Le patient atteint d'un lymphome

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HUB

26.11.2022

Hématologie et Soins Intensifs

- **Une relation complexe….**
  - **Cancer =**

  - **Cancer aux soins intensifs =**

Hématologie et Soins Intensifs

Authors	Publication	No. of patients	Mortality (%)			Prognostic indicators
			ICU	In-hospital	6 months	
Lloyd-Thomas and colleagues[3]	1988	60	63	78	N/A	APACHE II score, failure of malignancy to respond to chemotherapy, number of organ failures, leucopenia
Brunet and colleagues[4]	1990	260	43	57	81	SAPS II score, >1 organ failure, intractable sepsis
Yau and colleagues[15]	1991	92	N/A	77	N/A	Disease progression
Staudinger and colleagues[21]	2000	414	53	N/A	N/A	Respiratory insufficiency, mechanical ventilation, septic shock
Massion and colleagues[20]	2002	84	38	61	75	Respiratory failure, fungal infection, number of organ failure, transplant status
Kroschinsky and colleagues[19]	2002	104	44	N/A	67	SAPS II score, mechanical ventilation, C-reactive protein
Benoit and colleagues[6]	2003	124	42	54	66	Leucopenia, vasopressor use, urea >0.75
Owczuk and colleagues[16]	2005	40	65	N/A	N/A	SAPS II score, SOFA score, APACHE II score, neutropenia, thrombocyte count, mean arterial pressure, and necessity of catecholamine administration
Lamia and colleagues[18]	2006	92	N/A	58	N/A	SAPS II, LODS, ODIN, SOFA scores
Lim and colleagues[23]	2007	55	69	N/A	N/A	Bilirubin, inotropic support, multiple organ failure
Cuthbertson and colleagues[8]	2008	714	39	55	N/A	Cardiopulmonary resuscitation within 24 h, mechanical ventilation, inotropic support, APACHE II score
Hampshire and colleagues[11]	2009	7689	43	59	N/A	Age, length of hospital stay before ICU admission, severe sepsis, Hodgkin's lymphoma, transplant, tachypnoea, low Glasgow Coma scale, systolic hypotension, sedation, Pa_{O_2}:$F_{I_{O_2}}$ ratio, acidaemia, oliguria, hyponatraemia, hypernatraemia, haematocrit, uraemia, alkalaemia

Bird et al. Br. J. Aenesth. 2012

Hématologie et Soins Intensifs

= **5%** des admissions aux SI

Table 1 Patient characteristics

Patient characteristic data (*n*=199)	
Age (yr) [median (IQR)]	58 (46–66)
Male [*n* (%)]	112 (56.3)
Haematopoietic stem cell transplantation [*n* (%)]	84 (42.2)
Neutropenia [*n* (%)]	89 (44.7)
Graft-*vs*-host disease [*n* (%)]	22 (11.1)
Haematological malignancy [*n* (%)]	
Acute leukaemia	67 (33.7)
Chronic leukaemia	24 (12.1)
Myeloma	27 (13.6)
Lymphoma	80 (40.2)
Other	1 (0.5)
Primary reason for ICU admission [*n* (%)]	
Respiratory	67 (33.7)
Cardiac	14 (7.0)
Renal	16 (8.0)
Gastrointestinal	6 (3.0)
Neurology	5 (2.5)
Postoperative	40 (20.1)
Sepsis	42 (21.1)
Other	3 (1.5)
Unknown	6 (3.0)

40% non-onco!
40% non-onco!

Mortalité SI **34**%, hospitalière **46**%, à 6 mois **59**%

Table 4 Variables predictive of in-hospital mortality on multivariate analysis

Variable	Odds ratio	95% confidence interval
Invasive mechanical ventilation	3.03	1.33–6.90
Failure of ≥2 organ systems	5.62	2.30–13.70

Bird et al. Br. J. Aenesth. 2012
Hill. Blood Rev. 2010

Hématologie et Soins Intensifs

= **5%** des admissions aux SI

61% allo

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Unknown	6 (3.0)

Pneumonie bactérienne
>> virale, PCP, fungique
HH, tumeur obstructive

ICU admission data	
APACHE II score [median (IQR)]	21 (16–25)
Number of organ failures [median (IQR)]	2 (1–4)
Number of emergency admissions [*n* (%)]	103 (51.7)
Organ support on ICU [*n* (%)]	
Invasive mechanical ventilation	95 (51.9)
Renal replacement therapy	79 (40.9)
Vasopressors	87 (51.5)
Inotropes	13 (8.1)

Temps médian de séjour aux SI = 5 jours
Temps médian de séjour hospitalier = 27 jours

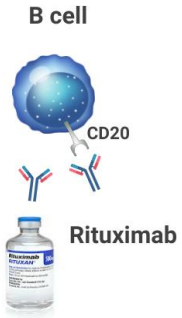
Bird et al. Br. J. Aenesth. 2012

Hématologie et Soins Intensifs

- **Centre dédié au cancer** (40,000 patients/an)
  - Expérience: 5% des admissions aux SI versus 1- 1,5%
- **Triage** efficient patients
- **Admission précoce**
- Bonne **collaboration** entre 2 spécialités, disponibles on site
  - Interactions avec infectiologie
- **Thérapies** (hémato/SI) **meilleures**
  - Moins toxiques, plus performantes

Outcome	
Mortality, *n* (%)	
Unit	3,312 (43.1)
Hospital[a]	4,239 (59.2)

Hampshire et al. Crit. Care.. 2009



Bird et al. Br. J. Aenesth. 2012

INSTITUT JULES BORDET

Hématologie et Soins Intensifs

Outcomes of Critically Ill Patients With Hematologic Malignancies: Prospective Multicenter Data From France and Belgium—A Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique Study

Elie Azoulay, Djamel Mokart, Frédéric Pène, Jérôme Lambert, Achille Kouatchet, Julien Mayaux, François Vincent, Martine Nyunga, Fabrice Bruneel, Louise-Marie Laisne, Antoine Rabbat, Christine Lebert, Pierre Perez, Marine Chaize, Anne Renault, Anne-Pascale Meert, Dominique Benoit, Rebecca Hamidfar, Mercé Jourdain, Michael Darmon, Benoit Schlemmer, Sylvie Chevret, and Virginie Lemiale

N=1011

Table 1. Patient Characteristics at Intensive Care Unit Admission

Variable	No. of Patients	%
Age, years*		
Median	60	
IQR	49-70	
Sex, male	614	61
Underlying malignancy		
Non-Hodgkin's lymphoma	320	31.6
Hodgkin's disease	25	2.5
Acute myeloid leukemia	275	27.2
Acute lymphocytic leukemia	76	7.5
Myeloma	126	12.5
Chronic myeloid leukemia	19	1.9
Chronic lymphocytic leukemia	76	7.5
Myelodysplastic syndrome	46	4.5
Other	51	5
BMT/HSCT recipient*	252	24.9
Autologous	107	10.6
Allogeneic	145	14.3
Reason for ICU admission		
Acute respiratory failure	632	62.5
Shock	428	42.3
Acute kidney injury	308	30.5
Coma	226	22.3
Chemotherapy in high-risk patients†	71	7.1
Circumstances of ICU admission	451	44.6
Time between hospital and ICU admission < 24 hours*		
Median, days	4	
IQR, days	0-16	
Direct admission to the ICU	267	26
Neutropenia*	289	28.6
More than one request from the hematologist before admission	105	10.4

Azoulay et al. JCO. 2013

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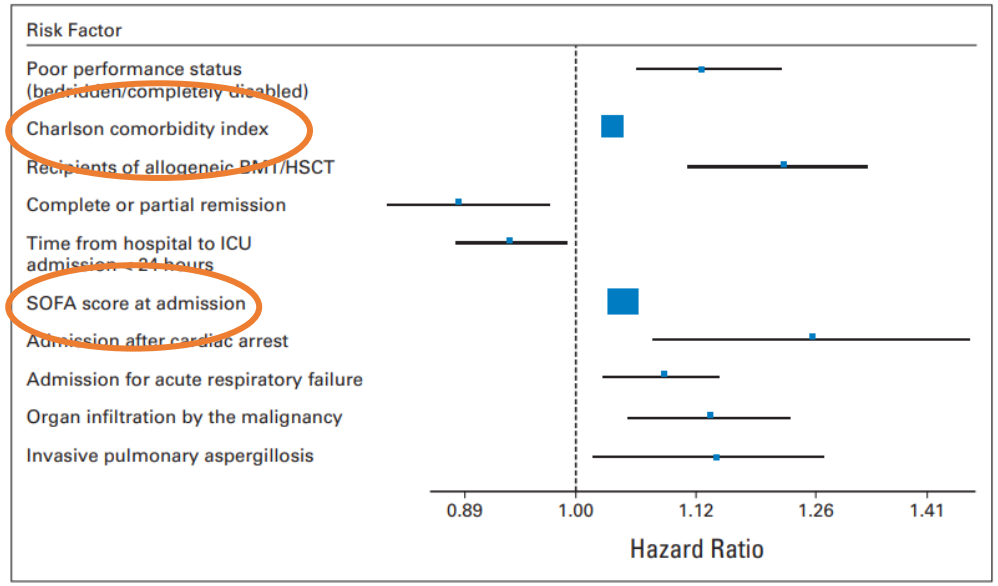
Mortalité hospitalière: 39%
à 90 jours: 47,5%
à 1 an: 56,7%

