CART Initiatives in Europe

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The efficacy of chimeric antigen receptor T cells (CARTs) in B cell neoplasms, ALL, large B cell lymphoma, and now multiple myeloma has been one of the great achievements in the fight against cancer in recent decades (Porter et al. 2011). However, there is still a need to increase the proportion of responses (especially in NHL) (Locke et al. 2019) and to decrease the proportion of relapse (especially in ALL) (Grupp et al. 2013). More importantly, currently, commercial CAR-T products are not available for T cell neoplasms, myeloid malignant haemopathies, or solid tumours. As a reflection of the necessary efforts to expand the efficacy of CARTs, more than 500 clinical trials are currently underway worldwide, mostly led by American or Chinese groups. Unfortunately, European institutions are under-represented in these initiatives. It is our duty to push and harmonize European academic clinical trials. We identified 35 early clinical trials promoted by European groups in Eudract and ClinTrialsGov (20 February 2021) (Table 5.1). Among them, 20 are initiatives from academic institutions, and 15 are initiatives from European companies allied with European academic institutions. In this summary, CART clinical trials promoted by European academic centres or by small to medium European companies are listed. The aim is to inform European groups treating haemato-oncology diseases of the current situation in this field, facilitating the inclusion of patients in these clinical trials. We aim to support the groups promoting these studies to increase collaboration.

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Table 5.1 Ongoing CART clinical trials in Europe

Title	Clinical Trial Gov Identifier	EudraCT Number	Institution	Target	Age Population	Disease
EUROPEAN CLINICAL TRIALS PROMOTED BY ACADEMIC CENTER						
Evaluation of CAR19 T-cells as an Optimal Bridge to Allogeneic Transplantation (COBALT)	NCT02431988	2015-000348-40	University College London	CD19	all ages	NHL DLBC
CAR19 Donor Lymphocytes for Relapsed CD19+ Malignancies Following Allogeneic Transplantation (CARD)	NCT02893189		University College London	CD19	Adult	CD19+ diseases
CARPALL: Immunotherapy With CD19 CAR T-cells for CD19+ Haematological Malignancies	NCT02443831		University College London	CD19	Pediatric	ALL
Immunotherapy with CD19 CAR gene-modified EBV-specific CTLs after stem cell transplant in children with high-risk ALL	NCT01195480	2007-007612-29	University College London	CD19	Pediatric	ALL
Phase 1 . open label study of CRISPR-CAR genome edited T cells (TT52CAR19) in R/R B Cell ALL		2019-003462-40	Great Ormond Street Hospital	CD19	Pediatric	ALL
A Cancer Research UK Phase I Trial of Anti-GD2 CAR Transduced T-cells (1RG-CART) in Patients With R/R Neuroblastoma	NCT02761915		Great Ormond Street Hospital/CaResearchUK	GD2	all ages	Neuroblastoma
Phase I Trial: T4 Immunotherapy of Head and Neck Cancer	NCT01818323		King's College London	ErbB receptor	Adult	Head and Neck Cancer
Phase I Study for the Adoptive Transfer of Re-directed FAP-specific T Cells in the Pleural Effusion of Patients With Malignant Pleural Mesothelioma.	NCT01722149		University of Zurich	FAP	Adult	Mesothelioma
Targeting Leukemic Stem Cell Expressing the IL-1RAP Protein in CML	NCT02842320		Centre Hospitalier Universitaire de Besancon	IL-1RAP	Adult	CML
Phase I/II Study of Anti-GD2 CAR-Expressing T Cells in Pediatric Patients Affected by High Risk and/or R/R Neuroblastoma or Other GD2-positive Solid Tumors	NCT03373097	2017-002475-26	Bambino Gesù Hospital and Research Institute	GD2	Pediatric	Neuroblastoma
Phase I/II Study of Anti-CD19 Chimeric Antigen Receptor-Expressing T Cells in Pediatric Patients Affected by R/R CD19+ ALL and NHL	NCT03373071	2017-002088-16	Bambino Gesù Hospital and Research Institute	CD19	Pediatric	CD19+ diseases
Phase 1-2a Trial to Determine the Feasibility and Safety of a Single Dose of Transposon-manipulated AlloCARCIK-CD19 Cells in R/R B-cell ALL, After HSCT	NCT03389035	2017-000900-38	Fondazione Matilde Tettamanti Menotti De Marchi Onlus	CD19	all ages	ALL
Pilot Study on the Infusion of Differentiated Autologous T-cells with Anti-CD19 Specificity CAR (ARI0001)in Patients With R/R CD19+ Leukemia or Lymphoma	NCT03144583	2016-002972-29	Hospital Clinic Barcelona	CD19	all ages	CD19+ diseases

