INTRODUCTION

Cell-based cancer immunotherapy represents a promising option for patients lacking treatment alternatives. It comprises the use of the immune system to destroy the tumour, ideally establishing an immunological memory response against the tumour. A very efficient method of attacking the tumour is to use effector cells, such as NK or T cells, either preselected in the tumour (tumour infiltrating lymphocytes, TILs) or with enhanced functions, such as tumour targeting through genetic manipulation.1-6

In the latter, targeting of cells is achieved by overexpression of an antigen receptor, either a natural T cell Receptor (TCR), or an artificial Chimeric Antigen Receptor (CAR). These receptors will guide the effector cell to its target and trigger cytotoxic activity of the lymphocytes. This approach has proven very successful in liquid tumours; however, advanced solid tumours are more challenging to treat. It is becoming obvious that the two main pitfalls in solid tumour CAR development are the identification of cancer-restricted targets and the negative influence of the tumour microenvironment (TME).

Ovarian cancer (OC) is one of the most lethal gynaecologic malignancies. Most OCs are epithelial ovarian carcinomas, with the most common of these being the serous type, which includes low and high-grade tumours. Women are usually diagnosed only at the advanced stage of the disease. Standard treatment comprise debulking surgery with the aim to remove all macroscopic tumour, preferably upfront, or after neoadjuvant chemotherapy. Surgery is followed by adjuvant chemotherapy and maintenance treatment in selected cases. However, even with a good initial response, the...
majority of patients will relapse or eventually develop chemotherapy-refractory disease. Therefore, alternative therapeutic approaches are needed.7

CAR is a generic name which defines an artificial molecule able to bind a target antigen on the extracellular space and transmit a signal inside the expressing cell. As shown in Figure 1, CARs are usually composed of conserved elements: an antigen-binding part which is often the single-chain fragment of an antibody, but may also be the extracellular part of a defined receptor (see later for NKG2D), a linker domain composed of a hinge separating the receptor part from the cytoplasmic membrane, and a transmembrane domain. The intracellular part is usually composed of the signalling domains of immune receptors. Since most of the CARs are expressed in T cells, the TCR signalling components have been favoured, but alternative designs such as NK receptor signalling components are in development.8 Upon binding to its target, CAR molecule clustering will trigger intracellular stimulation, leading to cellular changes that induce T cell cytotoxicity and cytokine release. To date, four generations of CARs have usually been used, although more complex molecular arrangements are emerging.9 The first-generation CAR utilized only the CD3ζ signalling domain. This conformation, although efficient in vitro, was shown not to provide a sustained response in vivo or in the clinic. Second- and third-generation CARs were created by the addition of signalling domains from proteins involved in the so-called ‘signal II’ or co-stimulation. Inclusion of these additional domains induced full activation, which resolved the problem of therapeutic duration. Enhanced CARs have recently been presented where additional molecules, such as cytokines or antibodies, were released from the CAR-expressing cells. These have been extensively reviewed by Rafiq and colleagues.10

**FIGURE 1** Overview of the different OC-CAR designed. At the centre, a prototype CAR construct is depicted with the different parts compositing it. The antigen-binding domain is mainly made of an scFv molecule, but it can be part of a receptor or a peptide. Around are the different designs and combination with the variety of fourth-generation CARs improving the TME-resistance or the general safety.
Over the last decade, great efforts have been made to develop CARs targeting OC, and comprehensive descriptions of promising CAR candidates have recently been published. However, the focus of these reviews was restricted to only a few targets, ‘the usual suspects’. This review aims to provide an overview of most of the CAR targets so far proposed to fight OC and highlights the efforts to find innovative solutions. As we will discuss, many different strategies have been tested leading to some clinical hope. The paths followed, sometimes unsuccessfully, might yet be useful to treat other types of solid tumour. Another hallmark of OC is its strong immunoinhibitory status. Here we will present some of the specific targets that may be aberrantly expressed on OC cells, and which have been used to direct CAR T cells to the tumour. Finally, we will describe the challenges relating to the particular TME of OC, and how CAR-expressing cells have been improved to reach the tumour site and more efficiently exert their effector functions.

2 | THE USUAL SUSPECTS

**MUC16** belongs to the mucin family and is a highly glycosylated protein composed of two main parts: a large and cleavable domain (CA125), and a short and retained domain (MUC16ecto). As a mucin, MUC16 is known to play a role in cellular homeostasis and the protection of epithelial surfaces. However, its interaction with mesothelin can play a role in OC metastasis. CA125 is an established serum marker for OC diagnostics, a high CA125 serum level correlating with a poor prognosis. Based on the assumption that CA125 should barely be present on the cell surface, and that circulating CA125 could potentially inhibit a CAR targeted against this portion of the full-length protein, Chekmasova and colleagues generated a CAR targeting the MUC16ecto using the murine hybridoma 4H11. A second-generation 4H11-CD28/CD3ζ CAR demonstrated efficient cytotoxicity in vitro, either against OC cell lines that overexpressed MUC16ecto, or against primary cancer cells in ascites from OC patients. In vivo studies in SCID-Beige mice using a modified MUC16ecto + target cell line showed that CAR T cell treatment was able to significantly reduce peritoneal tumours and enhance survival. However, the effect was transient, probably as a consequence of low CAR T cell persistence in the strongly immunosuppressive TME, and several days after T cell injection, a relapse was observed in 75% of treated mice. As discussed below, these results could be improved by expressing this CAR together with cytokines. It is important to note that these experiments were performed using cell lines that overexpressed MUC16ecto, which raises the question of whether this target is expressed at sufficient levels on primary OC cells and is accessible to the 4H11-based CAR. Importantly, efficient targeting of MUC16ecto was recently shown using a Bi-specific T cell engager (BiTe) named REGN4018, suggesting that the target is valid. As expected, and in contrast to anti-CA125 antibodies, REGN4018 was not sensitive to circulating CA125. However, it has also been reported that anti-CA125 antibody had a therapeutic effect against OC (NCT01335958). Moreover, Aithal et al recently described that after cleavage of MUC16 in OC cell lines such as OVCAR3, the CA125 subunit remained non-covalently bound to MUC16ecto. This was supported by co-immunoprecipitation experiments. The studies with the 4H11 CAR did not compare any CA125-targeting constructs, yet it was speculated that targeting of MUC16ecto should be more efficient than targeting CA125. An argument against this can be found in the historical design of the anti-CD22 CAR, with the location of the epitope evidently having a direct impact on efficiency. If CA125 associates with MUC16ecto, the 4H11 epitope might be buried, explaining the need to overexpress the target in the in vivo experiments. Finally, the assumption that circulating CA125 would impact a CA125-based CAR construct needs to be tested: it was recently demonstrated that a CAR target should be presented as a dimer to lead to CAR clustering and signalling. Therefore, CA125 continues to be an interesting target for alternate CAR designs.

