Adoptive Cellular Therapies in Ovarian Cancer

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Contributor: Lucy Davis , Rowan E Miller , Yien Ning Sophia Wong

Ovarian cancers are typically poorly immunogenic and have demonstrated disappointing responses to immune checkpoint inhibitor (ICI) therapy. Adoptive cellular therapy (ACT) offers an alternative method of harnessing the immune system that has shown promise, especially with the success of chimeric antigen receptor T-cell (CAR-T) therapy in haematologic malignancies. ACT has led to modest results in the treatment of solid organ malignancies.

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1. Types of Adoptive Cellular Therapy (ACT)

1.1. Chimeric Antigen Receptor T (CAR-T) Therapy

A chimeric antigen receptor T (CAR-T) cell consists of a T-lymphocyte that has been modified *in vitro* to express a specific antigen receptor. A CAR is itself a fusion of a single-chain variable region capable of recognising tumour-associated antigens and intracellular portions of the T-cell receptor that have the crucial property of transducing the signal to activate T-lymphocytes [1]. There is a wealth of evidence that CAR-T cells have been used successfully to improve outcomes for patients with haematologic malignancies [2][3][4]. Their unique properties are now being exploited in the treatment of solid organ cancers including ovarian cancer.

Challenges of CAR-T cells in OC include the heterogenous nature of these tumours, leading to difficulty identifying antigens that are tumour-specific yet sufficiently expressed to induce a response. Lack of persistence and trafficking of CAR-T cells *in vivo* has been an additional barrier to maximising clinical response rates [5]. This is likely due to the hostile TME, poor vascular integrity, and downregulation of adhesion molecules [6]. It is known that immunosuppressive mechanisms are at play in the TME, including the presence of regulatory T-cells and cytokines that may attenuate the effect of CAR-T cells.

In terms of side effects, there are hurdles to be overcome in the use of CAR-T cells in solid organ malignancies. Target antigens are often expressed to varying degrees in healthy tissues and the phenomenon of the ‘on-target, off-tumour’ effect is observed when CAR-T cells destroy healthy tissue and give rise to adverse clinical effects [7]. A further potential toxicity of this treatment is the cytokine release syndrome (CRS). CRS presents with a spectrum of severity ranging from flu-like symptoms to circulatory shock due to the massive release of cytokines that can occur on lymphocyte activation. Earlier clinical trials in this area focused on the safety profile of CAR-T therapy and how this is affected by co-administration of other systemic anticancer agents.

A variety of tumour-associated antigens have been identified in OC as suitable targets for CAR-T cells and formed the basis of phase I and II clinical trials in recent years. A popular antigenic target utilised in CAR-T cell therapy in OC is mesothelin, a membrane glycoprotein expressed in particularly high levels in serous epithelial ovarian cancers as well as normal mesothelial tissues [8]. It has been reported that non-specific toxicity rates are lower due to low-level expression of mesothelin in normal tissues, making it an attractive target for CAR-T therapy [9]. In 2014, Haas et al. showed that mesothelin-directed CAR-T cells can persist in the peripheral blood, with peak levels at 6–14 days following a single infusion in 19 subjects with mesothelin positive tumours, including five with OC [10]. This expansion *in vivo* was enhanced with the administration of cyclophosphamide, suggesting that LD chemotherapy prior to administration of CAR-T cells may serve to potentiate their anti-cancer effect. Wang et al. reported similar peak serum levels of CAR-T directed against mesothelin at 7–14 days in 15 subjects, including one OC patient with mesothelin-positive tumour tissue [11]. In contrast to the Haas et al. [10] study, the single CAR-T cell infusion was given without any LD chemotherapy.

