Cancéropôle Île-de-France

RÉPUBLIQUE FRANÇAISE
INSTITUT NATIONAL DU CANCER

4CMMRD care for

International Replication Repair Deficiency Consortium

Lymphomes associés au CMMRD (constitutional mismatch repair deficiency)

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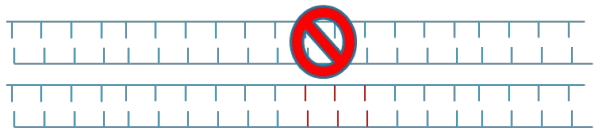
Cancers liés au aux altérations du système MMR

Sd de Lynch

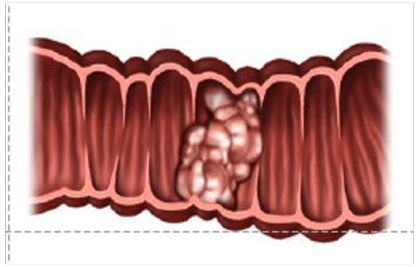


Lynch jeune

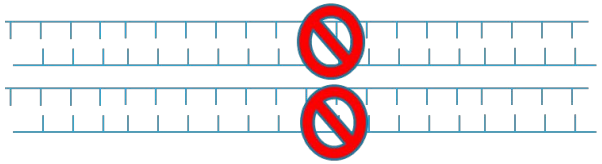
1 Hit

Age moyen au diagnostic 48 ans

Cas familiaux de cancers Digestifs /Génitaux



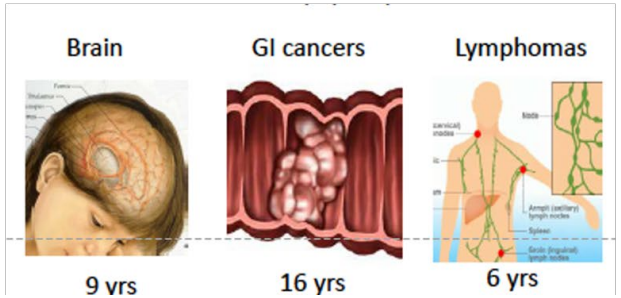
CMMRD



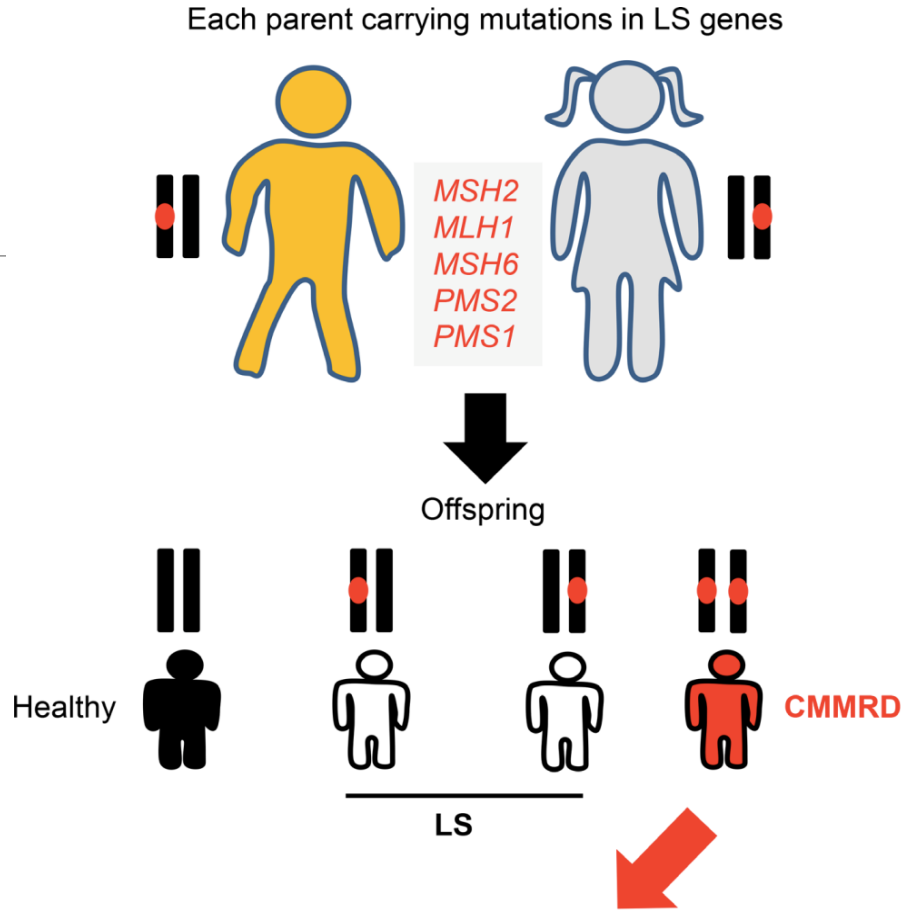
