ROAD MAP CAR-T

PROSPETTIVE ATTUALI E FUTURE DELL'USO DELLE CAR-T IN ITALIA

2019 MOTORE SANITÀ
Gestire il Cambiamento

GESTIONE DELLA TOSSICITÀ E DELLE COMPLICANZE

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PALERMO

POLICLINICO "PAOLO GIACCONE"

AULA DELL'ACCADEMIA
DELLE SCIENZE MEDICHE

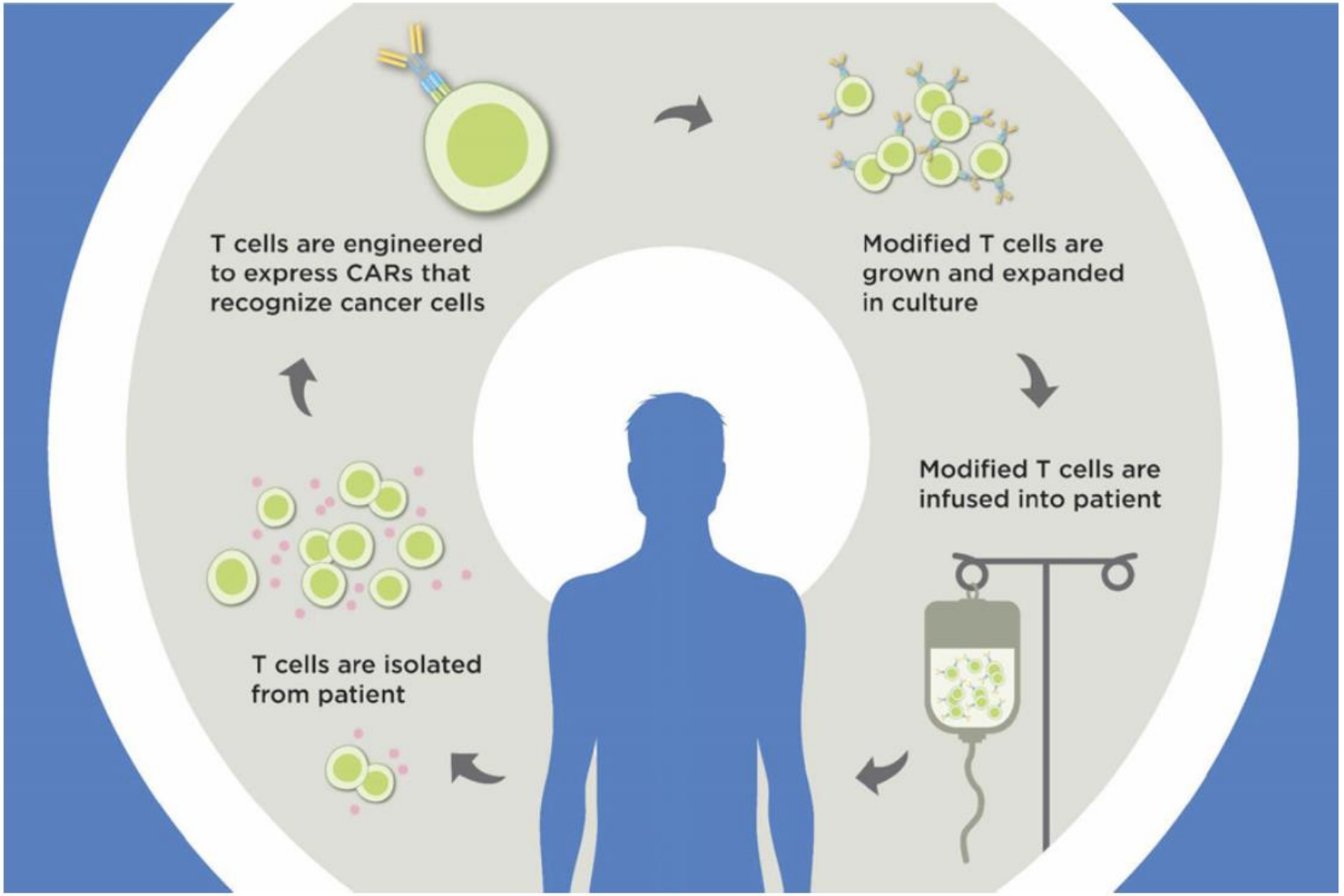
Via del Vespro, 129

3 LUGLIO 2019

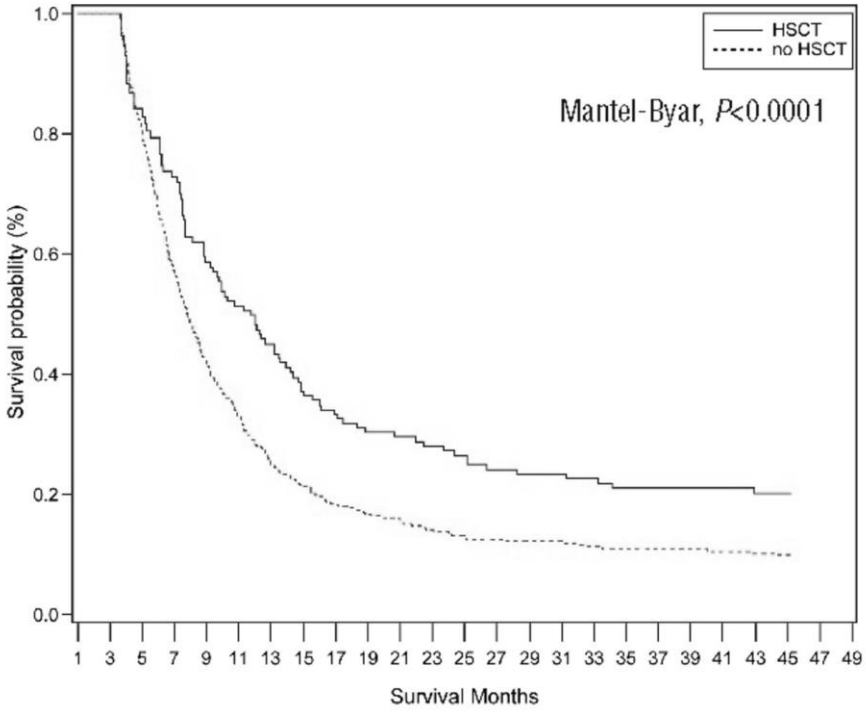
AGENZIA ITALIANA DEL FARMACO
Ufficio Segreteria Organismi Collegiali

La CTS ha ritenuto utile sottolineare, innanzitutto, che la scelta dei Centri clinici che potranno essere sottoposti alla qualifica da parte delle ditte spetta necessariamente alle Regioni. A tal fine, la Commissione ritiene opportuno proporre i seguenti criteri minimi, che ovviamente dovranno affiancarsi alle autorizzazioni previste per legge:

