Titolo rivista/libro: Annals of oncology

Titolo articolo/sezione: Current strategies of cell and gene therapy for solid tumors: results of the joint international ESMO and CTIWP-EBMT survey

Autore/i: Comoli P , Pentheroudakis G , Ruggeri A , Koehl U , Lordick F , Mooyaart JE , Hoogenboom JD , Urbano-Ispizua A

ISSN: 0923-7534

DOI: 10.1016/j.annonc.2023.12.009

Anno: 2023

Volume: -

Fascicolo: -

Editore:

Pag. iniziale: -

Pag. finale: -

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

LETTER TO THE EDITOR

Current strategies of cell and gene therapy for solid tumors: results of the joint international ESMO and CTIWP-EBMT survey

Despite the encouraging success of industry-manufactured chimeric antigen receptor (CAR)-T-cell therapy for hematologic cancers, clinical trials with advanced therapy medicinal products (ATMPs) face unique challenges in solid tumors (STs) because of the immunosuppressive tumor microenvironment, and the hurdle of T-cell trafficking to and within scarcely accessible tumor sites.[1,2] Because of the variety of programs and infrastructures involved in ATMP manufacturing and delivery, the availability of information on ongoing studies in ST is limited.[3,4] A joint questionnaire-based survey was launched to capture the landscape of ATMP treatment of STs from January 2018 to December 2020 within the ESMO and European Society for Blood and Marrow Transplantation (EBMT) centers.

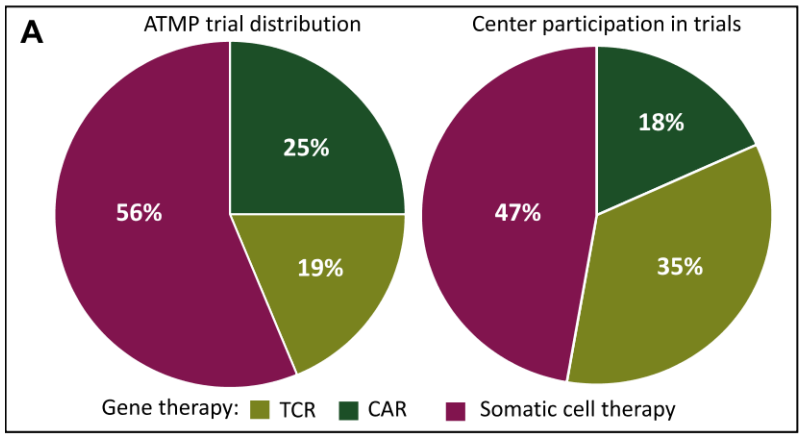
A total of 149 questionnaires valid for descriptive analysis were received from 53 countries. Of these, 23% of the respondents were involved in cell and/or gene therapy trials during the study period and 15% indicated their intention to start a cell therapy/gene therapy program. Details of the products used in clinical trials and other adjunct treatments are reported in Figure 1, and details on the clinical trials are reported in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.12.009. Survey results showed that a sizeable portion of the studies are using tumor-infiltrating lymphocytes or other types of somatic cell therapy mostly directed at unspecified autologous tumor-associated antigens, likely to broaden specificity and increase feasibility. Although increasingly used, gene-modified T cells represent ∼40% of ATMPs used in patients with ST, with gene therapy clinical trials running in 51% centers, which is different from the overwhelming prevalence of CAR gene therapy in the setting of hematological malignancies worldwide, the latter fueled by efficacy and availability of commercial products.[5] Indeed, about two-thirds of the ESMO/EBMT centers indicate having an ATMP product used in clinical studies that is manufactured by academic institutions, either at the 'point of care' (54%) or off-site (15%), although industry-sponsored trials are running in at least half of the centers. Of the seven centers that declared more than one study with different ATMPs, three ran both academic and industry-driven trials.