A well-known biomarker of OC is CA-125, which is itself a domain of a large transmembrane glycosylated protein called MUC16 that has become a focus of CAR-T therapy in OC over recent years [12]. MUC16 has been shown to be overexpressed in ovarian cancers and linked to promoting cell proliferation, migration and invasion [13]. O'Cearbhaill et al. published a study in 2020 in which 18 heavily pretreated patients with ovarian, fallopian tube and primary peritoneal cancers received CAR-T cells directed at MUC16 and engineered to secrete IL-2 [14]. They were able to first establish a maximum tolerated dose that was then administered both intravenously and intraperitoneally to a cohort of patients after receiving LD chemotherapy. A best response of stable disease (SD) was observed, along with serum levels of CAR-T cells peaking at 7–28 days. However, two of the three patients who received LD chemotherapy experienced dose-limiting toxicity (DLT) in the form of macrophage activation-like syndrome, leading to this cohort being closed for further recruitment. Although the sample size was small, these data suggest that LD chemotherapy may increase the risk of toxicity, especially in the context of IL-2 secretion. Looking forward, an ongoing study (NCT03907527) is recruiting a similar cohort of patients with advanced, platinum-resistant OC at an estimated larger sample size of 71 subjects. They are planned to receive CAR-T cells directed at MUC16 either intravenously or intraperitoneally and with or without prior LD chemotherapy. This should allow for comparison of maximum tolerated dose and efficacy between these different routes of administration.

An additional protein that has been studied as a target for CAR-T cells is the folate receptor alpha (FRα), which has been shown to be expressed in at least half of ovarian cancers of a diverse range of phenotypes [15] and of limited expression in healthy tissues [16]. A pioneering study treated subjects with recurrent epithelial OC with CAR-T cells directed at FRα. They were able to demonstrate safety when given alone but showed grade 3–4 adverse effects when co-administered with IL-2 [17]. Furthermore, no objective reduction in tumour burden was seen in these patients, likely linked to the low levels of radio-labelled CAR-T cells detected in the tumour and peripheral blood after a few weeks. Currently ongoing is a study (NCT03585764) that is recruiting those with persistent and pretreated high grade serious ovarian cancer (HGSOC) to receive FRα CAR-T cells via the intraperitoneal route and with or without LD chemotherapy. Perhaps it will find that the addition of lymphoreductive treatment is associated with increased persistence of the FRα CAR-T cells and better anti-tumour response. The transmembrane glycoprotein B7-H3 is highly expressed in human OC and has shown a correlation with CD8 [18].

CAR-T cells directed at B7-H3 are currently being evaluated in cohorts of patients with epithelial OC (NCT04670068) and recurrent OC (NCT05211557). Other CAR-T targets, such as TAG-72 (NCT05225363) and ALPP (NCT04627740), are currently under investigation in clinical trials.

1.2. Genetically Engineered T Cell Receptor (TCR) Therapy

TCR therapy consists of, in most cases, peripheral blood lymphocytes that have been modified to express the T-cell receptor specific to a certain cancer-associated antigen. In contrast to CAR-T cells, TCR-T cells recognise cancer antigens in an MHC-restricted manner and these targets tend to be of the cancer testis antigen (CTA) type, often consisting of normal developmental proteins whose expression has been abnormally upregulated in malignant tissue [19]. An advantage of TCR-T cells over CAR-T cells is their ability to also target intracellular antigens, which may increase their cytotoxic and anti-tumour activity.

A popular CTA target for TCR-T cells in solid tumours is the melanoma-associated antigen (MAGE), which has been shown to be overexpressed in a high percentage of OCs and in some reports has been associated with decreased progression-free survival [20]. A phase I study treating patients with a range of MAGE-A4-positive tumours following LD chemotherapy has reported results in 2023 [21]. Grade 3–4 haematological toxicity was observed in all patients, leading to an adjustment of the LD chemotherapy dose. Two trial-related deaths were recorded, including one OC patient who experienced grade 3 neurological toxicity followed by death due to cerebrovascular accident. Overall, 74% of the patients had SD or partial response (PR), including five with OC. A sub-study of this trial is underway to explore whether the use of radiotherapy may work synergistically with TCR therapy with a more favourable adverse effects profile than LD chemotherapy. A phase II randomised study (NCT05601752) is currently recruiting participants with recurrent OC to receive TCR-T cells directed against MAGE-A4 as a monotherapy or with the immune checkpoint inhibitor (ICI) Nivolumab.

A commonly studied CTA, which has been the focus of some early-phase TCR-T clinical trials in OC over recent years is the New York Esophageal-1 antigen (NY-ESO-1). This antigen has been found to be expressed in around 40% of a diverse range of OC tumours and higher expression has been associated with later stages, poorer response to initial treatment and a serous phenotype [22]. A 2016 study (NCT02869217) has recruited participants with a wide range of NY-ESO-1-positive solid tumours to receive cyclophosphamide followed by either a single dose or repeated intravenous doses of TCR-T cells directed at NY-ESO-1. Early results have so far shown mild CRS and a small amount of G3–G4 toxicity following a single TCR-T infusion. More promisingly, out of the nine participants treated by 2019, two had a PR and another five had SD [23].