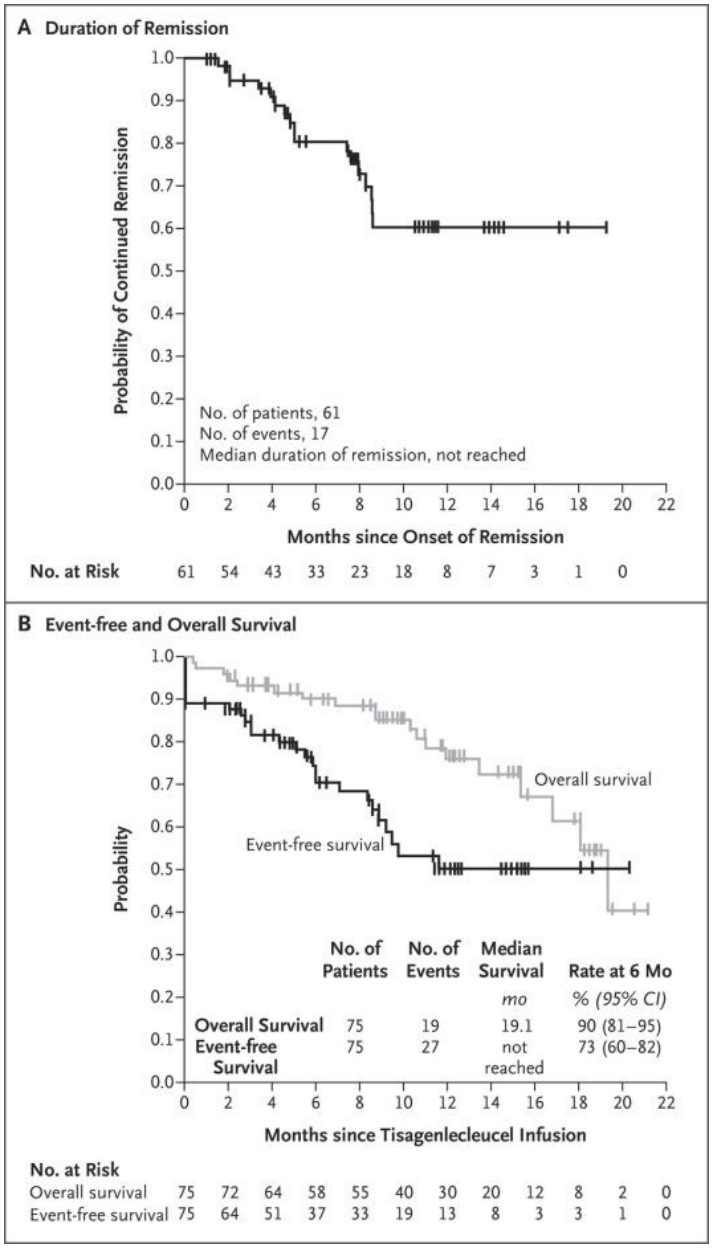
- Certificazione del Centro Nazionale Trapianti in accordo con le Direttive EU;
- Accreditamento JACIE per trapianto allogenico comprendente unità clinica, unità di raccolta ed unità di processazione;
- Disponibilità di un'unità di Terapia Intensiva e rianimazione;
- Presenza di un team multidisciplinare adeguato alla gestione clinica del paziente e delle possibili complicanze.


T cells are engineered to express CARs that recognize cancer cells
Modified T cells are grown and expanded in culture
Modified T cells are infused into patient
T cells are isolated from patient

Leucemia Linfoblastica acuta ricaduta e resistente



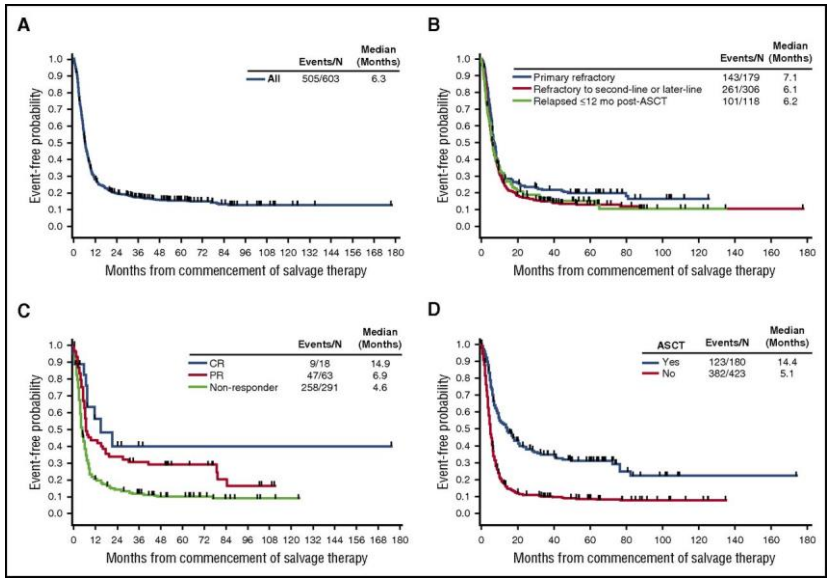
Nicola Gökbuget et al. Haematologica 2016;101:1524-1533