51% Amines
48% Ventilation mécanique
31% Ventilation non invasive
26% Dialyse



Azoulay et al. JCO. 2013

Hématologie et Soins Intensifs

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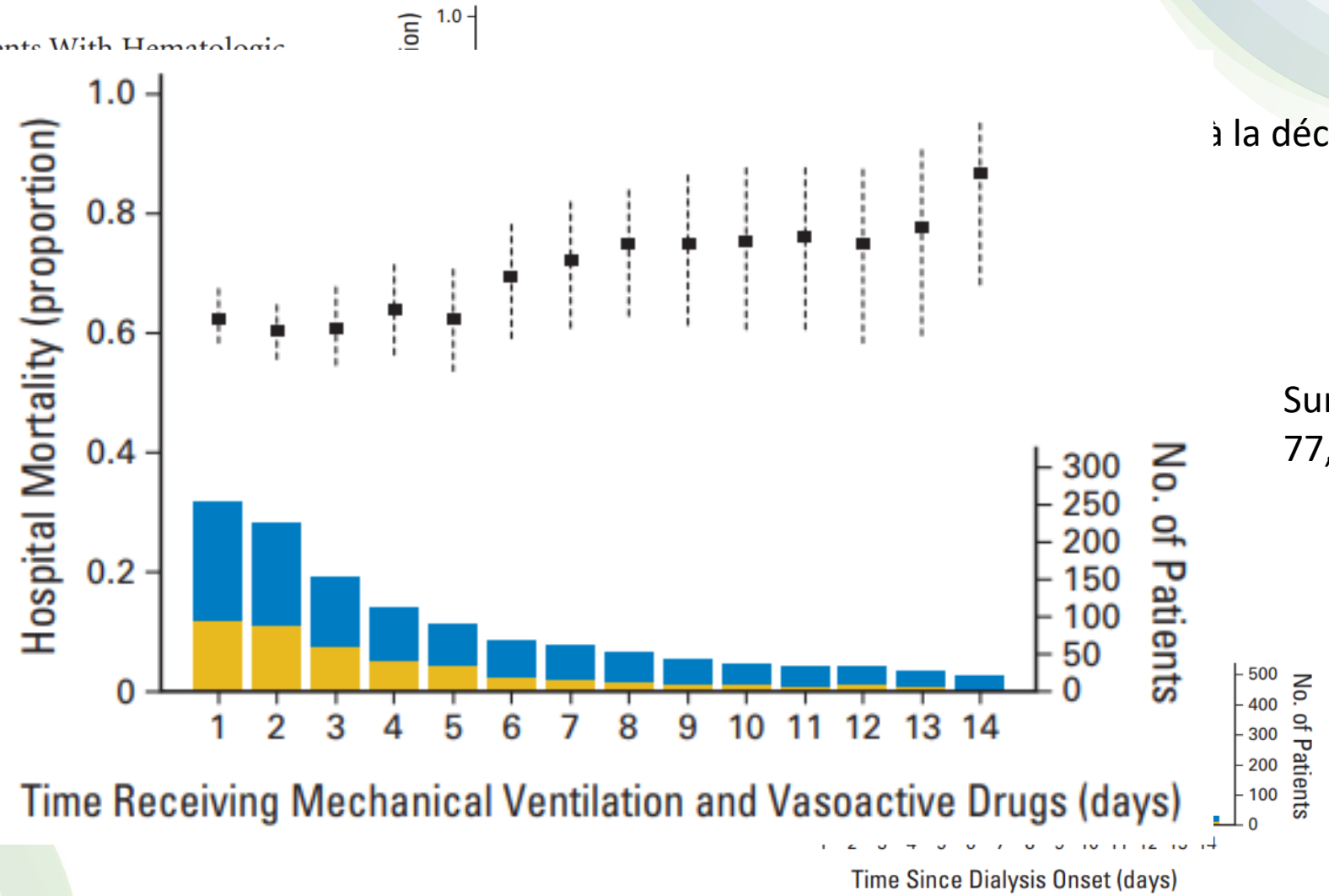

… la décharge

Survie à la décharge
77,5%

Survie à la décharge
81,3%

Azoulay et al. JCO. 2013

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→ Survie patients avec pathologie onco-hématologique largement améliorée
→ Admission précoce aux SI est corrélée à une meilleure survie
→ Une défaillance organique unique est de bon pronostic
  → même si celle-ci est prolongée!
  → ≠ défaillances organiques cumulées/prolongées

→ Nécessité de discussions

Azoulay et al. JCO. 2013

Hématologie et Soins Intensifs

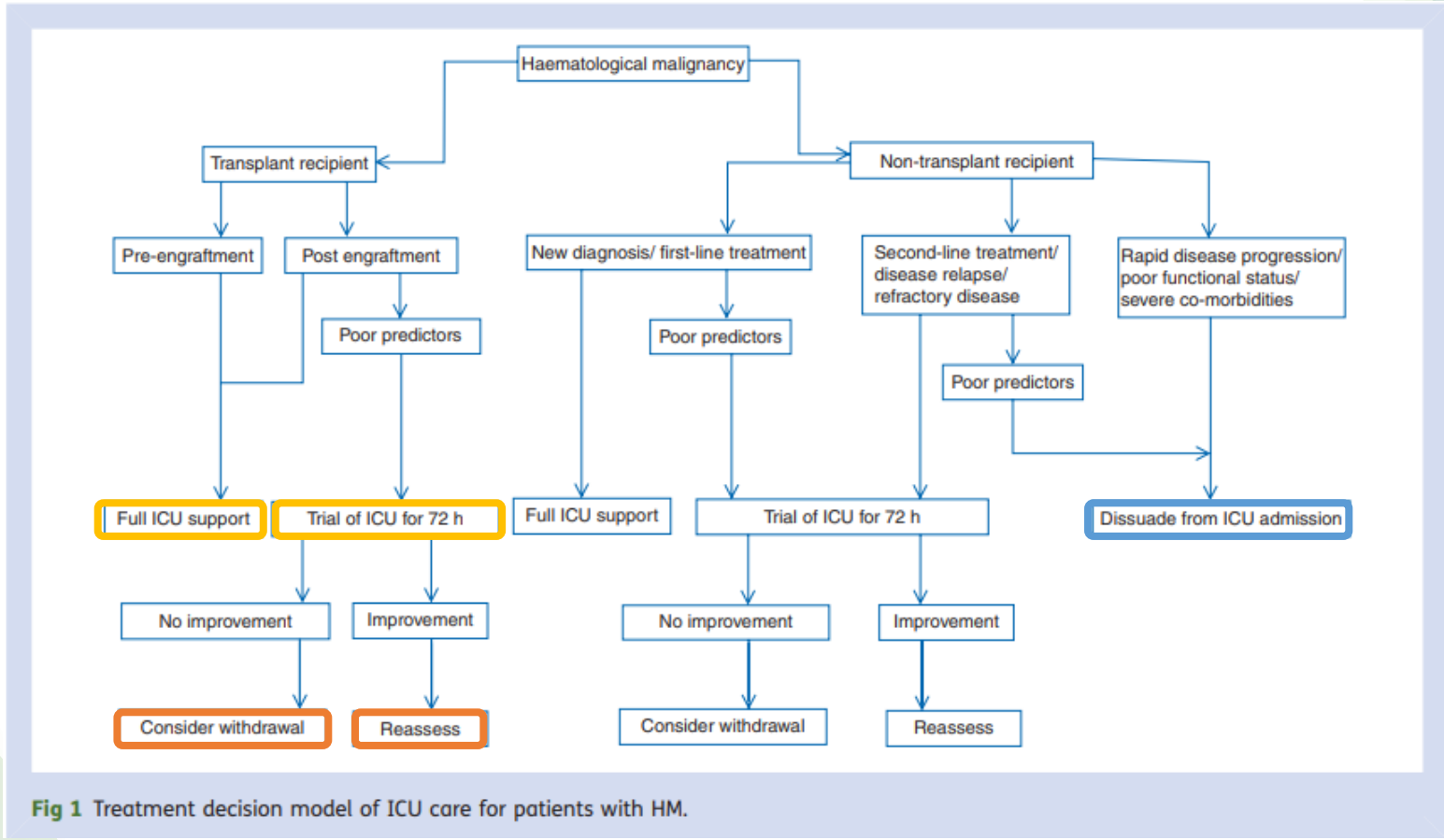


Fig 1 Treatment decision model of ICU care for patients with HM.

Bird et al. Br. J. Aenesth. 2012

Et le lymphome dans tout ça

Nouvelle classification WHO 2022 (5è édition)

- Classées selon caractéristiques anatomopathologiques, génétiques, cliniques
- 120 entités...

Hodgkin lymphoma
Classic Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma

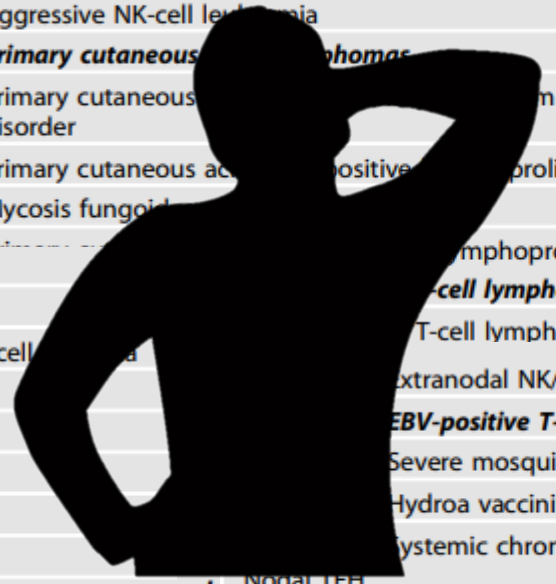
Tumour-like lesions with B
Reactive B-cell-rich lympho lymphoma
IgG4-related disease
Unicentric Castleman disea
Idiopathic multicentric Cast
KSHV/HHV8-associated mu

Tumour-like lesions with T
Kikuchi-Fujimoto disease
Indolent T-lymphoblastic proliferation
Autoimmune lymphoproliferative syndrome

Mesenchymal dendritic cell neoplasms
Follicular dendritic cell sarcoma
EBV-positive inflammatory follicular dendritic cell
Fibroblastic reticular cell tumour
Myofibroblastic tumour
Intranodal palisaded myofibroblastoma
Spleen-specific vascular-stromal tumours
Splenic vascular-stromal tumours
Littoral cell angioma
Splenic hamartoma
Sclerosing angiomatoid nodular transformation of spleen

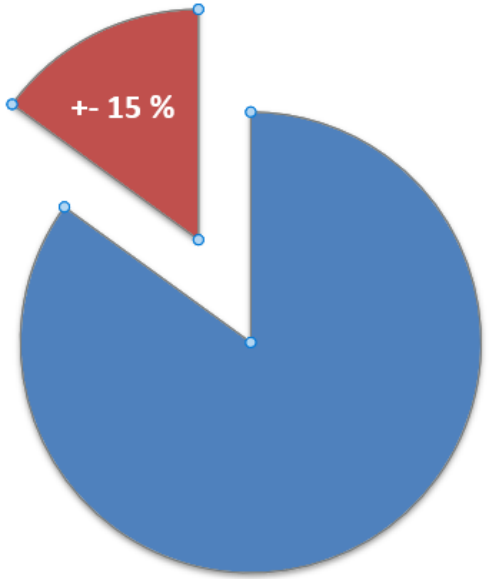
Mature T-cell and NK-cell neoplasms
Mature T-cell and NK-cell leukaemias
T-prolymphocytic leukaemia
T-large granular lymphocytic leukaemia
NK-large granular lymphocytic leukaemia
Adult T-cell leukaemia/lymphoma
Sezary syndrome
Aggressive NK-cell leukaemia
Primary cutaneous lymphomas
Primary cutaneous disorder
Primary cutaneous
Mycosis fungoi
Indolent NK cell lymp
Enteropathy-associat
Monomorphic epithe
Intestinal T-cell lymp
T-cell lymphoproliferative
proliferative disorder
mphoproliferative disorder:
-cell lymphoma
T-cell lymphoma
xtranodal NK/T-cell lymphoma
EBV-positive T- and NK-cell lymphoid proliferations and lymphomas of childhood
Severe mosquito bite allergy
Hydroa vacciniforme lymphoproliferative disorder
ystemic chronic active EBV disease
Nodal TFH
Nodal TFH Systemic EBV-positive T-cell lymphoma of childhood
Nodal TFH cell lymphoma, NOS
Other peripheral T-cell lymphomas
Peripheral T-cell lymphoma, not otherwise specified
EBV-positive NK/T-cell lymphomas
EBV-positive nodal T- and NK-cell lymphoma

