Trial Watch: Adoptive cell transfer for oncological indications

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Abbreviations: ACT, adoptive cell transfer; CAR, chimeric antigen receptor; CIK, cytokine-induced killer; CMV, cytomegalovirus; CTL, cytotoxic CD8+ T lymphocytes; DC, dendritic cell; EBV, Epstein–Barr virus; HPV, human papillomavirus; HSC, haematopoietic stem cell transplantation; IL, interleukin; mAb, monoclonal antibody; MAGEA3, melanoma antigen family A3; MDSC, myeloid-derived suppressor cell; MLANA, melan-A; NK, natural killer; PBL, peripheral blood lymphocyte; PBMC, peripheral blood mononuclear cell; PMEL, premelanosome protein; TAA, tumor-associated antigen; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte; TLR, Toll-like receptor

Introduction

One particular paradigm of anticancer immunotherapy relies on the administration of (potentially) tumor-reactive immune effector cells. Generally, these cells are obtained from autologous peripheral blood lymphocytes (PBLs) ex vivo (in the context of appropriate expansion, activation, and targeting protocols), and re-infused into lymphodepleted patients along with immunostimulatory agents. In spite of the consistent progress achieved throughout the past two decades in this field, no adoptive cell transfer (ACT)-based immunotherapeutic regimen is currently approved by regulatory agencies for use in cancer patients. Nonetheless, the interest of oncologists in ACT-based immunotherapy continues to increase. Accumulating clinical evidence indicates indeed that specific paradigms of ACT, such as the infusion of chimeric antigen receptor (CAR)-expressing autologous T cells, are associated with elevated rates of durable responses in patients affected by various neoplasms. In line with this notion, clinical trials investigating the safety and therapeutic activity of ACT in cancer patients are being initiated at an ever increasing pace. Here, we review recent preclinical and clinical advances in the development of ACT-based immunotherapy for oncological indications.

Keywords: checkpoint blockers, chimeric antigen receptor, GM-CSF, TCR, TLR agonists, tumor-associated antigens

One strategy to eradicate established malignant lesions involves the intravenous administration of autologous or allogeneic immune effector cells that are naturally or artificially endowed with tumoricidal activity and expanded/activated ex vivo.1-3 This approach, which is known as “adoptive cell transfer” (ACT) or “adoptive cell therapy”, relies on immune cell populations that mediate direct tumoricidal effects, including conventional cytotoxic CD8+ T lymphocytes (CTLs), given alone or together with helper CD4+ T cells, natural killer (NK) cells, and so-called “cytotoxic-induced killer” (CIK) cells (i.e., CD3+CD56+ NK cell-like non-MHC restricted CTLs).4,5 Therefore, ACT-based anticancer immunotherapy should be conceptually differentiated from both haematopoietic stem cell transplantation (H SCT) and dendritic cell (DC)-based vaccination. In the former scenario, neoplastic bone marrow progenitors are ablated by high dose chemoradiotherapy, and histocompatible haematopoietic stem cells are subsequently provided to reconstitute normal lympho-, myelo- and erythropoiesis.10-12 In the latter setting, autologous DCs are loaded ex vivo with a source of tumor-associated antigens (TAAs) and re-administered to patients along with immunostimulatory interventions, a protocol that aims at the elicitation of an endogenous, TAA-specific immune response.13-16 Thus, whereas the efficacy of DC-based anticancer interventions fully relies on the host immune system (implying that DC-based vaccination constitutes a bona fide example of active immunotherapy), this is not completely the case of ACT-based regimens. Nonetheless, the full-blown efficacy of ACT-based immunotherapy depends on the persistence, expansion and activation of
re-infused cells in vivo, which are supported by cellular and humoral components of the host immune system. Thus, ACT-based immunotherapeutic regimens cannot be considered as pure instances of passive immunotherapy.3,17

