**C’è una soglia di età anagrafica al di sopra della quale un paziente non dovrebbe essere candidato alla terapia cellulare CAR-T?**

**Presentazione del quesito**

M. Martino (Reggio Calabria)

Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022

| | Disease status | MSD allo | MUD allo | MMAD allo | Auto | CAR-T |
|---|---|---|---|---|---|---|
| LBCL | CR1 (intermediate/high IPI at diagnosis) | GNR/III | GNR/III | GNR/III | CO/I | GNR/III |
| | Untested relapse | GNR | GNR | GNR | GNR | S/I |
| | Chemosensitive early relapse, ≥CR2 | CO/II | CO/II | D/III | CO/I | S/II |
| | Chemosensitive late relapse, ≥CR2 | CO/II | CO/II | D/III | S/II | CO/II |
| | Chemosensitive relapse after auto-HSCT failure | CO/II | CO/II | CO/III | GNR/III | S/II |
| | Refractory disease | CO/II | CO/II | CO/III | GNR/I | S/I |
| | Primary CNS lymphoma | GNR/III | GNR/III | GNR/III | S/II | D/III |
| FL | CR1, untransformed | GNR/III | GNR/III | GNR/III | GNR/II | GNR/III |
| | CR1, transformed into high-grade lymphoma | GNR/III | GNR/III | GNR/III | CO/III | GNR/II |
| | Chemosensitive relapse, ≥CR2 | CO/III | CO/III | GNR/III | S/II | GNR/III |
| | ≥CR2 after auto-HSCT failure | S/II | S/II | D/III | GNR/III | CO/II |
| | Refractory | CO/II | CO/II | CO/III | GNR/III | CO/II |
| MCL | CR1 | GNR/III | GNR/III | GNR/III | S/I | GNR/III |
| | CR/PR >1, no prior auto-HCT | CO/III | CO/III | D/III | CO/II | S/II |
| | CR/PR >1, after prior auto-HCT | CO/II | CO/II | CO/III | GNR/II | S/II |
| | Refractory | CO/II | CO/II | CO/III | GNR/II | S/II |

J.A. Snowden et al. Bone Marrow Transplantation (2022) 57:1217 – 1239

**Table 1. Patient eligibility criteria for CAR-T**

| 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.<br>Real-world CAR-T data suggest 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 were comparable in both groups to the rest of the population. |

P. J. Hayden et al. Annals of Oncology 2022

| | DLBCL<br>Limite età | MCL<br>Limite età | FL<br>Limite età |
|---|---|---|---|
| Axi-Cel | III linea<br>75 anni | No limiti | IV Linea<br>No limiti |
| Tisa-Cel | III linea<br>75 anni | | III<br>No limiti |
| Axi-Cel | II linea<br>75 anni | | |