2 Hits

Age moyen au diagnostic 9 ans

Consanguinité, cancers multiples dans l'enfance



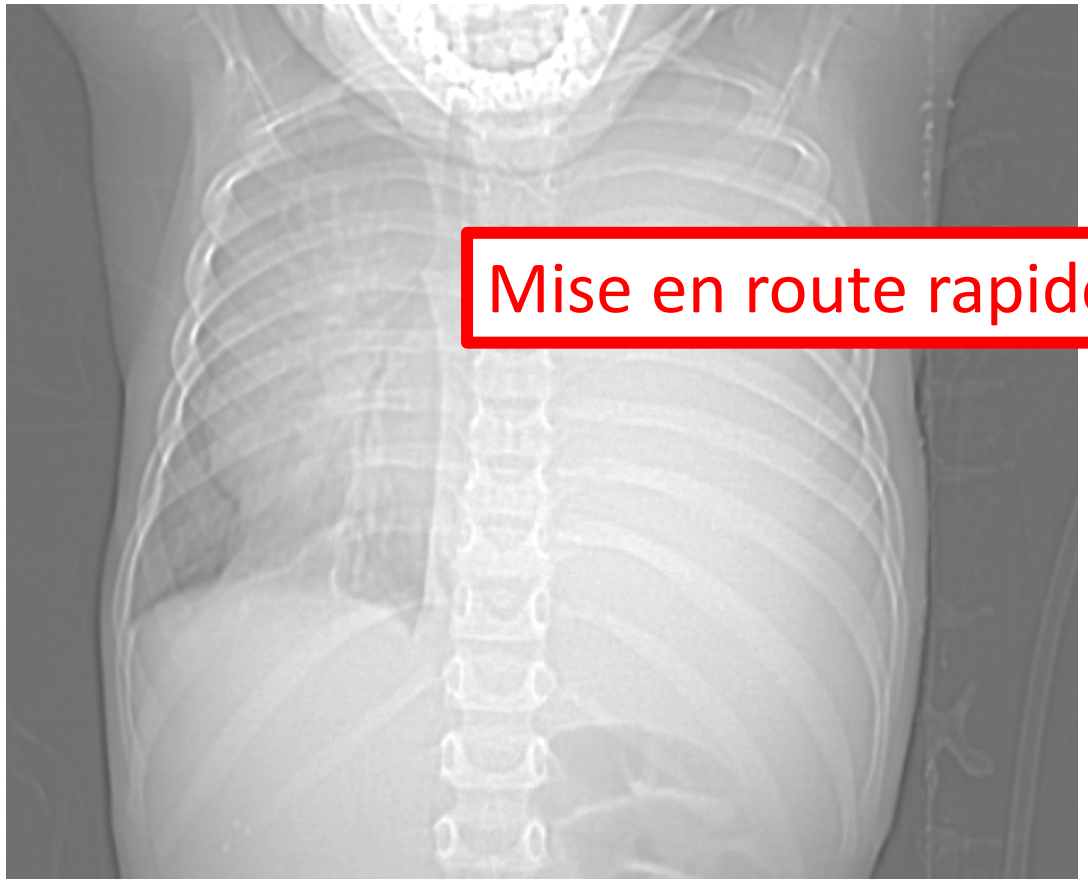
CMMRD, incidence ≈ 1:1,000,000

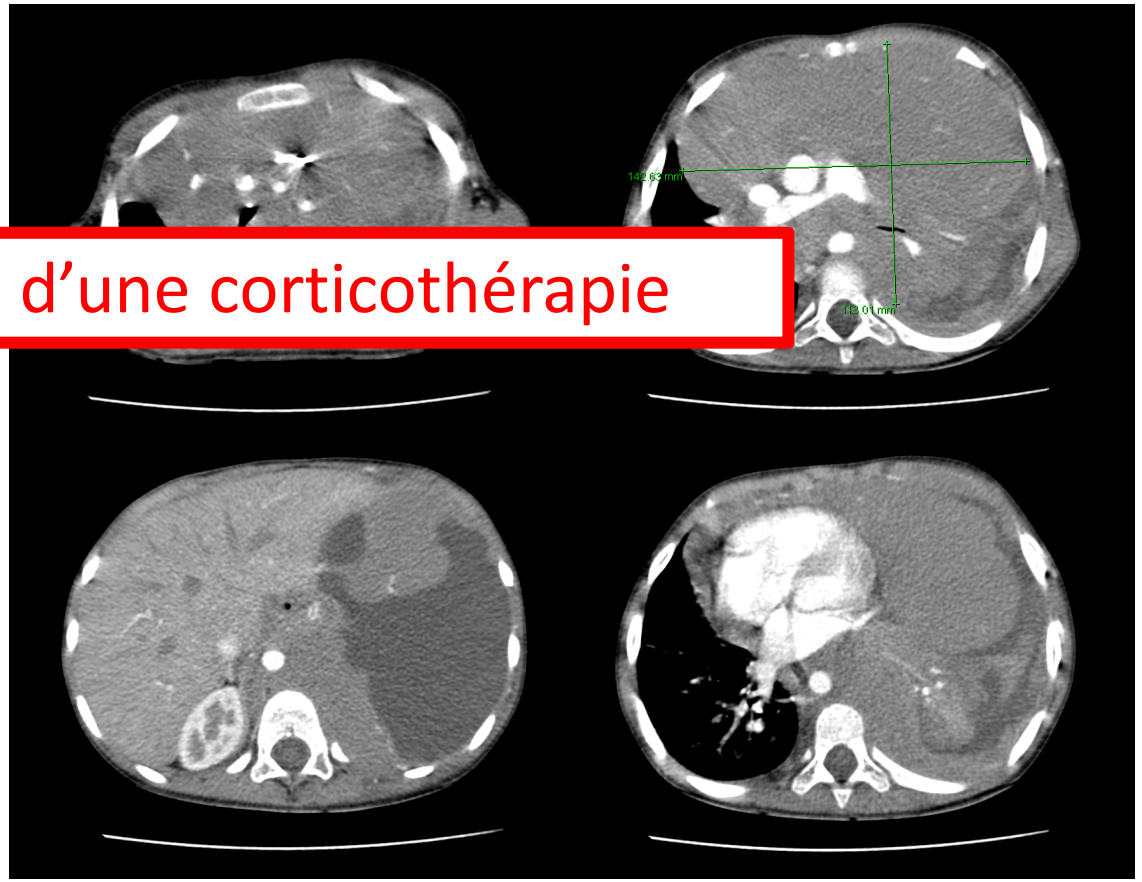


Brain tumors (from age 2 years),
Digestive tract cancer (from age 8-10 years.
Haematological malignancies (from age 1 year),
Leukaemia (from age 1 years),
LS associated cancers (from age 20 years),
Other cancers?

Abedalthagafi M. et al, Oncotarget, 2018

Valentine, 4 ans: lymphome lymphobastique T





Mise en route rapide d'une corticothérapie

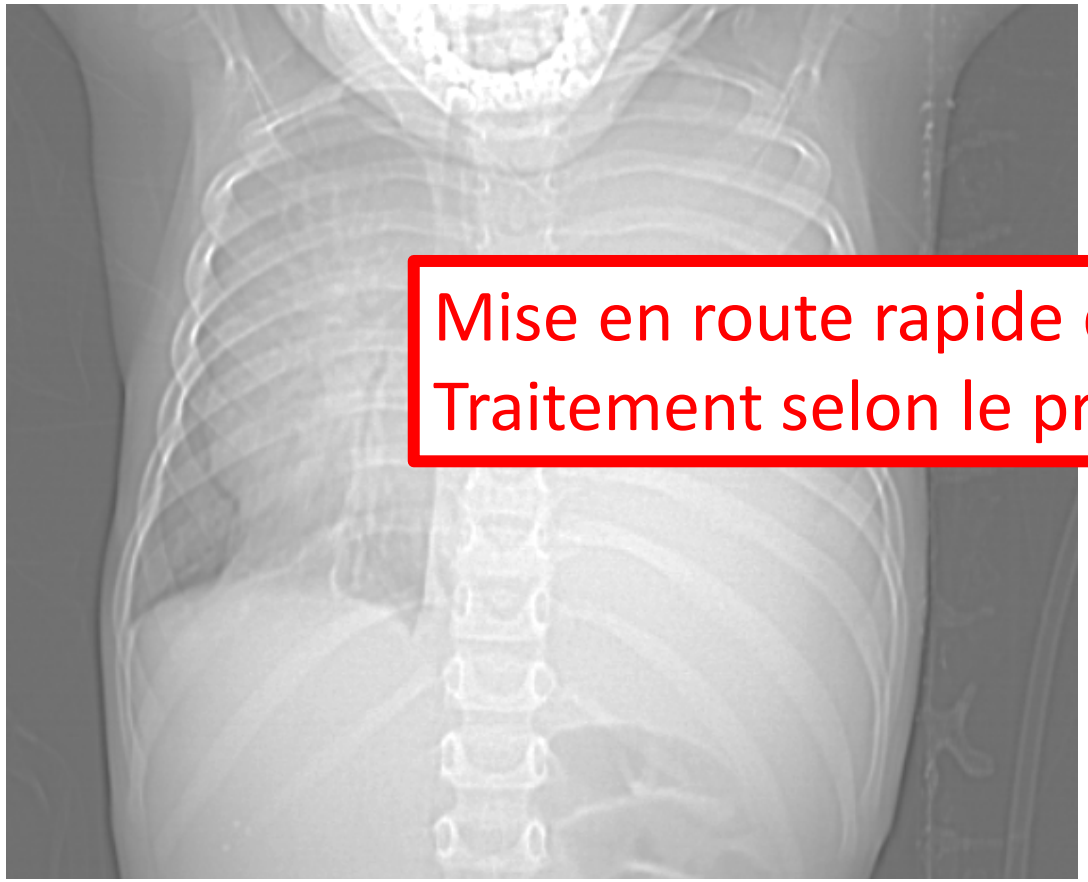
Valentine, 4 ans: lymphome lymphobastique T