**Mesothelin** is a glycoprotein found at low expression levels on normal tissue and overexpressed in different tumour tissues such as mesothelioma cells and epithelial ovarian cancer cells, as well as stomach, lung and pancreatic tumours. Mesothelin plays an important role in metastasis of OC by binding to CA125. Its overexpression can be related to chemotherapy and poor survival in OC. It is expressed in 82% of serous epithelial OCs, making mesothelin an attractive target. Importantly, antibody-based therapies have already shown promising results. In addition, mesothelin as a target has the highest number of clinical trials, completed or ongoing, for CAR-based treatment of OC and other solid tumours. Based on good results from the preclinical study of the SS1 CAR used in a transient system, a clinical trial including mesothelioma and pancreatic cancer patients was conducted (NCT01355965). Importantly, despite the presence of mesothelin in healthy tissues, and thus the use of a transient system, no ‘on target, off tumour’ toxicity was observed. However, severe adverse events of anaphylaxis and cardiac arrest were reported after the third infusion in one patient. This anaphylaxis correlated with an increase of antibodies against the murine SS1 scFv that was used in this CAR. Of interest, a clinical study on pancreatic cancer, including two constructs—one recognising mesothelin and the other targeting the general B-cell marker CD19—has been registered. The rationale is to enhance mesothelin CAR activity, but there is no indication as to whether they expect to counteract the appearance of anti-scFv antibodies (NCT03497819). A second trial was conducted using the same SS1-CAR in a lentiviral vector, for stable expression. Despite positive results from the preclinical study, low clinical effects were observed due to
poor persistence of the CAR T cells (NCT02159716). In addition, two phase I trials using a fully human scFv are ongoing, with one including OC patients (NCT03054298 and NCT03323944). Another CAR was tested using the P4 scFv; transduced CAR T cells demonstrated improved performance in terms of cytokine production and cytotoxicity in vitro, and efficient anti-tumour activity in a xenogenic human OC model was observed.36 Mesothelin, like MUC16, is a cleavable protein and interestingly; in these studies, it was shown that in the presence of high levels of the soluble part, CAR T cell efficiency remained unaffected. These promising results with a fully humanized anti-mesothelin CAR were recently confirmed in a preclinical pancreatic cancer model.37 Another attractive strategy has been to combine electroporation with a humanized anti-mesothelin CAR (CARMA-hMeso). CARMA-hMeso showed good performance both in vitro and in vivo in an OC model.38 Using this strategy of a CARMA™, non-viral, mRNA-based platform, the company MaxCyte has developed the CAR MYC-M11. Recruitment for a clinical trial is ongoing, including patients with OC (NCT03608618). Nevertheless, the preclinical study was performed using target cells modified to express human mesothelin. The question of the efficacy of CARMA-hMeso against primary cancer cells was not resolved. Furthermore, the low persistence due to mRNA degradation could lead to only a transient effect. NK cells have been engineered to express a particular NK-adapted anti-mesothelin SS1 CAR.39 A more recent study confirmed the therapeutic effect of these CAR NK cells in OC.40 This original approach will be used in an upcoming clinical trial involving OC patients (NCT03692637). A phase I/II trial was started in 2012 using a SS1 scFv CAR to treat patients with metastatic cancer, including OC. However, the study was terminated due to slow/insufficient accrual (NCT01583686). In addition to SS1- and P4-derived scFvs, a YP218-derived scFv was recently used for a second-generation CAR design and tested against OC. In a side-by-side comparison with SS1, which targets the distal region of mesothelin, and YP218, which targets the proximal region, the authors showed that YP218 was more effective in terms of cytokine production and cytotoxic activity, in vitro and in vivo.41 As discussed above, the presence of mesothelin in healthy tissues may be a serious concern. Therefore, in order to increase tumour specificity, a fourth-generation CAR was tested in the context of OC. In this study, the CD3ζ signalling domain was physically separated from the co-stimulatory module CD28. To achieve this, two distinct CARs targeting two different antigens (mesothelin (P4) and Folate receptor α (MOv19)) were designed, with the P4 scFv linked to CD3ζ, and MOv19 linked to CD28. The study concluded that the so-called trans-signalling CAR was as efficient as a second-generation construct in killing assays, but more potent in cytokine release. Importantly, it was safer since its in vivo activity was more pronounced against double-positive target cells. Although convincing, this does not preclude the recognition of healthy cells bearing only mesothelin, but the tandem format will attenuate such reactivity.42 Finally, another strategy to increase mesothelin CAR safety is to also add a suicide gene to delete reactive CAR cells, in case of toxicity.43 One such strategy is to induce apoptosis via iCaspase9 release. When exposed to the synthetic dimersing drug AP1903, iCaspase9 is activated, leading to CAR T cell apoptosis.44 Two clinical trials using this suicide strategy alongside mesothelin CAR are presently recruiting patients with either malignant pleural disease from mesothelia, lung cancer, breast cancer or advanced breast cancer (NCT02414269 and NCT 02 792 114). Interestingly, the feasibility of intrapleural injection, post-lymphodepletion and after PD-1 blockade, was reported for other cancer types and could well be used for OC.45 This suicide gene strategy has been discussed and criticized, due to the cost of the cell product preparation. Alternative strategies to reduce or tune down CARs rather than eliminating the CAR T cells are being developed.46,47