Elevated amounts of natural tumor-infiltrating lymphocytes (TILs) have been correlated with improved disease outcome in cohorts of patients affected by various neoplasms.18-23 Thus, TILs would represent a convenient source of potentially tumor-reactive cells for ACT-based immunotherapy.24-26 However, TILs are not always available since (1) not all neoplastic lesions can be surgically resected/biopsied, and (2) some tumors contain limited amounts of TILs. When TILs are not available, ACT-based immunotherapy relies upon PBLs that are artificially endowed (by genetic engineering) with tumouridal functions.5 This can be accomplished by stably transfecting PBLs with a construct coding for a TAA-specific T-cell receptor (TCR).5,27-30 or a so-called chimeric antigen receptor (CAR).31-37 The latter consists in the antigen-binding domain of a TAA-specific immunoglobulin fused in-frame with an intracellular signaling tail composed of one or more immunostimulatory modules.31-37 This technology is advantageous since it endows PBLs with the ability to recognize and kill (malignant) cells that express the CAR target in an MHC-independent manner.35,38-41 Additional advantageous features can be provided to PBLs via genetic engineering, including (but not limited to) (1) superior proliferative potential and in vivo persistence;46-49 (2) improved effector functions (i.e., cytotoxicity and cytokine secretion);47,50,51 and (3) enhanced tumor-homing capacities.52-53 Moreover, PBLs can be genetically modified and expanded/activated in the presence of pharmacological agents that prevent (at least to some extent) terminal differentiation.54-57 This is particularly relevant because terminally differentiated CTLs are generally characterized by reduced proliferative capacity and functional exhaustion.55,58-59

Cancer patients allocated to ACT-based immunotherapy are generally subjected to lymphodepleting chemo(radio)therapeutic regimens.60 A large body of clinical data indicates that this approach is indeed associated with improved disease outcome, presumably since (1) it efficiently relieves the immunosuppressive network established within malignant lesions and systemically by myeloid-derived suppressor cells (MDSCs) and CD4⁺CD25⁺FOXP3⁺ regulatory T cells (Tregs);61-69 and (2) it consistently blunts the so-called “cytokine sink”, i.e., the ability of endogenous lymphocytes to compete with re-infused T, NK or CIK cells for critical cytokines like interleukin (IL)-7 and IL-15.70,71 Similarly, accruing preclinical and clinical evidence demonstrates that various chemo- and immunotherapeutic interventions can improve the efficacy of ACT.72-74 These interventions include (though presumably are not limited to) (1) various cytokines that support the expansion, survival or effector functions of re-infused lymphocytes (e.g., granulocyte-macrophage colony stimulating factor, GM-CSF; IL-2; IL-7);75-78 (2) Toll-like receptor (TLR) agonists (which normally function as immunological adjuvant);79-82 (3) conventional chemotherapeutics with off-target immunostimulatory effects, such as cyclophosphamide (an alkylating agent employed for the treatment of several neoplasms),83-88 gemcitabine (a nucleoside analog commonly used against pancreatic carcinoma patients),89-91 and oxaliplatin (a platinum salt approved for use in advanced colorectal carcinoma patients);92-94 (4) monoclonal antibodies (mAbs) that block immunological checkpoints, such as the cytotoxic T lymphocyte associated protein 4 (CTLA4)-targeting agent ipilimumab and nivolumab;95-97 (5) angiogenesis inhibitors (because they favor the normalization of the tumor vasculature, hence restoring/promoting the access of re-infused lymphocytes to the tumor bed);98,99 and (6) colony stimulating factor 1 receptor (CSF1R) inhibitors, which inhibit MDSCs and other immunosuppressive cell population, like tumor-associated macrophages.100-102

