O'Cearbhail-2019 [116]	II	*Epithelial ovarian, fallopian tube, or peritoneal cancer* in second or third complete remission	Mixed	CH	86	range:40-89		+

Note 1: Grey highlight indicates studies with both breast and ovarian cancer patients. These studies are mentioned twice in this table.
Note 2: In case that information on response criterion for ORR is available, presented in parentheses.
aTL: Autologous tumour lysate, CEA: Carcinoembryonic antigen, CH: Carbohydrate, DC: Dendritic cell, ER: oestrogen receptor, HLA: Human leukocyte antigen, HER2: Human epidermal growth factor receptor 2, MAM-A: Mammaglobin-A, MUC1: Mucin 1, PR: Progestin receptor, WTC: Whole tumour cell, WT1: Wilms tumour 1.

[a] There were also 18 patients of stage I-II with no measurable disease.
[b] Information for age is provided for a wider cohort of patients than the subgroup used for the meta-analysis.
[c] There were also 15 patients with no evidence of disease (NED).
[d] Mean age is available.
[e] Only 19 patients with available info for ORR.
[f] Seven patients with NED and info available only for OS; one patient (PD before vaccine) with available info for ORR.
[g] Median age for seven NED patients; for one patient with PD before vaccination age = 40 years.
[h] There were also seven patients with NED.
[i] There were also five patients with NED.
[j] There was also one patient with NED.
[k] Only 25 patients with available info for ORR.
[l] Seven patients with NED and three patients with disease (info for ORR is available only for the three patients with disease while OS/PFS for all ten patients).
[m] Seven patients with NED and info available only for OS; three patients (PD or SD before vaccine) with available info for ORR.
[n] Median age for the seven NED patients, for the three patients with SD or PD before vaccine median age = 60 years.

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Most of the studies (51; 76.1% of the 67) are phase I or II and the year of publication ranges from 2000 for BC or 2002 for OC, up to 2019 (Table 2). Only 8 trials were randomised, with vaccination in one or both arms.

Among the 67 eligible studies, only information distinctly provided for BC/OC patients was retained, i.e., efficacy or toxicity information for other types of cancers or patients treated with other therapies without vaccines, were excluded.

More details on the treatments administered, i.e., vaccine type and other treatments given in combination, are summarised in Table S4.

Quality assessment for the included studies according to Cochrane's and ROBINS-I tool is presented in Table S5, while publication bias is evaluated through funnel plots separately for BC/OC studies (Fig. S1,a-b). Due to inclusion of 10 BC, 5 OC trials with no OR observed, the Egger's test is significant. Apparent publication bias shows that trials with high ORR are missing from the literature, i.e., positive ones (instead of negative ones with low ORR, the usual target of such an investigation).

3.2. Cohorts

A total of 1698 BC patients, receiving vaccine treatment, are gathered from the 46 BC studies. Almost all BC patients are metastatic and pre-treated. The 32 OC studies include 426 OC patients having received vaccine treatment.

Of note, in 12 (26.1%) BC and 11 (34.4%) OC studies, the number of participating BC/OC patients is only up to five and these studies are only included in a sensitivity analysis, presented in the supplement.

Most BC studies included DC vaccine, administered in 144 (8.5%) patients (16 studies) followed by peptide vaccines in 143 (8.4%) patients (10 studies).The cohort on carbohydrate (CH) vaccine was the largest with 1114 (65.6%) patients in four studies, but ORR is not provided in them. In addition, 103 (6.1%) and 43 (2.5%) patients received, protein and virus vaccines, respectively, delivered in four studies each. Fifty-two (3.1%) patients (3 studies) received WTC vaccines, while multi-antigen vaccines and DNA vaccines were given in 70 (4.1%) and 22 (1.3%) patients respectively (2 studies each). Autologous tumour lysate (aTL) vaccine was administered only in one study with 7 (0.4%) BC patients.

In the case of OC patients, the most frequent vaccines administered were peptide vaccines in 146 (34.3%) OC patients (13 studies) and DC vaccines in 110 (25.8%) patients (10 studies). Virus vaccines were administered in 57 (13.4%) patients (4 studies) and protein vaccines in 20 (4.7%) patients (2 studies). WTC vaccines, carbohydrate vaccines and *L. monocytogenes* strain vaccines were given in only one (3.1%) study each − three in total with 93 (21.8%) patients.

More details for the type of treatments, including vaccine preparation and administration, are available in Table S1. In most of the studies treatment with vaccine only was administered, in 31 (67.4%) for BC and 21 (65.6%) for OC.

3.3. Objective response rate

Information on tumour response was available in 33 BC studies (71.7% of 46 total) and 24 OC studies (75.0% of 32 total), corresponding to 459 (27.0%) BC and 222 (52.1%) OC patients, respectively.