Folate is essential in rapidly dividing cells, and there are multiple modes of uptake by the cells. Folate receptor alpha (FRα) is one of a family of folate receptors and is normally expressed at low levels in normal tissue (e.g. kidney, lung, choroid plexus). In all but the kidney, it is found on the apical surface of the epithelium, away from the circulation.48 High-level expression is found in ovarian, lung and breast cancers.49 Monoclonal antibodies against FRα (e.g. Farletuzumab, MOv18, MOv19) have a long history of development, variously being used for diagnosis and prognosis, as well as delivery of therapeutic agents (mostly Farletuzumab), and as part of bispecific antibodies (MOv18 with anti-CD3).50 MOv18 provided the basis of the first anti-FRα CAR, utilising an Fcy signalling domain.51 Whilst safe, this treatment gave no clinical benefit to patients (NCT00019136). This has been attributed to low CAR expression and poor persistence.52 A MOv19 CAR construct was tested with CD3ζ or 4-1BB/CD3ζ (‘BBζ’) signalling domains. Both designs demonstrated anti-tumour efficacy in a mouse xenograft model, whilst the BBζ domain gave enhanced persistence.53 Co-stimulation with CD27 was also beneficial.54 A phase I trial with the BBζ design is planned and currently recruiting (NCT03585764). In a comparison using the MOv19 CAR with a CD3ζ first generation, a CD28/CD3ζ second-generation design, and a CD28/4-1BB/CD3ζ third-generation design, the second and third-generation designs showed enhanced reactivity and proliferation, with better inhibition of tumour growth and improved survival in a xenograft model.55 The MOv19 sequence was used as the basis for guided selection with human heavy and light chains, resulting in the C4 derivative.56 This was also used as the basis for CAR designs; an mRNA electroporation protocol of a C4 CAR with CD27/CD3ζ signalling domains facilitated regression of human OC xenografts in mice.57 More recently, NK92 cells with
lentiviral C4-based CARs also showed efficacy against OC cells in vitro. Here, first-generation (CD3ζ signalling domain), second-generation (CD28/CD3ζ) and third-generation (CD28/4-1BB/CD3ζ) designs were all effective in vitro, but the third-generation design exhibited higher cytotoxicity and functionality, as well as greater proliferation, and reduced antigen-induced apoptosis of the NK92 cells. This corresponded to greater survival in xenograft models, versus non-CAR controls.58 FRα is an attractive target for CAR therapy, invoking good reactivity. This approach holds some promise if a suitable platform can be found, and efficacy can be demonstrated in clinical trials.

HER2 (aka HER2/neu, ErbB2, CD340) is one of a family of four transmembrane tyrosine kinase receptors and is able to dimerize with each of the other members. Overexpression has been recorded in a variety of solid cancers, including OC. It has classically been detected by IHC, though this method may be underestimating the rate of positive samples; in a survey of 50 high-grade ovarian serous carcinomas, 29% were positive by IHC; however, qPCR, Western blotting and flow cytometry indicated that all were positive.59 These levels were above normal ovarian surface epithelial cells, as was reflected in the fact that CAR T cells (C6.5 scFv) reacted against all OC samples, but not normal tissues.59 Amongst a series of CARs that have been developed against HER2, an early CAR therapy trial against solid tumours used a third-generation CAR against colon cancer, with a scFv based upon the 4D5 antibody (Trastuzumab). This resulted in the death of one patient, which was attributed to CAR reactivity against low-level HER2 expression on lung epithelial cells.60 Subsequently, a range of other CAR designs have been pursued. Of direct relevance to OC, HER2 is overexpressed in OCs, lentiviral CAR administration eradicated established xenografts in vivo. Thus, it appears that targeting of integrin αvβ6 with CAR therapy has potential for the treatment of OC, though care will need to be taken to avoid adverse reactivity against expression of this integrin in non-target tissues.

In normal tissues, EpCAM (CD326) is only expressed by simple epithelia, at the basolateral surface and thus is somewhat inaccessible to cells and large molecules. It is upregulated in a variety of epithelial-derived carcinomas (including colon, stomach, pancreas, lung, ovary, breast) where it is typically distributed across the cell surface, including the apical surfaces. Anti-EpCAM CARs have previously been tested in various solid tumours, with some success. With respect to OCs, lentiviral CAR administration eradicated established xenografts in a mouse model. Also, repeated administration of mRNA CAR was able to delay disease progression.69 The changes in cellular localization of this target in cancerous cells should in principal translate to a good level of safety for cell-based therapy.

