EBMT

EBMT Recommendations for CAR-T Cell Treatments

SFGM-TC Annual Meeting

Nov 18th, 2021

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Chair. EBMT Cellular Therapy & Immunobiology Working Party

DISCLOSURES OF COMMERCIAL SUPPORT

Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Scientific Advisory Board	Other
Sanofi SA	X		X				X
Bellicum Pharmaceuticals			X			X	
Kite / Gilead			X			X	X
BMS / Celgene			X			X	X
Novartis			X				X
Janssen			X			X	
Terumo BCT			X				X

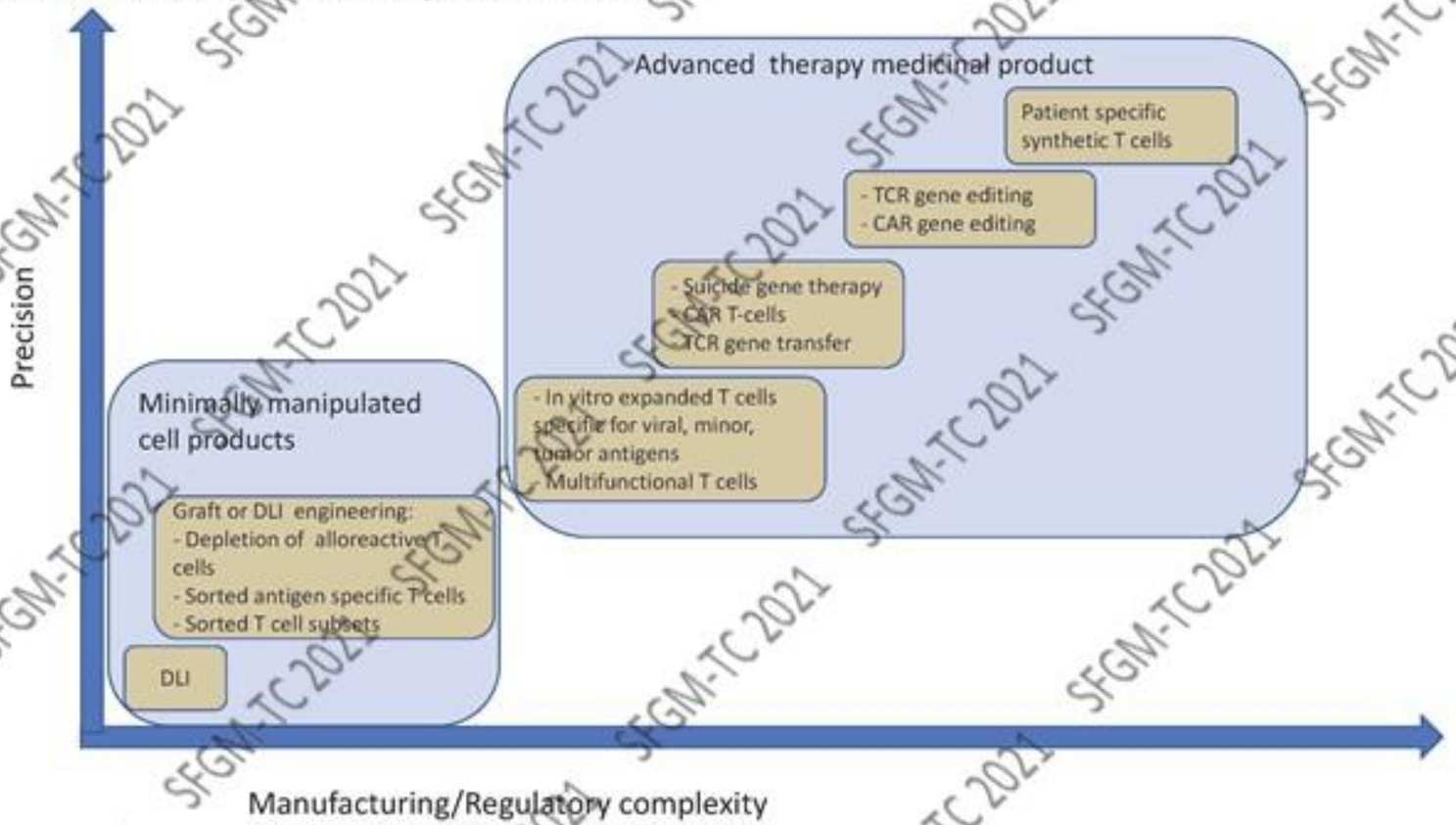
SCIENCE TRANSLATIONAL MEDICINE | REVIEW

CANCER

Hematopoietic stem cell transplantation in its 60s: A platform for cellular therapies

Christian Chabannon,[1]* Jurgen Kuball,[2] Attilio Bondanza,[3] Francesco Dazzi,[4] Paolo Pedrazzoli,[5] Antoine Toubert,[6] Annalisa Ruggeri,[7,8] Katharina Fleischhauer,[9] Chiara Bonini[10]*

FIGURE 4- T cell therapy in the era of precision medicine



The nature of CAR-T Cells

CAR-T Cells are gene therapy medicinal products (GTMP, a subcategory of Advanced Therapy Medicinal Products or ATMPs, as per EU Regulation 2007/1394) that are manufactured from autologous or allogeneic human T cells, through 4 essential steps

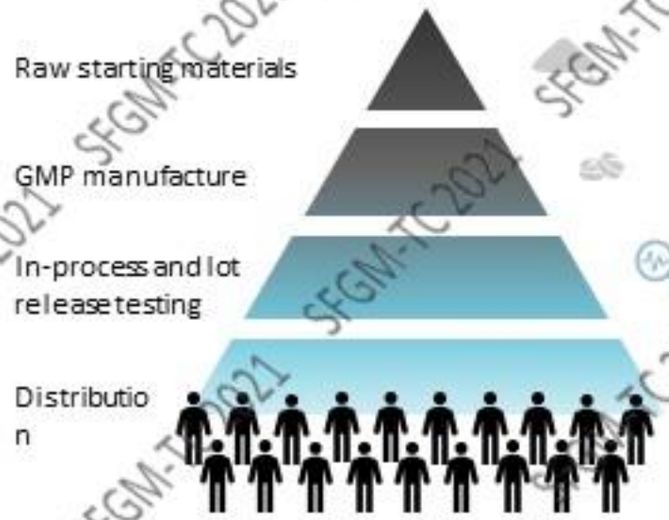
- The collection of blood mononuclear cells, whether from the patient (autologous CAR-T Cells) or from healthy donors (allogeneic CAR-T Cells)
- Ex-vivo immune selection of T-cells or T-cell subsets
- Genetic modification of immune-selected T cells to induce CAR expression at their surface
- Ex vivo expansion / amplification of genetically modified T-Cells

CAR T cell manufacturing process differs of the production of conventional drug products

CAR T cell manufacturing process:

- Personalised to each patient[1]
- Inherent variability of starting product[1]
- Limited batch size[2]
- Complex manufacturing process[1,2]
- Specialised facility with highly trained personnel[3]
- OOS production[1]

Conventional manufacture[4]



CAR: chimeric antigen receptor; GMP: good manufacturing practice; OOS: out of specification

1. Bersenev A & Kiss S. *Cell Gene Ther Insights* 2018; 4:1051–1058. 2. Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (Jun 2017; available at https://ec.europa.eu/health/sites/health/files/files/eudralex/vol4/2017_11_22_guidelines_gmp_for_atmps.pdf). 3. Yescarta SmPC (May 2019; available at www.ema.europa.eu). 4. Adapted from Scientific and Regulatory Considerations for Gene Modified T Cell Therapy (Nov 2017; available at https://pharm.ucsf.edu/sites/pharm.ucsf.edu/files/cersi/media-browser/Graeme%20Price%20and%20Kristin%20Baird.pdf).