According to the results of various clinical trials, the re-infusion of autologous PBLs genetically modified to express TAA-specific TCRs or CARs is well tolerated by cancer patients, and can induce considerable rates of objective, long-lasting clinical responses, in particular among young individuals affected by hematological neoplasms.1-3,103 ACT-based immunotherapy is associated with a sizeable (though limited) risk of potentially lethal autoimmune reactions. These generally originate from the activation of adoptively transferred cells against healthy tissues that express TAA-related antigenic determinants.8,104-106 As a standalone example of such risk, 2 y ago Morgan and colleagues reported the unexpected death of two among nine subjects with melanoma antigen family A3 (MAGEA3) tumors treated with autologous PBLs expressing a MAGEA3-specific TCR.8,106 Such an unfortunate occurrence was subsequently attributed to the ability of adoptively transferred PBLs to cross-recognize MAGEA12-expressing cells in the brain.106 Besides these potentially fatal (but fortunately rare) toxicities, ACT is associated with relatively mild side effects, including the so-called “cytokine release syndrome”, which reflects the massive activation of adoptively transferred cells against their targets.105 Such events, however, are generally manageable by the administration of corticosteroids or more specific immunosuppressive agents, such as the IL-6-targeting mAb tocilizumab.5,72,73,108-111 Of note, despite encouraging preclinical results,112-118 the adoptive transfer of NK cells to cancer patients appears to mediate limited therapeutic effects, for hitherto unclear reasons.119-121 Efforts are currently being devoted to the development of novel approaches to fully harness the cytotoxic potential of NK cells for ACT-based immunotherapy.122-126

In spite of an accruing body of compelling clinical data, no ACT-based immunotherapeutic regimen is currently approved by the US Food and Drug Administration or equivalent regulatory agency for use in cancer patients. Along the lines of our monthly Trial Watch series,127,128 here we summarize recent preclinical, translational and clinical progress in the development of ACT-based immunotherapeutic regimens for cancer therapy.

**Update on the development of ACT-based anticancer immunotherapy**

**Completed clinical studies**

Since the submission of our most recent Trial Watch discussing this topic (April 2014),129 data from no less than 20 clinical trials investigating the therapeutic profile of ACT-based
immunotherapy have been published in the peer-reviewed scientific literature (source http://www.ncbi.nlm.nih.gov/pubmed), and preliminary results from five additional studies have been presented at the American Society of Clinical Oncology (ASCO) annual meeting (source http://meetinglibrary.asco.org/). Reflecting previous, very encouraging clinical findings, a significant fraction of these studies involved CAR-expressing autologous T cells.\(^{130-137}\) These were redirected against CD19, which is expressed by various forms of leukemia,\(^{130,136,137}\) CD20, a lymphoma-associated antigen,\(^{131}\) melan-A (MLANA), which is selectively expressed by melanocytes,\(^{132}\) NY-ESO-1, a cancer/testis antigen expressed by multiple malignancies,\(^{133}\) mutant epidermal growth factor receptor (EGFR), which is found at the surface of cancer cells of various origin,\(^{134}\) or mesothelin, another relatively widespread TAA.\(^{135}\) In this context, CAR-expressing T cells were administered as standalone immunotherapeutic interventions,\(^{133-136}\) combined with standard chemotherapy,\(^{131}\) in conjunction with tumor-targeting mAbs,\(^{137}\) or in the context of DC-based vaccination.\(^{132}\)

In addition, various studies relied on the administration of autologous TILs or peripheral blood mononuclear cells (PBMCs) expanded \textit{ex vivo} generally (but not always) upon selection for antigen specificity, or exposure to a source of TAs in the presence of activating stimuli.\(^{138-149}\) In particular, three of these trials involved CTLs specific for so-called viral TAs, i.e., TAs encoded by oncogenic viruses (uniquely expressed by malignant cells),\(^{144,145,149}\) namely cytomegalovirus (CMV), which is implicated in the pathogenesis of several tumors including glioblastoma and nasopharyngeal carcinoma,\(^{144}\) Epstein–Barr virus (EBV), which is etiologically linked to lymphomagenesis,\(^{145}\) and human papillomavirus type 16 and 18 (HPV-16 and HPV-18), which are associated with a considerable proportion of cervical carcinoma cases.\(^{149}\) Two studies relied on the administration of CTLs selected for their ability to react against shared TAs, including \textit{erb-b2} receptor tyrosine kinase 2 (ERBB2), which is overexpressed by an elevated fraction of breast carcinomas,\(^{147}\) MLANA and premelanosome protein (PMEL), both of which are expressed by melanoma cells.\(^{140}\) One study utilized a preparation of TILs highly enriched in polyfunctional CD4\(^+\) T\(_{\text{IL}}\) cells specific for a patient-specific mutation in \textit{erb}b2 interacting protein (ERBB2IP).\(^{142}\) The remaining studies investigated the therapeutic profile of unselected TILs or PBMCs, expanded \textit{ex vivo} according to conventional procedures.\(^{138,141,143,146,148}\) In these clinical settings, ACT was employed as a standalone immunotherapeutic intervention,\(^{146-149}\) performed in the context of DC- or peptide-based anticancer vaccination,\(^{138}\) or combined with total body irradiation.\(^{143}\)