The Roswell Park Cancer Institute has conducted multiple trials with NY-ESO-1-targeted TCR-T cells in patients with recurrent epithelial ovarian, primary peritoneal or fallopian tube carcinoma and platinum-refractory or -resistant disease. Six participants in an early trial beginning in 2012 received low dose LD chemotherapy followed by a single IV infusion of NY-ESO-1 TCR-T cells. No appreciable reduction in tumour burden was seen and, furthermore, five of the six patients reported serious adverse effects [24]. A number of techniques have been employed in later studies to try and enhance the anti-tumour effect of NY-ESO-1 TCR-T cells. For example, one

trial (NCT03017131) utilised the pyrimidine nucleoside analogue Decitabine as well as IL-2 with TCR-T cells, aiming to measure toxicity, persistence of TCR-T cells and disease response. In addition to this, researchers plan to sample tumours in any disease recurrence following TCR-T treatment to assess for MHC/NY-ESO-1 levels and better understand treatment resistance mechanisms. An ongoing third study by the same group (NCT03691376) employs a Melphalan myeloablative conditioning regimen before intravenous autologous TCR lymphocytes and haemopoietic stem cells directed against NY-ESO-1 to assess whether this strategy increases TCR survival and clinical response.

A novel approach using TCR-T cells in solid cancers, including OC, is being trialled with an estimated enrolment of 271 participants in a phase II study that started in 2018 (NCT03412877). The most tumour-reactive TILs from each participant's tumour sample will be selected, their TCR isolated and genetically expressed in autologous peripheral blood lymphocytes to create a TCR-T product. This personalised approach aims to combine the specificity of TIL with the cytotoxicity of effector T cells. One cohort will also receive PD-1 blockade with Pembrolizumab to assess whether this strategy can further enhance survival of TCR-T cells and improve response rates.

1.3. Tumour-Infiltrating Lymphocytes

Tumour-infiltrating lymphocytes have become increasingly recognised over recent years as playing an important role in the growth and control of solid tumours. TIL therapy, unlike engineered T-cell therapy, is associated with fewer incidences of CRS or immune effector cell-associated neurotoxicity (ICANS), resulting in a more favourable toxicity profile [25]. The use of high-dose non-myeloablative lymphodepletion (NMA-LD) and IL-2 post-transfer has, however, been linked to high-grade adverse events associated with TIL therapy.

NMA-LD is frequently reported to be associated with high-grade haematological adverse events, whilst recombinant IL-2 can lead to multi-organ toxicities, including heart, kidneys and lungs, as well as systemic toxicity, such as capillary leak syndrome [26]. Although these aspects of TIL therapy often lead to a requirement for inpatient management with specialist support, in most cases these high-grade toxicities occur acutely and can be addressed within the same inpatient admission [26][27]. Additionally, the 'one-off' nature of TIL therapy, in contrast to the majority of current standard-of-care anti-cancer approaches, makes it less time-consuming for patients and avoids the need for frequent appointments.

A 2017 prospective study by Goode et al. of over 5500 patients with OC found that TILs were often present in the epithelial tumour islets, with the highest infiltration found in HGSOC [28]. Importantly, an association was observed between increased levels of TILs and overall survival, which was most significant in the HGSOC group. These cells can be harvested from the patient's tumour tissue, expanded *ex vivo* and transferred back to them as a form of ACT. A key difference between this approach and CAR-T cells and TCR-T cells is the reliance on pre-existing TILs in the patient's tumour sample and the challenge of expanding this cell population *ex vivo*.

Earlier trials in the 1990s compared giving TILs vs. TILs with chemotherapy and showed some promising results. For example, Aoki et al. reported complete response in seven out of ten patients with advanced epithelial OC who

received TILs with a cisplatin-based chemotherapy regimen [29]. Following on from this, Fujita et al. conducted a study to compare TIL plus standard chemotherapy vs. standard chemotherapy alone in the adjuvant setting following primary debulking of epithelial OC [30]. A significantly greater long-term survival rate was observed in the TIL group, suggesting that TILs could play a crucial role in preventing disease recurrence in epithelial OC and work synergistically with standard chemotherapy.

