6th POSTGRADUATE
Lymphoma
Conference

# Refractory and Relapsed PCNSL

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Rome,
September 7-9
2022

VOI Donna Camilla Savelli Hotel

President:
P.L. Zinzani

# Disclosures

| Company name | Pre-clinical Research support |
|---|---|
| Astra-Zeneca | X |
| GossamerBio | X |
| Hangzhou Hezheng Pharmaceutical | X |

## Incidence of R/R PCNSL: Informations from the LOC database « RWE »

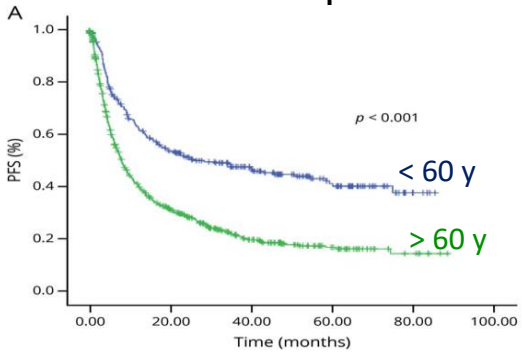
Jan 2011-March 2016: N = 1002 newly-diagnosed PCNSL from 32 centers

Median age= 68 y (18 – 91); DLBCL : 97 %

MTX HD in first-line= 92 % + Rituximab in 50-87 %

Median follow-up = 44 months

50% refractory to first-line treatment or relapse after first-line treatment




Median PFS = 28.4 months

Median PFS = 8 months

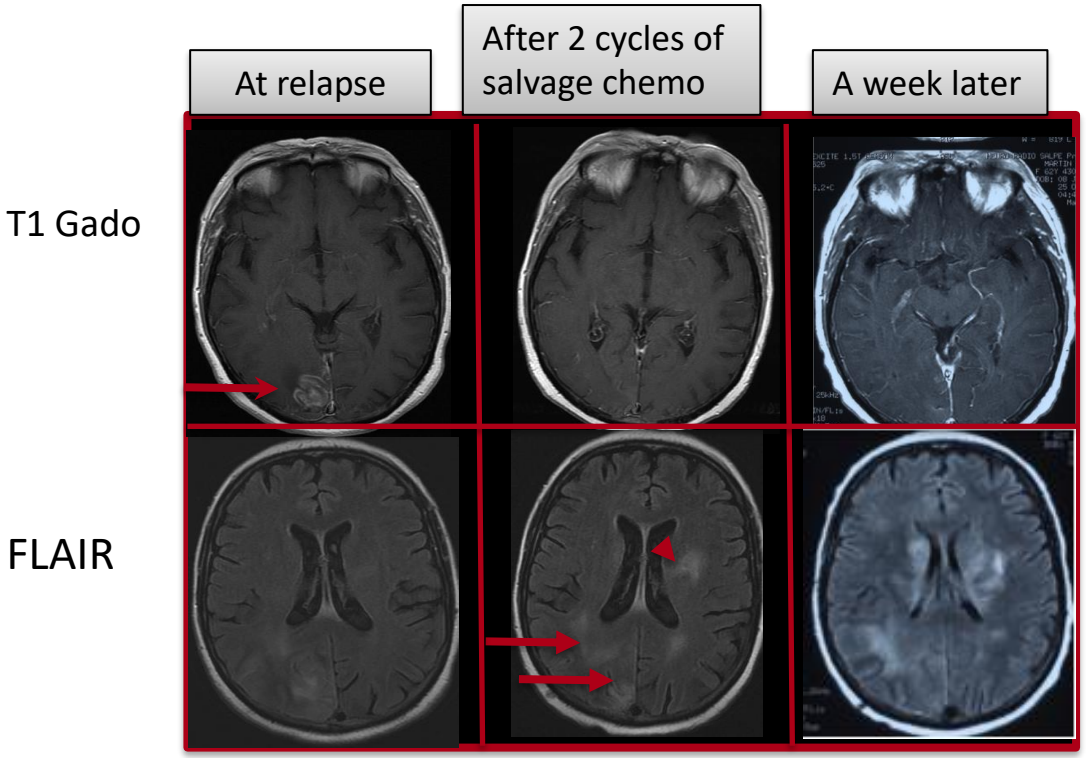
*Houillier et al, Neurology 2020*

## Specificities in PCNSL

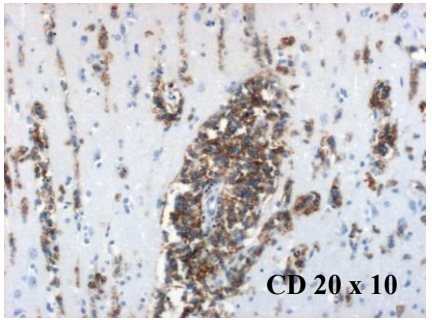
- Site of relapse (LOC Database)
  - Brain : 92 % (often in spatially distinct site of the brain)
  - IO : 10 %
  - Systemic: 3 %
- Late relapse > 60 months
- Asymptomatic relapsed in 20-25% of cases (brain and IO relapse)