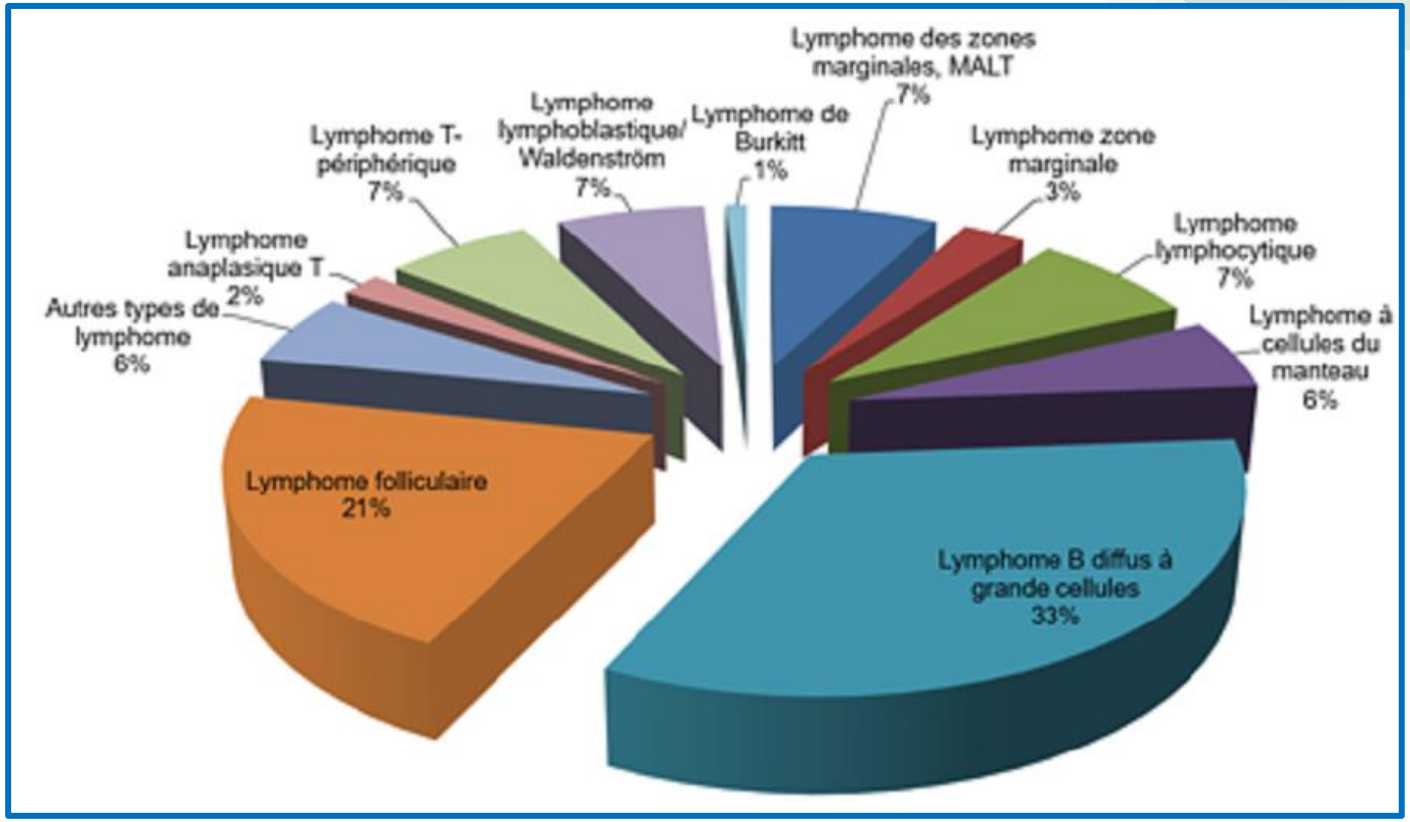
Mature B-cell neoplasms
Pre-neoplastic and neoplastic small lymphocytic proliferations
Large B-cell lymphomas
Diffuse large B-cell lymphoma, NOS
T-cell/histiocyte-rich large B-cell lymphoma
ymphoma/ high grade B-cell lymphoma
rearrangements
-cell lymphoma
ma with *IRF4* rearrangement
lasms and other diseases with
nopathies
isease
gammopathy of undetermined significance
onal gammopathy of undetermined
nopathy of renal significance
noclonal immunoglobulin deposition
related (AL) amyloidosis
inoglobulin deposition disease



Alaggio et al. Leukemia. 2022

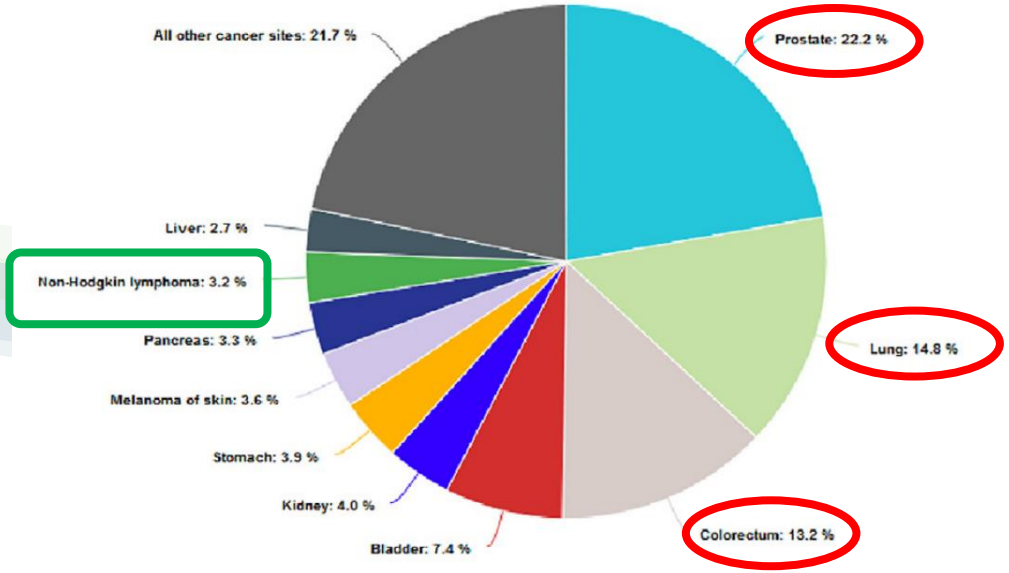
Et le lymphome dans tout ça?

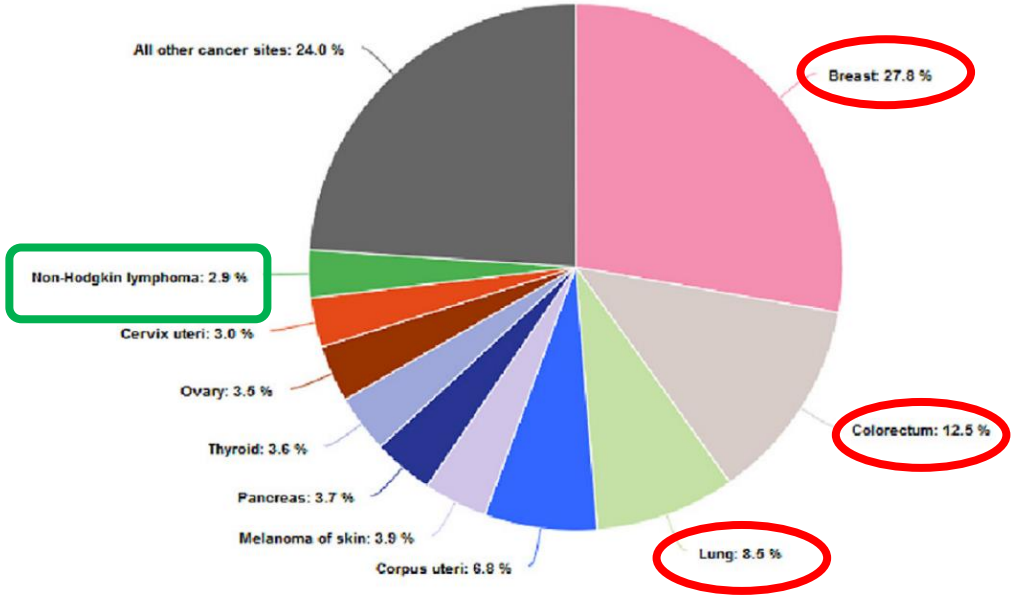




Thandra et al. Med Sci. 2021

Incidence des lymphomes

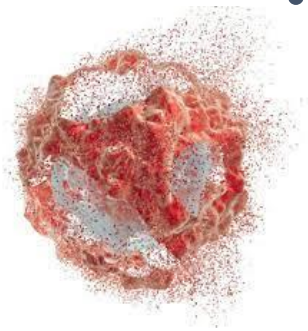




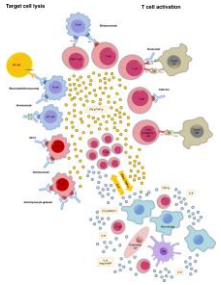
~ 120,000 nouveaux cas/an
(2800 en Belgique)

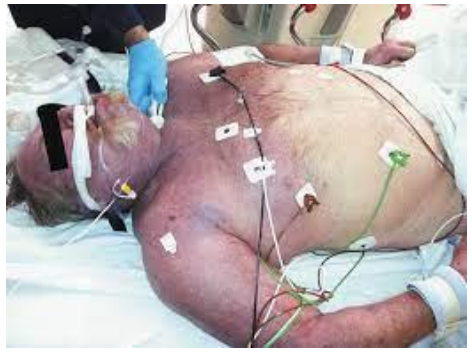
Dyba et al. European Cancer Burden in 2020. Eur J Cancer. 2021
Globocan 2020 < WHO

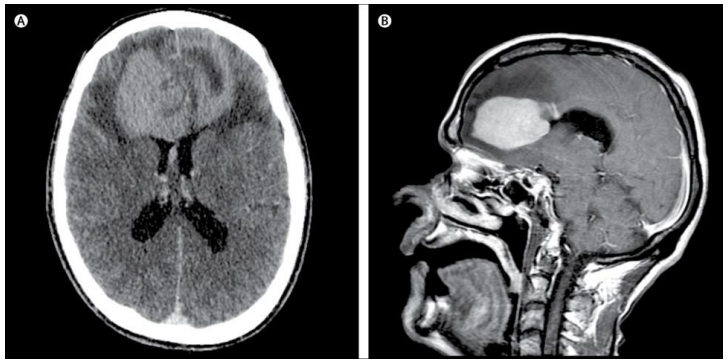
Et le lymphome dans tout ça?