Clinical Trial Using Humanized CART Directed Against BCMA (ARI0002h) in Patients With Relapsed/Refractory Multiple Myeloma to Proteasome Inhibitors, Immunomodulators and Anti-CD38 Antibody	NCT04309981	2019-001472-11	Hospital Clinic Barcelona	BCMA	Adult	MM
Phase 2 Study of the Infusion of ARI-0001 Cells in Patients With CD19 + Acute Lymphoid Leukemia Resistant or Refractory to Therapy (CART19-BE-02)	NCT04778579		Hospital Clinic Barcelona	CD19	Adult	ALL
Immunotherapy with differentiated T lymphocytes genetically modified to express a chimeric receptor with anti-CD30 specificity in patients with classic Hodgkin's lymphoma and NHL-T CD30+		2019-001263-70	IIBSP-Sant Pau Hospital	CD30	Adult	Hodgkin lymphoma and T-NHL CD30+
CD19-targeting 3rd generation CAR T cells for refractory B cell malignancy - a phase I/IIa trial.	NCT03068416	2013-001393-19	Uppsala University	CD19	all ages	CD19+ diseases
T lymphocytes transduced by RV-SFG-CD19-CD28 4-1BBzeta retroviral vector - A unicenter Phase I /II clinical trial	NCT03676504	2016-004808-60	University Hospital Heidelberg	CD19	all ages	CD19+ diseases
CD19-targeting 3rd generation CAR T cells for refractory B cell malignancy - a phase I/IIa trial. A phase II trial.		2016-004043-36	Uppsala University	CD19	all ages	CD19+ diseases
A phase I/IIa clinical trial to assess feasibility, safety and antitumor activity of autologous SLAMF7 CAR-T cells in MM	NCT04499339	2019-001264-30	Universitätsklinikum Würzburg	SLAMF7	Adult	MM
EUROPEAN CLINICAL TRIALS PROMOTED BY EUROPEAN COMPANIES						
A Phase I-IIa trial to assess the safety and antitumor activity of autologous CD44v6 CAR T-cells in AML and MM expressing CD44v6.	NCT04097301	2018-000813-19	MolMed S.p.A.	CD44v6	all ages	MM
A Single-Arm, Open-Label, Multi-Centre, Phase I/II Study Evaluating the Safety and Clinical Activity of AUTO3, a CAR T Cell Treatment Targeting CD19 And CD22 in Paediatric And Young Adult Patients With R/R -ALL	NCT03289455	2016-004680-39	Autolus Limited	CD19/CD22	Pediatric	ALL
A Single Arm, Open-label, Multi-centre, Phase I/II Study Evaluating the Safety and Clinical Activity of AUTO3, a CAR T Cell Treatment Targeting CD19 and CD22 With PD1 Antibody in Patients With R/R DLBCL	NCT03287817	2016-004682-11	Autolus Limited	CD19/CD22	Adult	HNL DLBC
A Single Arm, Open-Label, Multi-centre, Phase I/II Study Evaluating the Safety And Clinical Activity of AUTO4, a CAR T Cell Treatment Targeting TRBC1, in patients With R/R TRBC1 Positive Selected T cell NHL	NCT03590574	2017-001965-26	Autolus Limited	TRBC1	Adult	T-NHL
A Single Arm, Open-Label, Multi-Centre, Phase I/II Study Evaluating the Safety and Clinical Activity of AUTO3, a CAR T Cell Treatment Targeting CD19 and CD22 with Anti PD-1 Antibody in Patients with R/R DLBCL		2016-004682-11	Autolus Limited	CD19/CD22	Adult	HNL DLBC
A Single Arm, Open-Label, Multi-Centre, Phase I/II Study Evaluating the Safety and Clinical Activity of AUTO2, a CAR T Cell Treatment Targeting BCMA and TACI, in Patients with R/R MM	NCT03287804	2016-003893-42	Autolus Limited	CD19	Adult	MM
An Open-Label, Multi-Centre, Phase Ib/II Study Evaluating The Safety and Efficacy of AUTO1, A CAR T Cell Treatment Targeting CD19, in Adult Patients With R/ R B-ALL.	NCT04404660	2019-001937-16	Autolus Limited	CD19	Adult	ALL