CAR-T cells approved indications for hematological malignancies

CID	MAH	Date of MA in Europe	Indications	Targeted tumor antigen
tisagenlecleucel	Novartis	August 2018	r/r ALL (< 26 years old) r/r NHL	CD19
axicabtagene ciloleucel	Kite / Gilead	August 2018	r/r NHL & PMBCL	CD19
brexucabtagene autoleucel	Kite / Gilead	December 2020	r/r MCL r/r ALL	CD19
lisocabtagene maraleucel	Celgene / BMS	not yet approved	r/r NHL	CD19
idecabtagene vicleucel	Celgene / BMS	August 2021	adv Multiple myeloma	BCMA
ciltacabtagene autoleucel	Legend Pharm. / Janssen Pharm. / J&J	not yet approved	adv Multiple myeloma	BCMA

ICD (commercial name)	MAH	Indication(s)	Date MA was granted	Vector type	Co-stimulation domain	Registration studies	Real World Data (RWD)	ORR	CRS / ICANS incidence (all grades)
tisagenlecleucel	Novartis	r/r B cell ALL *	August 2017 (FDA) August 2018 (EMA)	lentiviral	4 1BB	ELIANA Maude SL et al. N Engl J Med. 2018 Feb 1;378(5):439 448. doi: 10.1056/NEJMoa1709866	Pasquini MC et al. Blood Adv. 2020 Nov 10;4(21):5414 5424. doi: 10.1182/bloodadvances.2020003092.	81%	77% / 40%
		r/r DLBCL	October 2017 (FDA) August 2018 (EMA)			JULIET Schster SJ et al. N Engl J Med. 2017 Dec 28;377(26):2545 2554. doi: 10.1056/NEJMoa1708566. Epub 2017 Dec 10	Iacoboni G et al. Cancer Med. 2021 May;10(10):3214 3223. doi: 10.1002/cam4.3881. Epub 2021 May 1.	52%	58% / 21%
axicabtagene ciloleucel	Kite / Gilead	r/r DLBCL r/r PMBCL	October 2017 (FDA) August 2018 (EMA)	retroviral	CD28	ZUMA 01 Neelapu SS et al. N Engl J Med. 2017 Dec 28;377(26):2531 2544. doi: 10.1056/NEJMoa1707447. Epub 2017 Dec 10.	Jacobson CA et al. J Clin Oncol. 2020 Sep 20;38(27):3095 3106. doi: 10.1200/JCO.19.02103. Epub 2020 Jul 15.	82%	93% / 64%
relmacabtagene autoleucel	IM therapeutics	r/r DLBCL	September 2021 (National Medical Products Administration (NMPA) of China)			RELIANCE	Zhu J, et al. ASH 2020. Abstracts 1186		

Inter-trial comparisons should not be made due to differences in study design, patient populations, treatment interventions, and duration of follow-up, among others. We cannot make direct comparisons or draw conclusions from one trial to another. For descriptive purposes, efficacy results for each of the studies mentioned are listed.

Chabannon C et al. Bull Cancer. 2021. in press

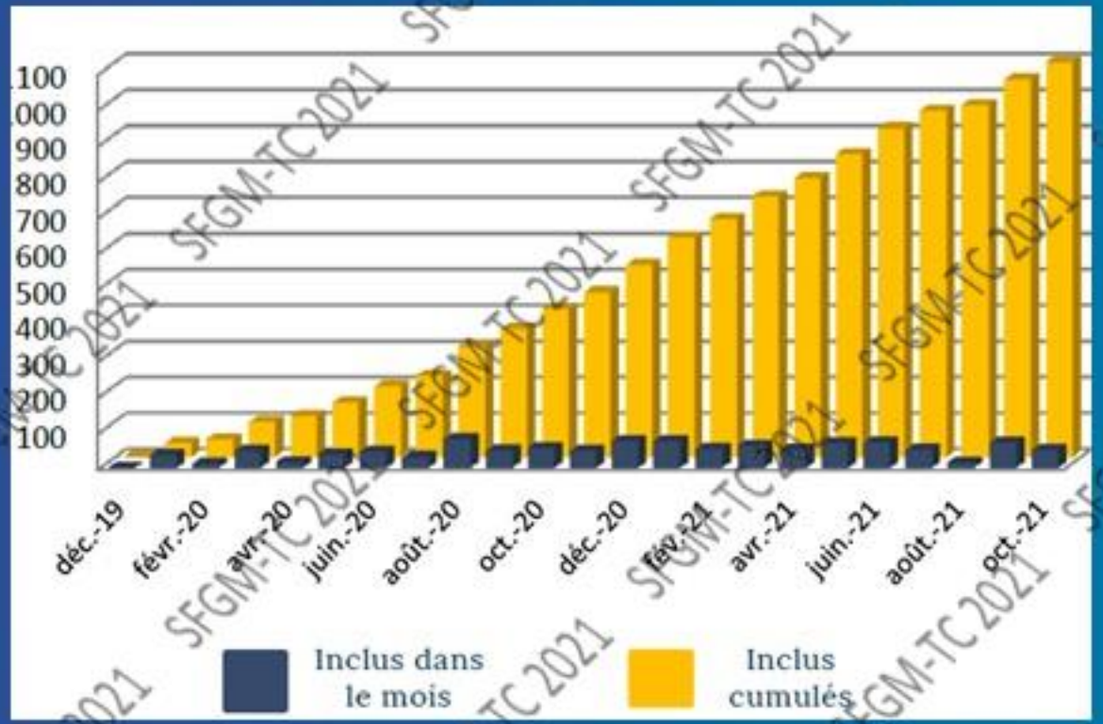
ICD (commercial name)	MAH	Indication(s)	Date MA was granted	Vector type	Co-stimulation domain	Registration studies	Real-World Data (RWD)	ORR	CRS / ICANS incidence (all grades)
brexucabtagene autoleucel	Kite / Gilead	r/r MCL	July 2020 (FDA) December 2020 (EMA)	retroviral	CD28	ZUMA 02 Wang M et al. N Engl J Med. 2020 Apr 2;382(14):1331 1342. doi: 10.1056/NEJMoa1914347	NA	85%	91% / 63%
lisocabtagene maraleucel	BMS (Celgene)	r/r DLBCL	February 2021 (FDA)	lentiviral	4 1BB	TRANSCEND Abramson JS et al. Lancet. 2020 Sep 19;396(10254):839 852. doi: 10.1016/S0140 6736(20)31366 0. Epub 2020 Sep 1	NA	74%	42% / 30%
idecabtagene vicleucel	BMS (Celgene)	MM progression after treatment with one agent from the three major classes	March 2021 (FDA) / August 2021 (EMA)	lentiviral	4 1BB	KARMMA Munshi NC et al. N Engl J Med. 2021 Feb 25;384(8):705 716. doi: 10.1056/NEJMoa2024850	NA	73%	84% / 18%
ciltacabtagene autoleucel	Janssen (J&J / Legend Therapeutics)	MM progression after treatment with one agent from the three major classes		lentiviral	4 1BB	CARTITUDE Berdeja JG et al. Lancet. 2021 Jul 24;398(10297):314 324. doi: 10.1016/S0140 6736(21)00933 8. Epub 2021 Jun 24	NA	97%	95% / 21%

Chabannon C et al. Bull Cancer. 2021. In press

Inter-trial comparisons should not be made due to differences in study design, patient populations, treatment interventions, and duration of follow-up, among others. We cannot make direct comparisons or draw conclusions from one trial to another. For descriptive purposes, efficacy results for each of the studies mentioned are listed.
US FDA has approved liso-cel for the treatment of R/R DLBCL . Liso-cel is not approved by EMA in Europe.
Cilta-cel is not approved by any Regulatory agency.