- **Risques associés au lymphome récemment diagnostiqué:**
  - **Métaboliques: hypercalcémie, lyse tumorale**
    - Myélomes, lymphomes agressifs
  - **Inflammatoires: syndrome d'activation macrophagique**
    - Lymphomes de Hodgkin, lymphomes T
  - **Tumoraux: compression d'organes, de vaisseaux, HTIC**
    - Lymphomes primitifs du médiastin, du SNC, B diffus à grandes cellules, intravasculaires,…







Algrain. Leuk and Lymph. 2015

Et le lymphome dans tout ça?

- **Expérience d'un hôpital universitaire – Saint Louis – 650 lits/12 lits USI/**
  - Environ 800 admissions USI par an – 25% hématologiques
  - Période d'étude: 2000-2010
    - 4000 nouveaux lymphomes – **5%** ont nécessité une admission aux SI

Table I. Baseline patient characteristics ($n = 190$).

Characteristic	n (%) or median [IQR]
Year of admission	
2000–2004	47 (25)
2005–July 2010	143 (75)
Demographics	
Male gender	124 (65)
Age, years	49 [35–63]
Type of lymphoma	
Hodgkin lymphoma	14 (7)
Non-Hodgkin lymphoma	176 (93)
Diffuse large B-cell lymphoma	55 (29)
Burkitt lymphoma	45 (24)
Primary cerebral lymphoma	6 (3)
Other B lymphomas	36 (19)
T lymphoma	34 (18)
Lymphoma prognostic factors	
Performance status ≥ 2	120 (63)
Ann Arbor stage	
I	4 (2)
II	7 (4)
III	10 (5)
IV	169 (89)
Elevated LDH rate	138 (85)
IPI for NHL ($n = 176$)	
0–2	27 (17)
3–5	136 (83)
IPS for HL ($n = 14$)	
0–3	5 (36)
4–7	9 (64)

Algrain. Leuk and Lymph. 2015

Et le lymphome dans tout ça?

Reason for ICU admission	
Renal failure	68 (36)
Hemodynamic failure	53 (28)
Respiratory failure	49 (26)
Neurological failure	42 (22)
Monitoring	23 (12)
SOFA score at ICU admission	4 [1–7]
Inaugural complications of lymphoma	
Tumor lysis syndrome	59 (31)
Hemophagocytic syndrome	46 (24)
Clinically documented infection	40 (21)
Leukopenia	17 (9)
Treatments in ICU	
Chemotherapy	140 (74)
Renal replacement therapy	78 (41)
Mechanical ventilation	75 (39)
Vasopressive agents	57 (30)
Non-invasive mechanical ventilation	12 (6)

26% ont eu besoin de support ventilatoire, hémodynamique et/ou de dialyse

Algrain. Leuk and Lymph. 2015

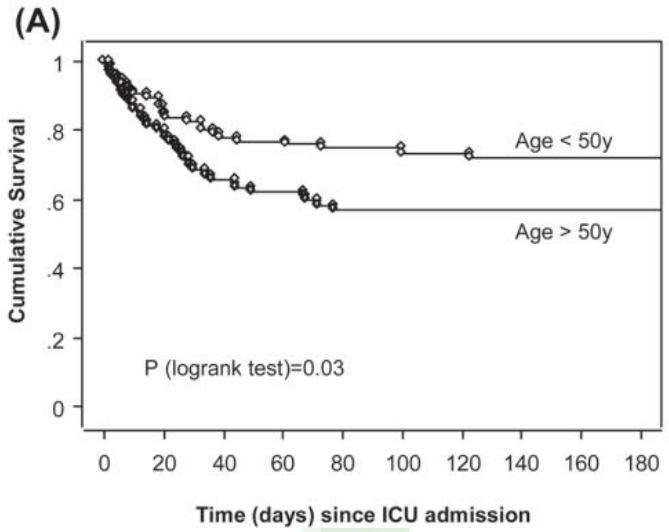
Et le lymphome dans tout ça?

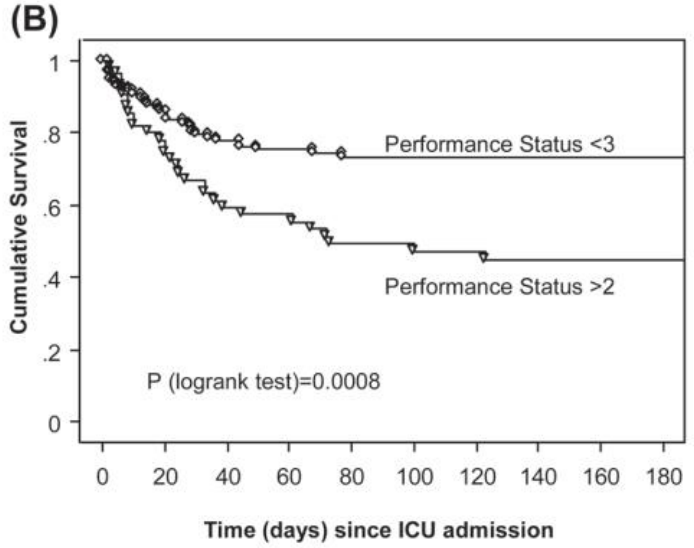
Survival

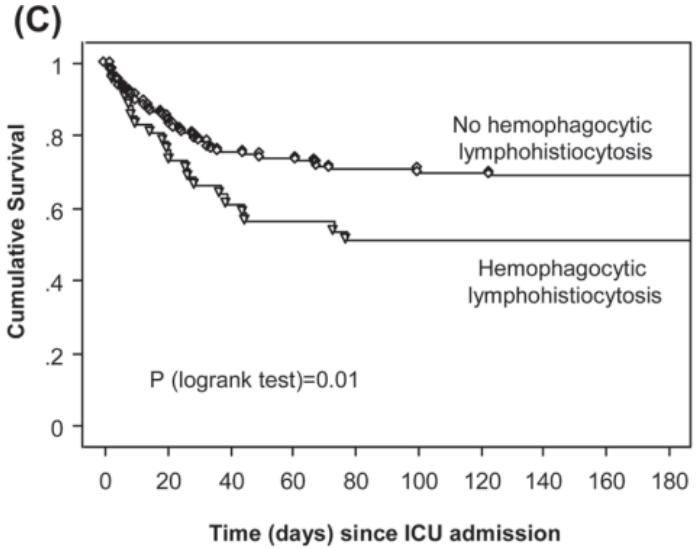
Discharged alive from ICU	148 (78)
Discharged alive from hospital	119 (63)
Alive after 1 year	93 (49)

	Multivariate analysis*		
	OR	95% CI	*p*-Value
Age > 50 years	2.23	1.02–4.90	0.0001
Hemophagocytic syndrome	2.57	1.03–6.40	0.04
Performance status > 2	3.36	1.47–6.54	0.003
Burkitt lymphoma	3.36	1.38–8.19	0.008
Primary cerebral lymphoma	7.32	1.06–50.54	0.04
SOFA score	1.15	1.04–1.27	0.006
Admission after 2004	0.35	0.15–0.78	0.01

83-72-52%







Algrain. Leuk and Lymph. 2015

Et le lymphome dans tout ça?

Incidence of intensive care unit admission, outcome and post intensive care survival in patients with diffuse large B-cell lymphoma

N=331 DLBCL
(2000-2014)
Vienne

11,2%

	ICU patients ($n = 37$)
Sex (f/m; n)	15/22
Age at diagnosis	57 (30.5–65.5)
Lymphoma diagnosis	
Advanced stage (III/IV)	28 (75.7%)
Bulky disease	13 (35.1%)
IPI[a]	
Low/intermediate (score 0–2)	15 (45.5%)
High (score 3–5)	18 (54.5%)
Comorbidity[a]	
CCI 0 points	23 (62.2%)
CCI 1–2 points	12 (32.4%)
CCI 3–4 points	1 (2.7%)
CCI ≥5 points	1 (2.7%)

= 7% ND

Table II. Etiologies of organ failures in different hematologic settings.

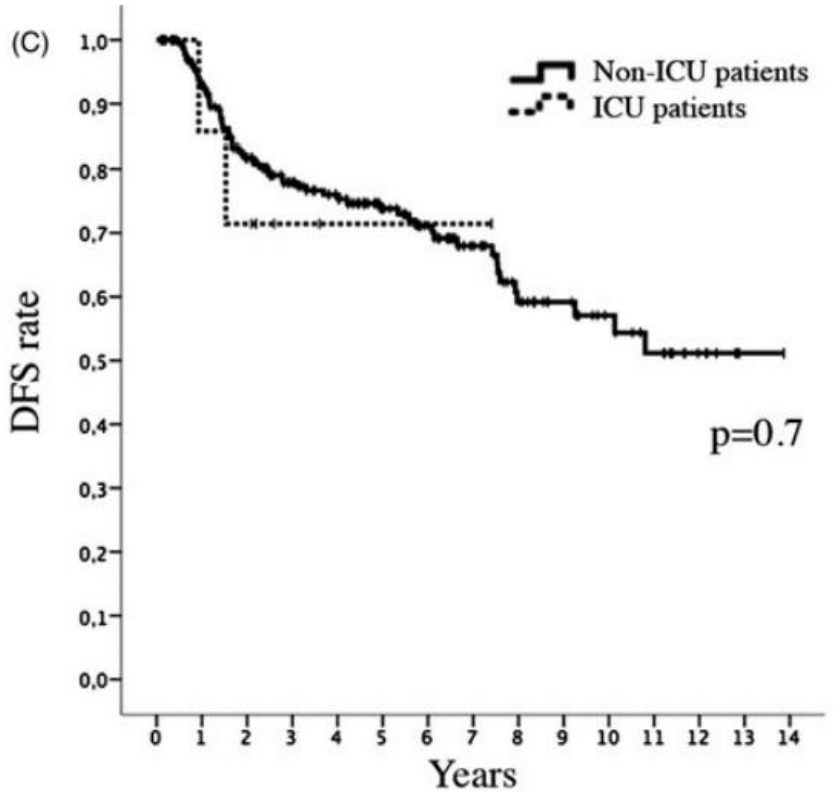
	Newly diagnosed ($n = 18$)	First-line beyond cycle one ($n = 6$)	Relapsed/ refractory ($n = 13$)
Compression/infiltration of organs	9 (50%)		
Tumor lysis	3 (17%)		
Bleeding	3 (17%)		2 (15%)
Infection	3 (17%)	4 (66%)	5 (38%)
Central nervous system relapse			4 (31%)
Embolism		1 (17%)	1 (8%)
Others		1 (17%)	1 (8%)