**Table 2. Patient's characteristics in pivotal trials and real-life retrospective reports**

| | | Pivotal trials | | | Real-life retrospective reports | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Study | | ZUMA-1[4] | JULIET[5] | TRANSCEND NHL 001[6] | Nastoupil JCO 2020[43] | Jacobson JCO 2020[44] | Pasquini Blood adv 2020[46] | Landsburg ASH 2021[47] | Locke ASH 2021[45] |
| Product | | Axi-cel | Tisa-cel | Liso-cel | Axi-cel | Axi-cel | Tisa-cel | Tisa-cel | Axi-cel |
| Patients | Enrolled | 111 | 165 | 344 | 298 | 135 | NA | NA | 1500 |
| | Manufacturing success | 110 (99%) | 153 (93%) | 342 (99%) | 298 (100%) | 134 (99%) | NA | NA | NA |
| | Infused | 101 (91%) | 111 (67%) | 269 (78%) | 275 | 122 | 155 | 682 | 1500 |
| | Eligible for clinical trial (%) | 100% | 100% | 100% | 57% | 38% | NA | 32% | 49% |
| | Median age (range) - yr | 58 (23-76) | 56 (22-76) | 63 (54-70) | 60 (21-83) | 62 (21-79) | 65 (18-88) | 66 (14-91) | 62 |
| | Age ≥ 60 yr | NA | NA | NA | 154 (52%) | NA | NA | NA | NA |
| | Age ≥ 65 yr | 24 (24%) | 25 (23%) | 112 (42%) | NA | NA | 83 (54%) | 377 (55%) | 509 (38%) |
| | Age ≥ 75 yr | NA | NA | 27 (10%) | NA | NA | 27 (10%) | 120 (18%) | NA |
| | Male sex | 68 (67%) | 72 (65%) | 174 (65%) | 192 (64%) | NA | 91 (54%) | 400 (59%) | 872 (65%) |
| | ECOG-PS 0 | 42 (42%) | 61 (55%) | 110 (41%) | 76 (26%) | 36 (30%) | NA | NA | NA |
| | ECOG-PS 1 | 59 (58%) | 50 (45%) | 155 (58%) | 164 (55%) | 74 (61%) | NA | NA | NA |
| | ECOG-PS ≥ 2 | 0 | 0 | 4 (1%) | 58 (19%) | 12 (10%) | 8 (5%) | 137 (20%) | 59 (4%) |
| | Prior ASCT | 21 (21%) | 54 (49%) | 90 (33%) | 98 (33%) | 31 (25%) | 40 (26%) | 176 (26%) | 359 (27%) |
| | Prior allo-SCT | 0 | 0 | 9 (3%) | 7 (2%) | 4 (3%) | 5 (3%) | 11 (2%) | 25 (2%) |
| | Renal disease[a] | 0 | 0 | 51 (19%) | 21 (7%) | NA | NA | NA | 30 (2%) |
| | Cardiovascular disease[b] | 0 | 0 | 13 (5%) | 10 (3%) | 2 (2%) | NA | NA | 169 (13%) |
| Toxicity | Non-relapse mortality (%) | 2% | 0 | 3% | 4.4% | 6% | 1.2% | NA | NA |

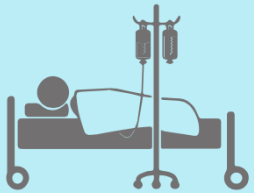
Vic S, et al. Eur J Cancer. 2022 Nov;175:246-253.

# Considerations For CAR T Cell Therapy May Differ From Criteria For Stem Cell Transplants[1]

It is important to recognize that eligibility for CAR T cell therapy may differ from criteria for stem cell transplants[1]

**General considerations for candidates for stem cell transplant:**

- Age[2]
- Adequate patient fitness, performance status, and organ function[2]
- Tolerant of high doses of chemotherapy[3,4]
- Chemosensitivity (precise recommendations may vary by institution)[4,5]



**Additional considerations:**

- Socioeconomic factors[2]
- Caregiver support[2]
- Social work evaluation[2]

**References: 1.** Li C, et al. *JCI Insight*. 2019;4(16):e130195. **2.** Tay J, et al. *Bone Marrow Transplant*. 2019;54:368-382. **3.** Gisselbrecht C, Van Den Neste E. *Br J Haematol*. 2018;182(5):633-643. **4.** Memorial Sloan Kettering Cancer Center. Autologous Stem Cell Transplant: A Guide for Patients & Caregivers. Accessed August 12, 2021. https://www.mskcc.org/pdf/cancer-care/patient-education/autologous-stem-cell-transplant-guide-patients-caregivers. **5.** Gisselbrecht C, et al. *J Clin Oncol*. 2010;28(27):4184-4190.

# Considerations for CAR T Cell Therapy

**General considerations for candidates for CAR T cell therapy:**

- Have a disease as defined in commercial indication or in clinical trial[1]
- Adequate marrow function[2]
- Adequate patient fitness, performance status, and organ function[3]
- No active, uncontrolled infections, including hepatitis B, hepatitis C, or HIV[3]
- Absence of clinically relevant comorbidities (eg, select cardiovascular, neurologic, or immune disorders)[3]
- Cumulative chemotherapy exposure may adversely affect quality of circulating T cells[2]
  - Eg, bendamustine may adversely affect T cell numbers and function[4]
- Allogeneic stem cell transplant before CAR T cell therapy increases the risk of GVHD because the manufactured CAR T cells will be derived mostly from the engrafted donor T cells[5]

Precise criteria for eligibility vary by malignancy, treatment regimen or protocol, and CAR T cell product[3]

**Additional considerations:**

- Socioeconomic factors[1]
- Caregiver support - a dedicated caregiver should be available 24 hours a day[6]
- Social work evaluation[7]
- Stay in close proximity of treating institution for at least 4 weeks after CAR T cell infusion[6]

GVHD, graft-versus-host disease.