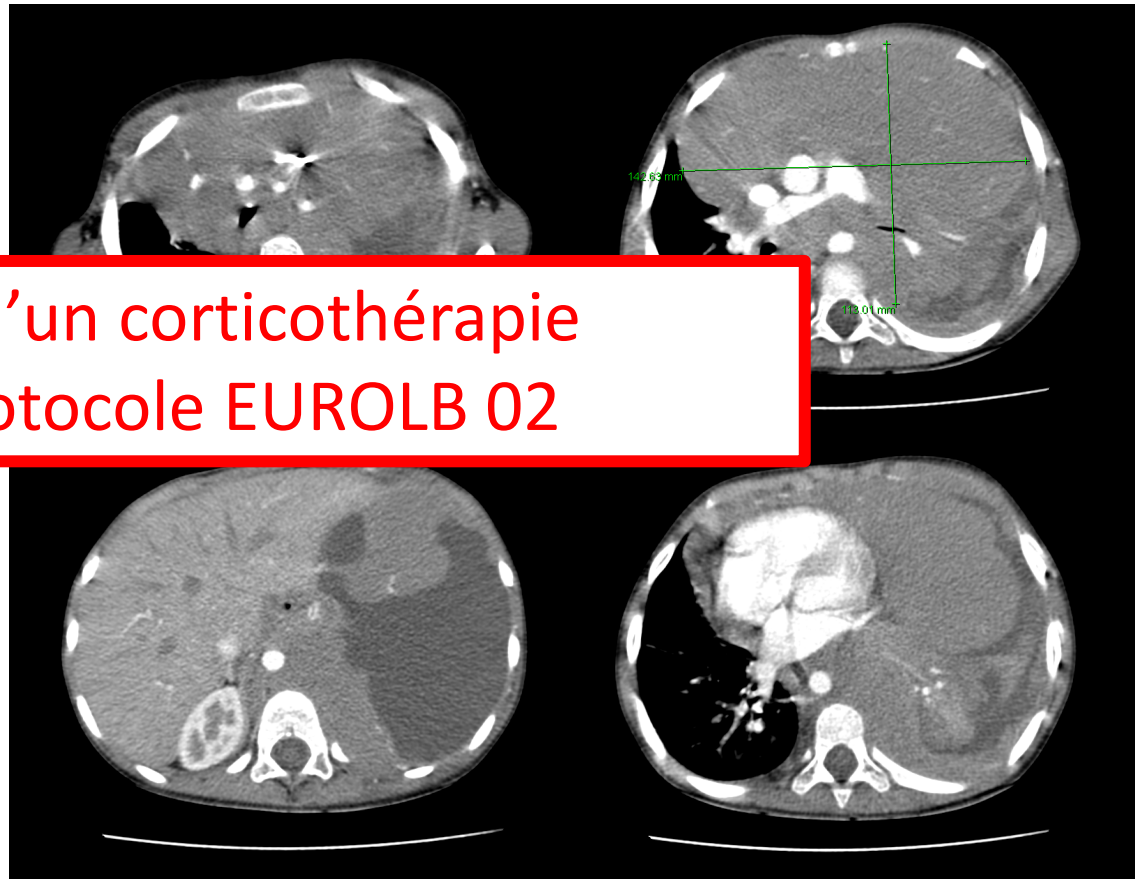
- Présence de taches « café au lait »
- Et chez d'autres membres de la famille
- Parents non consanguins
- Histoire familiale peu bruyante

Valentine, 4 ans: lymphome lymphobastique T

CMMRD ???

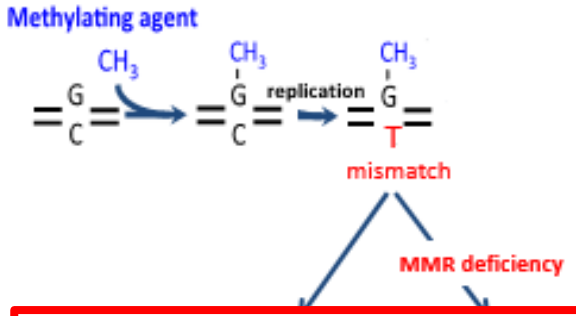
Valentine, 4 ans: lymphome lymphobastique T