Wohlfarth et al. Leuk and Lymph. 2016

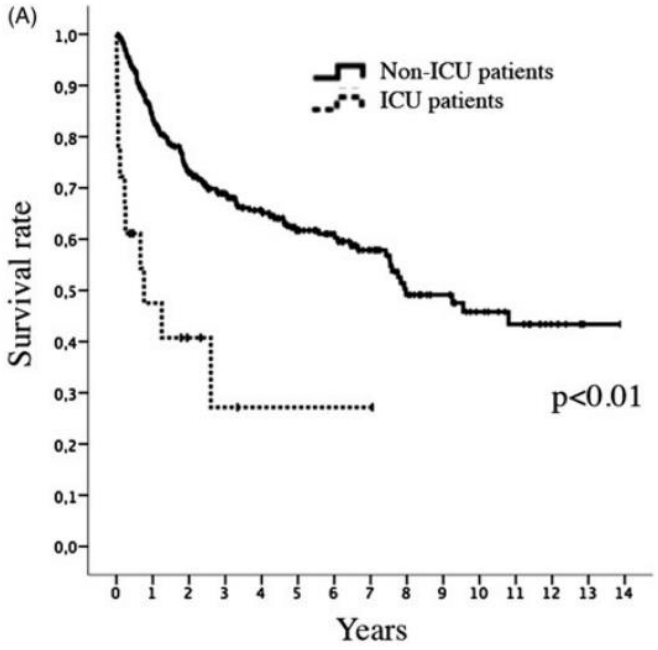
Et le lymphome B diffus dans tout ça?

Incidence of intensive care unit admission, outcome and post intensive care survival in patients with diffuse large B-cell lymphoma

N=331 DLBCL
(2000-2014)
Vienne



Survie aux SI: **76%** ; hospitalière: **70%**



Pas de différence significative lors de l'ajustement à l'IPI!!

Wohlfarth et al. Leuk and Lymph. 2016

Et le lymphome B diffus dans tout ça?

Outcomes after intensive care unit admission in newly diagnosed diffuse large B-cell lymphoma patients: A real-life study

N=828 DLBCL
(2008-2018)
France

72 patients ont eu besoin de SI (= 8,7%)
dont 45 sont des ND (= 5,4%)

Reason for ICU admission	
Acute respiratory failure	18 (40.0)
Septic shock	15 (33.3)
Acute kidney failure	5 (11.1)
Multiorgan failure	2 (4.4)
Neurological failure	2 (4.4)
Others	3 (6.6)

Age at diagnosis (y)	63.2 ± 11.8		23 (51.1)
	64 [57-72]		8 (17.8)
Gender			18 (40.0)
Female	16 (35.6)		
Male	29 (64.4)		
B signs	25 (55.6)		
Ann Arbor staging			
I–II	1 (2.2)		
III–IV	44 (97.8)		
IPI			
0-2	7 (15.6)	75 [57-100]	<.0001
3-5	38 (84.4)	79 ± 26	
Vasopressive drugs	11 (36.7)	12 (80.0)	.006
Lactate	519.7 ± 916.4		

= 4 jours

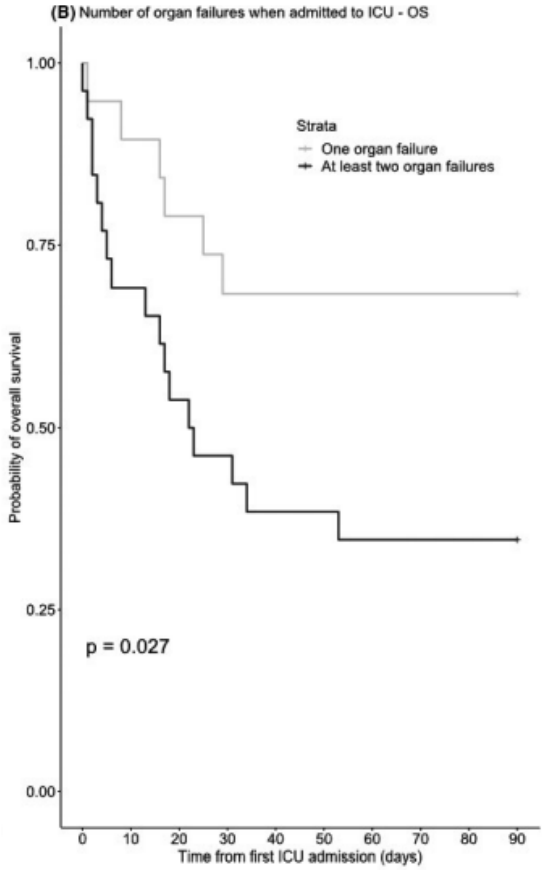
cements aux SI: 26,7%

Zduniak et al. Eur. J Haematol. 2020

Et le lymphome B diffus dans tout ça?

Outcomes after intensive care unit admission in newly diagnosed diffuse large B-cell lymphoma patients: A real-life study

N=828 DLBCL
(2008-2018)
France



Number of organ failures when admitted to ICU		
One organ failure	1	0.12
At least two organ failures	1.89 (0.85-4.17)	

→ Transfert précoce!

Zduniak et al. Eur. J Haematol. 2020

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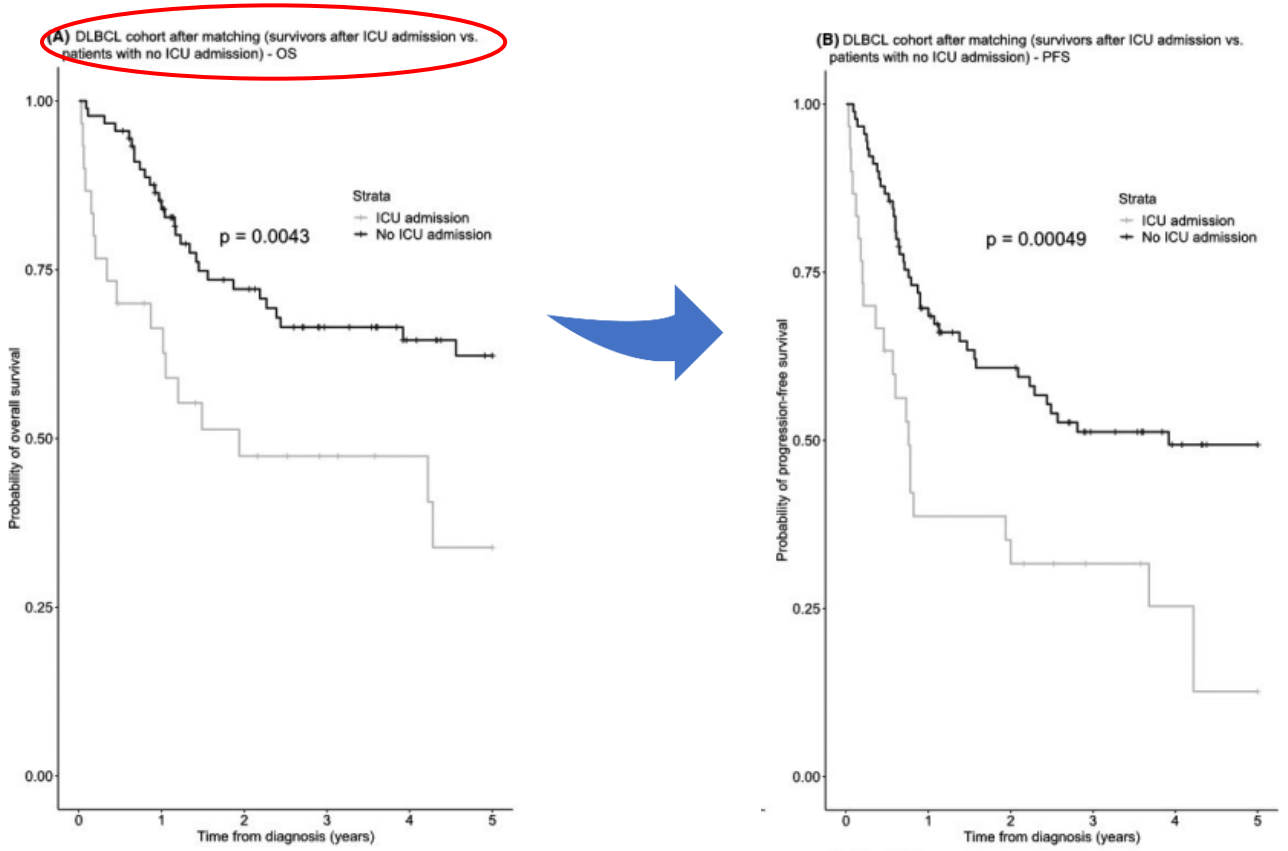

< Traitement moins intensif ultérieur?

!! Dose-intensité // survie

Zduniak et al. Eur. J Haematol. 2020

En conclusion

- **Hématologie et Soins intensifs: une relation complexe?** **NON**
- **5%** patients atteints de lymphomes nécessitent une prise en charge USI autour du diagnostic
  - < Sepsis/Insuffisance respiratoire/Lyse tumorale
  - Pronostic bien meilleur depuis 10 ans!!! - **50% à 1 an** (60% de survie < non-onco)
    - En première ligne de traitement ; meilleures thérapeutiques hémato-USI
    - Peu importe la pathologie sous-jacente
    - D'autant plus que la prise en charge est **PRECOCE**
    - D'autant plus que le traitement oncologique est administré sans/avec peu de délai!
    - En cas de survie (70-80%), idem patients non-USI???