Much like endogenous T-cells, transferred TILs will be susceptible to the well-characterised immune regulation at play in the TME, which may be overcome by using combination therapy with ICIs [31]. The National Center for Cancer Immune Therapy has produced several clinical trials using TIL in OC patients, including in combination with ICIs. An initial pilot trial treated six platinum-resistant OC participants with TILs following LD chemotherapy and found 3–5 month SD in most, followed by progression [32]. Of note, they observed high levels of TIL 'exhaustion markers' such as PD-1 and LAG-3 post infusion, as well as increased expression of MHC-II and PD-L1 in the tumour tissue, which may be impeding the efficacy of the treatment. Based on these results, a similar follow-up study of six patients was conducted with the addition of the ICI Ipilimumab prior to TIL harvest. At 12 months, five participants had SD and one had PR, indicating that the addition of ICIs may increase TIL yield and augment the cytotoxic effect of these cells in the tumour. Analysis of the tumour samples again found expression of the inhibitory coreceptor LAG-3, which is known to interact with MHC-II on tumour cells. This was thought to be an additional target that could be utilised in improving the outcome of TIL therapy. A third study began in 2021 (NCT04611126) with an estimated recruitment of around 18 participants with advanced ovarian, fallopian tube and primary peritoneal cancer. One cohort will receive the same regimen of ICI along with TILs whilst another cohort will also receive the LAG-3 inhibitor Relatlimab with PD-1 inhibitor Nivolumab. This trial remains in the recruitment phase and aims to provide data on safety profile and response rates of this combinatorial approach.

A similar approach is being adopted in an ongoing study (NCT03158935) in which a cohort of patients with platinum-resistant OC will receive TILs followed by the PD-1 inhibitor Pembrolizumab [33]. An additional trial with an estimated enrolment of 15 participants with epithelial OC, fallopian tube or peritoneal cancer is currently recruiting (NCT03412526). Participants will receive LD chemotherapy followed by a single treatment of 2Gy whole-body radiotherapy before infusion of TILs and recombinant IL-2.

2. Vaccines (Cell-Based)

Although not an ACT as such, vaccines can provide an alternative method of harnessing the host cellular and humoral immune system to target cancer-associated antigens. Clinical trials over the last 20 years have tested vaccines against OC antigens in both the adjuvant setting and in those with recurrent or persistent disease. Advantages to vaccine therapy include vaccines' potential to induce immunity against multiple antigens, which may be particularly beneficial in OC owing to their heterogeneity. Vaccines may also be useful to enhance the effects of other immunotherapy agents, such as ICIs.

Vaccines have been studied in the setting of advanced metastatic OC as a method of achieving disease control, often used in conjunction with other modalities of treatment. A novel approach using dendritic cell-based vaccine in

combination with a VEGF inhibitor, Bevacizumab, with or without cyclophosphamide, was adopted by Tanyi et al. in a trial that began in 2010 involving 25 platinum pre-treated participants with recurrent advanced epithelial OC [34]. They reported a median time to disease progression of 15 months amongst those patients who had objective T-cell vaccine responses. Furthermore, the group that received cyclophosphamide had evidence of significantly increased expansion of vaccine-reactive T cells as well as increased OS when compared with the non-cyclophosphamide cohort. There are also peptide-based vaccines under investigation, such as the multi-epitope anti-folate receptor vaccine that was used in combination with a PD-L1 inhibitor, Durvalumab, in a heavily pre-treated population; it showed promising results with one PR and nine SD [35]. Overall, these findings suggest the potential benefit of vaccines, at least as an adjunctive therapy in combination with other standard-of-care treatments.