The designated as primary analysis for ORR in BC patients is based on the 21 from the 33 studies with BC sample size above five patients, including 428 patients with residual disease at enrollment. The pooled ORR in this cohort, based on 48 (11.2%) observed objective responses, was estimated as 9% (95%CI [5%, 13%]; REM, Cochran's Q $P < 0.001, I^2 = 73.1\%$, Fig. 2a). Of note, no OR was observed in 10 studies (176 patients in total), while ORR reached 63% (95%CI [45%, 79%]), in Higgings-2017 (35 BC patients).

In the OC case, primary ORR analysis was analogously based on 12 studies with 182 OC patients, and ten (5.5%) recorded responses. The pooled ORR estimate was 4% (95%CI[1%, 7%]; FEM, $P = 0.85, I^2 = 0.0\%$, Fig. 2b). No response was found in five studies (59 patients), while 33% was the highest observed ORR in two different studies (Kandalaft-2013; Dijkraaf-2015) with only six OC patients each.

Results of sensitivity analyses, including all studies irrespective of their sample size, are consistent with the above estimates of the primary analysis. For the BC, the pooled ORR estimate was 10% (95%CI [6%, 13%]; REM, $P < 0.001, I^2 = 63.0\%$, Fig. S2a), while for the OC5% (95%CI [2%, 8%]; FEM, $P = 0.99, I^2 = 0.0\%$, Fig. S2b).

3.4. Subgroup analysis by vaccine type

For the BC patients, the ORR estimate in 'DC vaccine' trials (7 trials, 81 patients) was only 5% (95%CI [1%, 10%], FEM; $P = 0.75$; $I^2 = 0.0\%$), while it was 8% (95% CI [2%, 13%], FEM; $P = 0.18, I^2 = 41.2\%$) in 'Peptide vaccine' trials (3 trials, 89 patients), and it reached 11% (95%CI [4%, 17%], REM; $P < 0.001, I^2 = 84.6\%$) in trials of other vaccine types (11 trials, 258 patients) (Fig. 3a). Observed differences were not significant (interaction $P = 0.80$).

In the case of OC, pooled ORR estimates among different vaccine types were very similar, with 5% (95% CI [0%, 9%], FEM; $P = 0.39, I^2 = 0.2\%$) in 'DC vaccines' (4 trials, 75 patients), 4% (95%CI [0%, 10%], FEM; $P = 0.50, I^2 = 0.0\%$) in 'Peptide vaccines' (4 trials, 55 patients), and 4% (95%CI [0%, 9%], FEM; $P = 0.81, I^2 = 0.0\%$) in trials of other vaccine types (4 trials, 52 patients) (Fig. 3b, interaction $P = 0.98$).