→ Importance de travail en équipe, de décisions conjointes et de réévaluations systématiques

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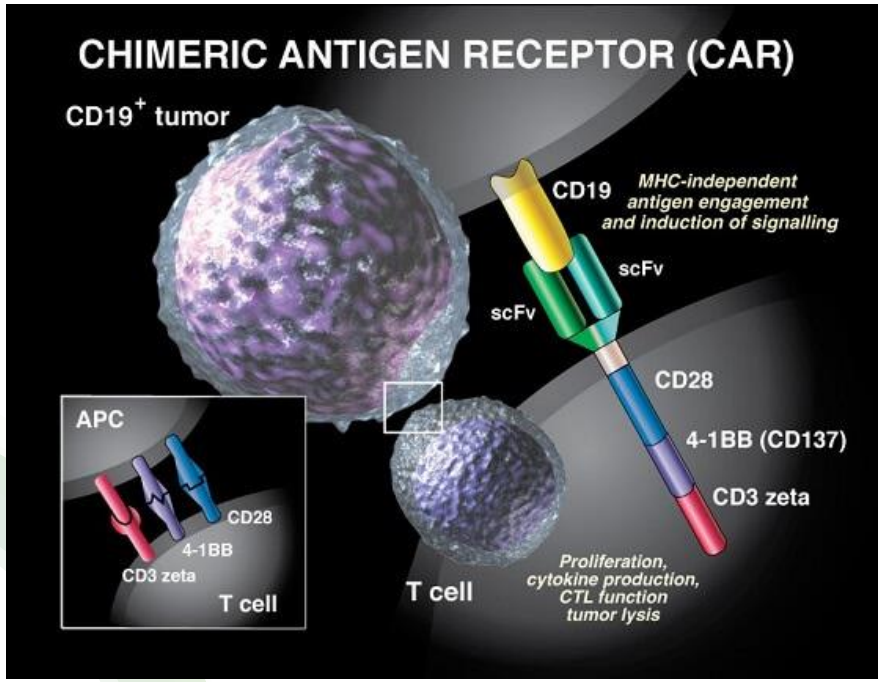
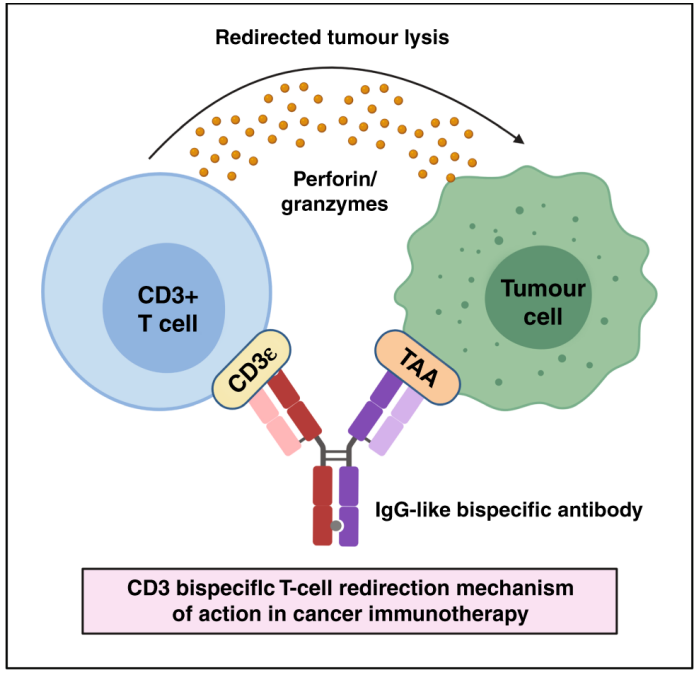
NON !!!

Quoi, c'est tout????

- **On ne cesse de s'améliorer… même en rechute!**
- LBDGC réfractaire/en rechute: mOS ~ 6 mois…





Jacobson et al. Trans Cell Ther. 2022

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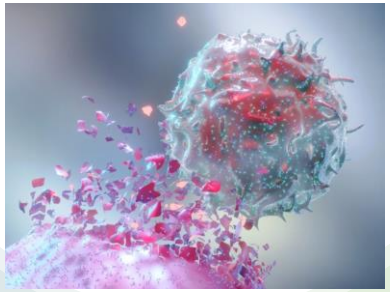

CAR T therapy

Real-world Evidence of Axicabtagene Ciloleucel for the Treatment of Large B-Cell Lymphoma in the United States

N= 1297
DLBCL/PMBCL/HGL

Measure (95% CI)	Overall N = 1297
ORR[a]	73.0 (70.5-75.4)
CR[a]	55.5 (52.8-58.2)
PR[a]	17.5 (15.5-19.7)
DOR[b]	
Median, months	NE (24.7-NE)
At 1 year	64.1 (60.6-67.4)
At 2 years	57.0 (51.5-62.1)

OS	
Median, months	21.8 (17.4-28.8)
At 1 year	62.3 (59.5-64.9)
At 2 years	49.5 (46.0-52.9)
PFS	
Median, months	8.6 (6.5-12.1)
At 1 year	47.3 (44.4-50.1)
At 2 years	39.2 (35.9-42.5)
NRM	
At 1 month	1.2 (0.7-1.9)
At 3 months	3.0 (2.1-4.0)
Median follow-up, months	12.9 (12.8-13.2)

Jacobson et al. Trans Cell Ther. 2022

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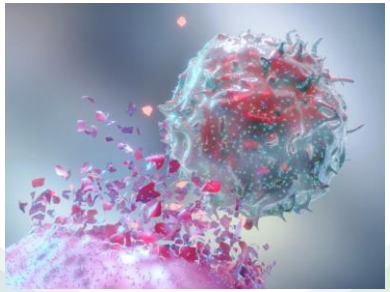

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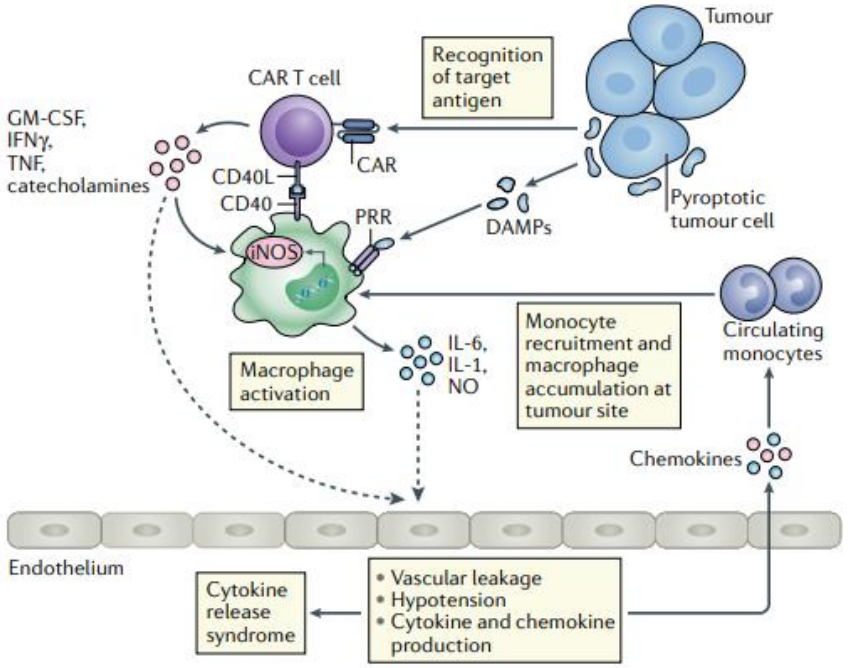
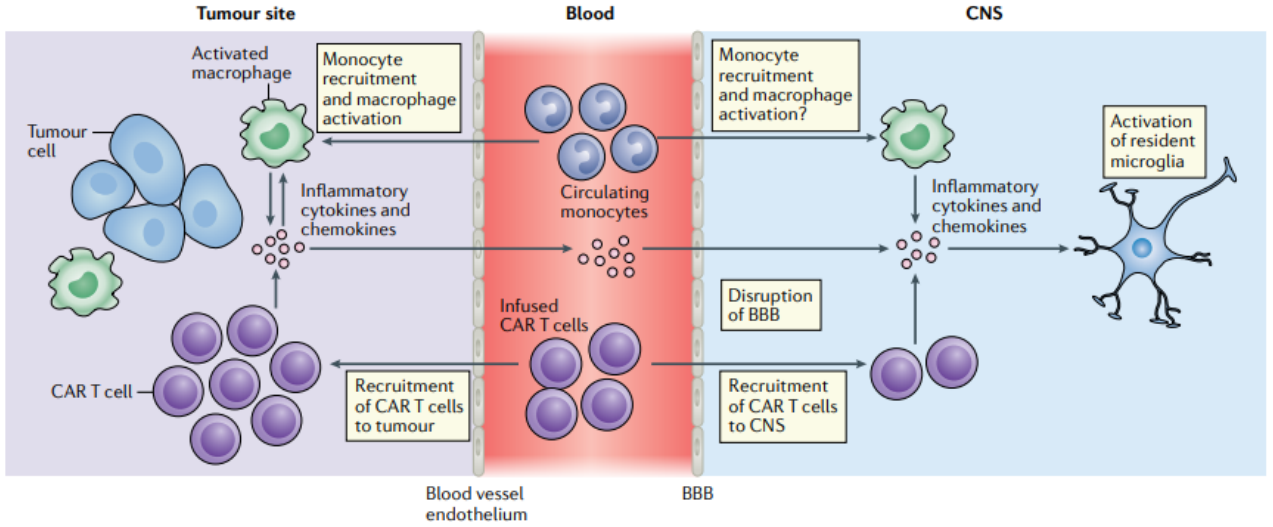
N= 1297
DLBCL/PMBCL/HGL

→ Effet secondaires redoutables, amenant les patients aux SI:
- Cytokine Release Syndrome, **CRS**
- Immune effector-cell associated Neurotoxicity syndrome, **ICANS**

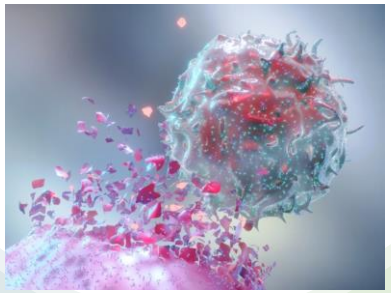




Jacobson et al. Trans Cell Ther. 2022
Morris et al. Nat Rev. 2022

INSTITUT JULES BORDET

CAR T therapy



- **CRS**

USI

CRS grading and management approaches

CRS grade 1	• temperature >38°C • flu-like symptoms • nausea	• infectious workup • broad spectrum antibiotic • supportive measures (antipyretics)
CRS grade 2	• temperature >38°C • hypotension not requiring vasopressors • hypoxia requirin low- flow nasal cannula or blow-by	• manage fever and symptoms as grade 1 • transfer to IMC/ICU • low dose vasopressor • tocilizumab 8mg/kg i.v.
CRS grade 3	• temperature>38°C • hypotension requiring one vasopressor with or with vasopressin • hypoxia requiring high- flow orfacemask	• manage fever and symptoms as grade 2 • repeat tocilizumab • low dose corticosteroids
CRS grade 4	• temperature >38°C • hypoxia requring positive airway pressure • hypotension requiring multiple vasopressors (excl. vasopressin)	• manage fever and symptoms as grade 2 • high dose corticosteroids • consider further individual treatment

Real-world Evidence of Axicabtagene Ciloleucel for the Treatment of Large B-Cell Lymphoma in the United States