Interestingly, while the majority of reported studies were early-phase trials, 11% of the academic studies versus none of the industry-sponsored ones were phase III trials. Despite most recent positive signals in early-phase clinical trials,[6] this observation still reflects the, to date, limited efficacy of most ATMPs for STs, and the current trends revolving around testing new targets, fine-tuning CAR/T-cell receptor interactions with the respective targets, and enhancing activity through technical improvements, mostly done by rapidly moving optimized products into early-phase clinical trials. In this scenario, academic centers may play an important central role in focusing preclinical and clinical research on *ex vivo* reprogramming of immune cells to maintain stemness and produce proinflammatory cytokines, and on exploiting systemic and local chemo/radiotherapy regimens and the added immunomodulatory effects of checkpoint inhibition to promote intratumoral cytokine and chemokine upregulation, tumor antigen presentation/cross-presentation, T-cell infiltration, and tumor microenvironment remodeling. This seems to be common practice in ESMO/EBMT centers, as more than half of the clinical studies (56%) associated adjunctive agents, mainly, immune checkpoint inhibitors or chemotherapy/radiotherapy, with ATMP treatment (Figure 1C).

Notwithstanding the essential contribution of academic centers in the research and development of ATMPs for STs, and the fact that the economic burden of early research and development activities rests on the noncommercial organizations, only 12% of the centers declared support by European Union funding for their projects. In perspective, while waiting for breakthrough cellular products to treat STs, network models for ATMP production and multi-stakeholder coalitions facilitating cooperation between not-for-profit organizations and companies may provide greater opportunities to ensure a faster and efficient 'bench-to-bedside' transition.

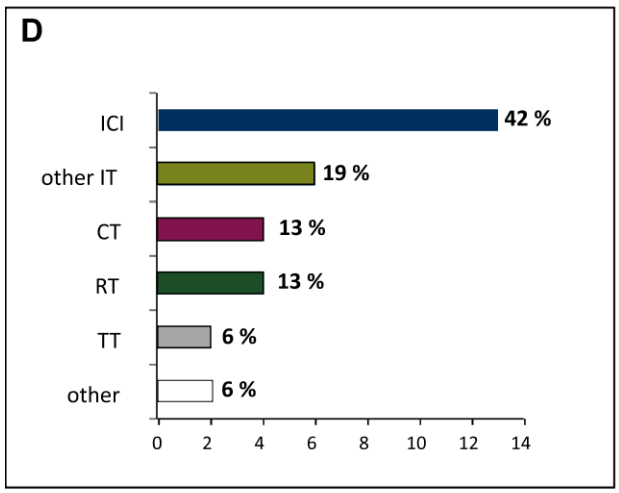
P. Comoli[1], G. Pentheroudakis[2], A. Ruggeri[3], U. Koehl[4], F. Lordick[5], J. E. Mooyaart[6], J. D. Hoogenboom[7], A. Urbano-Ispizua[8], S. Peters[9], J. Kuball[10], N. Kröger[11], A. Sureda[12], C. Chabannon[13], J. Haanen[14] & P. Pedrazzoli[15]*, on behalf of the EBMT Cellular Therapy & Immunobiology Working Party, and the European Society of Medical Oncology

[1]*Cell Factory and Pediatric Hematology Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy;*
[2]*European Society for Medical Oncology, Lugano, Switzerland;*
[3]*Pediatric Hematology and BMT Unit, San Raffaele Scientific Institute, Milan, Italy;*
[4]*Institute of Clinical Immunology and Fraunhofer Institute for Cell Therapy and Immunology, Leipzig;*
[5]*Medical Oncology, Universitätsklinikum Leipzig, Leipzig, Germany;*
[6]*EBMT Statistical Unit, Leiden;*
[7]*EBMT Leiden Study Unit, Leiden, The Netherlands;*
[8]*Hematology Department, Clinic University Hospital, Barcellona, Spain;*
[9]*Multidisciplinary Oncology Center, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland;*
[10]*Department of Hematology and Center for Translational Immunology, UMC Utrecht, Utrecht, The Netherlands;*
[11]*University Medical Center Hamburg, Hamburg, Germany;*



B

Type of antigen	N = 61
AFP	5 (8.2%)
EGFR	6 (9.8%)
GD2	1 (1.6%)
HER2	3 (4.9%)
LAGE	4 (6.6%)
MAGE	10 (16%)
MART-1	1 (1.6%)
NY-ESO-1	10 (16%)
MUC-1	2 (3.3%)
survivin	1 (1.6%)
WT1	2 (3.3%)
CD70	2 (3.3%)
Claudin-6	2 (3.3%)
EBV antigens	1 (1.6%)
Autologous tumor/TIL/other	11 (18%)