Registration of patients treated with CAR-T Cells in Europe

Registration of patients treated with CAR-T Cells in France



DESCAR-T

Newsletter 2 novembre 2021

DESCAR-T

Registre français des patients souffrant d'une hémopathie, éligibles à un traitement par cellules CAR-T

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haematologica
Journal of The Ferrata Storti Foundation

Management of adults and children undergoing CAR t-cell therapy: best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE)

by Ibrahim Yakoub-Agha, Christian Chabannon, Peter Bader, Grzegorz W. Basak, Halvard Bonig, Fabio Ciceri, Selim Corbacioglu, Rafael F. Duarte, Hermann Einsele, Michael Hudecek, Marie José Kersten, Ulrike Köhl, Jürgen Kuball, Stephan Mielke, Mohamad Mohty, John Murray, Arnon Nagler, Stephen Robinson, Riccardo Saccardi, Fermin Sanchez-Guijo, John A. Snowden, Micha Srour, Jan Styczynski, Alvaro Urbano-Ispizua, Patrick J. Hayden, and Nicolaus Kröger

Haematologica 2019 [Epub ahead of print]

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GUIDELINE ARTICLE

Management of adults and children undergoing chimeric antigen receptor T-cell therapy: best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE)

Ibrahim Yakoub-Agha,[1] Christian Chabannon,[2] Peter Bader,[3] Grzegorz W. Basak,[4] Halvard Bonig,[5] Fabio Ciceri,[6] Selim Corbacioglu,[7] Rafael F. Duarte,[8] Hermann Einsele,[9] Michael Hudecek,[10] Marie José Kersten,[11] Ulrike Köhl,[12] Jürgen Kuball,[13] Stephan Mielke,[14] Mohamad Mohty,[15] John Murray,[16] Arnon Nagler,[17] Stephen Robinson,[18] Riccardo Saccardi,[19] Fermin Sanchez-Guijo,[20] John A. Snowden,[21] Micha Srour,[22] Jan Styczynski,[23] Alvaro Urbano-Ispizua,[24] Patrick J. Hayden[25] and Nicolaus Kröger[26]

Ferrata Storti Foundation

Haematologica 2018
Volume 105(2):297-316

Table 11. Monitoring of patients during medium-term follow-up.

Test	Purpose	Frequency	Comment
FBC, biochemistry panel, LDH, fibrinogen, CRP	Standard follow-up	At every visit and as clinically indicated	
CMV, EBV, adenovirus	Viral reactivation	As clinically indicated	
Quantitative immunoglobulins or serum protein electrophoresis	Immune reconstitution	Monthly	Consider IV immunoglobulins
Peripheral blood immunophenotyping – CD3/4/8/16+56/19+	Immune recovery	Once monthly for first 3 months, three monthly thereafter in first year	Guide to anti-infective prophylaxis
CAR T-cell monitoring where kits are available for routine monitoring of anti-CD19 CAR T-cells	CAR T-cell persistence	Peripheral blood flow cytometry or transgene by molecular methods as clinically indicated	Not recommended by CAR T-cell manufacturers

FBC: full blood count; LDH: lactate dehydrogenase; CRP: C-reactive protein; CMV: cytomegalovirus; EBV; Epstein-Barr virus; IV: intravenous; CAR: chimeric antigen receptor.

TITLE:

'Management of Adults and Children receiving CAR T-cell therapy: 2021 Best Practice Recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA)'

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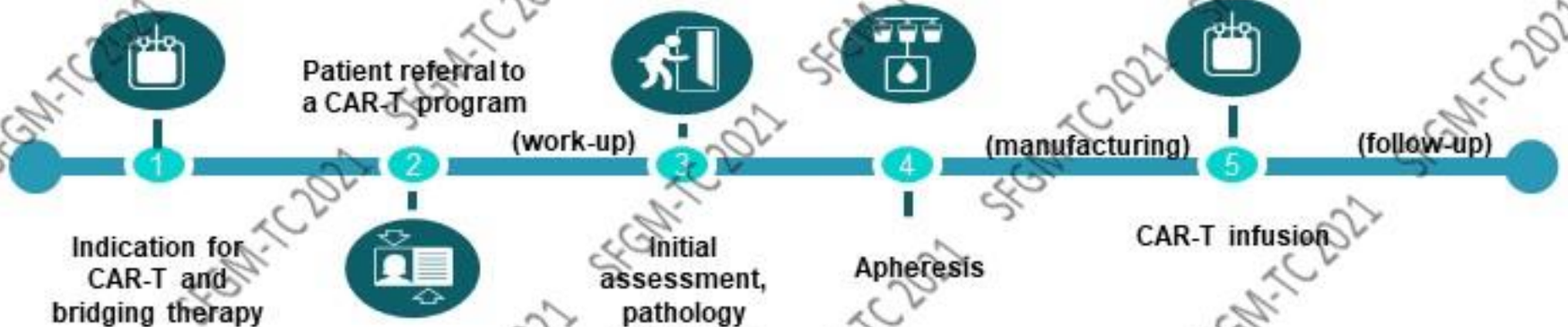
* Participated equally to this work and should be considered as first author.

These practical recommendations prepared on behalf of EBMT-JACIE and the European Haematology association (EHA) update and expand on the first EBMT CAR-T guidelines published in 2019 and cover all aspects of patient care and supply chain management, from patient selection to long-term follow-up, post-authorisation safety surveillance and regulatory issues

Patient journey



➔ **Turnaround time from patient identification to apheresis and infusion can be a significant constraint.**

CAR T WORKING GROUP

The aim is to provide practical, clinically relevant recommendations on the use of these high-cost, logistically complex therapies for haematologists/oncologists, nurses and other stakeholders including pharmacists and health sector administrators involved in the delivery of CAR-T in the clinic

These European recommendations are not prescriptive and are intended as best practice guidance in the use of this therapeutic class.