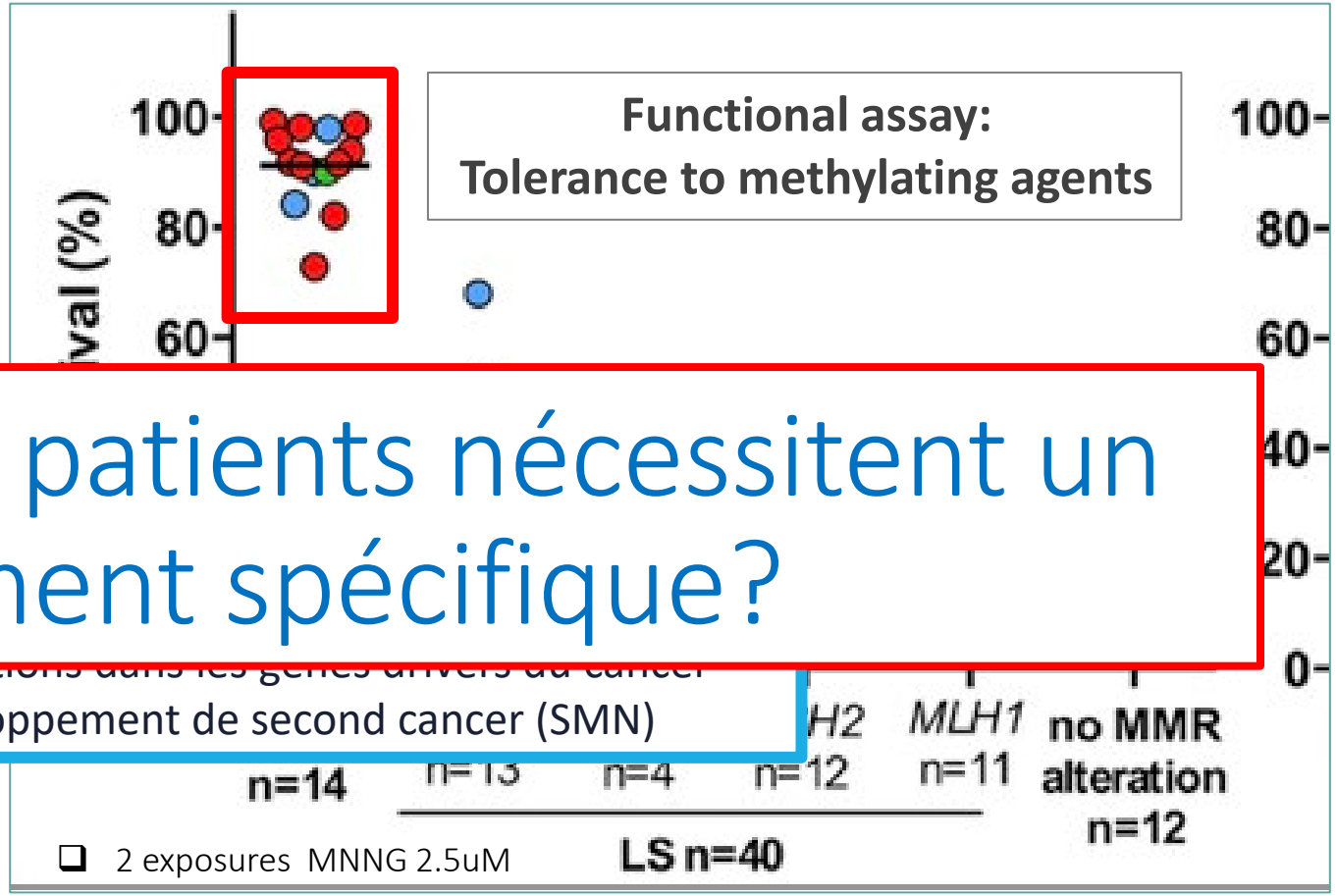




Mise en route rapide d'un corticothérapie
Traitement selon le protocole EUROLB 02

Chimiosensibilité des tumeurs CMMRD





Au
l'ina
aug
certains agents genotoxique
comme les agents méthylants et les analogues des purines

=> developpement de second cancer (SMN)

Est-ce que ces patients nécessitent un traitement spécifique?

Bodo S et al. Gastroenterology 2015

Lymphoma in CMMRD

OBJECTIVES

TO DESCRIBE in an unselected cohort of patients :

- Lymphomas associated with CMMRD
- Pattern of response to cytotoxic agents
- Toxicity of treatment
- Risk of second malignancies

METHODS

TO REVIEW DATA of alllymphomas in CMMRD patients identified through several sources

- the C4MMRD database
- the IRRDC database
- or declared by IBFM/EICNHL members

3 different sources

C4CMMRD database	IRRDC database	EICNHL/iBFM
36 patients 48 Lymphoma	18 patients 23 Lymphoma	27 patients 36 Lymphoma

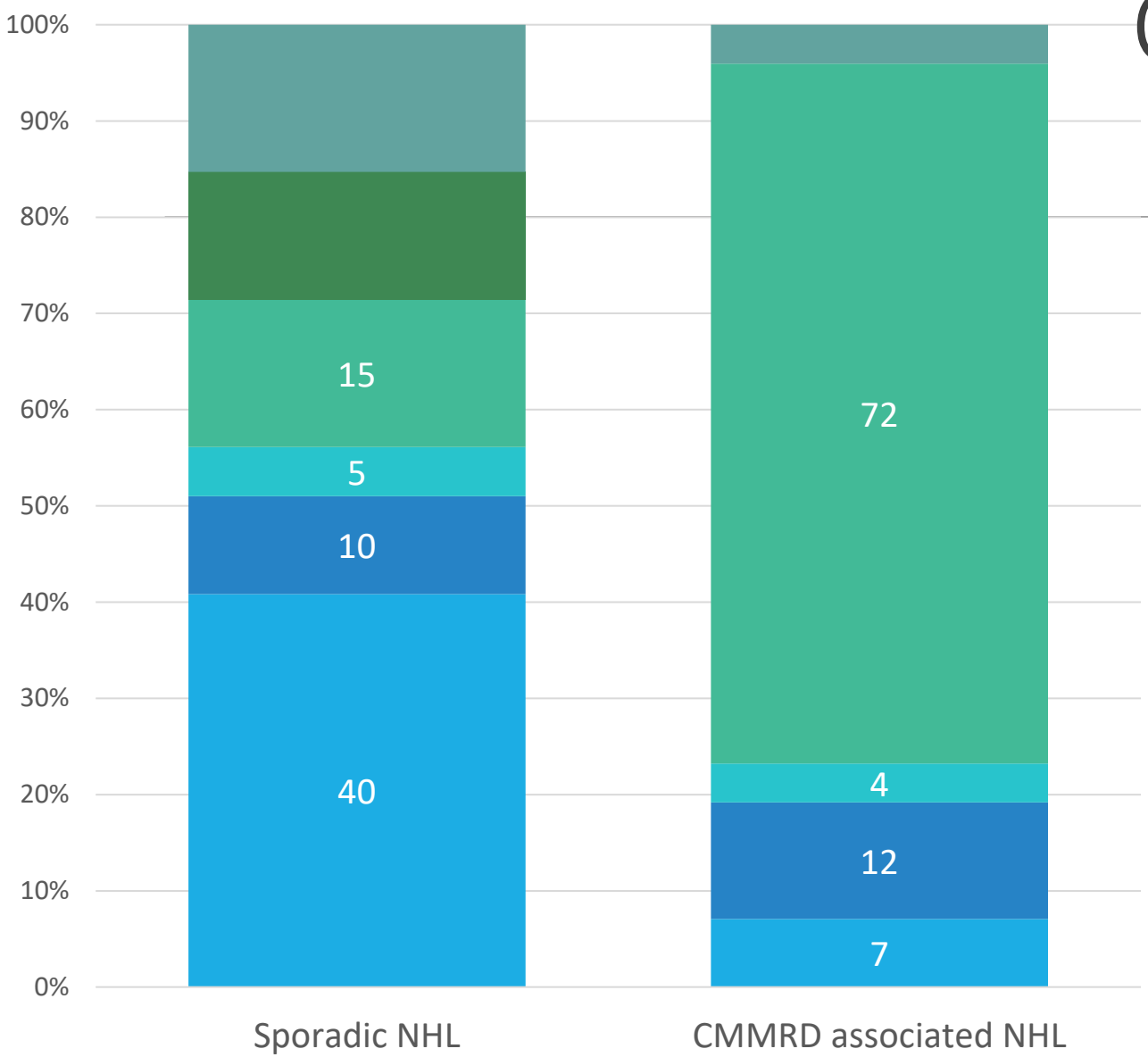
Excluded = 7 patients
5 :registered in both consortium databases / 2 : too much missing data.