L1-CAM (CD171) is not expressed in normal ovaries, but is frequently overexpressed in OCs, and is associated with a poor clinical outcome.70 A CAR based upon an antibody targeting the CE7 epitope mediated reactivity against OC cells and induced regression in a xenograft model, giving a survival advantage compared with mock-transduced controls.65

Müllerian inhibiting substance type II receptor (MISIIR) is involved in regression of Mullerian ducts in male embryos. It is overexpressed in the vast majority of epithelial OCs, endometrial carcinomas, uterine sarcomas, cervical carcinomas and other gynaecologic malignancies. It is also upregulated in breast, prostate, and lung cancers, and ocular melanoma. MISIIR signalling naturally causes growth inhibition; however, suitable ligands (synthetic, transgenic, antibody) which have been tested, have not yet entered clinical trials. High expression of MISIIR is correlated with a better prognosis where lymphocytes are able to infiltrate tumour tissues. Therefore, it is potentially safe and effective. Screening of

3 | THE EMERGING TARGETS

In parallel to the usual suspects, an increasing number of targets have emerged with potential to be used for CAR T cell therapy. Integrin αvβ6 is an epithelial-specific integrin, which is expressed at undetectable or very low levels in normal tissues, except during development and epithelial remodelling. By contrast, it is overexpressed in many solid cancers (pancreas, head and neck, breast colon, stomach, lung, cervix, fallopian tube, ovary). Expression correlates with poor prognosis, as it has role in the activation of TGFβ, tumour cell migration, invasion and epithelial-to-mesenchymal transition.65 A few CAR molecules have been designed to target integrin αvβ6b. ‘Bpep’, a high-affinity peptide identified by phage display, was incorporated into a first-generation CAR, resulting in specific killing of αvβ6-positive ovarian tumour targets.66 Another peptide with high affinity to integrin αvβ6, ‘A20’, was derived from the foot and mouth disease virus. This peptide has been used in a second-generation CAR alone (CD28/CD3ζ)67 or co-expressed with a CXCR2 receptor.68 These designs resulted in efficacy against a range of tumour xenografts in vivo. Thus, it appears that targeting of integrin αvβ6 with CAR therapy has potential for the treatment of OC, though care will need to be taken to avoid adverse reactivity against expression of this integrin in non-target tissues.

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scFvs derived from a number of antibody sequences identified a candidate with antigen-specific reactivity, and a second-generation (CD27/CD3ζ) lentiviral CAR based upon this was able to clear MISIIR-positive tumours in vivo.72 The distribution of this antigen lends itself to potentially safe and effective clinical use of MISIIR-targeting CARs.

Another type of target for OC is the over-glycosylation often found on the surface of cancer cells. Tumour-associated glycoprotein 72 (TAG72) is a sialyl-Tn O-glycan carbohydrate hapten that can be overexpressed on cancer cells. This feature is found in various cancer types, including OC. In 2000, in the context of gene transfer by recombinant adenovirus vector, TAG72 was shown to be a good epitope to selectively target OC.73 Using a second-generation CAR T cell against TAG72, Priceman et al have shown a potent and antigen-dependent activity in vitro. However, in vivo, despite good anti-tumour activity and prolonged survival, a lack of persistence of the CAR T cell resulted in tumour recurrence. The limited effect of the CAR T cell therapy was due to antigen escape by the recurring tumour and low IL-2 production. This mitigated result highlights the importance of CAR design in order to overcome TME immunosuppression.74

Glypican-3 (GPC3) is considered a target for ovarian clear cell carcinomas (OCCC), a less frequent type of OC. GPC3 is known to regulate cell proliferation signalling and play a role in the proliferation and differentiation of embryonic cells.75,76 A clinical trial using a GPC3 peptide vaccine demonstrated anti-tumour efficacy in advanced OCCC, indicating that GPC3 could be used as a target for CAR T cell therapy.77,78 Recently, iPSCs were transduced with anti-GPC3, CAR with the objective of producing NK/innate lymphoid cells (NK/ ILC). These CAR NK/ILC cells showed good activity in vitro, and anti-tumour activity in vivo, without observed toxicity. A clinical trial using this approach will start in Japan for OC treatment.79

Another emerging target is the oncofoetal antigen 5T4. 5T4 is expressed at very low levels on normal tissues, but found at higher levels on different cancers, such as OC.80 Moreover, 5T4 was shown to be associated with cancer spreading,81 making 5T4 a good candidate for CAR T cell therapy. Harrop and colleagues compared two 5T4-specific scFvs with different affinities (H8 and 2E4) in a second-generation CAR design. In vitro assays showed that the higher-affinity H8-CAR secreted higher levels of cytokines (INFγ and IL-2) compared to the 2E4-CAR. Similar results were obtained in vivo, where the high-affinity CAR significantly improved the survival of mice compared to the low affinity CAR. However, one drawback with high-affinity scFvs is that, besides highly expressing tumour cells, they can also recognize cells with low-level expression of the target, such as in normal tissues.82

Claudin 6 was recently demonstrated to be a CAR target.83 In this report, the authors confirmed the cancer specificity of this protein and introduced a novel approach to deliver CAR molecules through mRNA-nanoparticles. Claudin 6 is a tight junction protein that was already targeted with therapeutic antibodies in clinical trials (NCT02054351) and has been announced to be tested in a basket trial including OC patients.84

4 | THE IMMUNE TARGETS

Solid tumours have been reported to express receptors otherwise found on immune cells. Such receptors may contribute to the immunosuppressive environment or more directly protect the cancer cells from being destroyed by effector cells. OCs have been shown to express certain of these molecules, and an attractive strategy would be to use them as targets in order to differentiate malignant tissues from healthy ones. In this respect, CD47 is a very interesting marker, known in immunology as the ‘don’t eat me signal’ that protects cells from phagocytosis. It was found to be expressed in around 80% of OCs, and low expression of CD47 correlated to a good response to adjuvant therapy, suggesting that its presence might have a protective role for the tumour cells.85,86 At this stage, only one CD47-specific CAR has been reported to react against OC cell lines, with in vivo results generated using a pancreatic xenograft model.87 Thus, whether this construct is an option to treat OC remains to be explored.