Three studies investigated the clinical profile of autologous CIK cells,\(^{150,151}\) administered with either standard chemotherapy,\(^{151}\) or DC-based interventions.\(^{150,152}\) Finally, two studies assessed the safety and efficacy of adoptively transferred NK cells,\(^{153,156}\) given either upon HSCT,\(^{153}\) or in combination with autologous DCs.\(^{154}\)

Taken together, the results of these studies corroborate the notion that ACT-based immunotherapy is well tolerated and can induce durable clinical responses in a consistent proportion of patients affected by various neoplasms. As a single exception, Chandran and colleagues (National Cancer Institute, NIH, Bethesda, MD, USA) reported that the administration of highly avid PMEL- and MLANA-specific CTLs together with IL-2 was unable to produce objective therapeutic benefits in a cohort of 15 patients with refractory metastatic melanoma, despite normal clonal engraftment and documentable cytototoxic activity against melanocytes.\(^{140}\)

**Preclinical and translational advances**

Among the preclinical and translational studies dealing with ACT-based immunotherapy published during the last 13 months in peer-reviewed scientific journals, we found of particular interest the works of (1) Crompton and colleagues (from the National Cancer Institute, NIH, Bethesda, MD, USA), who demonstrated that chemical inhibitors of \textit{v-akt} murine thymoma viral oncogene homolog 1 (AKT1) can be employed to expand tumor-specific CTLs with memory T-cell features;\(^{155}\) (2) Geng and collaborators (from the University of Maryland, Baltimore, MD, USA), who genetically engineered TAA-specific CTLs to secrete bacterial flagellin (a TLR5 agonist), resulting in superior antitumor activity;\(^{156}\) (3) Soto-Pantoja and co-workers (from the National Cancer Institute, NIH, Bethesda, MD, USA), who found that the expression of CD47 (an anti-phagocytic signal)\(^{157-159}\) considerably blunts the ability of radiation therapy to promote the activation of adoptively transferred CTLs;\(^{160-162}\) (4) Huang et al. (from the Harvard Medical School, Boston, MA, USA), who demonstrated that carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) heterodimerizes with heparitin A virus cellular receptor 2 (HAVCR2, best known as TIM-3) on the surface of activated CTLs, and that this interaction is required for the immunosuppressive activity of TIM-3;\(^{163}\) (5) Lin and colleagues (from the Duke University Medical Center, Durham, NC, USA), who identified miR-23a as a strong repressor of the transcription factor PR domain containing 1, with ZNF domain (PRDM1, also known as BLIMP1), which is involved in CTL effector functions;\(^{164}\) (6) Caruana and collaborators (from the Baylor College of Medicine and Houston Methodist Hospital, Houston, TX, USA), who engineered CAR-expressing CTLs to recover the ability to secrete heparanase (an enzyme involved in the degradation of the extracellular matrix), resulting in improved tumor infiltration and accrued antineoplastic activity;\(^{165}\) and (7) Motz and coworkers (from the University of Pennsylvania School of Medicine, Philadelphia, PA, USA), who found that the neoplastic endothelium actively counteracts tumor infiltration by adaptively transferred CTLs by expressing pro-apoptotic FAS ligand (FASLG).\(^{166-168}\)