Total included
74 Patients / 100 Lymphoma

Population

- **100 lymphomas in 74 patients**
  - Period of treatment : **1983-2020**
  - Median age at diagnosis of 1st lymphoma: **7.9 y (6 m -25.6 y)**
  - Only 5 patients less than 2 yo
- **27 patients with previous malignancy**
  - 22 with brains tumors (15 GBM, 3 medulloblastoma, 5 other), 5 CRC, 1 ALL, 1 wilms tumor, 1 salivary gland carcinoma; 1 sarcoma

CMMRD lymphoma subtype



Hodgkin Lymphoma = 0

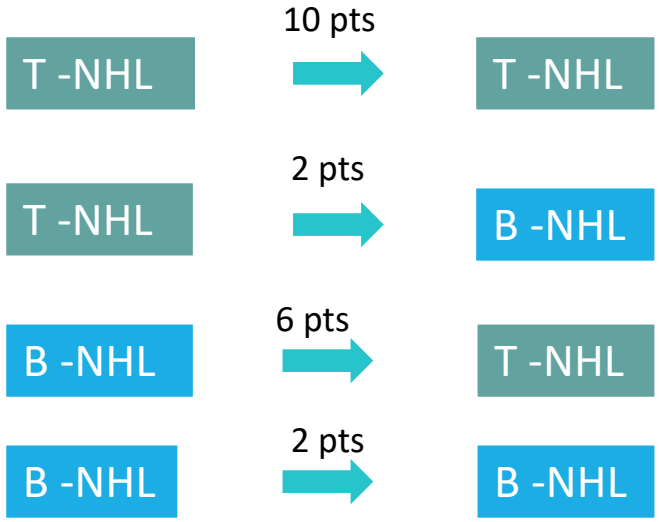
Staging (St Jude)
90% stage 3-4

Beishuizen, Lancet Hematol 2023

Multiple lymphoma

- **20 patients**:
  - **14** with 2 NHL
  - **6** with 3 NHL
- Median interval: **4.3 y (range: 1,1-20)**
- NB: not considered as relapse if more than 3y after 1st NHL diagnosis

- Histological subtype



Treatment and response: all NHL

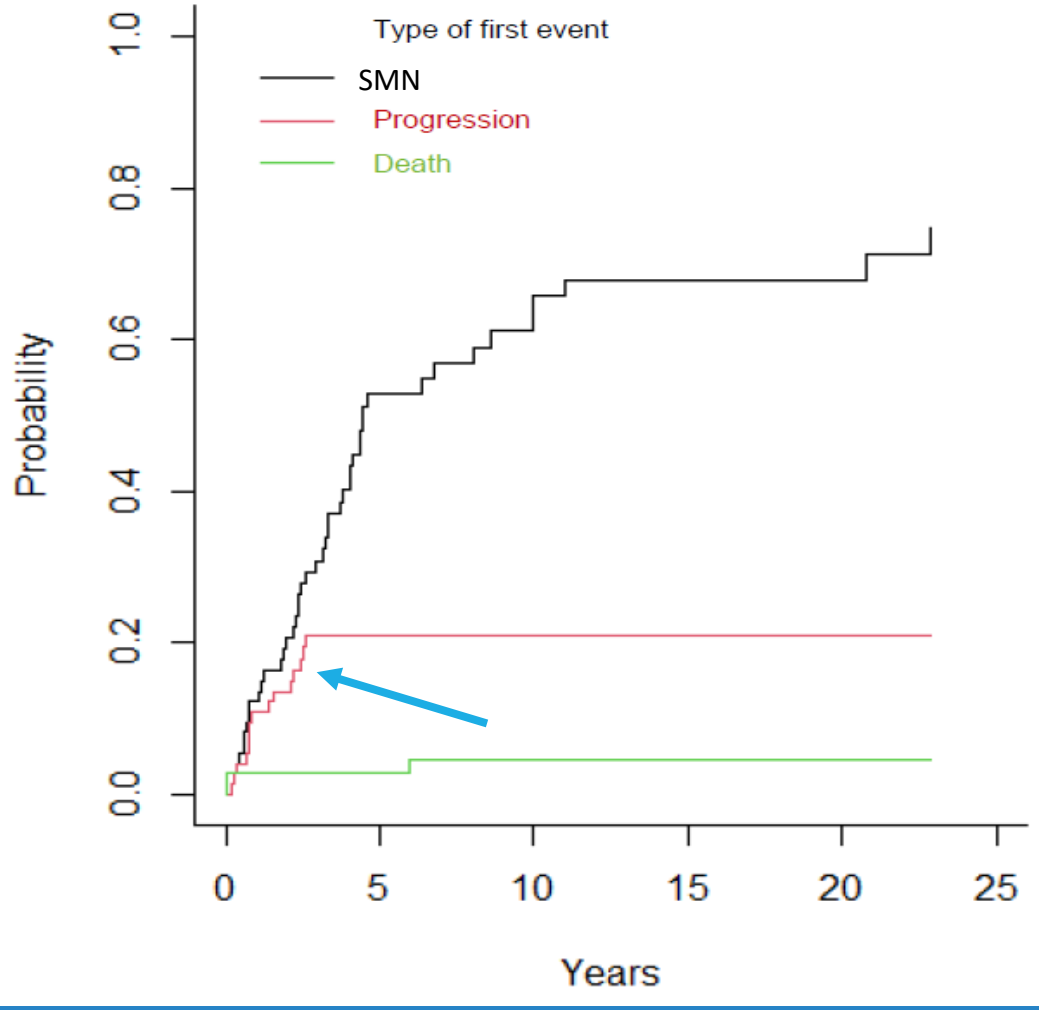
- **Treatment according to the protocol adapted to the histological subtype**

- **Response to treatment**

	1st NHL (N=74)	2nd NHL (N=20)	3rd NHL (N=16)	Total (N=100)
Response to treatment				
CR	64	16	4	84 (84%)
No CR	10	4	2	16*
Evolution after treatment				
Relapse/progressions	15	2	2	19