Measure (%)	Overall N = 1297
CRS	
Any grade	1073 (83)
≥ grade 3[a]	107 (8)
Grade 4[a]	53 (4)
Grade 5[a]	22 (2)
Median time to onset (range), days[b]	4 (1-28)
Median duration (range), days[b]	6 (1-121)
Resolution rate by Day 21 since onset (95% CI)[b]	92.2 (90.4-93.6)

Jacobson et al. Trans Cell Ther. 2022

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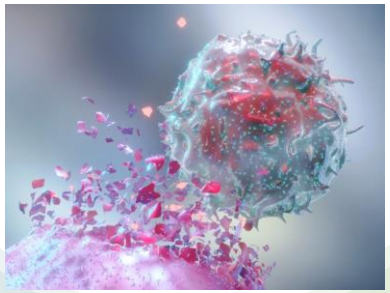
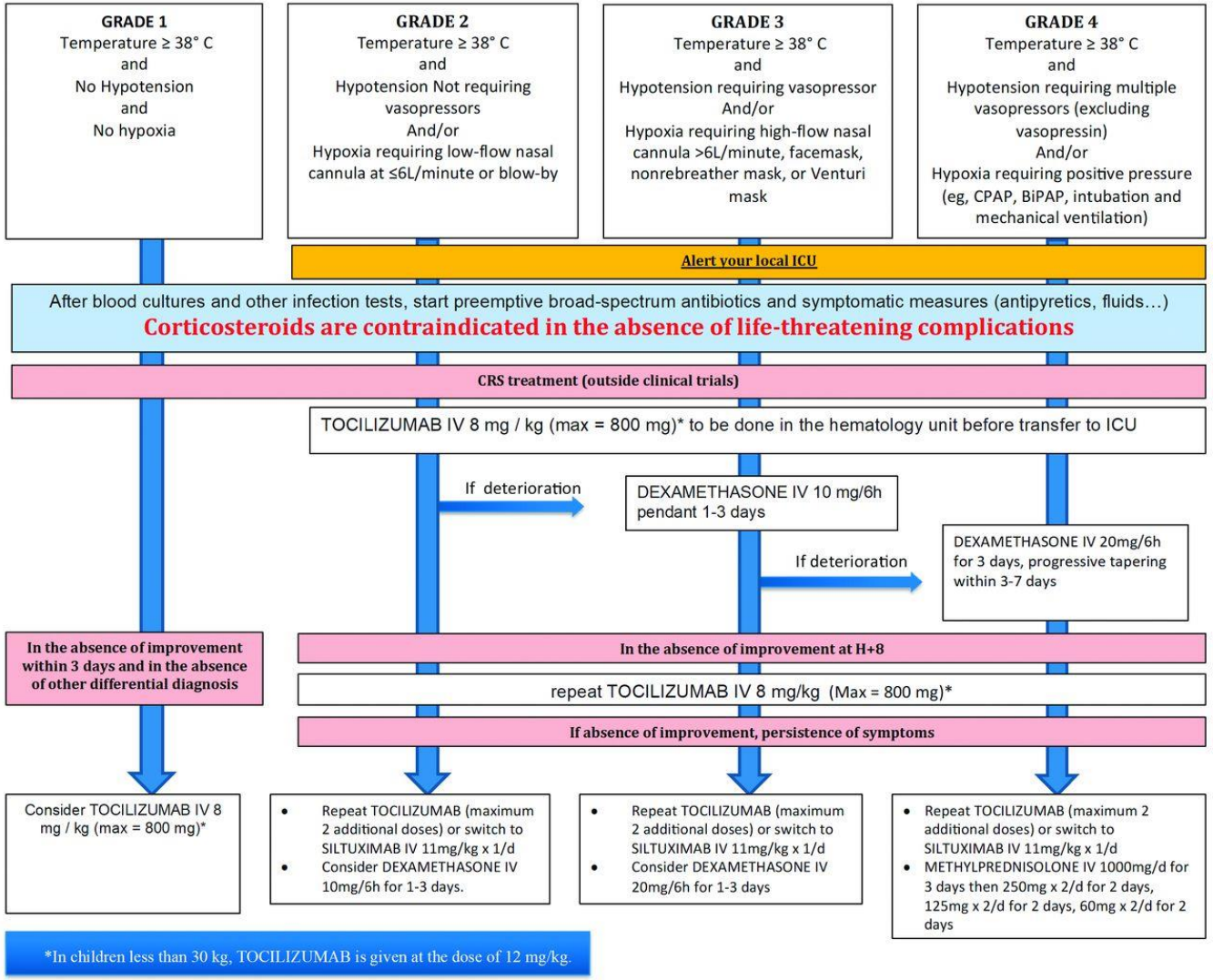
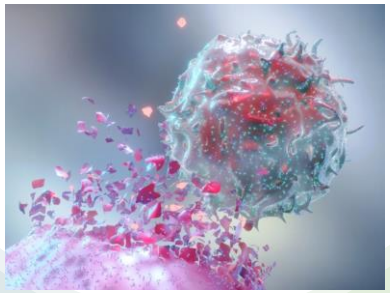


CAR T therapy



Yakoub-Agha et al. Haematologica. 2020

CAR T therapy



- **ICANS**

USI

CRS grading and management approaches

ICANS grade 1	• awakens spontaneously • fatigue • ICE: 7-9 points	• supportive care • IV hydration • neurology consultation • EEG/MRI • consider antiepileptic drug
ICANS grade 2	• awakens to voice • delirius/somnolent • ICE: 3-6 points	• supportive care as grade 1 • consider ICU transfer • consider antiepileptic drug, if not started • low dose corticosteroids (i.e. dexamethasone 10mg)
ICANS grade 3	• awakens to tactile stimulus • ICE: 0-2 points • local edema on imaging • seizure, that resolves with intervention	• Supportive care as grade 2 • ICU transfer • continous corticosteroids (i.e. dexamethasone 10mg every 6 hours) and antiepileptic drugs • repeat MRI
ICANS grade 4	• comatose • ICE:0 • cerebral edema • life-threatening (>5min) seizure • motor weakness	• supportivecareasgrade3 • highdosecorticosteroids specific neurointensive treatment (status epilecticus, brain edema) • consider further individual treatment

Real-world Evidence of Axicabtagene Ciloleucel for the Treatment

ICE[14]

Orientation: Orientation to year, month, city, hospital: 4 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
Attention: Count backward from 100 by 10: 1 point

Jacobson et al. Trans Cell Ther. 2022

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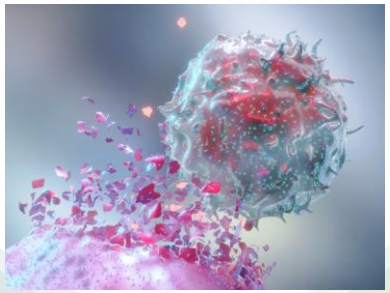

CAR T therapy

GRADE 1	GRADE 2	GRADE 3	GRADE 4
- Decreased level of consciousness (Awakens spontaneously) - ICE Score (age ≥ 12) = 7-9 or CAPD (age<12) = 1-8	- Alteration level of consciousness affecting activities of daily living (Awakens to voice) - ICE Score (age ≥ 12) = 3-6 or CAPD (age<12) = 1-8	- 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 resolve with intervention - Focal/local oedema on neuroimaging - ICE Score (age ≥ 12) = 0-2 or CAPD (age<12) > 8	- Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma - Life-threatening prolonged seizure (>5 min); 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 edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad - ICE score or CAPD impossible

Contact your local ICU,
Alert your referral neurologist

Symptomatic measures: raised head 30 °, suspend oral nutrition, replace oral drugs by IV

Specific ICANS treatment (outside clinical trials)

- Systematic EEG in 1st place
- MRI and LP as clinically indicated (differential diagnosis)
- Close monitoring

- Daily EEG, fundus, MRI and then LP in the absence of CI, transfer to ICU

- If seizure (clinically or EEG): CLONAZEPAM IV 1 mg (0.015 mg / Kg up to 1 mg), and introduce levetiracetam 500 mg x2 (paediatric dose 30 mg / Kg x 2, max 3g daily)
- If persistence or recurrence of seizure, repeat clonazepam 5 min once, otherwise, to be treated as a "état de mal"

- If papillary oedema : consider ACETAZOLAMIDE IV 1000 mg then 250-1000 mg/12h (5 mg/Kg/12h)

- If cerebral oedema: consider hyperosmolar therapy

If associated with CRS grade ≥ 1 (fever): TOCILIZUMAB IV 8 mg / kg (max = 800 mg); see management of CRS

If ICANS without CRS (afebrile): consider corticosteroid therapy

- DEXAMETHASONE IV 10 mg/6h for 1-3 d
- DEXAMETHASONE IV 20 mg/12h for 1-3 d

- METHYLPREDNISOLONE IV 1000 mg/4h for 3 d then 250 mg x 2/d for 2 d, 125 mg x 2/d for 2 d, 60 mg x 2/d for 2 d
- Discuss other alternative: high dose cyclophosphamide, anti-IL1R (Anakinra), antiIL6 (Siltuximab)

In children:
Grade 2-3: dexamethazone 0,5mg/kg /6h (maxi 10 mg/dose) ou methylprednisone 1 to 2 mg/kg/d.
Grade 4 : High-dose

EEG monitoring until resolution: if seizure: e.g. ICANS grade 2
Daily fundus until resolution: if papillary oedema: e.g ICANS grade 3
MRI and LP to be reassessed according to evolution
CAR-T cell checklist 2 times a day*