*Ambady et al, J Clin Oncol 34, 2016 (suppl; abstr e19051); Ghesquieres et al, Annals Oncol 2010; Houillier et al. Neurology 2020; Fossard et al, ASH 2013; Langnier-Lemercier et al, Neuro-Oncol 2016*

# Non-enhanced pattern of relapse




## Autopsy



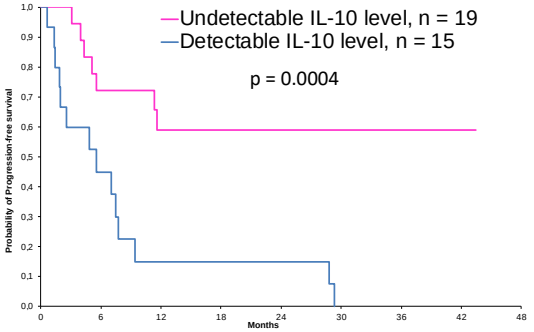
# Biomarkers as Prognostic factors ?



- **In the CSF**
  - **IL10 at the end of the treatment in CR patients**

  *N'Guyen et al. Eur J Cancer 2016*

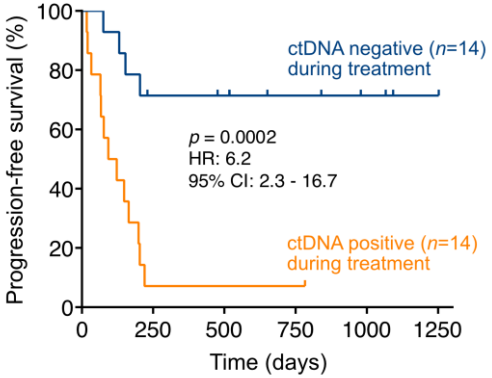
PFS according to IL10/CSF at the end of treatment




- **in the CSF and/or the plasma**
  - **Ct DNA**

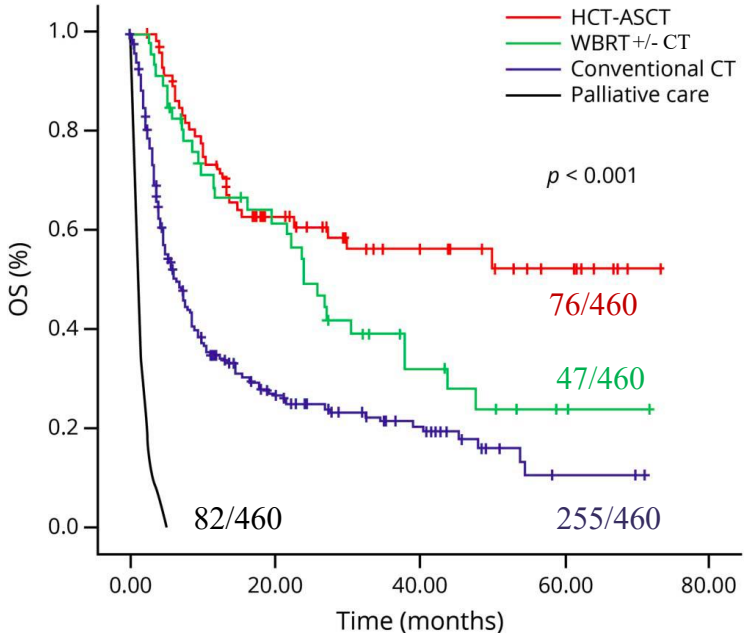
  *Mutter et al. Blood (2021) 138 (Supplement 1): 6*

PFS according to ctDNA/CSF+/-plasma during treatment



# Prognosis of R/R

OS according to treatment at relapse
LOC Database (N = 460 R/R PCNSL)




Whole population:
- 3-y OS = 25 %
- Median = 6.7 months

After ASCT:
- 3-y OS = 57%
- Median OS = NR

*Houillier er al. Neurology 2020*

# TREATMENT OPTIONS AT RELAPSE

Entering a « no standard » area

# CONVENTIONAL TREATMENTS

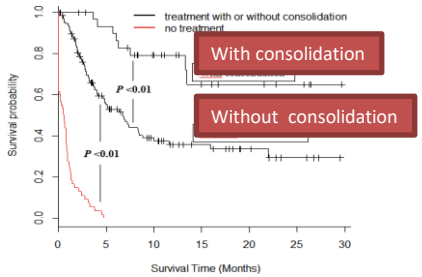


| | |
|---|---|
| WBRT | ORR: 74 %; Median OS = 11 months |
| Re-HD MTX | In selected cases with long lasting CR1 with previous course of MTX |
| HD Ara-C or Ifosfamide based Chemo (e.g R-DHAP, R-ICE) | **ORR: 60-80 %,** |