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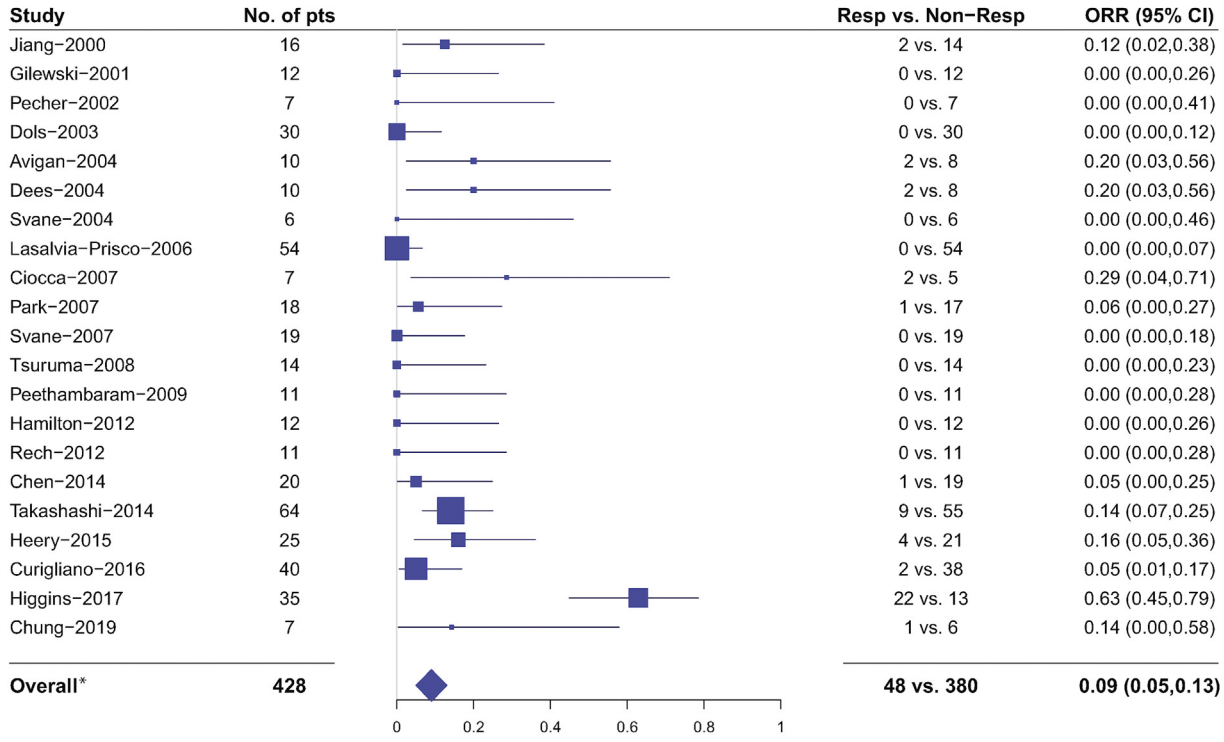
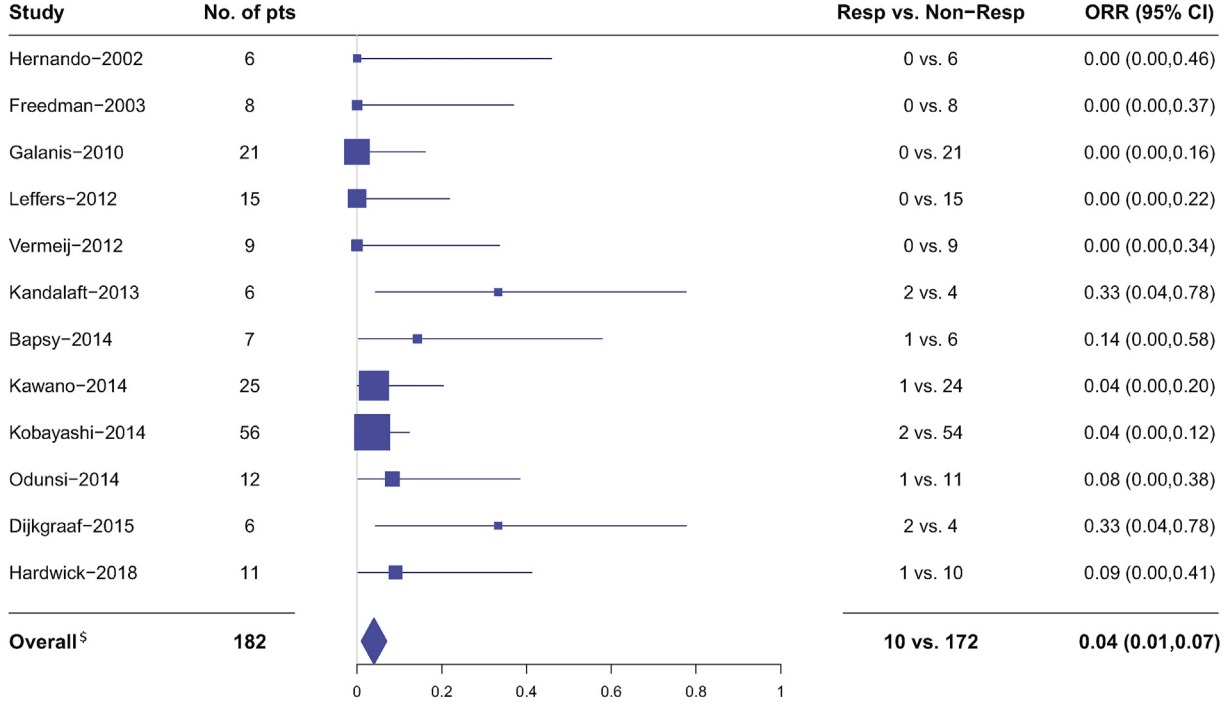
a



* Estimates of ORR (95% CI) based on random effects model
Cohran's Q: p<0.001
I^2=73.1%

b



$ Estimates of ORR (95% CI) based on fixed effect model
Cohran's Q: p=0.85
I^2=0.0%

Fig. 2. a: Forest plot for ORR; breast cancer (studies with N > 5). b: Forest plot for ORR; ovarian cancer (studies with N > 5).