C

Type of tumor	N = 92
Bone sarcoma (excluding Ewing sarcoma, skeletal)	5 (5.4%)
Breast cancer	2 (2.2%)
Central nervous system tumors (include CNS PNET)	2 (2.2%)
Colorectal	3 (3.3%)
Ewing sarcoma (ES)/PNET	3 (3.3%)
Germ cell tumor	4 (4.3%)
Head and neck	5 (5.4%)
Hepatobiliary	7 (7.6%)
Kidney cancer excluding Wilms' tumor	3 (3.3%)
Lung cancer, non-small-cell	13 (14%)
Lung cancer, small-cell	3 (3.3%)
Medulloblastoma	1 (1.1%)
Melanoma	17 (18%)
Neuroblastoma	1 (1.1%)
Other	9 (9.8%)
Ovarian (carcinoma)	8 (8.7%)
Pancreatic	1 (1.1%)
Prostate	1 (1.1%)
Renal cell	1 (1.1%)
Soft tissue sarcoma (excluding Rhabdo and ES/PNET)	3 (3.3%)

Figure 1. Distribution and characteristics of the ATMP-based clinical trials for solid tumors in Europe and in the countries affiliated to EBMT, based on the results of the EBMT—ESMO survey. Among the 35 active centers that answered the survey and declared involvement in cell and/or gene therapy, the majority treated an approximate number of one to five adult patients, while a minority exclusively or partially treated children. Only 23% of the centers enrolled >20 patients. Among the centers that indicated having at least one ATMP treatment from January 2018 to December 2020, 33 ATMP trials were identified, in which some centers indicated multiple types of ATMPs (maximum three types of ATMPs, five different products). ATMP trials were mainly based on *ex vivo* manipulated T or NK lymphocytes, cultured and, in 39% of the cases, gene modified either with CAR sequence or T-cell receptor transgene (A, left graph). Of the 61% somatic cell therapy products, T-cell therapies, including TILs and EBV-CTLs, and DC vaccination, were equally distributed (24% each), with NK-based and other ATMPs accounting for 12%. In panel A (right graph), center participation into cell therapy trials according to the type of ATMP, is shown. Antigens preferably used as a target for generating ATMPs are reported in panel B. NYESO-1 and MAGE were more largely used, followed by EGFR and LAGE. Many of the somatic cell therapy products were directed to autologous tumors. Among the tumors targeted, melanoma (18%) and lung cancer (17%, including both small- and non-small-cell) were the most common; GI tract tumors, gynecological cancers, bone sarcomas, head and neck, and breast cancer were also targeted (C). ATMPs were combined with other treatment modalities, largely represented by ICIs, alone or with CT, in 56% of the centers; IL2 with or without other conventional active therapies were also administered along with ATMPs (D). Note: Centers could indicate multiple ATMPs, other treatment modalities, types of tumors treated, and types of antigens targeted.

AFP, alpha-fetoprotein; ATMP, advanced therapy medicinal product; CAR, chimeric antigen receptor; CT, chemotherapy; CNS, central nervous system; CTL, cytotoxic T lymphocyte; EBMT, European Society for Blood and Marrow Transplantation; EBV, Epstein—Barr virus; EGFR, epidermal growth factor receptor; GD2, disialoganglioside GD2; GI, gastrointestinal; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; IL, interleukin; IT, immunotherapy (mainly rhIL-2); LAGE, L-antigen; MAGE, melanoma antigen gene; MART-1, melanoma antigen recognized by T cells 1; MUC-1, mucin 1; NK, natural killer; NY-ESO-1, New York esophageal squamous cell carcinoma-1; PNET, primitive neuroectodermal tumor; RT, radiotherapy; TIL, tumor-infiltrating lymphocyte; TT, targeted therapy; WT1, Wilms' tumor 1.

[12]*Institut Català d'Oncologia—Hospital Duran i Reynals, Barcelona, Spain;*
[13]*Centre de Thérapie Cellulaire & Centre d'Investigations Cliniques en Biothérapies Inserm CBT-1409, Institut Paoli-Calmettes, Marseille, Cedex, France;*
[14]*Medical Oncology, Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands;*
[15]*Oncology Department, Fondazione IRCCS Policlinico San Matteo, Pavia, Dept of Internal Medicine and Medical Therapy, University of Pavia, Pavia, Italy*
(*E-mail: p.pedrazzoli@smatteo.pv.it).