Eligibility Criteria	EBMT/EHA recommendations	Comments
Age limit	No age limit	Decision should be based on physical condition rather than age, although ability to collect sufficient cells by apheresis can be a limiting factor in infants and small children. Real-world CAR-T data suggests that 5.9% of treated patients with B-ALL were <3 years old and 53.5% of treated patients with NHL were >65 years old and that CR rates was comparable in both groups to the rest of the population.
Performance Status	ECOG <2, Karnofsky > 60% or Lansky >60%	Although patients with ECOG>1 were treated outside clinical trials, it was associated with significantly decreased OS and PFS. The detrimental effect may be less significant in cases where poor performance status is due to active disease.
Life expectancy	More than 6-8 weeks	Requires careful consideration in terms of risk-benefit ratio.
High tumour burden	Risk-benefit assessment required	High tumour burden in B-ALL and LBCL is a risk factor for treatment failure and greater toxicity and careful consideration of the individual risk-benefit ratio is required.
History of malignancy	Absence of active malignancy requiring treatment other than non-melanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast).	Requires careful consideration of the risk-benefit ratio.
Prior allo-HCT	Not a contra-indication	Not a contra-indication when off immunosuppression but in ALL may increase risk of CAR-T associated toxicity
Prior treatments directed towards antigenic target of CAR-T e.g. bispecific antibodies/ prior CAR-T	Not a contra-indication, but antigen negative escape should be excluded at relapse post-targeted therapy and prior to CAR-T especially in B-cell ALL	Reduced CD19 expression may not decrease the efficacy of anti-CD19 CAR-T in B-ALL; however, prior treatment with blinatumomab may impair efficacy A second infusion of anti-CD19 CAR T-cells may be feasible and can induce remission in a subset of patients.
Immunosuppressive treatment	Relative contra-indication	Any systemic immunosuppressive treatment may impair the efficacy of CAR-T Intermittent topical, inhaled, or intranasal corticosteroids are permitted.
Bacterial or fungal infections	Active infection is a contra-indication	Infection should be treated and well controlled such that the patient should be stable prior to leukapheresis. In most cases, active infection requires only a temporary deferral.

Prior to Apheresis	EBMT/EHA recommendations	Comments
Performance status	ECOG <2, Karnowski > 60%	At discretion of leukapheresis practitioner
Interval following exposure to chemotherapy	Allow sufficient time for recovery from cytotoxic chemotherapy/ immunosuppression/ steroids (see Table 4 for washout periods)	Adequate marrow recovery from prior chemotherapy required
Interval following exposure to steroids	A minimum of 3 days prior to leukapheresis. Optimally, 7 days to minimise impact on leukapheresis	Physiological replacement doses of hydrocortisone permitted, Topical and inhalational steroids also permitted
Blood oxygen saturation	≥ 92% on room air	
Hepatitis B, Hepatitis C, HIV, Syphilis, and HTLV	To be done within 30 days of leukapheresis. Results must be available at the time of collection and shipment. Mandatory in some countries	In some countries, only serological testing is required; nucleic acid testing (NAT) is not necessary if all serological testing is negative
COVID-19 PCR	Not a contraindication in asymptomatic patients. Contraindication in symptomatic patients	Apheresis physician and manufacturing facility should be informed if positive PCR
COVID-19 vaccination	Recommended	Though data is limited, patients should be vaccinated against COVID-19, where possible, prior to admission for CAR-T.
Standard electrolytes and renal function	Required	Leukapheresis can be complicated by electrolyte imbalance and fluid shifts during the procedure
Haemoglobin	Haemoglobin>80 g/L recommended Haematocrit >0.24 recommended	To help establish a good interface during leukapheresis
Absolute Lymphocyte count (ALC)	≥ 0.2x10^9/L recommended	Low counts indicate insufficient haematological recovery and may predict for production failure. Higher count required in small children Of note, 0.2x10^9/L CD3$^+$ count is the minimum recommended threshold
Platelet count	> 30x10^9/L recommended	Transfuse as required, particularly for insertion of central line prior to leukapheresis.
Full Blood Count (FBC)	To be repeated at the end of apheresis procedure	Apheresis can remove more than 30% of circulating platelets

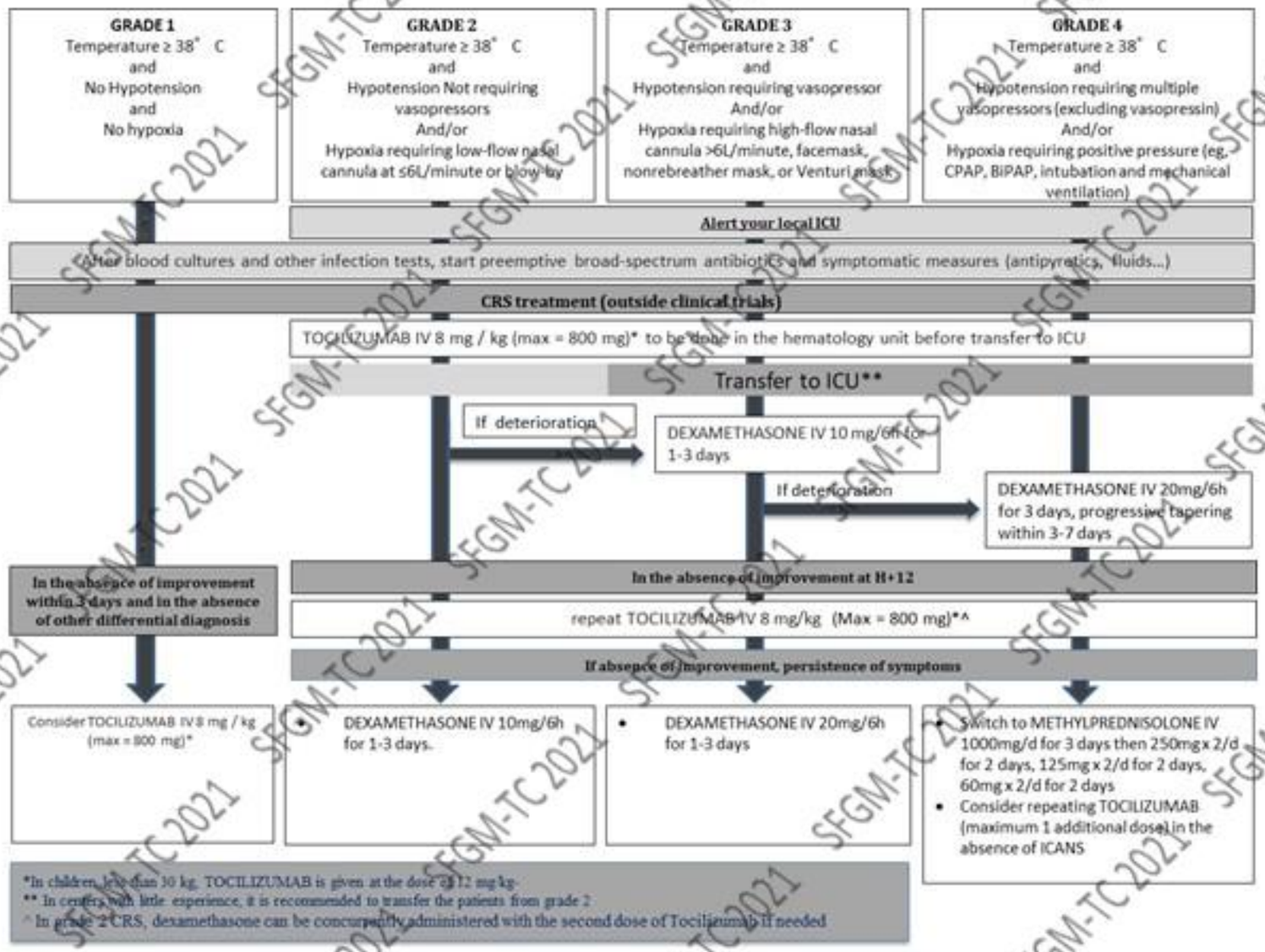
Table 3. Checklist prior to leukapheresis