**Recently initiated clinical trials**

Since the submission of our latest Trial Watch dealing with this topic (April 2014),\(^{129}\) no less than 67 different clinical trials have been launched to test the safety and efficacy of ACT-based immunotherapy in cancer patients (source http://clinicaltrials.gov/). A considerable proportion of these studies investigate the therapeutic profile of autologous PBMCs expanded \textit{ex vivo} and
genetically modified to express a TAA-specific CAR (NCT02081937; NCT02107963; NCT02111850; NCT-02132624; NCT02134262; NCT02135406; NCT02146924; NCT02153580; NCT02159495; NCT02186680; NCT-02194374; NCT02203825; NCT02208362; NCT02215967; NCT02228096; NCT02247609; NCT02259556; NCT-02277522; NCT02311621; NCT02315612; NCT02349724; NCT02395250). With a few exceptions, namely NCT02208362 (a Phase I study enrolling brain cancer patients), NCT02395250 (a Phase I trial recruiting individuals with hepatocellular carcinoma), NCT02311621 (a Phase I study enrolling subjects with neuroblastoma), as well as NCT02107963 and NCT02349724 (two Phase I studies recruiting patients with solid neoplasms), all these trials involve patients with hematological malignancies (mainly, acute lymphoblastic leukemia, B-cell lymphoma and multiple myeloma). In virtually all these studies, ACT is performed as a standalone immunotherapeutic intervention upon lymphodepleting chemotherapy. We found of particular interest the approach adopted by NCT02065362, in which EBV-specific CTLs are genetically modified to express a dominant negative variant of transforming growth factor, β receptor 1 (TGFB1), rendering these cells resistant to transforming growth factor, β 1 (TGFB1)-driven immunosuppression (Table 1).

Another considerable fraction of the clinical trials initiated during the last 13 months to assess the safety and efficacy of ACT-based immunotherapy in cancer patients involves autologous PBMCs expanded ex vivo and genetically engineered to express a TAA-specific TCR (NCT02059850; NCT02062359; NCT02070406; NCT02096614; NCT02153905; NCT-02210104; NCT02280811; NCT02319824; NCT02366546; NCT02390739). The vast majority of these studies specifically target NY-ESO-1 (NCT02059850; NCT02062359; NCT-02070406; NCT02210104; NCT02319824; NCT02366546) or members of the melanoma antigen protein family such as MAGEA3 and MAGEA4 (NCT02096614; NCT02153905). In addition, NCT02390739 (a Phase I/II study) tests the therapeutic profile of autologous PBMCs transduced with a construct coding for a murine TCR specific for thyroglobulin (TG), which is selectively expressed by thyrocytes, in thyroid cancer patients; NCT02173093 (a Phase I/II trial) investigates the safety and efficacy of CTLs coated with a bispeciﬁc antibody targeting ganglioside GD2 (a neuroblastoma-associated antigen) in neuroblastoma and osteosarcoma patients; and NCT02274506 initially intended to assess the clinical profile of allogenic CTLs genetically redirected against CD19 in subjects with leukemia or lymphoma. NCT02274506, however, has been withdrawn prior to enrollment for undisclosed reasons (Table 1).

Some recently initiated clinical trials investigate the safety and efficacy of CTLs selected for pre-determined features, including TAA speciﬁcity (NCT02203903; NCT02239861; NCT02291848); activation state, based on the surface expression of tumor necrosis factor receptor superfamily, member 9 (TNFRSF9, also known as CD137 or 4-1BB), and differentiation, based on the reduced expression of CD45RA (NCT02337595). Moreover, a few recent study assess the therapeutic proﬁle of CTLs speciﬁc for viral antigens, including E6 and E7 from HPV-16/-18 (in cervical carcinoma patients) (NCT02280811; NCT02379520), EBV-encoded proteins (in subjects with EBV-associated hematological malignancies) (NCT02057445; NCT02065362) and CMV-derived antigens (in nasopharyngeal carcinoma patients) (NCT02210065). All these studies rely on ACT as a standalone immunotherapeutic intervention following lymphodepleting chemotherapy. We found of particular interest the approach adopted by NCT02065362, in which EBV-specific CTLs are genetically modiﬁed to express a dominant negative variant of transforming growth factor, β receptor 1 (TGFB1), rendering these cells resistant to transforming growth factor, β 1 (TGFB1)-driven immunosuppression (Table 1).