Maude SL et al. N Engl J Med 2018;378:439-448

blood®

Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study



Blood 2017 130:1800-1808;

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas

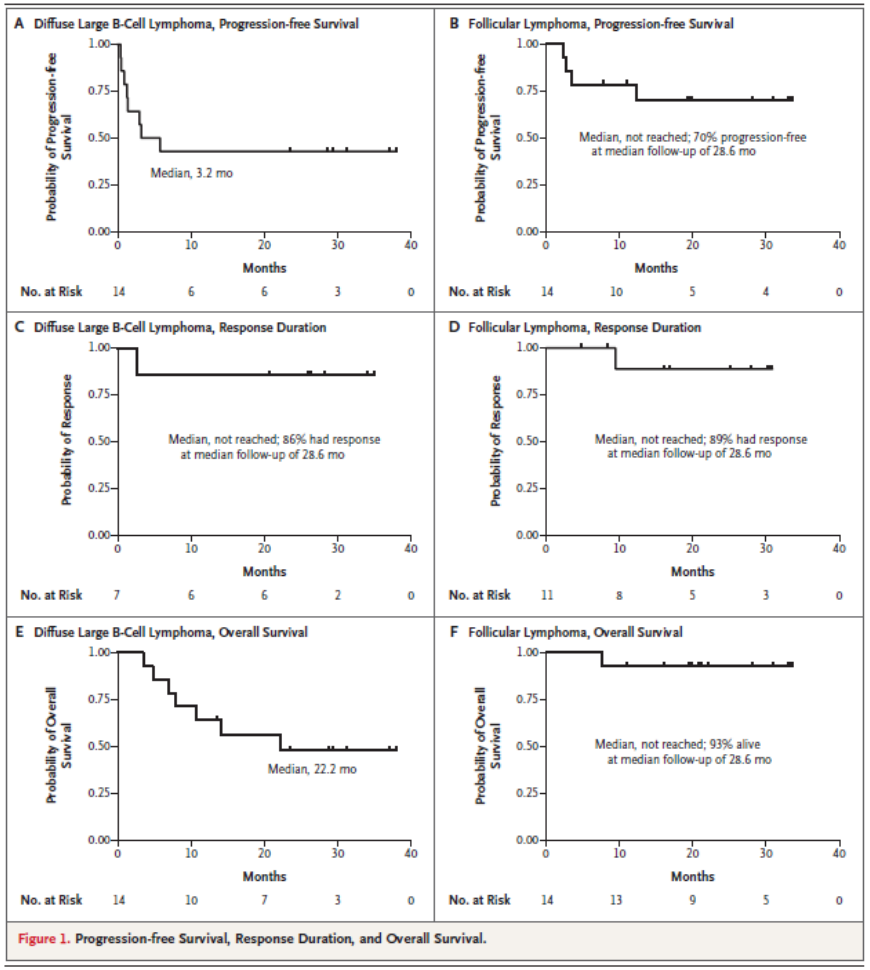


Figure 1. Progression-free Survival, Response Duration, and Overall Survival.