**but short duration of response**
**if no further consolidation ASCT**

Retrospective study

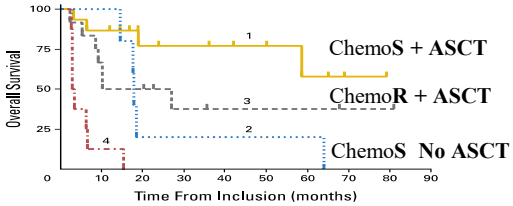
N = 256




*Morris, Lancet Neurol 2009; Plotkin, Lancet 2001; Plotkin, Clin Cancer Res 2004; Nguyen, JCO 2005; Soussain, JCO 2008; Sierra del Rio J Neuro-Oncol 2011; Mappa, Hematol Oncol 2012; Choquet, Hematol Oncol 2013, abst 44; Langnier-Lemercier, J Neuro-Oncol 2016*

# IC + ASCT in relapse for R/R PCNSL



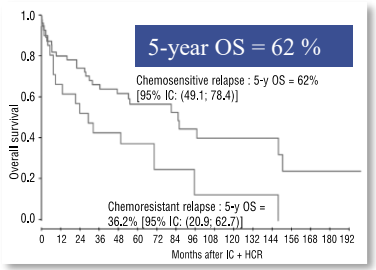



Multicentric prospective study N = 43

**TT-Bu-Cy**

Feasibility and efficacy of ASCT in consolidation after salvage treatment.

2-y PFS = 58 % in patients who received ASCT




French retrospective study N = 79

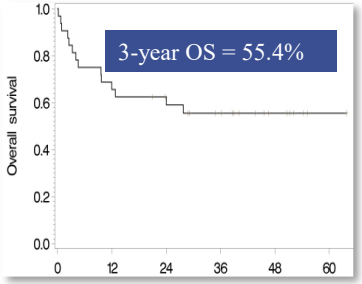
**TT-Bu-Cy**

Med FU = 56 months

Median age= 52.4 y (23-67)

5-y EFS = 44 % chimioS

TRM: n = 6 (8%)




German prospective study N = 32

**R-TT-BCNU**

Med FU = 45 months

Median age = 57 y (37-65)

2-year PFS = 46%

TRM: n = 4 (12 %)

*Soussain et al, J Clin Oncol 2008; Soussain, et al. Haematologica 2012; Kasenda et al, Leukemia 2017*

## **Type of ASCT: Retrospective study on the IBMTR** 2010-2018

3 types of IC used in PCNSL:

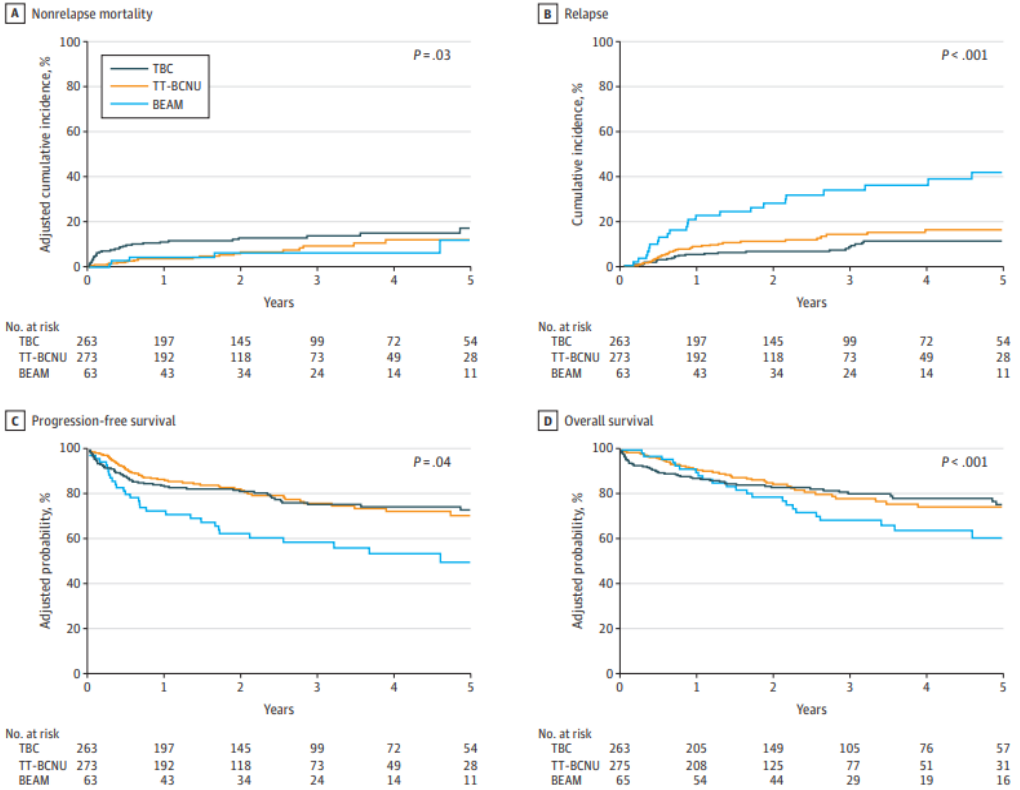
TBC: Thiotepa-Busulfan-Cyclophosphamide (n = 263)