References

1. Xu, X.; Qiu, J.; Sun, Y. The Basics of CAR T Design and Challenges in Immunotherapy of Solid Tumors—Ovarian Cancer as a Model. Hum. Vaccines Immunother. 2017, 13, 1548–1555.
2. Fowler, N.H.; Dickinson, M.; Dreyling, M.; Martinez-Lopez, J.; Kolstad, A.; Butler, J.; Ghosh, M.; Popplewell, L.; Chavez, J.C.; Bachy, E.; et al. Tisagenlecleucel in Adult Relapsed or Refractory Follicular Lymphoma: The Phase 2 ELARA Trial. Nat. Med. 2022, 28, 325–332.
3. Maude, S.L.; Laetsch, T.W.; Buechner, J.; Rives, S.; Boyer, M.; Bittencourt, H.; Bader, P.; Verneris, M.R.; Stefanski, H.E.; Myers, G.D.; et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N. Engl. J. Med. 2018, 378, 439–448.
4. Locke, F.L.; Ghobadi, A.; Jacobson, C.A.; Miklos, D.B.; Lekakis, L.J.; Oluwole, O.O.; Lin, Y.; Braunschweig, I.; Hill, B.T.; Timmerman, J.M.; et al. Long-Term Safety and Activity of Axicabtagene Ciloleucel in Refractory Large B-Cell Lymphoma (ZUMA-1): A Single-Arm, Multicentre, Phase 1–2 Trial. Lancet Oncol. 2019, 20, 31–42.
5. Sterner, R.C.; Sterner, R.M. CAR-T Cell Therapy: Current Limitations and Potential Strategies. Blood Cancer J. 2021, 11, 69.
6. Zhang, H.; Ye, Z.; Yuan, Z.; Luo, Z.; Jin, H.; Qian, Q. New Strategies for the Treatment of Solid Tumors with CAR-T Cells. Int. J. Biol. Sci. 2016, 12, 718–729.
7. Flugel, C.L.; Majzner, R.G.; Krenciute, G.; Dotti, G.; Riddell, S.R.; Wagner, D.L.; Abou-el-Enein, M. Overcoming On-Target, off-Tumour Toxicity of CAR T Cell Therapy for Solid Tumours. Nat. Rev. Clin. Oncol. 2023, 20, 49–62.
8. Ordóñez, N.G. Application of Mesothelin Immunostaining in Tumor Diagnosis. Am. J. Surg. Pathol. 2003, 27, 1418–1428.

9. Morello, A.; Sadelain, M.; Adusumilli, P.S. Mesothelin-Targeted CARs: Driving T Cells to Solid Tumors. Cancer Discov. 2016, 6, 133–146.
10. Haas, A.R.; Tanyi, J.L.; O'Hara, M.H.; Gladney, W.L.; Lacey, S.F.; Torigian, D.A.; Soulen, M.C.; Tian, L.; McGarvey, M.; Nelson, A.M.; et al. Phase I Study of Lentiviral-Transduced Chimeric Antigen Receptor-Modified T Cells Recognizing Mesothelin in Advanced Solid Cancers. Mol. Ther. 2019, 27, 1919–1929.
11. Wang, Z.; Li, N.; Feng, K.; Chen, M.; Zhang, Y.; Liu, Y.; Yang, Q.; Nie, J.; Tang, N.; Zhang, X.; et al. Phase I Study of CAR-T Cells with PD-1 and TCR Disruption in Mesothelin-Positive Solid Tumors. Cell. Mol. Immunol. 2021, 18, 2188–2198.
12. Felder, M.; Kapur, A.; Gonzalez-Bosquet, J.; Horibata, S.; Heintz, J.; Albrecht, R.; Fass, L.; Kaur, J.; Hu, K.; Shojaei, H.; et al. MUC16 (CA125): Tumor Biomarker to Cancer Therapy, a Work in Progress. Mol. Cancer 2014, 13, 129.
13. Zhai, Y.; Lu, Q.; Lou, T.; Cao, G.; Wang, S.; Zhang, Z. MUC16 Affects the Biological Functions of Ovarian Cancer Cells and Induces an Antitumor Immune Response by Activating Dendritic Cells. Ann. Transl. Med. 2020, 8, 1494.
14. O'Cearbhaill, R.E.; Park, J.H.; Halton, E.F.; Diamonte, C.R.; Mead, E.; Lakhman, Y.; Kane, P.; Riviere, I.C.; Brentjens, R.J. A Phase I Clinical Trial of Autologous Chimeric Antigen Receptor (CAR) T Cells Genetically Engineered to Secrete IL-12 and to Target the MUC16ecto Antigen in Patients (Pts) with MUC16ecto+ Recurrent High-Grade Serous Ovarian Cancer (HGSOC). Gynecol. Oncol. 2020, 159, 42.
15. Bax, H.J.; Chauhan, J.; Stavraka, C.; Santaolalla, A.; Osborn, G.; Khiabany, A.; Grandits, M.; López-Abente, J.; Palhares, L.C.G.F.; Chan Wah Hak, C.; et al. Folate Receptor Alpha in Ovarian Cancer Tissue and Patient Serum Is Associated with Disease Burden and Treatment Outcomes. Br. J. Cancer 2023, 128, 342–353.
16. Elnakat, H. Distribution, Functionality and Gene Regulation of Folate Receptor Isoforms: Implications in Targeted Therapy. Adv. Drug Deliv. Rev. 2004, 56, 1067–1084.
17. Kershaw, M.H.; Westwood, J.A.; Parker, L.L.; Wang, G.; Eshhar, Z.; Mavroukakis, S.A.; White, D.E.; Wunderlich, J.R.; Canevari, S.; Rogers-Freezer, L.; et al. A Phase I Study on Adoptive Immunotherapy Using Gene-Modified T Cells for Ovarian Cancer. Clin. Cancer Res. 2006, 12, 6106–6115.
18. Cai, D.; Li, J.; Liu, D.; Hong, S.; Qiao, Q.; Sun, Q.; Li, P.; Lyu, N.; Sun, T.; Xie, S.; et al. Tumor-Expressed B7-H3 Mediates the Inhibition of Antitumor T-Cell Functions in Ovarian Cancer Insensitive to PD-1 Blockade Therapy. Cell. Mol. Immunol. 2020, 17, 227–236.
19. Gibbs, Z.A.; Whitehurst, A.W. Emerging Contributions of Cancer/Testis Antigens to Neoplastic Behaviors. Trends Cancer 2018, 4, 701–712.