Tallantyre et al. J. Neurol. 2021

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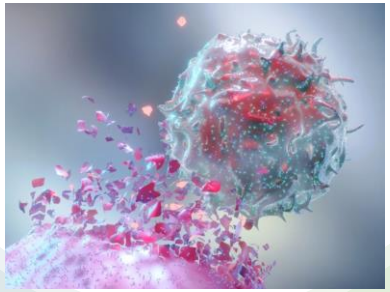
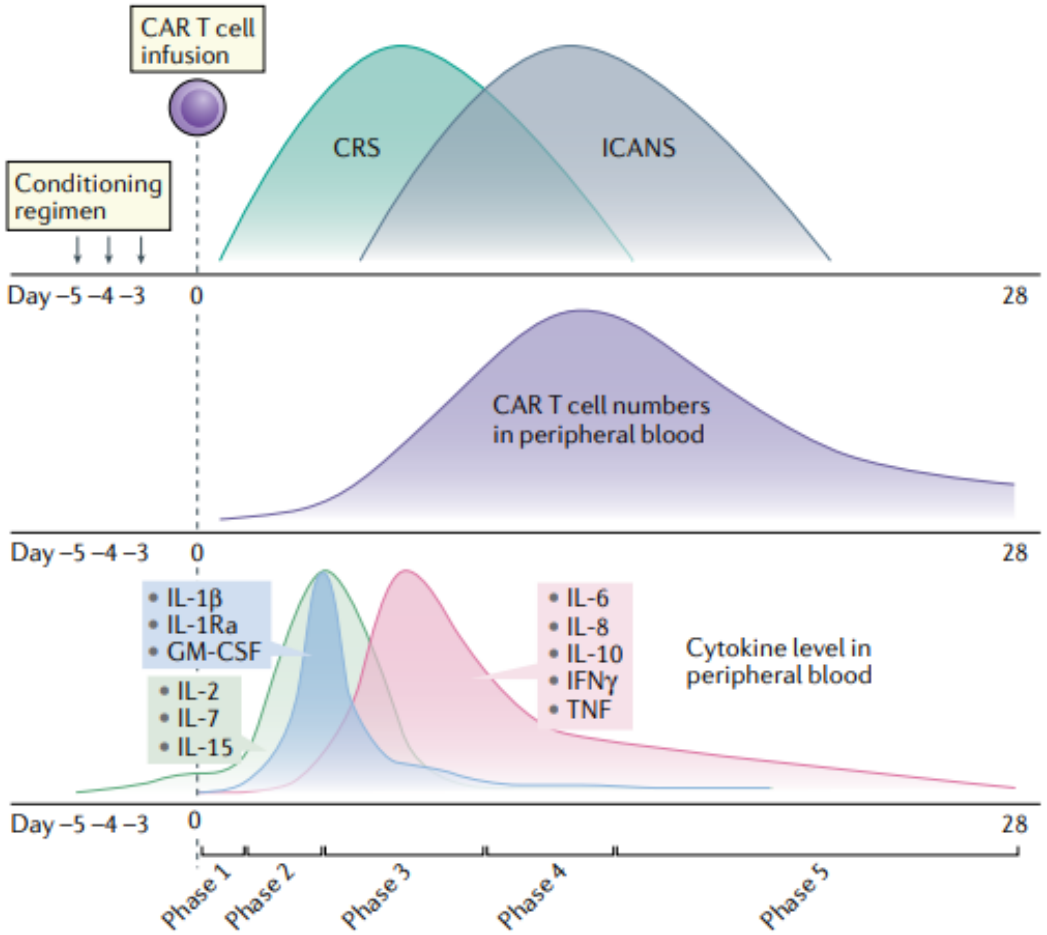


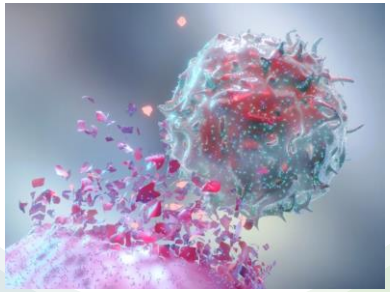
CAR T therapy



?? Implication du Tocilizumab dans le développement/aggravation des ICANS ??

Morris et al. Nat Rev. 2022

CAR T therapy



Outcomes in patients treated with chimeric antigen receptor T-cell therapy who were admitted to intensive care (CARTTAS): an international, multicentre, observational cohort study

N= 942 → **27% USI**

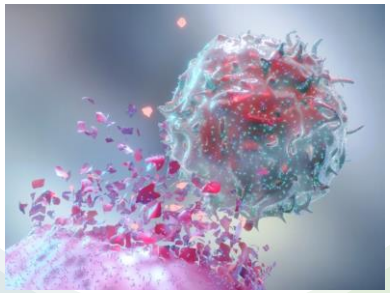
Time from CAR T-cell infusion to ICU admission, days	4·5 (2·0–7·0)
Underlying malignancy	
B-cell lymphoma or follicular lymphoma	206 (85%)
Acute lymphocytic leukaemia	31 (13%)
Multiple myeloma	4 (2%)
Number of chemotherapy lines before CAR T-cell therapy	3 (2–4)

Clinical diagnosis upon evaluation in the wards	
Clinical sepsis	39 (16%)
Isolated cytokine release syndrome	101 (42%)
Isolated ICANS	7 (3%)
Cytokine release syndrome and ICANS	93 (39%)
Large pleural effusion related to disease progression	1 (<1%)

Cytokine release syndrome grade 3 or 4 at initial evaluation in the wards	23/194 (12%)
Cytokine release syndrome grade 3 or 4 within 1 day after ICU admission	50/200 (25%)
ICANS grade 3 or 4 within 1 day after ICU admission	38/108 (35%)

Azoulay et al. Lancet Haematol. 2021

CAR T therapy



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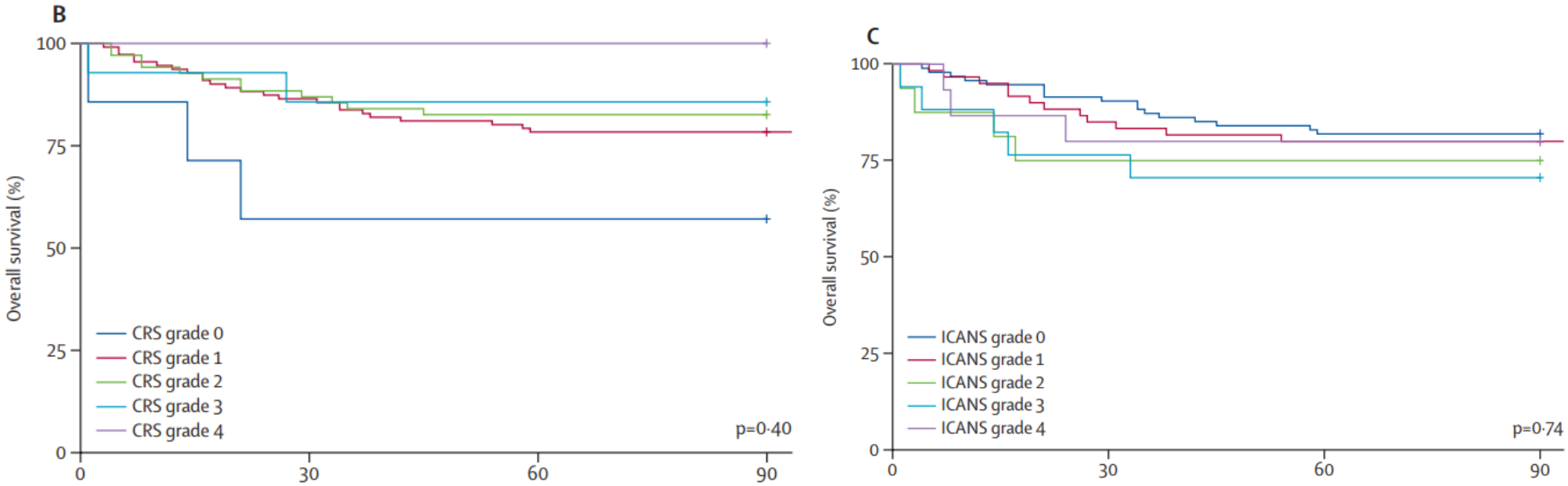
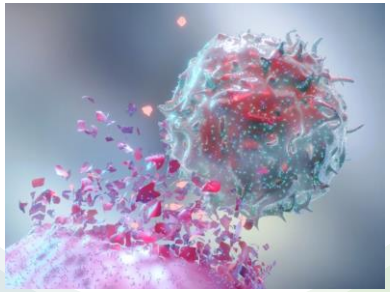


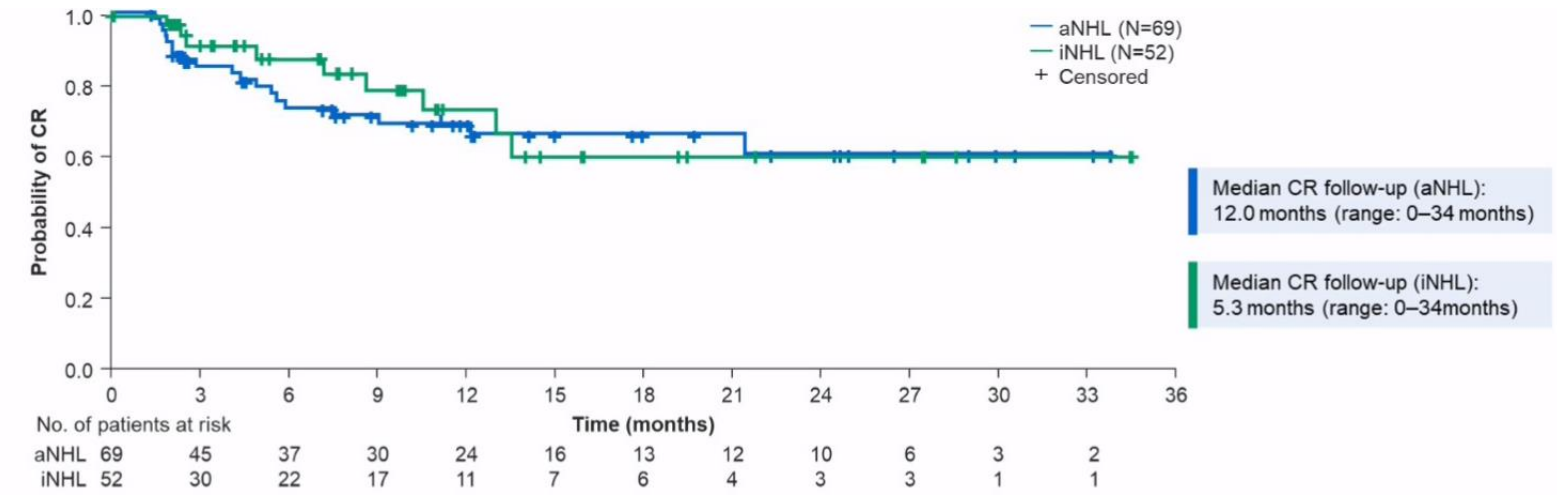
FR: fragilité, infection documentée, nécessité de life saving therapy < 24h admission SI

Azoulay et al. Lancet Haematol. 2021



Bite therapy

- Epcoritamab, Glofitamab, Mosunetusumab, X-mab….
- ORR **50-70% ;** CR **35% -** réponse prolongée (patients réfractaires ++)



CRS ~ 60%
grade ≥ 3: 5%
ICANS peu fréquents

Jacobson et al. Trans Cell Ther. 2022
Morris et al. Nat Rev. 2022

Take Home Messages

- Une nouvelle histoire d'amour commence…
  - Meilleur pronostic **frontline** pour la plupart de lymphomes
  - Thérapies spectaculaires chemo free en **rechute ou réfractaire**
  - Impact modéré (inexistant?) du séjour aux SI

  →**Lymphomes = EXCELLENTS candidats aux SI**

- Collaboration et disponibilité essentielles