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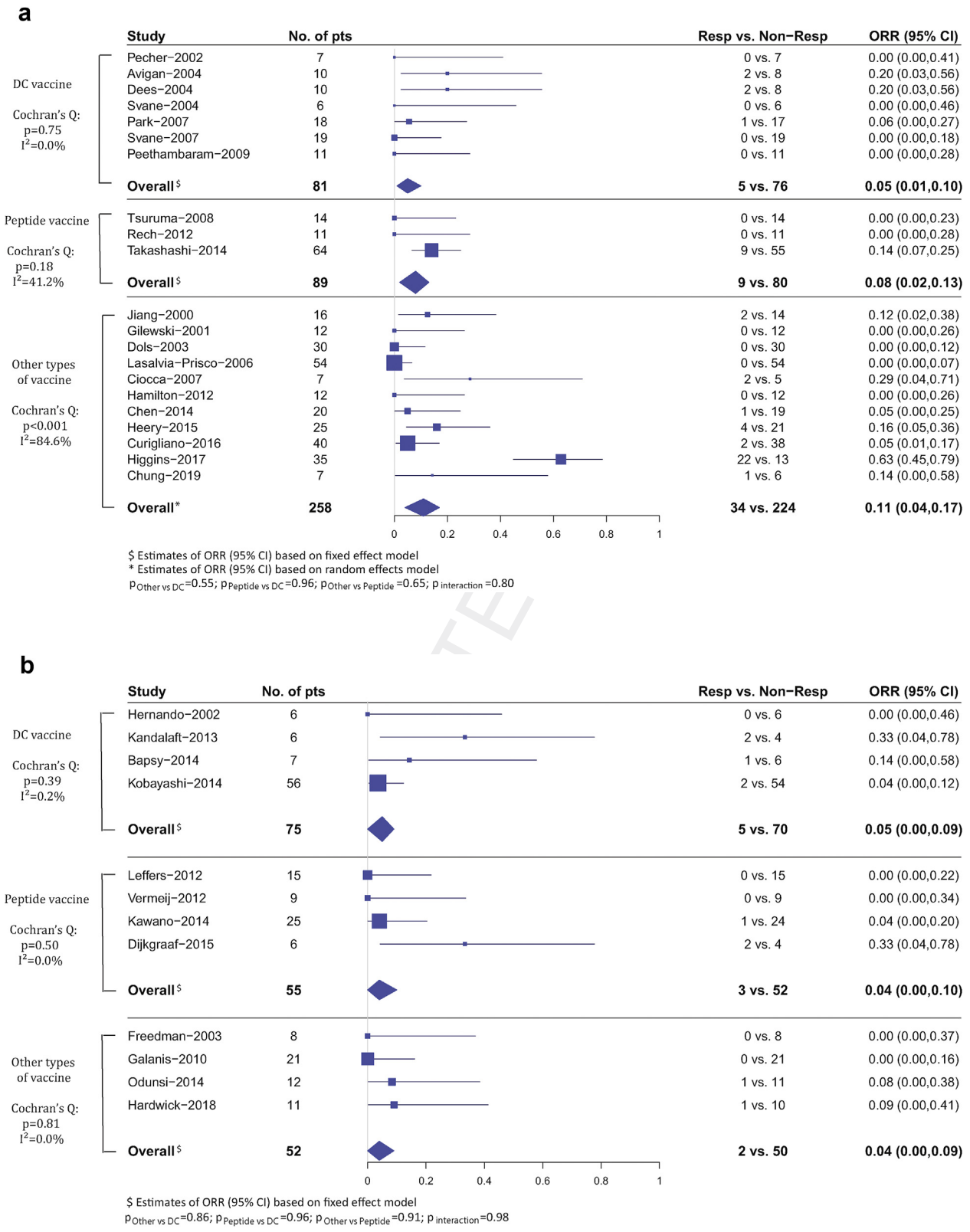

Fig. 3. a: Forest plot for ORR, by vaccine type; breast cancer (studies with N > 5). b: Forest plot for ORR, by vaccine type; ovarian cancer (studies with N > 5).

Differentiation in ORR estimates according to the therapy schema (only vaccine or in combination with other treatments) are summarised in Fig. 4,a-b. For the BC patients, the use of vaccine alone (8 trials, 130 patients) leads to an ORR of 4% (95%CI [1%, 7%], FEM; $P = 0.53, I^2 = 0.0\%$), while when used in combination