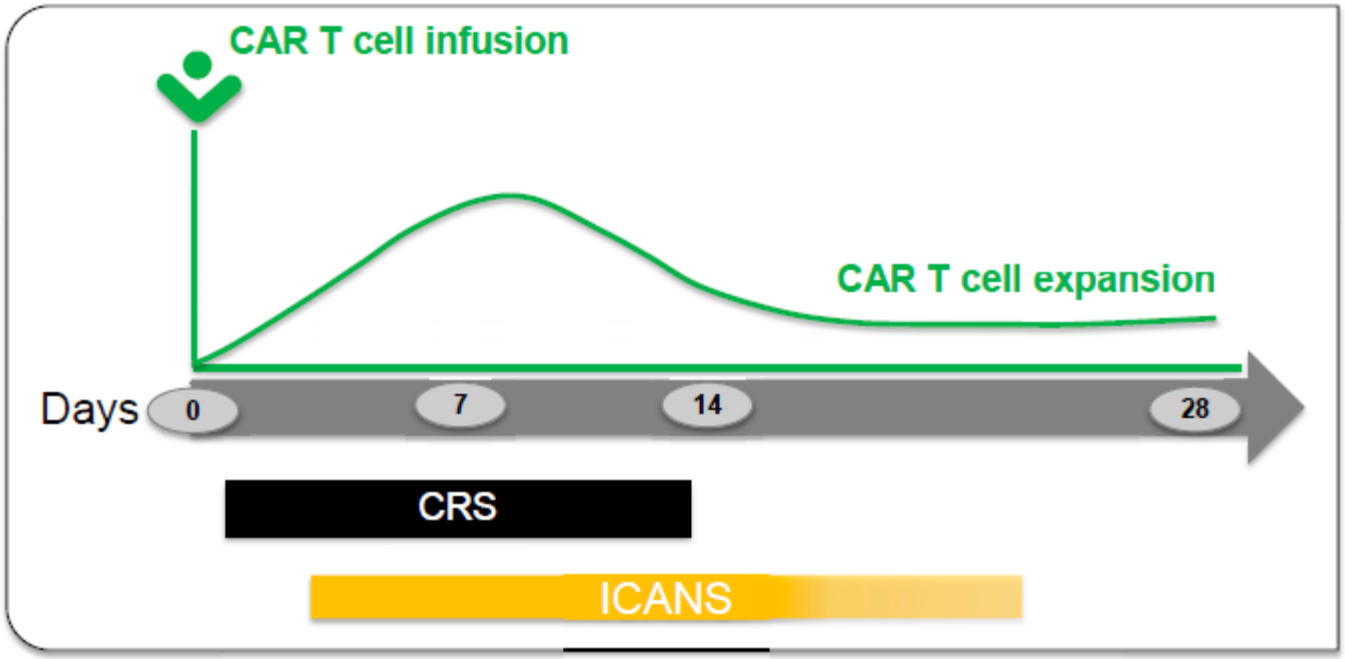


FIGURE 3. Onset and Resolution of CRS and ICANS

Abbreviations: CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune cell–associated neurologic syndrome.

Cytokine release syndrome

The Other Side of CAR T-Cell Therapy

TABLE 1. ASBMT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
With				
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or*				
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

Abbreviations: ASBMT, American Society of Blood and Marrow Transplantation; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome.

*CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause.

Immune effector cells-associated neurologic syndrome

TABLE 2. ASBMT ICANS Consensus Grading: Encephalopathy Assessment Tools for ICANS Grading

CARTOX-10[13]	ICE[14]
Orientation: Orientation to year, month, city, hospital, president/ prime minister of country of residence: 5 points	**Orientation:** Orientation to year, month, city, hospital: 4 points
Naming: Name 3 objects (e.g., point to clock, pen, button): 3 points	**Naming:** Name 3 objects (e.g., point to clock, pen, button): 3 points
	Following commands: (e.g., show me 2 fingers, close your eyes and stick out your tongue): 1 point
Writing: Ability to write a standard sentence (e.g., our national bird is the bald eagle): 1 point	**Writing:** Ability to write a standard sentence (e.g., our national bird is the bald eagle): 1 point
Attention: Count backward from 100 by 10: 1 point	**Attention:** Count backward from 100 by 10: 1 point

Abbreviations: ASBMT, American Society of Blood and Marrow Transplantation; CARTOX-10, CAR-T-cell-therapy-associated toxicity 10-point neurological assessment; ICANS, immune effector cell–associated neurologic syndrome; ICE, Immune Effector Cell Encephalopathy screening tool.

Immune effector cells-associated neurologic syndrome

TABLE 3. ASBMT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7–9	3–6	0–2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	NA	NA	Any clinical seizure focal or generalized that resolves rapidly; or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	NA	NA	NA	Deep focal motor weakness such as hemiparesis or paraparesis
Raised ICP/cerebral edema	NA	NA	Focal/local edema with or without hemorrhage on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing triad

Abbreviations: ASBMT, American Society of Blood and Marrow Transplantation; EEG, electroencephalogram; ICANS, immune effector cell–associated neurologic syndrome; ICE, Immune Effector Cell Encephalopathy screening tool; ICP, intracranial pressure; NA, not applicable.