Type of therapy	EBMT/EHA recommendations	Comments
Allo-HCT	Patients should be off immunosuppression and GvHD-free	A minimum of one month is recommended with the requirement to be GvHD-free and off immunosuppression
DLI	At least 4 weeks	6-8 weeks may be safer to rule out any GvHD
High-dose chemotherapy	3-4 weeks	Recovery from cytopenias is required
Intrathecal therapy	One week	
Short-acting cytotoxic/anti-proliferative drugs	3 days	Recovery from cytopenias is required
Systemic corticosteroids	Minimum of 3 days but ideally 7 days	ALC $\geq 0.2 \times 10^9$/L is recommended

Table 4. Washout period before leukapheresis [adapted from Kansangra et al, BBMT 2019[15]] Key. *Allo-SCT: allogeneic stem cell transplantation; GvHD: graft versus host disease; DLI: donor lymphocyte infusion; ALC Absolute Lymphocyte Count.*

Complications	EBMT/EHA recommendations	Comments
Active infection	Contra-indication	CAR T-cell infusion should be delayed until the infection is controlled
Clinical evidence of fluid overload or congestive cardiac failure	Contra-indication	Specific individualized risk-benefit; cardio oncology assessment is required
Cardiac arrhythmia not controlled with medical management	Contra-indication	Specific individualized risk-benefit; cardio oncology assessment is required
Hypotension requiring vasopressor support	Contra-indication	CAR T-cell infusion should be delayed until the hypotension has been fully treated
New-onset or worsening of another non-hematologic organ dysfunction ≥ Grade 3	Work-up is needed to identify the cause	Specific individualized risk-benefit assessment required
Significant worsening of clinical condition since start of LD	Work-up is needed to identify the cause	Specific individualized risk-benefit assessment required
Neurological evaluation including ICE score (adult) or CAPD score (children)	To be routinely performed	Serving as a baseline

Table 8. Potential complications to be ruled out before product thawing and CAR-T infusion. Key. *LD: lymphodepletion*

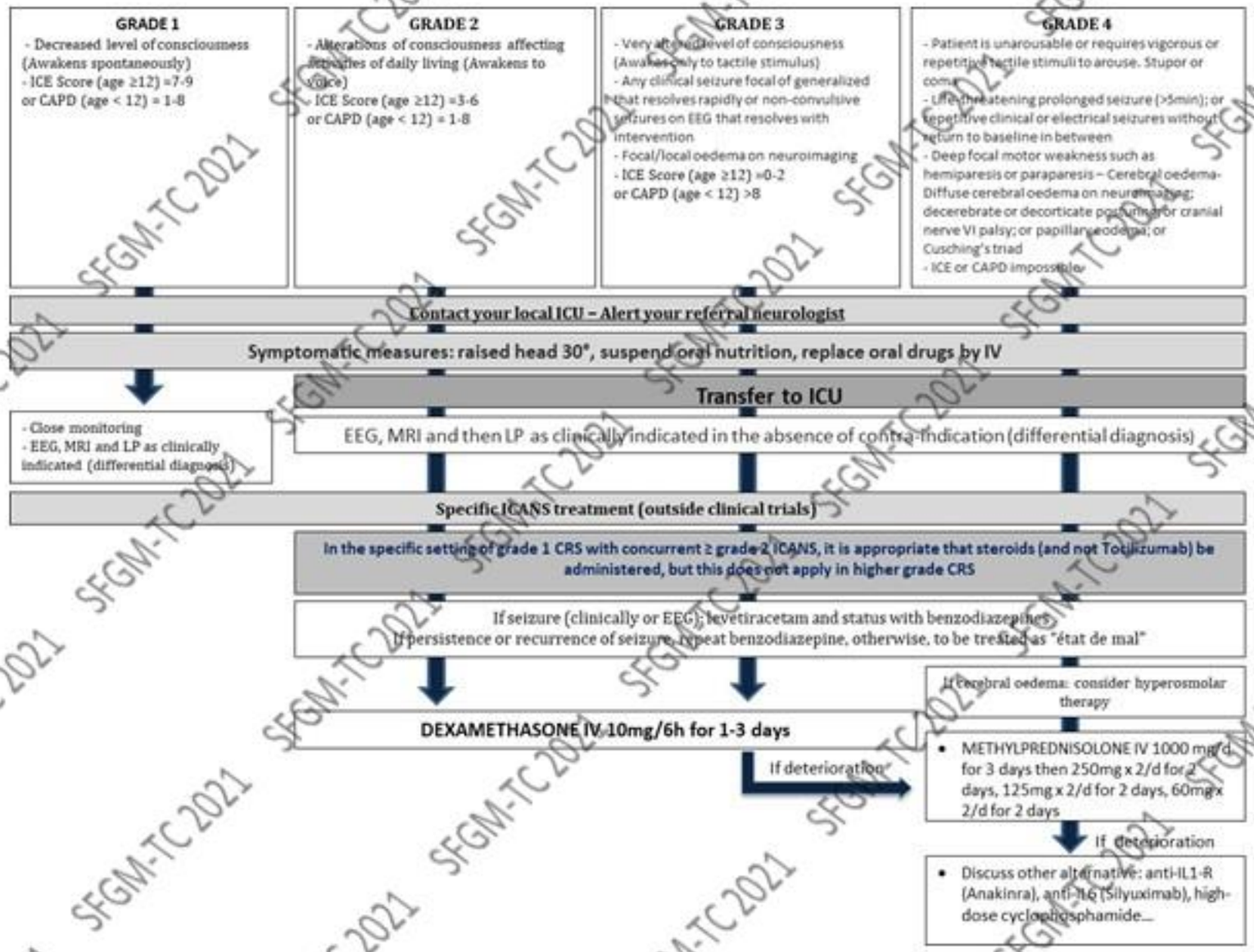

GRADE 1
Temperature ≥ 38° C
and
No Hypotension
and
No hypoxia
GRADE 2
Temperature ≥ 38° C
and
Hypotension Not requiring vasopressors
And/or
Hypoxia requiring low-flow nasal cannula at ≤6L/minute or blow-by
GRADE 3
Temperature ≥ 38° C
and
Hypotension requiring vasopressor
And/or
Hypoxia requiring high-flow nasal cannula >6L/minute, facemask, nonrebreather mask, or Venturi mask
GRADE 4
Temperature ≥ 38° C
and
Hypotension requiring multiple vasopressors (excluding vasopressin)
And/or
Hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)
Alert your local ICU
After blood cultures and other infection tests, start preemptive broad-spectrum antibiotics and symptomatic measures (antipyretics, fluids...)
CRS treatment (outside clinical trials)
TOCILIZUMAB IV 8 mg / kg (max = 800 mg)* to be done in the hematology unit before transfer to ICU
Transfer to ICU**
If deterioration
DEXAMETHASONE IV 10 mg/6h for 1-3 days
If deterioration
DEXAMETHASONE IV 20mg/6h for 3 days, progressive tapering within 3-7 days
In the absence of improvement within 3 days and in the absence of other differential diagnosis
In the absence of improvement at H+12
repeat TOCILIZUMAB IV 8 mg/kg (Max = 800 mg)*^
If absence of improvement, persistence of symptoms
Consider TOCILIZUMAB IV 8 mg / kg (max = 800 mg)*
• DEXAMETHASONE IV 10mg/6h for 1-3 days.
• DEXAMETHASONE IV 20mg/6h for 1-3 days
• Switch to METHYLPREDNISOLONE IV 1000mg/d for 3 days then 250mg x 2/d for 2 days, 125mg x 2/d for 2 days, 60mg x 2/d for 2 days
• Consider repeating TOCILIZUMAB (maximum 1 additional dose) in the absence of ICANS
*In children, less than 30 kg, TOCILIZUMAB is given at the dose of 12 mg/kg.
** In centers with little experience, it is recommended to transfer the patients from grade 2
^ In grade 2 CRS, dexamethasone can be concurrently administered with the second dose of Tocilizumab if needed