A relatively heterogeneous group of recent clinical trials assesses the safety and efﬁcacy of autologous PBLs or TILs (NCT02133196; NCT02277392; NCT02278887; NCT-02327390; NCT02342613; NCT02360579; NCT02375984) or allogeneic CTLs (NCT02065869) expanded ex vivo according to conventional protocols (optionally in the presence of activating stimuli, such as in NCT02277392; NCT02342613) or upon exposure to pharmacological agents that promote T-cell rejuvenation. These studies mainly enroll melanoma patients (NCT02278887; NCT02327390; NCT-02360579; NCT02375984) or subjects with hematological malignancies (NCT02065869; NCT02342613). Three clinical trials investigate the therapeutic efﬁcacy of CIK cells, either administered as standalone immunotherapeutic interventions (NCT02280278) or combined with DC-based vaccination (NCT02202928; NCT02215837), in patients with solid tumors. Finally, seven studies test the clinical proﬁle of autologous (NCT02118415; NCT02185781; NCT02229266) or allogeneic (NCT02100891; NCT02123836; NCT02316964) NK cells, in subjects affected by hematological malignancies (NCT-02123836; NCT02185781; NCT02229266; NCT02316964) or solid neoplasms (NCT02100891; NCT02118415) (Table 1).

As for the studies discussed in our previous Trial Watches dealing with ACT-based anticancer immunotherapy, the following trials have changed status during the last 13 months: NCT01722149, NCT01735604, NCT01740557, NCT-01853631, NCT01883297, NCT01897610, NCT01955460, NCT02027935, NCT02050347, and NCT02051257, which are now listed as "Recruiting"; NCT01585415, NCT01653717, NCT01683279, NCT01723306, NCT01815749, and NCT02030847, which are now listed as "Active, not recruiting"; NCT01716364, whose status is now "Unknown"; and NCT01747486, which now appears as "Completed" (source http://clinicaltrials.gov/). To the best of our knowledge, however, the results of NCT01747486 (a Phase II studies testing the
| Type                      | Indication(s)          | Phase | Status   | TAA(s) | Co-encoded molecule(s) | Notes                                                                 | Ref.          |
|--------------------------|------------------------|-------|----------|--------|------------------------|----------------------------------------------------------------------|---------------|
| **Allogenic CTLs**       | Hematological malignancies | I     | Recruiting | CD19   | None                   | Genetically modified, as standalone intervention                       | NCT02274506  |
|                          |                        |       |          |        |                        |                                                                       | NCT02057445  |
|                          |                        | I/II  | Recruiting | n.a.   | n.a.                   | Genetically modified, as standalone intervention                       | NCT02065869  |
|                          |                        | I     | Recruiting | EBV antigens | None                   | Genetically modified, as standalone intervention                       | NCT02123836  |
|                          |                        | I     | Recruiting | n.a.   | n.a.                   | Combined with decitabine-based chemotherapy                           | NCT02316964  |
| **Allogenic NK cells**   | ALL MDS                | I     | Recruiting | n.a.   | n.a.                   | As standalone intervention                                              | NCT02100891  |
|                          | Hematological malignancies | n.a. | Not yet recruiting | n.a. | n.a.                   | As standalone intervention                                              | NCT02065362  |
|                          | Solid tumors           | II    | Recruiting | n.a.   | n.a.                   | As standalone intervention upon HSCT                                   | NCT02186860  |
| **Autologous CTLs**      | Hematological malignancies | I     | Recruiting | Various | None                   | Enriched, in TAA-specific cells, as standalone intervention            | NCT02203903  |
|                          | MM                     | I     | Not yet recruiting | Various | None                   | Enriched, in TAA-specific cells, as standalone intervention            | NCT02291848  |
|                          | Nasopharyngeal carcinoma | I     | Recruiting | None    | DN TGFβR1              | EBV-specific cells, as standalone intervention                         | NCT02065362  |
|                          | Reproductive tract neoplasms | I     | Not yet recruiting | E6 E7 | None                   | As standalone intervention                                              | NCT02217393  |
|                          | Solid tumors           | I/II  | Recruiting | GD2    | None                   | Armed with GD2-specific bispecific antibody, as standalone intervention | NCT02173093  |
|                          |                        | I     | Recruiting | Various | None                   | Enriched, in TAA-specific cells, as standalone intervention            | NCT02100891  |
| **Autologous NILs**      | Melanoma               | I     | Not yet recruiting | n.a. | n.a.                   | As standalone intervention                                              | NCT02327390  |
| **Autologous NK cells**  | ALL                     | I     | Recruiting | n.a. | n.a.                   | As standalone intervention                                              | NCT02185781  |
|                          | AML                    | II    | Not yet recruiting | n.a. | n.a.                   | Combined with cytarabine-based chemotherapy                           | NCT02229266  |
|                          | NSCLC                  | II    | Recruiting | n.a.   | n.a.                   | As standalone intervention                                              | NCT02118415  |
| **Autologous PBMCs**     | Gynecological tumors   | I     | Recruiting | n.a.   | n.a.                   | As standalone intervention                                              | NCT02227392  |
|                          | Hematological malignancies | I/II  | Recruiting | n.a.   | n.a.                   | Depleted in CD45RA<sup>+</sup> cells, standalone intervention          | NCT02327390  |
|                          |                        | I     | Recruiting | n.a.   | n.a.                   | Enriched in CMV-specific cells, as standalone intervention            | NCT02100865  |
| **Autologous TILs**      | Hematological malignancies | I     | Not yet recruiting | n.a. | n.a.                   | As standalone intervention                                              | NCT02342613  |
|                          | Lung carcinoma         | II    | Not yet recruiting | n.a. | n.a.                   | As standalone intervention                                              | NCT02133196  |
|                          | Melanoma               | II    | Not yet recruiting | Recruiting | n.a.                   | As standalone intervention                                              | NCT02360579  |
|                          |                        | II    | Recruiting | n.a.   | n.a.                   | As standalone intervention                                              | NCT02111863  |
|                          |                        | III   | Recruiting | n.a.   | n.a.                   | As standalone intervention                                              | NCT02375984  |
| **CAR-expressing CTLs**  | ALL                    | I     | Active, not recruiting | CD19 | tEGFR                  | As standalone intervention                                              | NCT02146924  |
|                          |                        | I     | Recruiting | CD19   | None                   | As standalone intervention                                              | NCT02186860  |
|                          |                        | II    | Recruiting | CD19   | None                   | As standalone intervention                                              | NCT02228906  |
|                          | B-cell neoplasms       | I     | Recruiting | CD22   | None                   | As standalone intervention                                              | NCT02315612  |
|                          | Brain neoplasms        | I     | Not yet recruiting | IL13RA2 | tCD19                  | As standalone intervention                                              | NCT02208362  |
|                          | CLL NHL                | I/II  | Recruiting | CD16   | None                   | Combined with rituximab-based immunotherapy                           | NCT02315118  |