20. Daudi, S.; Eng, K.H.; Mhawech-Fauceglia, P.; Morrison, C.; Miliotto, A.; Beck, A.; Matsuzaki, J.; Tsuji, T.; Groman, A.; Gnjatic, S.; et al. Expression and Immune Responses to MAGE Antigens Predict Survival in Epithelial Ovarian Cancer. PLoS ONE 2014, 9, e104099.
21. Hong, D.S.; Van Tine, B.A.; Biswas, S.; McAlpine, C.; Johnson, M.L.; Olszanski, A.J.; Clarke, J.M.; Araujo, D.; Blumenschein, G.R.; Kebriaei, P.; et al. Autologous T Cell Therapy for MAGE-A4+ Solid Cancers in HLA-A*02+ Patients: A Phase 1 Trial. Nat. Med. 2023, 29, 104–114.
22. Szender, J.B.; Papanicolau-Sengos, A.; Eng, K.H.; Miliotto, A.J.; Lugade, A.A.; Gnjatic, S.; Matsuzaki, J.; Morrison, C.D.; Odunsi, K. NY-ESO-1 Expression Predicts an Aggressive Phenotype of Ovarian Cancer. Gynecol. Oncol. 2017, 145, 420–425.
23. Butler, M.O.; Saibil, S.; Bonilla, L.; Franke, N.; Hakgor, S.; Boross-Harmer, S.; Majeed, H.; Nelles, M.; Ohashi, P.S.; Ross, K.; et al. Effect of Minimal Lymphodepletion Prior to ACT with TBI-1301, NY-ESO-1 Specific Gene-Engineered TCR-T Cells, on Clinical Responses and CRS. J. Clin. Oncol. 2019, 37 (Suppl. S15), 2537.
24. Odunsi, K.; Cristea, M.C.; Dorigo, O.; Jazaeri, A.A.; Slomovitz, B.M.; Chagin, K.; Van Winkle, E.; Kari, G.; Iyengar, M.; Norry, E.; et al. A Phase I/IIa, Open Label, Clinical Trial Evaluating the Safety and Efficacy of Autologous T Cells Expressing Enhanced TCRs Specific for NY-ESO-1 in Patients with Recurrent or Treatment Refractory Ovarian Cancer (NCT01567891). J. Clin. Oncol. 2017, 35 (Suppl. S15), TPS3094.
25. Wolf, B.; Zimmermann, S.; Arber, C.; Irving, M.; Trueb, L.; Coukos, G. Safety and Tolerability of Adoptive Cell Therapy in Cancer. Drug Saf. 2019, 42, 315–334.
26. Haanen, J.B.A.G.; Rohaan, M.; Borch, T.H.; van den Berg, J.H.; Met, Ö.; Foppen, M.G.; Granhøj, J.S.; Nuijen, B.; Nijenhuis, C.; Beijnen, J.H.; et al. LBA3 Treatment with Tumor-Infiltrating Lymphocytes (TIL) versus Ipilimumab for Advanced Melanoma: Results from a Multicenter, Randomized Phase III Trial. Ann. Oncol. 2022, 33, S1406.
27. O'Malley, D.; Lee, S.; Psyrri, A.; Sukari, A.; Thomas, S.; Wenham, R.; Gogas, H.; Jazaeri, A.; Monk, B.; Rose, P.; et al. 492 Phase 2 Efficacy and Safety of Autologous Tumor-Infiltrating Lymphocyte (TIL) Cell Therapy in Combination with Pembrolizumab in Immune Checkpoint Inhibitor-Naïve Patients with Advanced Cancers. J. Immunother. Cancer 2021, 9 (Suppl. S2), A523.
28. Goode, E.L.; Block, M.S. Dose-Response Association of CD8 + Tumor-Infiltrating Lymphocytes and Survival Time in High-Grade Serous Ovarian Cancer. JAMA Oncol. 2017, 3, e173290.
29. Aoki, Y.; Takakuwa, K.; Kodama, S.; Tanaka, K.; Takahashi, M.; Tokunaga, A.; Takahashi, T. Use of Adoptive Transfer of Tumor-Infiltrating Lymphocytes Alone or in Combination with Cisplatin-Containing Chemotherapy in Patients with Epithelial Ovarian Cancer. Cancer Res. 1991, 51, 1934–1939.