Test	Points
Orientation: orientation to year, month, city, hospital	4
Naming: ability to name three objects (e.g., table, television, pillow)	3
Following commands: ability to follow simple commands (e.g., "smile" or "open your mouth")	1
Writing: ability to write a standard sentence (e.g., "Happy to have my family around")	1
Attention: ability to count backwards from 100 by 10	1

Table 9. ICE score for neurological toxicity assessment. Adapted from Lee et al[48]

Test	always	often	sometimes	rarely	never
Eye contact with caregiver	0	1	2	3	4
Purposeful actions	0	1	2	3	4
Aware of their surroundings	0	1	2	3	4
Being restless	4	3	2	1	0
Being inconsolable	4	3	2	1	0
Being underactive	4	3	2	1	0
slow response to interactions	4	3	2	1	0
Communicating needs and wants	5	4	3	2	40

Table 10. CAPD for encephalopathy assessment in children < 12 years, Adapted from Traube et al[51,52].


GRADE 1
- Decreased level of consciousness (Awakens spontaneously)
- ICE Score (age ≥12) =7-9
or CAPD (age < 12) = 1-8
GRADE 2
- Alterations of consciousness affecting activities of daily living (Awakens to voice)
- ICE Score (age ≥12) =3-6
or CAPD (age < 12) = 1-8
GRADE 3
- Very altered level of consciousness (Awakens only to tactile stimulus)
- Any clinical seizure focal or generalized that resolves rapidly or non-convulsive seizures on EEG that resolves with intervention
- Focal/local oedema on neuroimaging
- ICE Score (age ≥12) =0-2
or CAPD (age < 12) >8
GRADE 4
- Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
- Life-threatening prolonged seizure (>5min); or repetitive clinical or electrical seizures without return to baseline in between
- Deep focal motor weakness such as hemiparesis or paraparesis – Cerebral oedema- Diffuse cerebral oedema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilliary oedema; or Cusching's triad
- ICE or CAPD impossible
Contact your local ICU – Alert your referral neurologist
Symptomatic measures: raised head 30°, suspend oral nutrition, replace oral drugs by IV
Transfer to ICU
- Close monitoring
- EEG, MRI and LP as clinically indicated (differential diagnosis)
EEG, MRI and then LP as clinically indicated in the absence of contra-indication (differential diagnosis)
Specific ICANS treatment (outside clinical trials)
In the specific setting of grade 1 CRS with concurrent ≥ grade 2 ICANS, it is appropriate that steroids (and not Tocilizumab) be administered, but this does not apply in higher grade CRS
If seizure (clinically or EEG): levetiracetam and status with benzodiazepines
If persistence or recurrence of seizure, repeat benzodiazepine, otherwise, to be treated as "état de mal"
If cerebral oedema: consider hyperosmolar therapy
DEXAMETHASONE IV 10mg/6h for 1-3 days
If deterioration
• METHYLPREDNISOLONE IV 1000 mg/d for 3 days then 250mg x 2/d for 2 days, 125mg x 2/d for 2 days, 60mg x 2/d for 2 days
If deterioration
• Discuss other alternative: anti-IL1-R (Anakinra), anti-IL6 (Silyuximab), high-dose cyclophosphamide...

Tests	EBMT/EHA recommendations		Comments
	Purpose	Frequency	
FBC, Biochemistry panel, AST, ALT, bilirubin, LDH, Fibrinogen, CRP	Standard follow-up	At every visit and as clinically indicated	
CMV, EBV, Adenovirus, COVID-19	Viral reactivation/ infection (post-allo-HCT)	As clinically indicated	
Quantitative Immunoglobulins or Serum protein electrophoresis	Immune reconstitution	1-3 monthly	Consider IV (or SC) immunoglobulin replacement
Peripheral blood Immunophenotyping – CD3/4/8/16+56/19+	Immune recovery	Once monthly for first three months, three monthly thereafter in first year	Guide to anti-infective prophylaxis and vaccination schedule
CAR T monitoring	CAR T-persistence	Peripheral blood flow cytometry or transgene by molecular methods as clinically indicated	This is not feasible in most centres. For B-ALL, B-cell aplasia may be used as a surrogate for persistence

Table 11. Patient monitoring during medium-term follow-up. Abbreviations. *FBC: full blood count; CMV: cytomegalovirus; EBV; Epstein-Barr virus; IV: intravenous; SC: subcutaneous. * Additional tests and imaging can be performed as clinically indicated.*

	EBMT/EHA recommendation	Comments
Neutropenia	G-CSF to shorten duration of neutropenia from day +14 or after resolution of CRS or ICANS. Can consider starting earlier, e.g., day 5*, if patient is at high risk of infection, e.g., ALL, post-allo-HCT, high-dose steroids. For persistent neutropenia (<0.5 x 10^9/L) following Day +28, consider G-CSF.	Avoid if patient has CRS or ICANS
Antibacterial prophylaxis	Not routinely recommended**	Can be considered in case of prolonged neutropenia ar should be based on local guidelines e.g., with levoflox or ciprofloxacin.
Anti-viral	Valaciclovir 500 mg bid or aciclovir 800mg bd	Start from LD conditioning until one-year post-CAR T cell infusion AND until CD4 count >0.2x10^9/L
Anti-pneumocystis	Co-trimoxazole 480 mg once daily or 960 mg three times each week. To start from LD conditioning until one-year post-CAR-T cell infusion AND until CD4 count >0.2x10^9/L. Where there is prolonged myelosuppression, postpone start after ANC > 0.5 x 10^9/L.	Can be started later depending on centre guidelines. In case of co-trimoxazole allergy (or cytopenias precluding co-trimoxazole), pentamidine inhalation (3 mg once every month), dapsone 100 mg daily or atovaquone 1500 mg once daily can be considered.
Systemic anti-fungal prophylaxis	Not recommended routinely; consider Posaconazole (300mg/d) or fluconazole (200 mg/d) or Micafungin (50 mg i.v./d) in patients with severe (ANC < 0.5 x 10^9/L) or prolonged (> 14 days) neutropenia or in patients on long-term or high dose (> 72 h) corticosteroids or in patients post-allo-HCT.	In patients with prior allo-HCT, prior invasive aspergillosis and those receiving corticosteroids, posaconazole prophylaxis should be considered.
IV Immunoglobulin	Routine in children. Consider in adults with serious/recurrent infections with encapsulated organisms and hypogammaglobulinemia (< 4g/L).	Clinical evidence does not support routine use in adult following allo-HCT.