OC has been shown to express different NK cell markers, whilst NK cells are currently being tested in clinical trials to treat OC patients (reviewed in 88). Although attractive, NK cells have yet to demonstrate equivalent clinical potency to T cells; therefore, a strategy to target NK ligands on OC using NK cell receptors such as NKG2D may be feasible. This receptor has been tested either as a truncated extracellular domain fused to a signalling tail89 or as an enhanced full-length protein fused to CD3ζ.90 T cells expressing these constructs showed good reactivity against OC cell lines, but in vivo data have been generated with a murine construct. Thus, the efficacy of NKG2D-CAR against OC still needs to be tested against human NKG2D. To our knowledge, the NKG2D CAR strategy has not been further developed for the treatment of OC. An explanation for this may be the low NKG2DL presence on OC cells, since in this study, NKG2D was artificially upregulated by prior treatment of target cells with the histone deacetylase inhibitor sodium valproate (VPA).89 Nevertheless, NKG2D CARs are currently being tested in the clinic for other types of cancers.91

Another interesting immune target is CD24, which is a B-cell development marker often observed in solid tumours, and defined as a cancer stem cell marker (reviewed in 92). An anti-CD24 CAR construct was built from a validated scFv and tested in vitro as a third-generation construct expressed in NK-92 cells.92 Although in vitro killing of cell lines and primary OC cells was observed, no in vivo data were
TABLE 1  Catalogue of the OC-CAR and their use. Representative CAR design and clinical trials to treat OC are grouped according the targeted epitope. Trial information collected from ClinicalTrials.gov. Abbreviations: (m): murine scFv; (m/h): murine humanized scFv.

| Target epitope | Ab Generation | Structure | Specificity | ref | Clinical trial               |
|----------------|---------------|-----------|-------------|-----|-------------------------------|
| **Antibody-based CARs** | | | | | |
| MUC16          | 4H11 1st     | scFv-CD8h-CD8tm-CD3ζ | expressed in 80% of OC | 17 | |
|                 | 4H11 2nd     | scFv-CD8h-CD8tm-CD28-CD3ζ | | | |
| Mesothelin      | SS1(m) 2nd   | scFv-CD8h-CD8tm-4-1BB-CD3ζ | expressed in 80% of OC | 34 | NCT02159716, NCT03054298 |
|                 | undisclosed  | undisclosed | | | |
|                 | P4(m/h) 1st  | scFv-CD8h-CD8atm-CD3ζ | | 36 | NCT01583686 |
|                 | 2nd          | scFv-CD8h-CD8atm-CD28-CD3ζ | | | |
|                 | undisclosed  | undisclosed | | | |
|                 | 2nd (mRNA)   | scFv-CD8h-CD8tm-4-1BB-CD3ζ | | 38 | NCT03608618 |
| YP218           | 2nd          | scFv-CD8h-CD8tm-CD28-CD3ζ | | 41 | NCT03747965 |
|                 | undisclosed  | undisclosed | | | |
|                 | 4th          | undisclosed | | | |
|                 | undisclosed  | 3rd (in NK92) | scFv-CD8h-CD8tm-CD28-4-1BB-CD3ζ- | | |
| Folate receptor | MOv18 1st    | scFv-Fcγtm-Fcγ | 89% of tumours examined | 51 | NCT00019136 |
| FRα             | Mov19 2nd    | scFv-CD8h-CD8tm-4-1BB-CD3ζ | | 53 | NCT03585764 |
|                 | C4 (MOv19-derived) 2nd (mRNA) | scFv-CD8h-CD8tm-4-1BB-CD3ζ | | 54 | |
|                 | 1st (in NK92) | scFv-CD8h-CD8tm-CD27-CD3ζ | | | |
|                 | 2nd (in NK92) | scFv-igG1Fc-CD8h-CD28tm-CD3ζ | | | |
|                 | 3rd (in NK92) | scFv-igG1Fc-CD8h-CD28tm*CD28-CD3ζ | | | |
| TAG72           | CC49 2nd     | scFv-igG4h-CD4tm-4-1BB-CD3ζ | 90% epithelial OC | 74 | |
| GPC3            | G2 3rd       | scFv-CD8h-CD8tm-CD28-4-1BB-CD3ζ | 44% of clear cell adenocarcinomas | 79 | |
| 5T4             | H8 2nd       | scFv-CD8h-CD8tm-4-1BB-CD3ζ | 71% of the carcinomas | 80 | |
|                 | 2E4          | scFv-CD8h-CD8tm-4-1BB-CD3ζ | | | |
| Claudin 6       | scFv 2nd     | scFv-CD8h-CD8tm-4-1BB-CD3ζ | 69% | 83 | |
| CD24            | SWA11 3rd (NK-92) | scFv-CD28tm-4-1BB-CD28-CD3ζ | ca 80% of OC | 92 | Caused by OC |
| MISRII          | GM7 2nd      | scFv-CD8h-CD8tm-CD27-CD3ζ | 69% epithelial OC | 72 | |