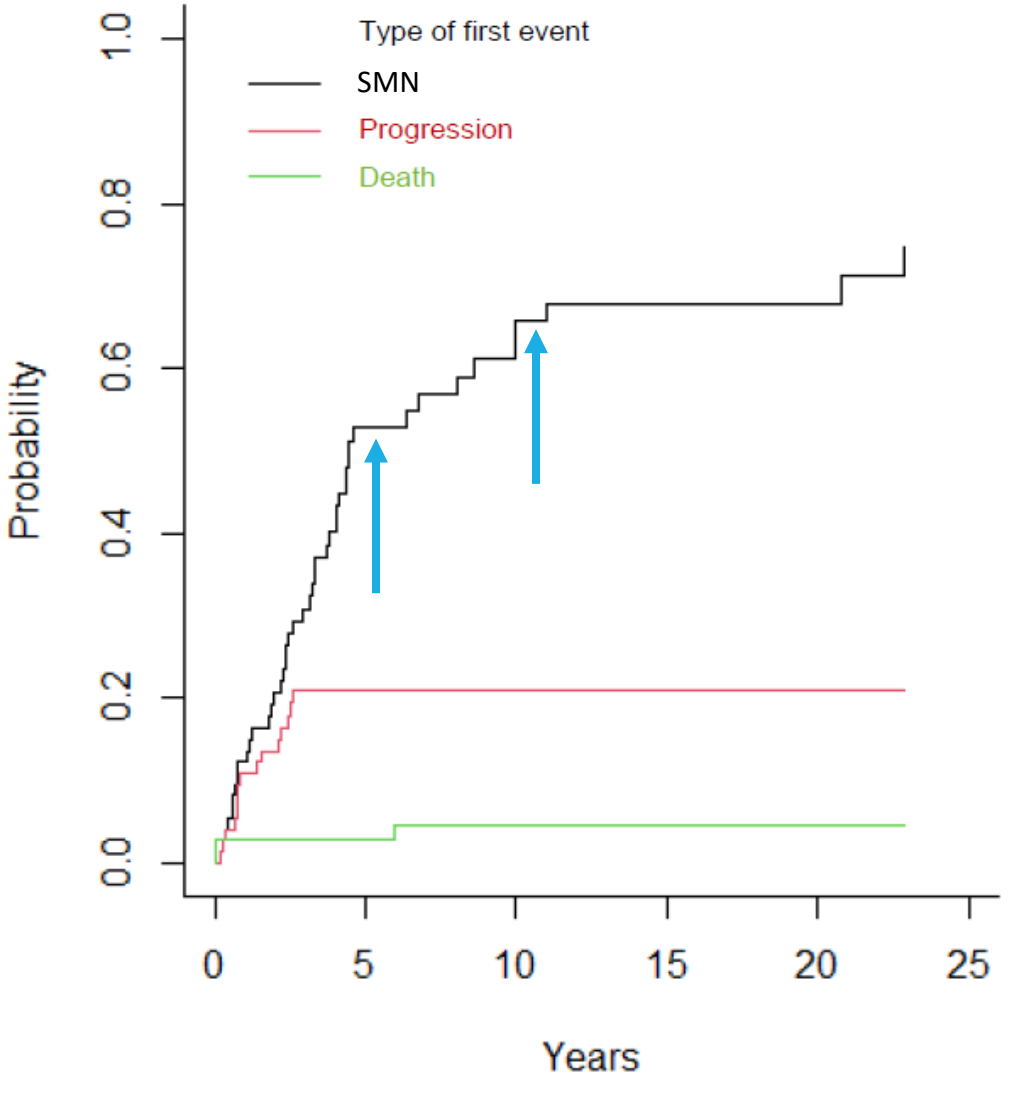
Treatment and response: all first NHL

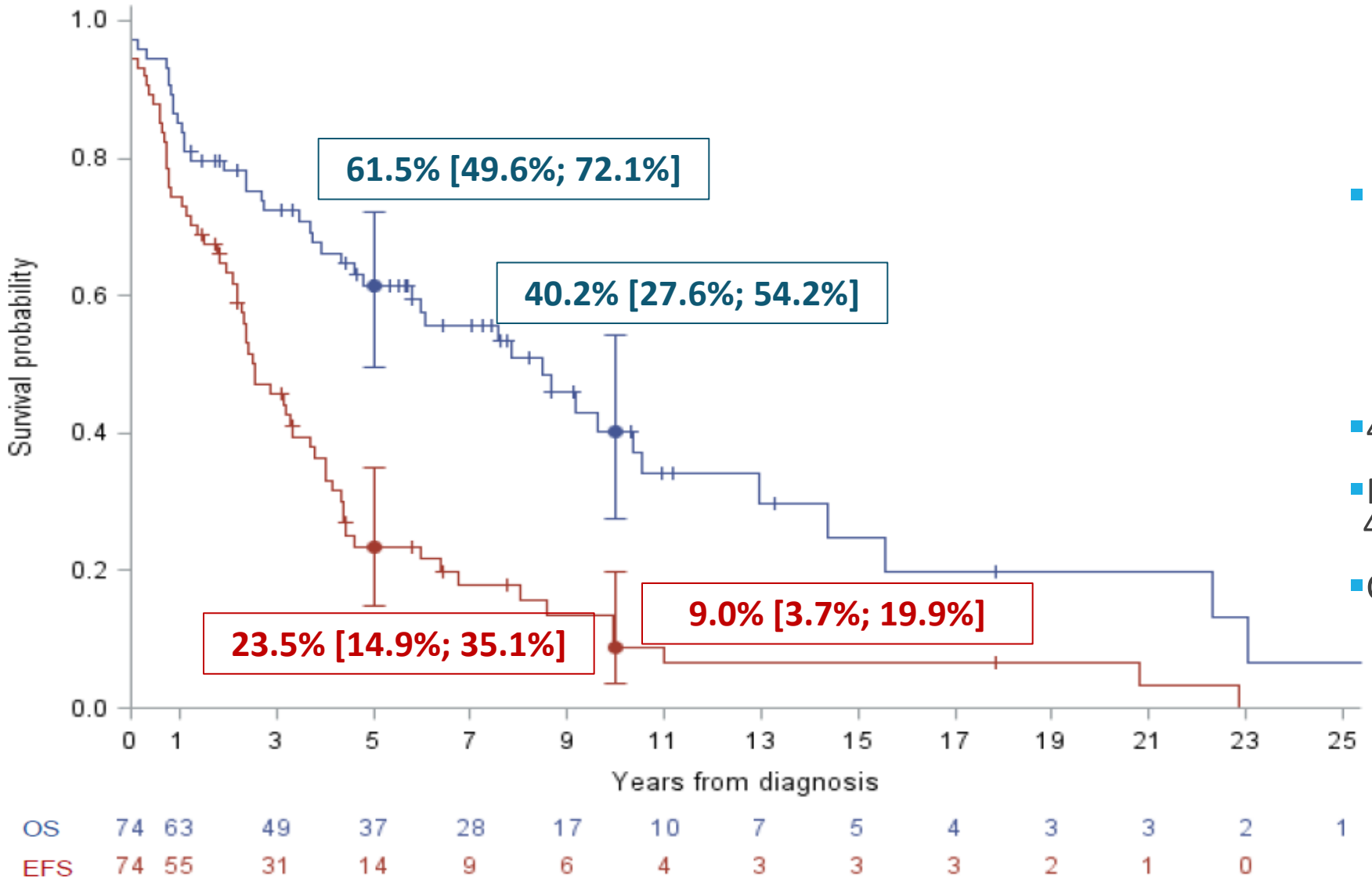
- Median FU: 8.7 years (IQ: 5.7 years – 17.8 years)
- 15 relapse/progression: med 10.1 months (1.9-30.7months)
- 3-year CIR after the first lymphoma was 20.8% (sd 4.8%)