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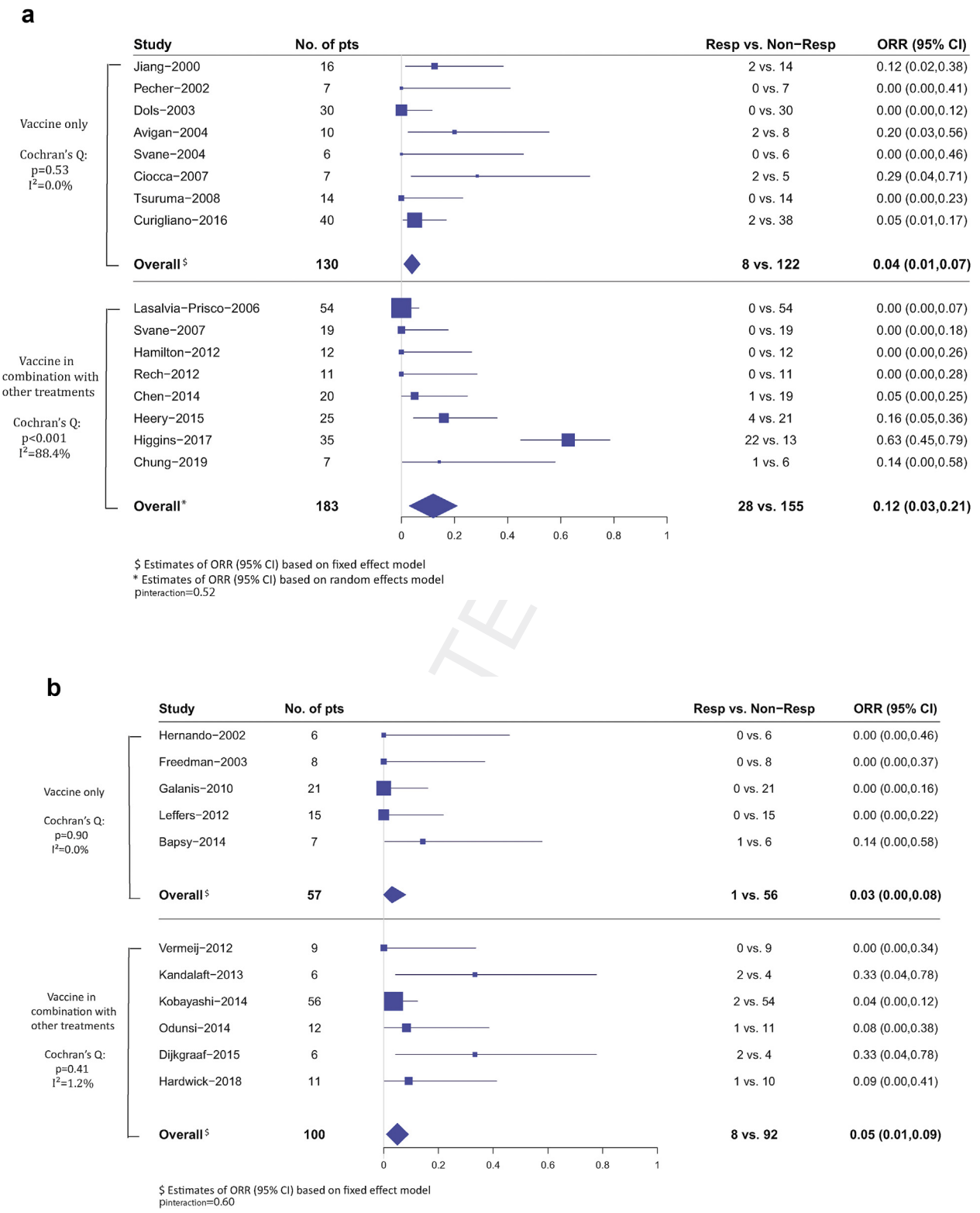

Fig. 4. a: Forest plot for ORR, by treatment; breast cancer (studies with N > 5). b: Forest plot for ORR, by treatment; ovarian cancer (studies with N > 5).

with other treatments (8 trials, 183 patients), ORR is estimated to be 12% (95%CI [3%, 21%], REM; $P < 0.001, I^2 = 88.4\%$) (of note the observed difference in benefit is not statistically significant, interaction $P = 0.52$). Analogously, in the OC case, with vaccine alone administered in 5 trials with 57 patients and in combination in six trials with 100 patients, the ORR with vaccine alone is 3% (95%CI [0%, 8%], FEM;

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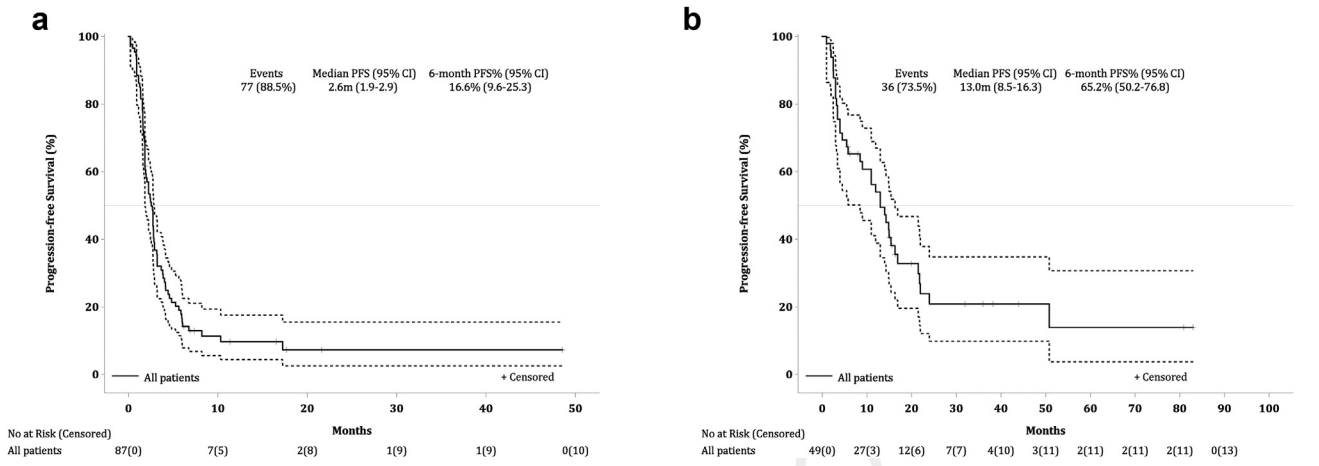