(Continues)
| Target epitope | Ab          | Generation | Structure                                      | Specificity     | ref | Clinical trial |
|---------------|-------------|------------|-----------------------------------------------|-----------------|-----|----------------|
| B7-H3         | 376.96 (m)  | 2nd        | scFv-CD28-CD3ζ/CD28-4-1BB-CD3ζ                | Ca 90%          | 95  | -              |
| CD47          | B6H12       | 2nd        | scFv-CD8h-CD28tm-CD28-CD3ζ                   | 100%            | 87  |                |
| L1-CAM        | CE7         | 2nd        | scFv-lg h-CD28tm-CD28-CD3ζ                   | 80%             | 65  |                |
| EpCAM         | 4D5MOC-B (m/h) | 3rd (lenti and mRNA) | scFv-CD8h-CD28tm-CD28-4-1BB-CD3ζ | 67%-100%        | 69  |                |
| B7-H4         | scFv 3#68 (yeast display library) | 2nd | scFv-CD8h-CD28tm-CD28-CD3ζ                   | Ca 90% OC       | 156 | -              |
| Her2 (ErbB)   | chA21 (m/h) | 2nd        | scFv-CD8h-CD28tm-CD28-CD3ζ                   | 100%            | 61  |                |
| PSMA          | C6.5        | 1st        | scFv-CD8h-CD28tm-CD3ζ                       |                 | 59  |                |
|               | J591        | 3rd        | scFv-CD8h-CD28tm-CD28-4-1BB-CD3ζ            | Detected in 75% | 125 |                |
| Ligand-based CARS |           |            |                                               |                 |     |                |
| CD70          | trCD27      | 2nd        | trCD27-CD27tm-4-1BB-1 (or CD28)-CD3ζ         | 17.4% OC        | 159 | NCT02713984    |
| NKG2DL        | trNKG2D     | 2nd        | scFv-4-1BB-CD3ζ                              | More than 80% OC| 89  |                |
| NKG2D FL (m)  |            | 1st        | scFv-CD3ζ                                   |                 | 90  |                |
| Integrin αvβ6 | B pep       | 1st        | ligand-Fch-CD4tm-CD3ζ                       | All epithelial OC samples surveyed | 66  |                |
|               | A20(FMDV2)  | 2nd        | scFv-CD28tm-CD28-CD3ζ, plus boosting/homing receptors |                 | 68  |                |
| TCR-like CARS |             |            |                                               |                 |     |                |
| WT-1p/HLA-A*0201/IL12 | ESK1 | 4th        | scFv-CD28tm-CD28-C3ζ-secreting IL-12         |                 | 162 |                |
| Enhanced CARS |             |            |                                               |                 |     |                |
| Mesothelin/ CXCR2/4 | SS1 | 4th        | scFv-CD8h-CD28tm-4-1BB-CD3ζ                  |                 | 137 |                |
| Mesothelin/A2aR | P4        | 4th        | scFv-CD8ah-4-1BBtm-4-1BB-CD3ζ-shRNA          |                 | 136 |                |
| MUC16/IL-12   | 4H11        | 4th        | scFv-CD8h-CD28tm-CD28-CD3ζ-secretating IL-12 |                 | 127 | NCT02498912    |
| MUC16/PD-1    | 4H11        | 4th        | scFv-CD28tm-CD28-CD3ζ-2PA-PD1 blocking scFv  |                 | 130 |                |
| Her2 (ErbB)   | T1E         | 2nd        | ligand-CD28h-CD28TM-CD28-CD3ζ                | Her2 (ErbB)     | 64  |                |
reported. Intriguingly, an anti-CD24 CAR combined with an anti-mesothelin CAR construct was used to improve efficacy against heterogeneous targets, but the authors did not observe any superior selectivity. Considering its expression in OC, CD24 deserves more attention, and it is tempting to speculate that the scFv used in the first report was not efficient enough in a CAR format, and therefore additional constructs, such as the recently reported humanized anti-CD24 antibody, hG7-BM3, should be tested.

Finally, two alternative markers which have already entered clinical use for other types of cancers, including CAR therapy, have been proposed to treat OC. These are members of B7 receptor group, with two members so far tested, namely B7-H3 (also known as CD276) and B7-H4. The first of these, B7-H3, is an immune inhibitory receptor which is expressed at low levels in normal tissues but can be found in various solid tumours. This receptor was recently shown to be actively involved in the progression of OC, making it a perfect target, since its presence is necessary for tumour progression. Dotti and co-workers recently reported a complete study on an anti-B7-H3 CAR where two CAR designs were tested in different tumour models. In addition, they performed a toxicity test against healthy tissues, which suggested that their CAR was safe despite low levels of B7-H3 expression. The second B7 receptor, B7-H4, is less studied and is expressed in healthy tissues. However, its expression is highly upregulated in OC samples. Here a complete study was presented on the development of anti-B7-H4 CAR; unfortunately, the in vivo experiments revealed strong CAR toxicity due to the presence of B7-H4 in murine healthy tissues, and a lower efficiency compared to anti-FR CAR, shown to be due to partial antigen loss. The authors proposed to test alternative clones in vivo from the four scFvs they isolated. Indeed, their selection criterion, as reported, was based on a cytotoxicity assay which might not be the most reliable method to predict in vivo efficacy. Recent reports have shown that testing several scFv clones might lead to the optimal CAR, but the predictors are still under investigation.

All the CAR designs discussed above, and their use in different clinical trials, are recapitulated in Table 1. The antigen expression and tissue localization of the CAR targets described are shown in Figure 2.

5 | DEALING WITH THE TME

Epithelial OC can metastasize through the transcoelomic, haematogeneous or lymphatic routes. Dissemination across the peritoneal cavity to other pelvic and peritoneal organs, facilitated via the peritoneal fluid (transcoelomic metastasis), is the most frequent pathway, and causes the highest morbidity and mortality. Relatively little is known about the mechanisms behind this process. In general, OC has a unique TME where the interactions between cancer cells and host cells are indispensable for tumour growth and progression.

Tumour-associated macrophages (TAM) and cancer-associated fibroblasts (CAFs) create a tumour-promoting and immunosuppressive TME. TAMs have been shown to mainly have an immunosuppressive M2 phenotype in OC, skewed by factors in the TME such as IL-6, IL-10, transforming growth factor beta (TGFβ) and arachidonic acid (AA) (reviewed in), which efficiently suppresses IL-12 production, the hallmark of a cytotoxic macrophage response against tumours.

IL-12 produced by macrophages and other antigen presenting cells (APC) is critical for the differentiation of naïve T cells into cytotoxic and type 1 helper T cells (Th1), as well as for activating NK cells, leading to IFN-γ production. One way of repolarising this response could therefore be to modify CAR T cells to secrete IL-12, either in a constitutive or inducible fashion. This has been shown to change the TME and activate T cells and NK cells, with reduced infiltration of T regs, in a solid tumour model. Epidermal growth factor (EGF)-secreting TAMs have been shown to promote tumour spheroid formation and growth at early stages of metastasis in mouse models for epithelial OC.