(continued)

Table 5.1 (continued)

Title	Clinical Trial Gov Identifier	EudraCT Number	Institution	Target	Age Population	Disease
An Open-label, Phase I Study to Assess the Safety of Multiple Doses of CYAD-101, Administered After Standard FOLFOLX or FOLFIRI Chemotherapy in Patients With Unresectable Metastatic Colorectal Cancer	NCT03692429		Celyad	NKG2D	Adult	Colorectal Cancer
A phase 1, open label, non-comparative, study to evaluate the safety and the ability of UCART19 to induce molecular remission in paediatric patients with relapsed /refractory B-cell acute lymphoblastic leukaemia		2015-004293-15	Servier	CD19	Pediatric	ALL
Phase I, Open Label, Dose-escalation Study Followed by a Safety Expansion Part to Evaluate the Safety, Expansion and Persistence of a Single Dose of UCART19 in Patients With R/R B-ALL	NCT02746952	2016-000296-24	Servier	CD19	Adult	ALL
Multicenter Phase I Trial of MB-CART20.1 for the Treatment of Patients With Metastatic Melanoma	NCT03893019		Miltenyi Biotec GmbH	CD20	Adult	Melanoma
A Phase I/II Safety, Dose Finding and Feasibility Trial of MB-CART20.1 in Patients With Relapsed or Resistant CD20 Positive B-NHL	NCT03664635		Miltenyi Biotec GmbH	CD19	Adult	NHL DLBC
A Phase I/II Safety, Dose Finding and Feasibility Trial of MB-CART19.1 in Patients With Relapsed or Refractory CD19 Positive B Cell Malignancies	NCT03853616	2017-002848-32	Miltenyi Biotec GmbH	CD19	all ages	CD19+ diseases
Phase I, open label dose-escalation study to evaluate the safety, expansion, persistence and clinical activity of multiple infusions of UCART123 in patients with adverse genetic risk AML		2018-001018-14	CELLECTIS SA Fr	CD123	Adult	AML
Assessing Feasibility of Expansion and Characterization of Gamma Delta T Cells of Patients With AML as Starting Product for Generation of CD33-CD28 Gamma Delta T Cells	NCT03885076		Royal Marsden NHS/TC Biopharm	CD33	Adult	AML
Phase I/IIa, First-in-human (FIH), Open-label, Dose Escalation Trial With Expansion Cohorts to Evaluate Safety and Preliminary Efficacy of CLDN6 CAR-T +/- CLDN6 RNA-LPX in Patients With CLDN6-positive Relapsed or Refractory Advanced Solid Tumors	NCT04503278	2019-004323-20	BioNTech Cell & Gene Therapies GmbH	CLDN6	Adult	Solid tumor

Abbreviations: R/R, relapsed/refractory; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; MM, multiple myeloma; NHL, non hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; CML, chronic myeloid leukemia; HSCT, hemopoetic stem cell transplantation

Twelve European institutions are responsible for the 20 academic clinical trials (University College London, $n = 4$; Hospital Clinic of Barcelona, $n = 3$; Great Ormond Street Hospital, $n = 2$; Bambino Gesù, $n = 2$; University of Uppsala, $n = 2$; King's College, $n = 1$; Matilde Tettamanti, $n = 1$; Hospital Sant Pau, $n = 1$; University of Heidelberg, $n = 1$; and University of Wurzburg, $n = 1$). The most frequent target is CD19 ($n = 12$; for ALL, $n = 5$; NHL, $n = 1$; all B-lymphoid neoplasms, $n = 6$). Other targets are BCMA ($n = 1$; MM), CD30 ($n = 1$; HL and T-NHL), SLAMF7 ($n = 1$; MM), GD2 ($n = 2$, neuroblastoma), ErbBR ($n = 1$, neck and head tumours), Fap ($n = 1$, mesothelioma), and IL-1 RAP ($n = 1$, CML). Of the 20 clinical trials, 8 only included adults, 5 only included children, and 7 included all ages.