Fig. 5. **a:** Progression-free survival curve and 95% confidence band for breast cancer (studies with N > 5)**. b:** Progression-free survival curve and 95% confidence band for ovarian cancer (studies with N > 5).

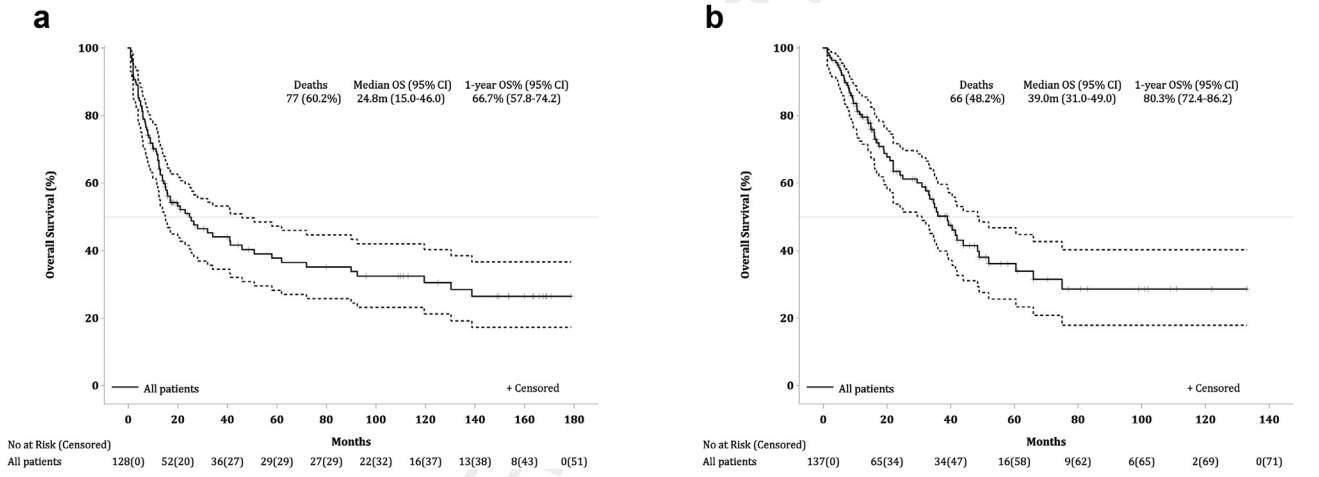

Fig. 6. **a:** Overall survival curve and 95% confidence band for breast cancer (studies with N > 5)**. b:** Overall survival curve and 95% confidence band for ovarian cancer (studies with N > 5).

$P = 0.90, I^2 = 0.0\%$), versus 5% (95%CI [1%, 9%], FEM; $P = 0.41, I^2 = 1.2\%$) in case of combination of vaccine with other treatments (interaction $P = 0.60$, non-significant).

3.5. Progression-free survival

Median PFS for BC patients (based on 87 patients in six studies with available patient-level data and sample size >5) is estimated to be 2.6 months (95%CI [1.9, 2.9]), 77 (88.5%) PFS events were observed overall, while the 6-month PFS rate is 16.6% (95%CI [9.6, 25.3]) (Fig. 5a).

All available information on PFS by study is summarised in Table S6a. For the majority of studies, the median PFS ranges from 2 to 5 months, with an extreme median observed at 17.7 months (Disis-2009).

In the OC setting, a median PFS value of 13.0 months (95%CI [8.5, 16.3]) is estimated, with a total of 36 (73.5%) PFS events and 6-month PFS rate 65.2% (95% CI [50.2, 76.8]) (based on 49 patients in five studies with available patient-level data and sample size >5) (Fig. 5b). All the information for PFS derived by each study is presented in Table S6b. In most of the cases, the 6-month PFS rate is over 50%, while wide range is observed with respect to the median PFS (3−22 months).