The omentum, an adipose tissue formed from a fold of mesothelium in the peritoneum, is a critical premetastatic niche for OC. A recent study in a mouse model of metastatic OC identified a unique subset of tissue-resident CD163+ Tim4+ macrophages in the omentum that could promote tumour progression. The acquisition of epithelial-mesenchymal transition (EMT) and cancer stem cell (CSC) characteristics by OC cells, followed by the development of invasive disease, were promoted by the presence of these omental TAMs. Their specific depletion effectively reduced tumour progression and downregulated genes associated with EMT and CSCs. Repolarization of these omental TAMs to tumouricidal macrophages could therefore be an important objective in OC therapy.

Other myeloid cells that are attracted to augment immunosuppression in OC are immature myeloid cells like myeloid-derived suppressor cells (MDSCs), which can inhibit both adaptive and innate anti-tumour immune responses. MDSCs can be attracted to OC sites by prostaglandin E2 (PGE2) through the CXCR4/CXCL12 pathway, but these mechanisms are still quite poorly understood. However, PGE2 has been shown to have a direct role in MDSC tolerogenic function through the upregulation of DNA methyltransferase 3A. Additionally, circulating monocytes can be attracted through the CCL2-CCR2 axis, which is overexpressed in OC, or through adenosine produced via a CD39-CD73-dependent mechanism. The latter results in the peritoneal accumulation of immature macrophages, which can produce TGFβ and PGE2, and thus attracts regulatory T cells (Tregs). A recent report demonstrated that disrupting the adenosine pathway through simultaneous blocking
of CD39 and CD73 effectively restored anti-tumour activity of human T cells from breast cancer patients. Anti-CD73 antibody is already being tested in clinical trials and has shown promising effects, alone or in combination with anti-PD-1 antibody (currently ongoing clinical trial: NCT04148937). Due to the unique and very immunosuppressive TME in OC, the use of such agents may be required in combination with CAR T cell therapy for the CAR T to sufficiently infiltrate the tumour and gain access to a less hostile environment.

The accumulation of fluid, or ascites, in the peritoneal cavity significantly contributes to poor quality of life and morbidity in OC. Ascites are rich in tumour growth factors and detached cancer cells. In addition to cancer cells, the most abundant cell types in ascites are macrophages and T lymphocytes, NK cells, fibroblasts, adipocytes and mesothelial cells. NK cells are present in ascites and infiltrate OC tissues, but their cytotoxicity is inhibited by several soluble factors, including macrophage migration inhibitory factor (MIF) and soluble B7-H6, which downregulate activating receptors on NK cells. Another immunosuppressive cell population often increased in OC and correlating with poor prognosis is Treg. These suppress anti-tumour immune responses through the production of inhibitory cytokines and chemokines.

Adipocytes in the omentum are also involved in cytokine signalling in OC through the secretion of IL-6, IL-8, CCL-2 and adiponectin, contributing to a tumour growth-promoting environment. Adipocytes can additionally alter their metabolism to provide fatty acids to cancer cells as an energy source.

Mesothelial cells line the peritoneum and the omentum. Below this lining is a basement membrane composed of collagen, fibronectin and laminin, which constitutes the extracellular matrix, also known to be important in OC metastasis. Mesothelial cells can also promote cancer growth, one mechanism being through the production of plasminogen activator inhibitor-1 (PAI-1). PAI-1 has been shown to induce the formation of cancer-associated mesothelial cells (CAMs), which secrete oncogenic factors like IL-8 (CXCL8) and CXCL5, further promoting OC cell growth in a feedback loop.

Highly proliferative, cells such as cancer cells, produce extracellular vesicles (EV) or exosomes to mediate transfer of proteins, lipids or nucleic acids between cells. EVs are present in ascites from OC patients where they influence immune escape, metastasis and drug resistance. EVs secreted from OC cells have been shown to inhibit the immune response by inducing powerful functional arrest of activated T cells, independent of antigen specificity. EVs can transport soluble molecules that directly affect tumour cell migration.

FIGURE 2 Expression and localization of the main OC-CAR Targets. Illustration of a human body showing the localization of the different targeted antigens in OC. In red, the antigens overexpressed in cancerous tissue and in blue the antigen expressed in the healthy tissue. Information was mainly collected from proteinatlas.org. Abbreviations: FRα: Folate receptor α. MSTN: Mesothelin. Images obtained from SMART.
as well as activated matrix metalloproteinases that degrade the extracellular matrix (ECM), enabling tumour cells to invade other tissues. EVs thus represent a challenge for CAR-modified immune cells, and they can be made resistant to certain factors carried by EVs. There are also numerous efforts to engineer EVs to exploit them as therapeutic delivery systems (recently reviewed in 118).

Increased numbers of CD8 + TILs correlate with improved prognosis in many cancers, including OC. However, activated TILs frequently upregulate immune checkpoint molecules such as PD-1 and LAG-3.119 Inhibiting these immune checkpoints whilst increasing tumour-specific CD8 T cell infiltration may therefore have a beneficial effect.120,121

6 | TME-RESISTANT CAR

For CAR T cell therapy to be successful in OC, they have to reconvert or overcome this immunosuppressive TME. Combined immune checkpoint blockade has been shown to enhance CAR T cell efficacy in haematological cancer.122 With gene editing possibilities, CAR T cells could also be made resistant to checkpoint inhibition (recently reviewed in 123) or equipped with decoy receptors for inhibitory molecules such as PD-1 and TGFβ (recently reviewed in 124). In this section, we will present the combination strategies that have been adopted to improve OC-CAR efficacy.