TABLE 5. CRS and ICANS in Refractory/Relapsed Acute B-Cell Lymphoblastic Leukemia

Parameter	Tisagenlecleucel (N = 75), Pedi AYA; Lentivirus-41BB[1]	FHCRC CAR T (N = 45), Pedi AYA; Lentivirus-41BB[39]	MSK CD19 CAR T (N = 53), Adult; Retrovirus-CD28[2]
Use of tocilizumab, %	37	37	11
Use of steroids, %	NR	23	21
CRS, all grades, %	77	93	85
CRS, ≥ 3, %	46	23	26
Median time to CRS onset (range), days	3 (1–22)	NR	2
Median duration CRS (range), days	8 (1–6)	NR	NR
NT/ICANS, all grades, %	40	49	62
NT/ICANS, ≥ 3, %	13	21	42
Median time to NT/ICANS onset (range), days			5 (2–11)
Nonrelapse fatal events, N	4 (5%) infections; 2 cerebral hemorrhages; 1 unknown	0 (0%)	1 (2%) CRS-multiorgan failure

Abbreviations: AYA, adolescent and young adult; CRS, cytokine release syndrome; FHCRC, Fred Hutchinson Cancer Research Center; ICANS, immune effector cell–associated neurologic syndrome; MSK, Memorial Sloan Kettering; NR, not reported; NT, neurotoxicity; pedi, pediatric.

TABLE 4. CRS and ICANS in Adult Patients With Refractory/Relapsed B-Cell Lymphoma

CAR T-Cell Product	Tisagenlecleucel, JULIET (N = 93); Lentivirus-41BB[4]	Axicabtagene Ciloleucel, ZUMA-1 (N = 108); Retrovirus-CD28[3]	Lisocabtagene Maraleucel, TRANSCEND (N = 102); Lentivirus-41BB[38]
Use of tocilizumab, %	15	45	17
Use of steroids, %	11	29	21
CRS all grades, %	58	93	37
CRS ≥ 3, %	23	12	1
Median time to CRS onset (range), days	3 (1–9)	2 (1–12)	5 (1–14)
Median duration CRS (range), days	7 (2–30)	8	NR
NT/ICANS all grades, %	NR	67	23
NT/ICANS ≥ 3, %	12	30	13
Median time to NT/ICANS onset (range), days			10 (3–23)
Nonrelapse fatal events, N	3 (4%) encephalitis; cerebral hemorrhage; mycosis (post-SCT)	3 (2.8%) cardiac arrests; HLH; pulmonary embolus	NR

Abbreviations: CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell–associated neurologic syndrome; NR, not reported; NT, neurotoxicity; SCT, stem cell transplant.

Conclusioni

- Le cellule CAR-T costituiscono una nuova classe estremamente potente di agenti terapeutici per il trattamento delle neoplasie ematologiche
- Numerosi trials hanno mostrato percentuali di risposta impressionanti in pazienti con neoplasie ematologiche recidivanti o refrattarie
- Sebbene questi risultati sono estremamente incoraggianti, si è anche verificata una importante morbidità e occasionalmente mortalità dovute alla tossicità
- Frequente è la necessità di trasferimento in ICU
- Per tale motivo è necessario che vengano utilizzate in Centri selezionati
- Il numero di posti letto necessari aumenterà non appena saranno completate le sperimentazioni attualmente in corso in altre patologie ematologiche e oncologiche
- Altro importante problema è il costo. E' attualmente estremamente elevato e non può ovviamente essere a carico delle strutture ospedaliere. Sono necessari un finanziamento ad hoc (? fondo farmaci innovativi) e dei DRG specifici.
- L'esperienza renderà nel prossimo futuro più maneggevole l'uso di queste terapie e questo porterà, insieme alle ulteriori indicazioni per altre patologie, ad aumentarne l'uso e , si spera, quindi a ridurne il costo