Second malignancies

- **75 SMN in 46 patients**
  - **26 NHL/** 23 Lynch spectrum associated K/ 20 brain tumors/ 6 others
- **Median interval: 4.4 y (0 - 9 y)**
- **CIR SMN:**
  - **5-y : 52.9%** (sd 6.2%)
  - **10-y : 65.7%** (sd 6.3%)





Survival

- 63 events
  - 45 SMN
  - 14 relapses/PD of NHL
  - 1 concomitant relapse + SMN
  - 3 deaths as first event
- 44 patients died.
- Median OS 8.5 years [95%CI: 4.8- 10.5 years].
- Causes of death:
  - NHL PD in 13 cases
  - SMN in 26 including 6 deaths related to a second or third NHL

First NHL : mature B-cell NHL

- **Mature B-NHL as first lymphoma: 17 patients**
- treated with standard protocols designed for pediatric B-NHL (LMB/BFM/R-CHOP)
- Complete response (CR) was obtained in 15/17
- No relapse if CR.
- **3-y PFS: 87.84% [64.72; 96.61].**
- **5 y CIR SMN: 64.7% (sd 12%)**

First NHL: T-Lymphoblastic lymphoma

	CMMRD associated T-LBL N = 53 (first NHL)	Sporadic T LBL N=233 (Burkhardt 2017)
Median age	7.7 y	8.7 y
Stage III/IV (MD = 3)	**85%/10%**	64%/18%
No CR	**7 *(13%)**	4 (1%)
5-year CIR	**25.6 % (sd 6%)**	**13 (sd2%)**
Second malignancies	**24 (44%)**	5 (2%)
3-year PFS	**70.43%** [56.15; 81.59]	82% ± 2%
5-year OS	20.6% [11.2 ; 34.8]	87% ± 2%

- **5 y CIR SMN: 50 % (sd 7.6%)**

*Comprising 3 patients who died during the 1st week of treatment

Conclusion

- **Large cohorte international**
- **LNH B-matures**
  - part du spectre CMMRD +++
  - **Chimio aussi efficace** que pour LNH sporadiques (3-y PFS: 87.8%)
- **LNH lymphoblastiques T**
  - Pas si mauvais mais quand même moins bons (CIR 25% vs 13%) => **Chimio- resistance ?**
  - Diminution de l'effet bio de la 6MP ?
  - Moins SMN que pour les B-matures

⇒ **Pas de modifications des traitements à ce stade**

Conclusion: toutes histologies

- **Les lymphomes CMMRD peuvent être guéris par les protocols standards**
- 2nd or 3rd LNH (vs rechute ?)
- OS à long terme mauvaise => Risque +++ de **second cancers**

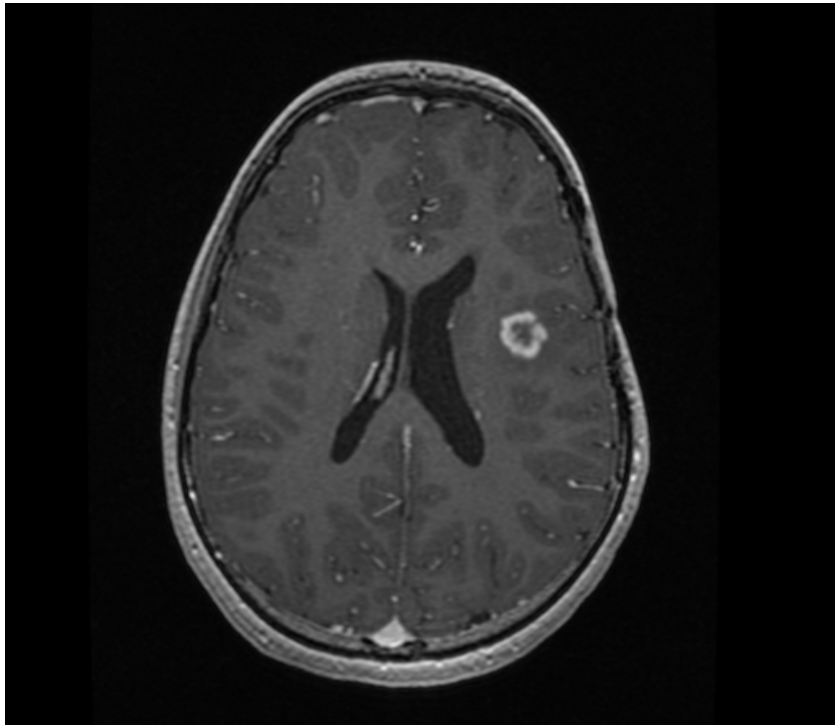
=> Mieux comprendre la physiopath des SMN est crucial!!!

=> +++ prevention des SMN

=> nouveaux agents => immune checkpoint inhibiteurs ?

Et Valentine ?

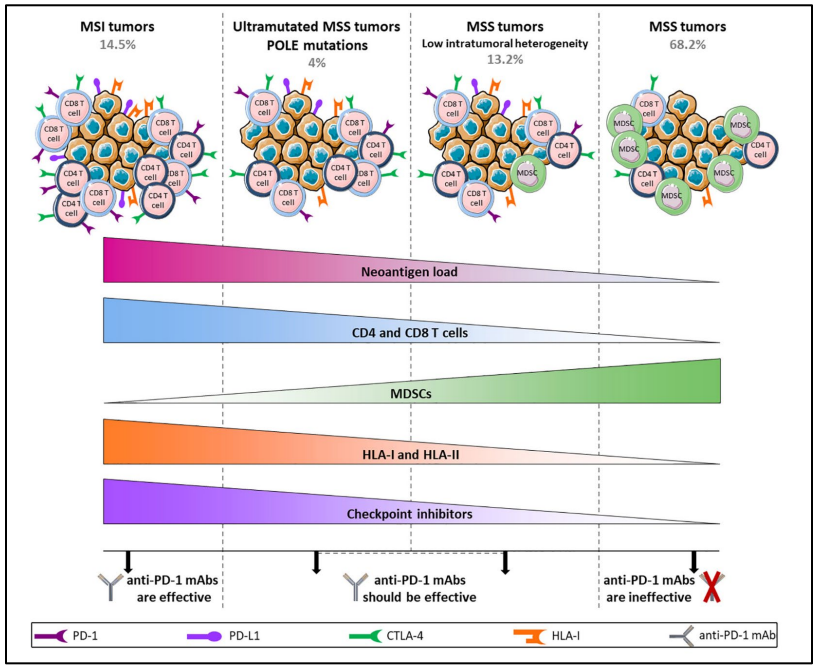
- **Actuellement guérie de son lymphome**
- **Diagnostic de gliome de haut grade en 2015**
- **Compréhension et prise en charge SMN ++++**
- **Mise en route d'un traitement par immunothérapie**
- **3ème « poussée »**
- **Va bien, bonne QdV**



Questions et perspectives: rôle des ICI dans les LNH CMMRD ?