In PFS sensitivity analysis, including all studies irrespective of their sample size, with available patient level data, results presented in Fig. S3,a-b, are in line with the primary analysis results.

3.6. Overall survival

Median OS for BC patients (based on 128 patients in 10 studies with available patient-level data and sample size >5) is estimated to be 24.8 months (95%CI [15.0, 46.0]), with 77 (60.2%) deaths observed overall, and a 12-

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month OS rate of 66.7% (95%CI [57.8, 74.2]) (Fig. 6a).OS available results by study are summarised in Table S7a, with median OS between 12 and 28 months for most of the studies.

In the OC setting, a median OS value of 39.0 months (95%CI [31.0, 49.0]), with a total of 66 (48.2%) deaths and 12-month OS rate of 80.3% (95%CI [72.4, 86.2]) are derived (based on 137 patients in eight studies with available patient-level data and sample size >5) (Fig. 6b). All available information on OS by study is summarised in Table S7b.The majority of studies display a median OS of over 2 years.

In the corresponding sensitivity analysis on OS, of all studies irrespective of their sample size, with available patient level data, results presented in Fig. S4,a-b, are in line with the primary analysis results.

3.7. Toxicity

Available information on toxicity is presented in Table S8,a-c for BC and Table S9,a-c for OC, respectively. The majority of reported adverse events (AEs) are only of Grade 1−2 (BC: 90% of any-cause AE and 92% among treatment-related; OC: 87% of any-cause AE and 81% of treatment-related). Injection site reaction of grade 1−2 is the most common AE experience by approximately half of the patients (55% of BC and 49% of OC patients), with fatigue, grade 1−2, also commonly experienced (23% BC, 15% OC). No fatal adverse events have been observed.

4. Discussion

In this study, we aimed to evaluate vaccination efficacy in two cancer types affecting women, BC (a heterogeneous disease, including non-immunogenic and immunogenic subtypes) and OC (considered as immunogenic), by compiling the results of different trials performed in a 20-year period (2000−2019). During this period, 141 studies were identified, and amongst them, 64 were not further analysed because no efficacy results were provided. Out of the 67 studies included in this meta-analysis, estimated ORR was 9% in BC and 4% in OC. These results are not very high, although higher than the ORR of 2.6% observed in the meta-analysis performed at the National Cancer Institute (NCI) under the US National Institutes of Health in 2004 [3]. Due to the high heterogeneity of patients treated in these studies, comparative analyses with standard treatments are not possible, a limitation of this meta-analysis.

Results were not found to be statistically different when comparing various types of vaccines: ORR in studies using DC vaccines is similar to the ORR using peptide vaccines or other types of vaccines, both in BC and in OC. Similarly, the use of vaccines alone or in combination with other treatments does not result in a significant change in ORR outcomes, either in BC or in OC, reflecting their use in later lines. However, it is interesting to note that some specific studies show higher ORR values than most other studies, both in BC and in OC, suggesting that some approaches may be more effective than others.

In general, however, ORR results show that there is still a large room for improvement, which should be guided by new developments in our understanding of tumour biology. For example, we now consider that neo-antigens are likely effective targets for T-cells and contribute to successful immunotherapy, although it is not currently clear whether TAAs/tumor cell lysates are better than neoantigens [4]. Significant efforts are therefore being made around the world to develop a tumour-specific antigen strategy that is unique to each individual, and developments in this area have shown interesting results [37,38]. Sequencing, immune peptidomic research, peptide production and the GMP production of neoantigen vaccines are, however, a long and costly drawback, although technological advances may result in lower costs.

The synergistic effect with inhibitors of the immune checkpoints (ICI), which already have a well-established profile in many tumour types, is another potential route to improving vaccine efficacy [39]. Yet, while Treg cells express most of the immune checkpoint molecules, the effect of ICI on these cells is still unclear [9]. Thus, it is noteworthy that the immunosuppressive role of Treg cells may be enhanced by ICIs targeting programmed cell death-1 (PD-1), whereas ICIs targeting the cytotoxic T-lymphocyte-antigen 4(CTLA-4) inhibitors may deplete these cells [9]. Interestingly, many Treg cell-targeting therapies are being tested, but most of these therapies have limited clinical efficacy due to the difficulty of selectively targeting Treg cells. Therefore, while Treg cell manipulation is a promising anticancer therapeutic strategy, further research is needed to control these cells.

Similarly, other potential combinations should be considered, such as vaccination and anti-angiogenic therapy (e.g. bevacizumab) [39], although initial clinical trials have failed to demonstrate clinical efficacy. Therefore, a better understanding and assessment of the immunological reshaping caused by anti-angiogenic therapy and the immunological stage is needed in the context of standard treatment for patients already on anti-angiogenic drugs, before considering combination with vaccination.