There were 16 additional clinical trials promoted by seven European pharma companies (Autolous, $n = 6$; Miltenyi, $n = 3$; Servier, $n = 2$; MolMed, $n = 1$; Celyad, $n = 1$; Cellectis, $n = 1$; TcBiopharm, $n = 1$, BioNTech, $n = 1$). Again, the most frequent target is CD19 ($n = 4$; for ALL, $n = 2$; NHL, $n = 1$; all B-lymphoid neoplasms, $n = 1$). Other targets are dual CD19/CD20 or CD19/CD22 ($n = 3$; ALL, $n = 1$; NHL, $n = 2$), CD20 ($n = 2$; melanoma, lymphoma), BCMA ($n = 1$; MM), CD123 ($n = 1$; AML), CD33 ($n = 1$, AML), NKG2D ($n = 1$, colon cancer), CD44v6 ($n = 1$, MM), TRCDB1 ($n = 1$, T-NHL), and CLDN6 ($n = 1$; colon cancer).

Hopefully, this list will grow as more clinical trials are set up. We intend to compile an ad hoc workshop to provide more comprehensive data, such as the characteristics of the genetic construct (type of costimulatory molecule, 2nd- or third-generation CAR), the vector (viral or nonviral), and the method of expansion (automated or manual) and the plans of these groups to go beyond a particular clinical trial (hospital exemption, EMA). We believe this information will be useful to increase efforts and fuel this field in Europe.

Two initiatives have recently been launched to foster collaboration and increase CART activity in Europe: GoCART and T2 EVOLVE Consortium.

GoCART is a strategic partnership between EBMT and EHA that includes a multistakeholder coalition of patient representatives, health care professionals, pharmaceutical companies, regulators, health technology assessment (HTA) bodies, reimbursement agencies, and medical organizations. Some of its most important aims include the following:

- Collaborate and share data and knowledge.
- Promote harmonization of data collection, education, standards of care, regulatory approval, centre qualification, and reimbursement processes.
- Set up a pre- and postmarketing registry that supports regulatory and shared research purposes.
- Develop a cellular therapy education and information program for patients and health care professionals.

T2EVOLVE is an alliance of academic and industry leaders in cancer immunotherapy under the European Union's Innovative Medicines Initiative (Supported from the European Union's Horizon 2020 Research and Innovation Programme). The key objective of T2EVOLVE is to accelerate development and increase the

awareness and access of cancer patients to immunotherapy with immune cells that harbour a genetically engineered TCR or CAR. Simultaneously, T2EVOLVE aims to provide guidance on sustainable integration of these treatments into the EU health care system. The T2EVOLVE consortium aims to achieve its goal by working on and improving the state of the art in the following key aspects:

- Selection of optimal lymphodepletion regimens.
- Optimization of preclinical models for the best safety and efficacy prediction.
- To involve and guide patients throughout their clinical journey.
- Definition of gold standard analytical methods pre- and post-engineered T cell infusion.
- Production of GMP guidance and establishment of standard product profiles.
- To produce excellent cancer therapies accessible to all European patients.

Key Points

1. Two initiatives have been launched to foster collaboration and increase CART activity in Europe: GoCART and T2 EVOLVE Consortium.
2. A large number of CAR-T cell clinical trials are underway.
3. Most clinical trials are occurring in the USA and China, and although Europe has lagged behind, there is evidence of increasing activity.
4. Initiatives to enhance clinical trial activity and cooperation across Europe are needed, and various initiatives are planned to facilitate this.

References

- Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor–modified T cells for acute lymphoid leukemia. *N Engl J Med*. 2013;368:1509–18.
- Locke FL, Ghobadi A, Jacobson CA, 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. [https://doi.org/10.1016/S1470-2045\(18\)30864-7](https://doi.org/10.1016/S1470-2045(18)30864-7).
- Porter DL, Levine BL, Kalos M, et al. Chimeric antigen receptor–modified T cells in chronic lymphoid leukemia. *N Engl J Med*. 2011;365:725–33.

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