30. Fujita, K.; Ikarashi, H.; Takakuwa, K.; Kodama, S.; Tokunaga, A.; Takahashi, T.; Tanaka, K. Prolonged Disease-Free Period in Patients with Advanced Epithelial Ovarian Cancer after Adoptive Transfer of Tumor-Infiltrating Lymphocytes. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 1995, 1, 501–507.
31. Sarnaik, A.A.; Hamid, O.; Khushalani, N.I.; Lewis, K.D.; Medina, T.; Kluger, H.M.; Thomas, S.S.; Domingo-Musibay, E.; Pavlick, A.C.; Whitman, E.D.; et al. Lifileucel, a Tumor-Infiltrating Lymphocyte Therapy, in Metastatic Melanoma. J. Clin. Oncol. 2021, 39, 2656–2666.
32. Pedersen, M.; Westergaard, M.C.W.; Milne, K.; Nielsen, M.; Borch, T.H.; Poulsen, L.G.; Hendel, H.W.; Kennedy, M.; Briggs, G.; Ledoux, S.; et al. Adoptive Cell Therapy with Tumor-Infiltrating Lymphocytes in Patients with Metastatic Ovarian Cancer: A Pilot Study. OncoImmunology 2018, 7, e1502905.
33. Ethier, J.-L.; Bonilla, L.; Boross-Harmer, S.; Bouchard-Fortier, G.; Cipollone, J.; Clarke, B.A.; Dhani, N.C.; Easson, A.M.; Franke, N.; Goldstein, D.P.; et al. A Phase Ib Trial of Pembrolizumab (Pembro) Following Adoptive Cell Therapy (ACT) in Patients with Platinum-Resistant Ovarian Cancer; The ACTIVATE (Adoptive Cell Therapy InVigorated to Augment Tumor Eradication) Trial. J. Clin. Oncol. 2018, 36 (Suppl. S15), TPS5611.
34. Tanyi, J.L.; Bobisse, S.; Ophir, E.; Tuyaerts, S.; Roberti, A.; Genolet, R.; Baumgartner, P.; Stevenson, B.J.; Iseli, C.; Dangaj, D.; et al. Personalized Cancer Vaccine Effectively Mobilizes Antitumor T Cell Immunity in Ovarian Cancer. Sci. Transl. Med. 2018, 10, eaao5931.
35. Zamarin, D.; Walderich, S.; Holland, A.; Zhou, Q.; Iasonos, A.E.; Torrisi, J.M.; Merghoub, T.; Chesebrough, L.F.; Mcdonnell, A.S.; Gallagher, J.M.; et al. Safety, Immunogenicity, and Clinical Efficacy of Durvalumab in Combination with Folate Receptor Alpha Vaccine TPIV200 in Patients with Advanced Ovarian Cancer: A Phase II Trial. J. Immunother. Cancer 2020, 8, e000829.