Available online xxx

https://doi.org/10.1016/j.annonc.2023.12.009

ACKNOWLEDGEMENTS

The authors are grateful to the EBMT and ESMO members who participated by completing the questionnaire.

FUNDING

None declared.

DISCLOSURE

PC reports receiving grants from Regione Lombardia (POR-FESR 2526393 Force-4-Cure) and Ministero della Salute (RC08069119 and RF-2019-12371492). GP is a part-time employee of ESMO as Chief Medical Officer. UK states that she is a consultant in immuno-oncology for AstraZeneca, Affimed, Glycostem, GammaDelta, and Zelluna; additionally, she is involved in collaborations with Novartis and Miltenyi Biotec regarding the production of CAR T cells. SP has received education grants, provided consultation, attended advisory boards, and/or provided lectures for the following organizations, from whom he has received honoraria (all fees to the institution)—consultation/advisory role: AbbVie, AiCME, Amgen, Arcus, AstraZeneca, Bayer, Beigene, Biocartis, BioInvent, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, ecancer, Eli Lilly, Elsevier, F-Star, Fishawack, Foundation Medicine, Genzyme, Gilead, GSK, Illumina, Imedex, IQVIA, Incyte, Ipsen, iTeos, Janssen, Medscape, Medtoday, Merck Sharp and Dohme, Merck Serono, Merrimack, Novartis, Novocure, OncologyEducation, Pharma Mar, Phosplatin Therapeutics, PER, Peerview, Pfizer, Regeneron, RMEI, Roche/Genentech, RTP, Sanofi, Seattle Genetics, Takeda, and Vaccibody; and board of director role: Galenica SA; talk in a company's organized public event: AiCME, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, ecancer, Eli Lilly, Foundation Medicine, GSK, Illumina, Imedex, Ipsen, Medscape, Merck Sharp and Dohme, Mirati, Novartis, PER, Peerview, Pfizer, Roche/Genentech, RTP, Sanofi, and Takeda; principal investigator in trials (institutional financial support for clinical trials) sponsored by Amgen, AstraZeneca, Beigene, Bristol-Myers Squibb, GSK, Merck Sharp and Dohme, and Roche/Genentech. JK reports grants from Gadeta, Novartis, and Miltenyi Biotech, and is the inventor of patents dealing with $\gamma\delta$T cell-related aspects and the co-founder of Gadeta, of which he was a shareholder. JH reports consultancy roles in Achilles Tx, BioNTech, BMS, CureVac, GSK, Immunocore, Imcyse, Instil Bio, Iovance, Bio, MSD, Molecular Partners, Novartis, Pfizer, PokeAcel, Roche, Sanofi, T-knife, Third Rock Ventures; Research grants from Amgen, Asher Bio, BioNTech, BMS, MSD, Novartis, and Sastra. All other authors have declared no conflicts of interest.

REFERENCES

1. Comoli P, Chabannon C, Koehl U, et al. European Society for Blood and Marrow Transplantation, Cellular Therapy & Immunobiology Working Party. Development of adaptive immune effector therapies in solid tumors. *Ann Oncol*. 2019;30(11):1740-1750.
2. Kloess S, Kretschmer A, Stahl L, Fricke S, Koehl U. CAR-expressing natural killer cells for cancer retargeting. *Transfus Med Hemother*. 2019;46(1):4-13.
3. Rohaan MW, Wilgenhof S, Haanen JBAG. Adoptive cellular therapies: the current landscape. *Virchows Arch*. 2019;474:449-461.
4. Xiao BF, Zhang JT, Zhu YG, et al. Chimeric antigen receptor T-cell therapy in lung cancer: potential and challenges. *Front Immunol*. 2021;12:782775.
5. Passweg JR, Baldomero H, Chabannon C, et al. European Society for Blood and Marrow Transplantation (EBMT). The EBMT activity survey on hematopoietic-cell transplantation and cellular therapy 2018: CAR-T's come into focus. *Bone Marrow Transplant*. 2020;55:1604-1613.
6. Majzner RG, Ramakrishna S, Yeom KW, et al. GD2-CAR T cell therapy for H3K27M-mutated diffuse midline gliomas. *Nature*. 2022;603:934-941.