Table 12. Infection prophylaxis post-CAR-T. Abbreviations. *G-CSF: granulocyte colony stimulating factor; CRS: cytokine release syndrome; LD: lymphodepleting conditioning; NCCN: The National Comprehensive Cancer Network; allo-HCT: allogeneic hematopoietic cell transplantation.*

Agent	EBMT/EHA recommendations		Comments
	Pre-CAR-T	Post-CAR-T	
Influenza Vaccine	Preferably vaccinate 2 weeks prior to LD. In B-cell aplasia low likelihood of serological response	> 3 months after CAR-T patients should be vaccinated irrespective of immunological reconstitution	Where there is incomplete immune reconstitution* or ongoing immunosuppression, there is a high likelihood of lower vaccine responses. Consensus view is that vaccination may still be beneficial to reduce rates of infection and improve clinical course
SARS-Cov-19	Preferably vaccinate prior to CAR-T therapy. In B-cell aplasia low likelihood of serological response	> 3 months after CAR-T-cell infusion.	No reports on vaccine response after CAR-T exist. However, SARS-Cov-19 vaccine-induced protection relies heavily on T-cell mediated immunity, therefore B-cell aplasia does not seem to be a contraindication; No T cell threshold has been defined. Post vaccination response monitoring is desirable.
Killed / Inactivated vaccines		> 6 months after CAR-T and > 2 months after immunoglobulin replacement	Contraindications include concurrent immunosuppressive or cytotoxic therapy.
Live and non-live adjuvant vaccines		1 year after CAR-T and fully immune reconstituted *	Contraindications include < 2 years post allo-HCT, < 8 months after completion of immunoglobulin replacement.

Table 13. Eligibility Criteria for Vaccination in patients receiving CD19-targeted CAR T-cell therapy [adapted from Hill and Seo. [63]***.*** ** Absolute CD4 T cells > 0.2x10⁹/L, CD19 or CD20 positive B-cells > 0.2x10⁹/L, no concomitant immunosuppressive or cytotoxic therapy*

Other relevant EBMT Recommendations

CORONAVIRUS DISEASE COVID-19: EBMT RECOMMENDATIONS VERSION 16 – May 27, 2021

COVID-19 vaccines. Version 7, October 3, 2021

Currently our assumptions and recommendations are:

1) HCT patients above the age of 12 years should be vaccinated against SAR-CoV-2. Patients could be given whatever vaccine is made available in their country as long as they are not live-attenuated or contain replicating viral vectors. However, only the two mRNA vaccines are licensed for adolescents.
2) Since the only studies so far reported have been performed with the mRNA vaccines, these vaccines seem preferable based on the currently existing information.
3) Response rates are lower than in healthy individuals especially if patients are vaccinated soon after HCT. Therefore, it makes sense to adapt the timing when vaccination should be initiated to the SARS-CoV-2 infection rate in the surrounding community.

Other important readings (1)

Biol Blood Marrow Transplant 25 (2019) 625–638

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Guideline

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells

Daniel W. Lee[1,#], Bianca D. Santomasso[2,#], Frederick L. Locke[3], Armin Ghobadi[4], Cameron J. Turtle[5], Jennifer N. Brudno[6], Marcela V. Maus[7], Jae H. Park[8], Elena Mead[9], Steven Pavletic[6], William Y. Go[10], Lamis Eldjerou[11], Rebecca A. Gardner[12], Noelle Frey[13], Kevin J. Curran[14], Karl Peggs[15], Marcelo Pasquini[16], John F. DiPersio[4], Marcel R.M. van den Brink[8], Krishna V. Komanduri[17], Stephan A. Grupp[18,*], Sattva S. Neelapu[19,**]

Other important readings (2)

Prérequis nécessaires pour la mise en place de protocoles de recherche clinique évaluant des thérapies cellulaires et géniques par lymphocytes T dotés de récepteur chimérique à l'antigène (CAR T-cells) : recommandations de la Société francophone de greffe de moelle et de thérapie cellulaire (SFGM-TC)

Ibrahim Yakoub-Agha [1,2], Christophe Ferrand [3], Yves Chalandon [4], Caroline Ballot [5], Cristina Castilla Llorente [6], Marina Deschamps [3], Jordan Gauthier [7], Myriam Labalette [2,8], Jérôme Larghero [9], Camille Maheux [10], Anne-Sophie Moreau [11], Pauline Varlet [2,3], Marie-Odile Pétillon [1], Marine Pinturaud [12], Marie Thérèse Rubio [13,14], Christian Chabannon [15,16]

Saisie des données des patients faisant l'objet d'un traitement par cellules CAR recommandations de la Société Francop de Greffe de Moelle et de Thérapie Cell (SFGM-TC)

Alyette Wasseur [1], Micheline Karam [1], Delphine Chaillou [2], Elodie Colonnese [3], Carole Dantin [4], Christelle Latiere [5], Youcef Meziane [6], Magny Pereira [7], Ibrahim Yakoub-Agha [8], Christian Chabannon [9], Nicole Raus [10]

Prise en charg encéphalopat cellules CAR-T recommandat de greffe de (SFGM-TC)

al Hadjeam [2,16], Gabrielle Emmanuelle Nicolas-Virelizi [2,8], Cécile Borel [11], Imran A

Le parcours de soins du patient dans le cadre des *CAR T-cell* : recommandations de la Société francophone de greffe de moelle et de thérapie cellulaire (SFGM-TC)

Mutualisation des outils de qualité pour les cellules CAR-T : recommandations de la Société francophone de greffe de moelle et thérapie cellulaire (SFGM-TC)

Rémy Duléry [1], Marie-Noëlle Lacassagne [2], Christine Giraud [3], Virginie Ader [4], Jean-Louis Beaumont [5], Sylvie Carnoy [6], Alexandre Carpentier [7], Nathalie Fegueux [8], Cécile Gibault-Joffe [9], Marie-Agnès Guerout-Verite [10], Thi Ngoc Phuong Huynh [11], Philippe Lewalle [11], Agnès Perrin [12], Sophie Plaza-Milhe [8], Agnès Bonnin [13], Ibrahim Yakoub-Agha [14], Nathalie Contentin [15]

Other important readings (3)

Suivi au moyen-terme
l'objet d'un traitemer
recommandations de
de greffe de moelle e

Tamim Al
Anne-Clai
Ibrahim Y.

Condition de réalisation
pour la mise à dispositic
biologique nécessaire à
***T-cells* commerciaux : av**
par la SFGM-TC

Sylvie Carnoy [1], Jean-Louis Beaumont [2], Tarik Kanoun [3], Nathalie Parquet [4], David Beauvais [5], Olivier Hequet [6], Justina Kanold [7], Caroline Ballot [8], Valérie Mialou [9], Lola Reppel [10], Gandhi Damaj [11], Ibrahim Yakoub-Agha [12], Christian Chabannon [13]

Lettre type pour les comptes rendus « CAR-T Cells » : recommandations de la Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC)

Florence Broussais [1], Alyette Vasseur [2], Micheline Karam [2], Delphine Chaillot [3], Maguy Pereira [4], Ibrahim Yakoub-Agha [5], Nicole Rahis [6]

Info suppl.