**References: 1.** Taylor L, et al. *Clin J Oncol Nurs*. 2019;23:20-26. **2.** Yakoub-Agha I, et al. *Haematologica*. 2020;105(2):297-316. **3.** Leukemia & Lymphoma Society. Facts about chimeric antigen receptor (CAR) T-cell therapy. 2020. **4.** Fang PQ, et al. *Front Oncol*. 2021;11:648655. **5.** Wall DA, Krueger J. *Curr Oncol*. 2020;27(suppl 2):S115-S123. **6.** Beaupierre A, et al. *J Adv Pract Oncol*. 2019;10(Suppl 3):29-40. **7.** Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24(6):1135-1141.

## Table 1. Groups and criteria based on ASCT and CAR T-cells eligibility

| Group | | Double eligible | Single eligible | Ineligible |
|---|---|---|---|---|
| **Transplant-eligible** | | + | - | - |
| **CAR T-eligible** | | + | + | - |
| | | **Eligibility criteria** | | |
| **Patient** | Fitness | Fit | **Not fit but not frail** | Frail |
| | *Age (years)* | *≤65-70* | *>65-70* | - |
| | *Performance status* | *Good* | *Intermediate* | *Poor* |
| | *Organ functions* | *Good* | *Intermediate* | *Poor* |
| | *Comorbidities* | *Low* | *Intermediate* | *High* |
| **Treatment** | Prior ASCT | No | **Yes** | - |
| **Graft** | Stem cell collection | Successful | **Failure** | - |
| **Tumor** | Tumour response | Remission | **Refractory** | - |

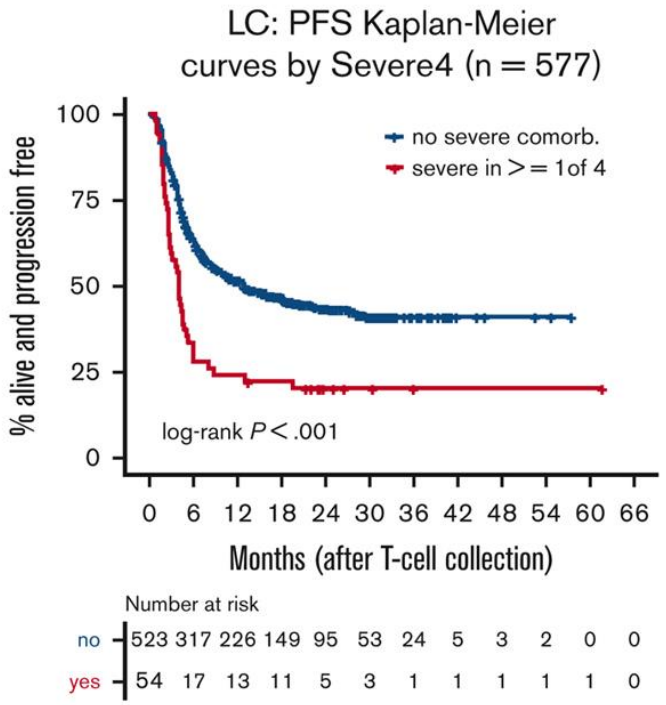
The abbreviation ASCT denotes autologous stem cell transplantation, CAR chimeric antigen receptor.

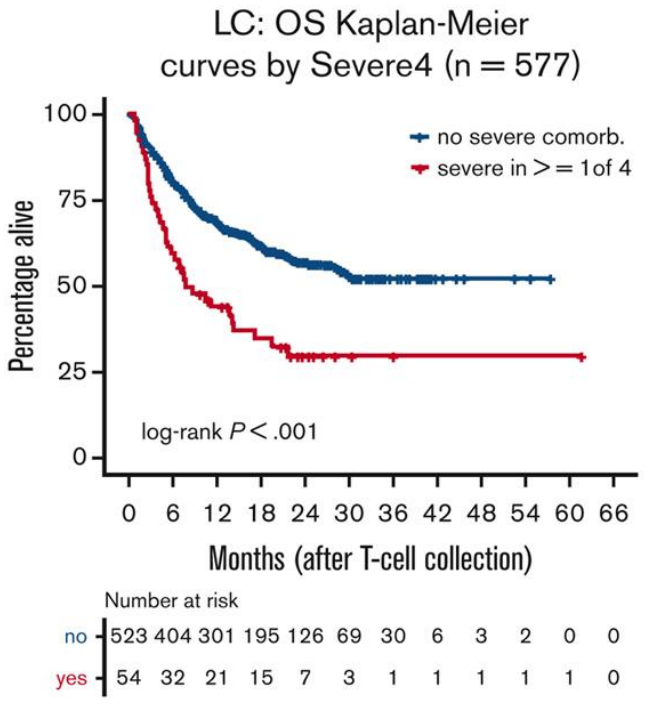
Vic S, et al. Eur J Cancer. 2022 Nov;175:246-253.