Numerous CAR strategies to affect TME have been proposed, either by directly aiming at cell surface components supporting the tumour, or by combining the tumour-targeted CAR with anti-immuno-inhibitory drugs such as checkpoint inhibitors. An original strategy was proposed by Coukos and colleagues six years ago where the common prostate marker, PSMA, which is also highly expressed in the endothelium of solid tumours, was targeted using an anti-PSMA CAR.125 The overall concept was to eliminate the ‘pipeline’ providing nutriment to the tumour, which was demonstrated in mice models where human proteins were overexpressed. Here, the tumour was not directly killed by the CAR; however, the effect was not complete. This was attributed to the presence of PSMA-negative endothelial cells. It could also be due to the scFv clone the authors used, which was recently compared to another construct (P-PSMA-101), and reported to be less efficient in triggering direct tumour cell killing in vivo.126

In order to prevent CAR T cell inhibition or depletion in the TME of solid tumours, resulting from Tregs or inhibition of immunological checkpoints, Koneru and colleagues127 tuned the second-generation 4H11-CD28/CD3ζ CAR by adding a construct allowing the secretion of IL-12, generating the 4H11-28zIL12 construct. This modification induced improved proliferation and INFγ secretion in vitro, and a more efficient anti-tumour activity in vivo, by increasing T cell persistence. The potential toxicity of IL-12 secretion was prevented by the incorporation of EGFRt as a ‘suicide’ gene. EGFRt is a truncated and non-functioning version of EGFR, and with the addition of cetuximab, it will induce death of the CAR T cells. This suicide gene strategy has been reported to be used in the clinic but only in combination with CD19CAR.128 Further studies using a syngeneic model of murine ovarian peritoneal carcinomatosis showed that 4H11-28z-IL12 T cells could overcome the suppressive effects of the TME by depleting TAMs, and resisting apoptotic and inhibitory signals.129 Based on these results, 4H11-28z-IL12 T cells were used in a phase I clinical trial.130 This trial aims to enrol 30 patients with a primary study estimated to start in August 2020 (NCT02498912).

Alternatively, CAR T cells have been used for targeting the delivery of checkpoint inhibitors. With this approach, an anti-PD-1 scFv was combined with a CAR and gave local protection to the expressing T cell from the immunosuppressive TME. In a proof-of-principle study, T cells expressing the 4H11 CAR combined with the PD-1 scFv demonstrated an enhanced in vivo efficacy and, importantly, bystander tumour-specific T cells were recruited.130 Of note, the in vivo study was performed using an OC cell line artificially overexpressing PDL-1. This could affect the balance of the response, and it would be interesting to repeat the experiment using human primary tumours, such as PDX models. Other studies and clinical trials using CAR T cells against mesothelin following the same strategy are presently under evaluation.131 Alternatively, one can also block the expression of PD-1 on the engineered CAR T cells, for example by using CRISPR/Cas9 to mediate PD-1 disruption in the CAR-expressing T cells.132 A preclinical study with a triple negative breast cancer model has shown that PD-1 disruption has little effect on CAR T cell proliferation, but found enhanced cytokine production and cytotoxicity by the KO PD-1 CAR T cells, compared to WT CAR T cells or CAR T cells combined with anti-PD-1 therapy.133 Using this approach, a clinical trial is recruiting, including patients with OC, to test the effect of the CRISPR-Cas9-mediated PD-1 knocked-out CAR T cells in the TME (NCT03747965). Another approach to disrupt PD-1 is to use a PD-1 small hairpin (sh) RNA blockade. A preclinical study has shown benefit in a pleural mesothelioma model.134 Recently, the same approach was exploited targeting the adenosine 2a receptor (A2aR) in OC, where the rationale was to improve resistance to the adenosine suppression signal present in the TME, which occurs through the A2aR.135 Using a second-generation CAR with the anti-mesothelin P4 scFv, the authors showed that CAR T cells combined with shRNA had a superior resistance to an adenosine analogue. They observed improved proliferation, cytokine production and no reduction of the cytotoxic function. These results still need to be confirmed in vivo.136

Furthermore, an alternative strategy has been to combine CAR with the expression of chemokine receptors. This is expected to increase the trafficking of the CAR T cells to the EVs.137
tumour. The chemokine receptor CCR2 was transduced with an anti-mesothelin CAR, and this modification was shown to increase transmigration and killing efficacy in vitro, and a significant increase of the T cell tumour infiltration in vivo, leading to an improved anti-tumour activity. Finally, CAR T cells tuning the cytokine level in the TME are also under investigation, with one strategy being the elimination of IL-10 with a blocking antibody, and another through CAR T overexpression of TNF-α and IL-2, enhancing and prolonging CAR T efficacy.

7 | CONCLUSIONS AND FUTURE PROSPECTS

We have here presented an exhaustive catalogue of the possible targets which have been exploited in CAR-based treatment of OC. Safety is a major concern, and single-target therapy no longer appears to be a safe option, mainly due to ‘off tumour, on target’ effects. Considering the number of markers which are potential CAR targets, an interesting approach would be to test combinations—as has already been proposed—but with targeting of the ‘usual suspects’ combined with immune checkpoint or emerging targets. This would allow a novel range of possibilities. In addition, the dual targeting design should be evolved and more restrictive, and as presented here; the strict recognition of double-positive targets is still not acquired. New types of design can also be exploited, like the use of TCR-like CAR constructs (see Table 1).

Our presentation of the OC TME clearly suggests that even the most efficient CAR will not manage to exert its full therapeutic effect on its own. The immunosuppressive TME needs to be tackled, and innovative solutions are currently being developed. An interesting strategy to test in OC could be to reshape the TME using nanoparticles prior to treatment with CAR T cells, as recently proposed, or to force the T cells into the tumour using magnetic targeting of T cells. These emerging methods are presently being developed for other cancer types and could well be of interest for OC.

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CONFICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the preparation of this review, EB and SW performed the final editing.

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