Traitement par inhibiteurs de PD1/PDL1 dans les tumeurs MMR deficientes

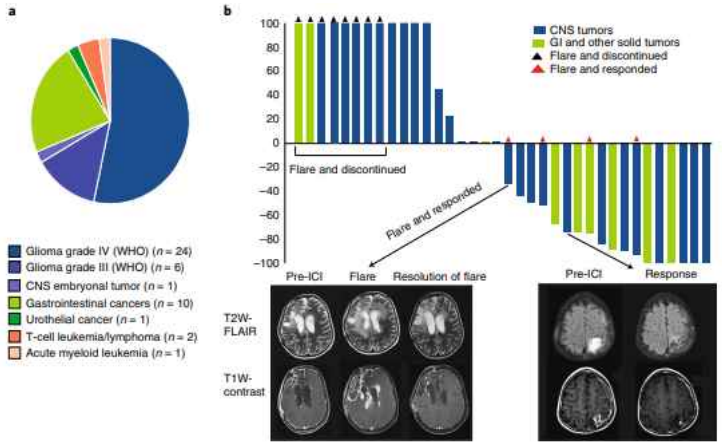
- Basé sur le taux très élevé de muations *(Campbell Cell 2017, Westdorp Cancer Lett 2017)*
- « Hot » tumors: *(Gubin Science 2015; Le NEJM 2015; Shlien Nat Genetic 2015)*
  - TIL++: CD3/CD8/FoxP3
  - Upregulation des IC: PD1/PDL1/IDO/CTLA4/LAG3..
- Efficacité dans CRC and noncolorectal MMR deficients / MSI high *(Uram NEJM 2015, Marabelle JCO 2020)*



En 2017, FDA approval du Pembrolizumab et du Nivolumab pour le traitement des cancers MMR-deficient (tous sites et histo confondus)

Questions et perspectives: rôle des ICI dans les LNH CMMRD ?

IRRCD series of 38 pats (28 CMMRD)



1 | Clinical response to ICI across cancer types in patients with germline DNA replication repair deficiency. a, Distribution of tumor types acro ents who developed 45 tumors. **b**, Waterfall plot of all radiological responses in non-haematological malignancies. Values show the best fractior ge in the 2 dimensions from baseline measurements as per RANO and RECIST criteria (Methods). Arrows point to representative T2-weighted T1-weighted contrast-enhanced MRI sequences in two patients showing flare and partial responses.

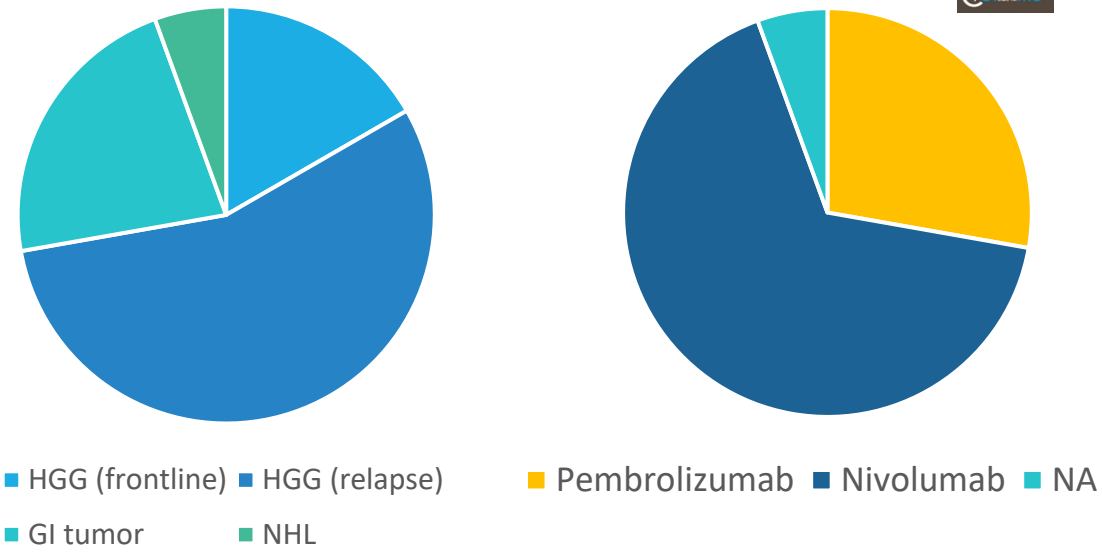
55.5% : response or stable disease

64%BT/100% other solid/0%ALL (no NHL)

Response sustained in 80% of the cases up (median duration 1.87 years).

Das A et al., Nat Med. 2022

C4CMMRD experience (18 CMMRD)



8/18 (44%) benefited from the treatment with a durable response and/or a stabilization

- 7 patients still alive (median FU=20 months)
- 11 patients died after a median survival of 5 months (9 HGG and 2 GI cancers)

Report from L Brugières, data extracted from C4CMMRD database

Questions et perspectives: rôle des ICI dans les LNH CMMI

- Update pour la prise en charge des patients CMMRD

ERN GENTURIS CMMRD guideline, update 2023
Manon Suerink, Katharina Wimmer, Chrystelle Colas, Laurence Brugières, Christian Kratz, Éloïse Ayuso, Léa Guerrini-Rousseau
Jurriaan Holzenspies

European Reference Network
for rare or low prevalence complex diseases
Network Genetic Tumour Risk Syndromes (ERN GENTURIS)

- Gliome de haut garde et K dig: immunotherapie (PD1-inhibiteur) +++, si possible dans un essai clinique, dès la première ligne.
- Pas recommander à ce jour pour les LNH
- Pas suffisamment de data pour prophylaxie/prevention des SMN par ICI
- Question ouverte pour les LNH: avantage à la mise en place d'une immunothérapie précoce en combo avec la chimio ou en maintenance ?
- Besoin+++ d'essais cliniques upfront et en combinaison

Acknowledgments

- International Replication Repair Deficiency Consortium
  - Uri Tabori
  - Vicky Forster
- eicnhl
  - Jan Loeffen
  - B Burkhardt
  - A Burke
  - E Macintyre
  - All clinicians
- 4CMMRD
  - All clinicians
  - Genetic review
    - K Wimmer
    - C Ponte Ruiz
    - M Pineda
    - S Horpaopan
- **Laurence Brugières**
- GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS
  - V Minard- Colin
  - L Guerrini-Rousseau
  - A Auperin
  - P Hoarau