# A validated composite comorbidity index predicts outcomes of CAR T-cell therapy in patients with diffuse large B-cell lymphoma

Severe4 Comorbidity Index: Presence of a CIRS grade 3 or higher comorbidity in either the respiratory, upper GI, renal, or hepatic systems.

| CIRS Category | Sample Medical Condition |
|---|---|
| Respiratory (Severe, CIRS score >2) | Oral steroids or daily prn inhalers, acute pneumonia, supplemental oxygen or ventilation support, lung or pleural neoplasm, 50 or more pack-year smoking history |
| Upper GI (Severe, CIRS score >2) | Documented PUD, acute or chronic pancreatitis, melena, prior gastric cancer, history of perforated ulcer |
| Renal (Severe, CIRS score >2) | Serum creatinine >3 mg/dl, active pyelonephritis, nephritic syndrome, colic symptoms, dialysis, renal carcinoma |
| Hepatic (Severe, CIRS score >2) | Active or chronic hepatitis/cirrhosis, marked elevation of transaminases or bilirubin (>3x ULN), acute cholecystitis, biliary obstruction, any liver or biliary tree carcinoma |




Geoffrey Et al. Blood Adv, 2023,

# Factors That May be Associated with CAR T Cell Toxicity[a]

Factors that may impact toxicity following CAR T cell therapy may include patient-specific characteristics and/or treatment-related factors[1]

**Factors associated with increased risk for CRS and for neurotoxicity:**[1,2]

- Higher CAR T cell doses and lymphodepletion regimens containing fludarabine
- Higher peak *in vivo* proliferation of CAR T cells
- Higher disease burden
- Baseline thrombocytopenia
- Baseline elevated markers of endothelial activation, including angiopoietin-2 and von Willebrand factor
- Poor ECOG status (PS 2)

**Factors associated with CRS:**

- CAR T cells without selection of CD8+ central memory T cells[3]
- Elevated baseline serum ferritin and CRP[3]

**Factors associated with neurotoxicity:**

- Elevated CRP after infusion[1]
- Select serum cytokines and proteins, including: IL-2, sIL-2Rα, IL-6, IL-8, IL-10, IL-15, INF-ϒ, TNF-α, granzyme B, soluble GM-CSF, and MCP-1[1]

ECOG, Eastern Cooperative Oncology Group; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-ϒ, interferon gamma; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; PS, performance status; TNF-α, tumor necrosis factor alpha.

[a]The factors listed here are based on multiple different clinical studies, however research on factors that influence CAR T cell toxicity are ongoing and may vary by disease, specific product, or other factors.

**References: 1.** Brudno JN, Kochenderfer JN. *Blood Rev*. 2019;34:45-55. **2.** Siddiqi T, et al. *Blood*. 2017;130 (suppl_1):193. **3.** Murthy H, et al. *Immunotargets Ther*. 2019:8.

# Factors That May be Associated with Poor Outcomes[a]

- Several baseline factors have been found to be independently associated with risk of relapse after CAR T cell therapy including:
  - Elevated LDH and CRP
  - Low albumin
  - High ferritin
  - Tumor burden[b]
  - Total metabolic tumor volume (TMTV)[c]

- Elevated LDH and CRP, low lymphocyte count, low albumin, and high ferritin have been associated with poor survival following CAR T cell therapy

[a]Characteristics at time of treatment; [b]Measured via CT scan; [c]TMTV computed with 41% maximum standardized uptake value threshold method.
CRP, C-reactive protein; LDH, lactate dehydrogenase; TMTV, total metabolic tumor volume.
**Reference:** Vercellino L, et al. *Blood Adv*. 2020;4(22):5607-5615.