(Continued on next page)
| Type | Indication(s) | Phase | Status | TAA(s) | Notes | Ref. |
|------|--------------|-------|--------|--------|-------|------|
| CAR-expressing CTLs | Hepatocellular carcinoma | I | Recruiting | GPC3 | None | As standalone intervention | NCT02395250 |
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| | Leukemia | I | Recruiting | CD19 | None | As standalone intervention | NCT02153820 |
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therapeutic profile of CTLs redirected against CD19 through the CAR technology in relapsing or refractory chronic lymphocytic leukemia patients) have not been released yet. The future will tell whether the expectations on the CAR technology will be met or whether another ACT regimen will obtain regulatory approval beforehand.

Concluding Remarks

The number of studies recently initiated to test the safety and efficacy of ACT-based immunotherapy in cancer patients does not cease to increase.12,72,73,129 Moreover, several startup companies focusing on the development of novel paradigms of ACT-based anticancer immunotherapy have recently been created.103 This reflects accumulating clinical data demonstrating that the adoptive transfer of CTLs is relatively safe and can induce durable responses in a large proportion of patients, especially when CTLs are genetically redirected against a specific TAA. Among all the ACT protocols currently being tested in the clinic, the infusion of autologous CTLs genetically engineered to express a TAA-specific CAR undoubtedly stands out as the most promising approach. Although security measures must be envisioned to avoid potentially lethal autoimmune reactions,179 CAR-expressing CTLs have the potential to become the first paradigm of ACT-based cancer immunotherapy approved for use in humans.

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