In recent years, poly-ADP ribose polymerase (PARP) inhibitors have become a new therapeutic option for OC patients [40]. Initially, this therapy was shown to improve PFS in women with platinum-resistant OC [41], although recently some beneficial effects on OS have been demonstrated [42], suggesting

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that further studies are needed to develop the potential of these drugs [43].

In this regard, it has been observed in other indications that in late-stage cancer showing compromised tumour microenvironment by inhibitory mechanisms, therapeutic vaccination functions favorably as monotherapy in pre-malignant disease but needs co-treatment in late-stage disease, for the reasons stated. Examples of this include: (1) co-treatment of peptide vaccination with SOC chemotherapy (carboplatin and paclitaxel) for late-stage cervical cancer [44] (mediated by chemotherapy depletion of immunosuppressive myeloid cells) and (2) co-treatment of peptide vaccination with anti-PD-1 for HPV16+ oropharyngeal cancer [45] (mediated by T cell release from immune checkpoint blockade in tumour micro-environment [TME]). Thus, similar approaches may also prove useful in BC and OC. Finally, we believe that currently available vaccine strategies targeting or utilising dendritic cells to present antitumour antigens may be incorporated into established clinical practice utilising prime − boost methods, although there are still significant obstacles [46].

Moreover, while DCs are the most common therapy for cell vaccination in cancer patients because of their essential role in initiating and maintaining immune responses, the limited therapeutic efficacy of the DC-vaccines should be considered. In this regard, B cells and macrophages provide additional immunotherapy opportunities that can be explored [47].

In the current meta-analysis, despite the low response rates obtained with therapeutic vaccines in BC and OC patients, the results achieved in both PFS and mostly OS are noteworthy with a median PFS of 2.6 and an OS of 24.8 months in BC patients and of 13 months and 39 months in OC patients, respectively. Although heterogeneity of patients included in these trials precludes formal analyses, most patients were late stage patients, heavily pretreated, and therefore such survival data as shown in this meta-analysis bring hope for the future application and potential of vaccines interventions. In addition, our analysis confirms the low toxicity induced by vaccination, which promotes an interest in maintaining efforts to improve the efficacy of this type of immunotherapy.

5. Conclusions

Despite their modest results in terms of ORR observed in clinical trials performed in the last 20 years, patients included in those trials have experienced relatively long survival rates, which is a noteworthy result in late stage patients for both BC and OC. Although a plethora of different approaches have been tested, it is clear that a better understanding of the underlying mechanisms is needed in order to further improve their efficacy. Indeed, new approaches and increased efforts are required to find treatments that address the needs of patients in these indications, probably using treatment combinations.

Funding

This study was supported by the Ovacure Foundation and institutional support, the Ludwig Institute for Cancer Research, and institutional funding of the University of Lausanne and the CHUV (no grant numbers apply).

Conflict of interest statement

UD has served as advisor/consultant for Roche.

GC has received grants, research support and/or is coinvestigator in clinical trials by BMS, Celgene, Boehringer Ingelheim, Roche, Iovance and Kite; has received honoraria for consultations or presentations by Roche, Genentech, BMS, AstraZeneca, Sanofi-Aventis, Nextcure and GeneosTx; has patents in the domain of antibodies and vaccines targeting the tumour vasculature as well as technologies related to T-cell expansion and engineering for T-cell therapy; and receives royalties from the University of Pennsylvania related to T-cell therapy.

KZ has provided consulting or participation in advisory boards of: AstraZeneca, Daiichi, Genomic Health (Exact Science), Lilly, MSD, Mylan, Novartis, Pfizer, Roche; has received travel funding by AstraZeneca, Pfizer, Roche, Pierre Fabre; has unrestricted funding for organisation of scientific events by AstraZeneca, Daiichi, Eisai, Exact Science, Lilly, MSD, Mylan, Novartis, Pfizer, Roche, Synlab; has research funding by Roche.

AS has served as advisor/consultant for Roche, AstraZenca, Tesaro-GSK, Celgene-BMS; has received travel/educational/research grants by Roche, AstraZenca-MSD, GSK, Celgene, Agen, BMS, Pfizer, Clovis, Novartis.

LK has received grants in clinical trials by BMS, BTG and Nestle.; has received honoraria for consultations GeneosTx.

All remaining authors have declared no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.10.014.

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Please cite this article as: Dafni U et al., Efficacy of cancer vaccines in selected gynaecological breast and ovarian cancers: A 20-year systematic review and meta-analysis, European Journal of Cancer, https://doi.org/10.1016/j.ejca.2020.10.014

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Please cite this article as: Dafni U et al., Efficacy of cancer vaccines in selected gynaecological breast and ovarian cancers: A 20-year systematic review and meta-analysis, European Journal of Cancer, https://doi.org/10.1016/j.ejca.2020.10.014