Carnet de suivi des patients recevant un traitement par CAR T-cell : recommandations de la Société francophone de greffe de moelle et de thérapie cellulaire (SFGM-TC)

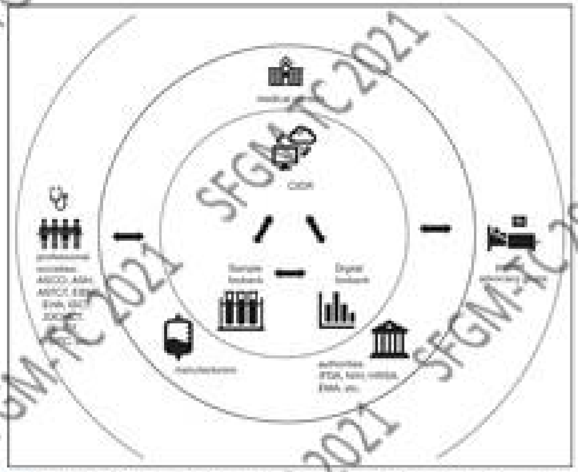
Maxime Berquier [1], Lucie Cherel [2], Dorothée Clerc Renaud [3], Carole Hospital Gustems [4], Anne Wallart Brejaud [6], Ibrahim Yakoub-Agha [5], David Beauvais [5]

Suivi immunologique des patients traités par cellules CAR-T pour hémopathie maligne: recommandations du groupe CARTi et de la Société francophone de greffe de moelle et de thérapie cellulaire (SFGM-TC)

Marie Thérèse Rubio [1], Pauline Vafet [2], Vincent Allain [3], Caroline Ballot [4], Alexis Cuffel [3], Marina Deschamps [5], Christophe Ferrand [6], Jacques Foguenne [6], Edouard Forcade [7], Anne Huynh [8], Amélie Guihot [9], Jean-Baptiste Latouche [10], Claude Lemarie [11], Guillaume Martinroche [12], Florence Morin [3], Stéphanie Nguyen [13], Kathleen Schmit [6], Sophie Servais [14], Federico Simonetta [15], Ibrahim Yakoub-Agha [16], Sophie Caillat Zucman [3]

Other important readings (4)

Suivi immunologique des patients traités par cellules CAR-T pour hémopathie maligne: recommandations du groupe CARTi et de la Société francophone de greffe de moelle et de thérapie cellulaire (SFGM-TC)



TO THE EDITOR:

Blueprint for the discovery of biomarkers of toxicity and efficacy for CAR T cells and T-cell engagers

Sophie Paczesny,[1] Marcelo C. Pasquini,[2] Steven Z. Pavletic,[3] Amit Agarwal,[4] Stephen Spellman,[5] Leslie Kean,[6] Chantale Bernatchez,[7] Juliane Gust,[8] Verena Staedtke,[9] and Miguel-Angel Perales[10]

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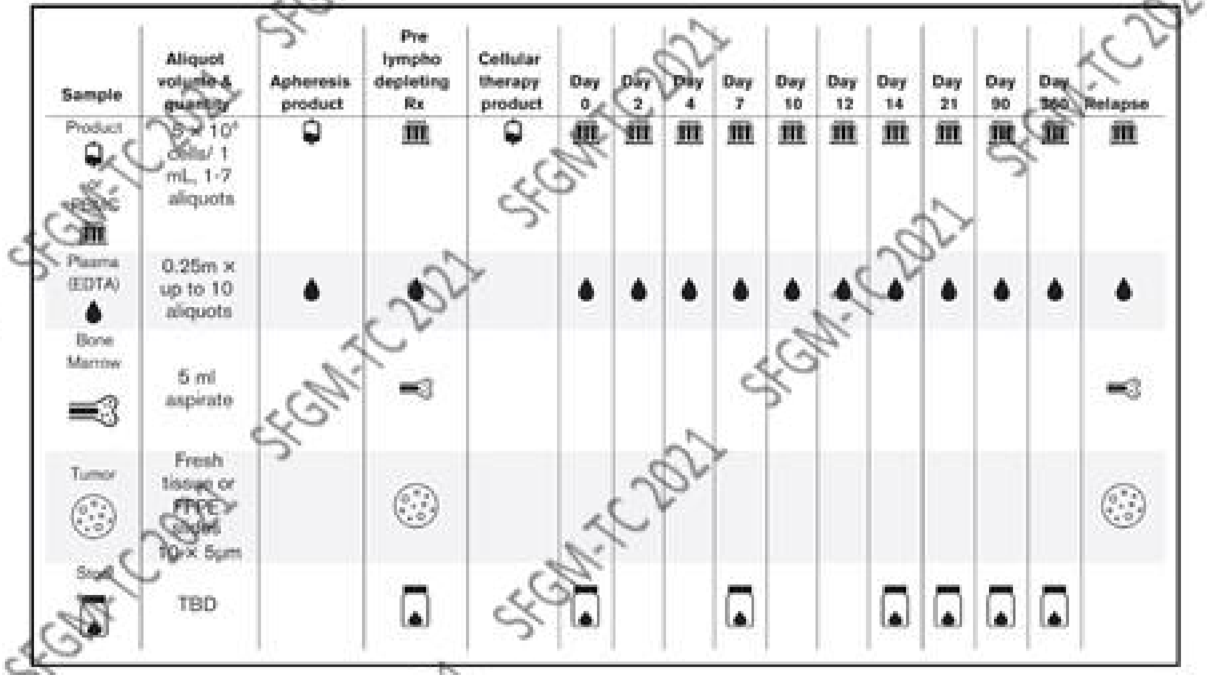

Figure 2. Proposed sample collection (eg, for CD19 CAR T cells). EDTA, ethylenediaminetetraacetic acid; FFPE, formalin fixed, paraffin embedded; TBD, to be determined.

We don't aim to break silos down, but to connect them

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GoCART COALITION

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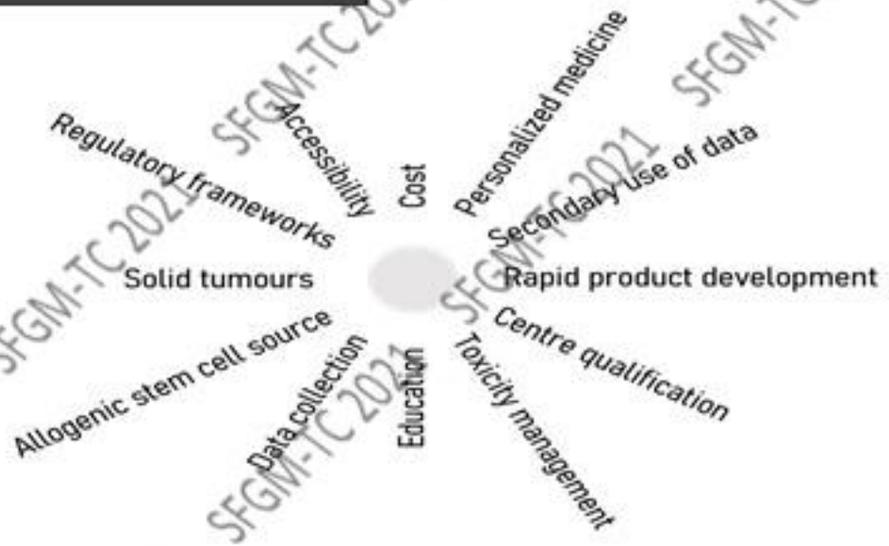
Challenges in the field of cellular therapies




EBMT
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EUROPEAN HEMATOLOGY ASSOCIATION
4th European CAR T-cell Meeting
Save-the-Date / February 3-5, 2022
SFGM-TC 2021

The EBMT – EHA CAR-T Handbook

Editors: Nicolaus Kröger, John Gribben, Christian Chabannon, Hermann Einsele, Ibrahim Yakoub-Agha

This Open Access first European CAR-T Handbook co-promoted by the European Society for Blood and Marrow Transplantation (EBMT) and The European Hematology Association (EHA) covers several aspects of CAR-T cells treatments, including the underlying biology, indications, management of side-effects, access to and manufacturing issues. This book, written by leading experts in the field, provides an unparalleled Overview of the CAR-T cell technology and its application in clinical care, to enhance readers' knowledge and practice skills.


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Thanks!