TT-BNCU: Thiotepa – BCNU (n = 273)

BEAM (n = 63)

*Scordo et al. JAMA Oncol 2021*

## Type of ASCT: Retrospective study on the IBMTR 2010-2018



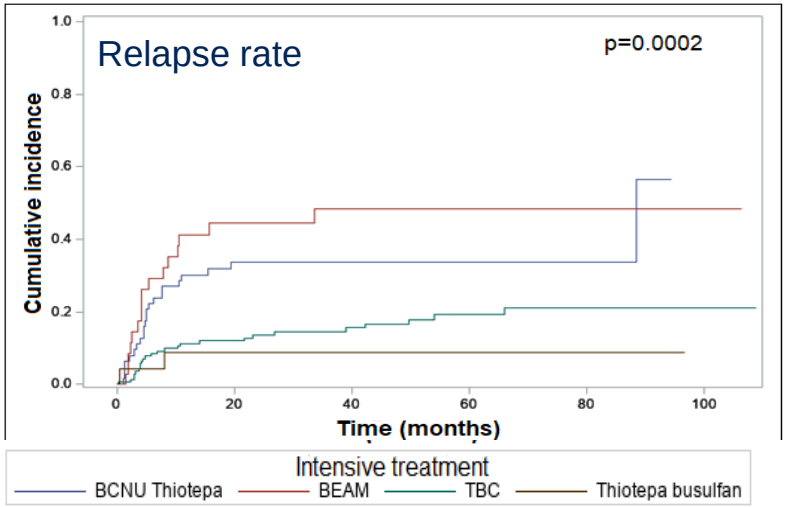

N= **603;**
mean age = 57 (range, 19-77) years

Relapse: BEAM > TT-BCNU > TBC
NRM: BEAM - TT-BCNU < TBC

*Scordo et al. JAMA Oncol 2021*

# Type of ASCT: RWE - LOC database N = 266 (2011-Nov 2019)

N = 266
Median age at IC-ASCT: 57 y (22-74)
Median FU = 43 months




| | TT-Bu N=24 | TBC N= 142 | TT-BCNU N=64 | BEAM N=36 |
|---|---|---|---|---|
| **RR at 2 years** | 9% | 14% | 34% | 44% |
| **RR at 5 years** | 9% | 19% | 34% | 48% |

.

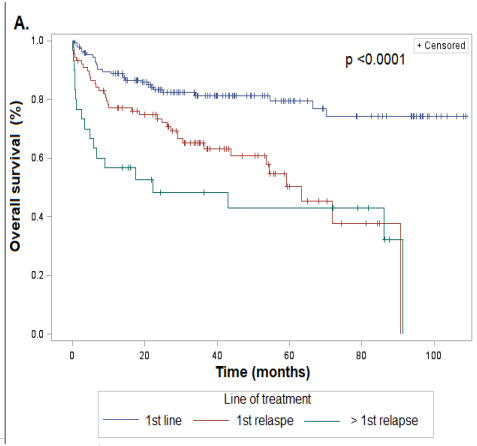
*Schenone et al. BMT 2022*

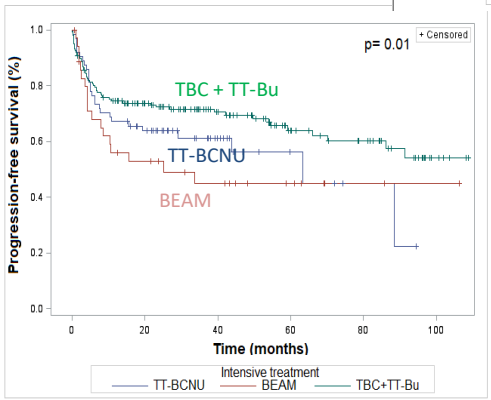
# Type and Timing of ASCT



First-line : N = 147
First-relapse : N = 88
> 1 relapse : N = 31

5-y OS: 80%; 50%, 43%



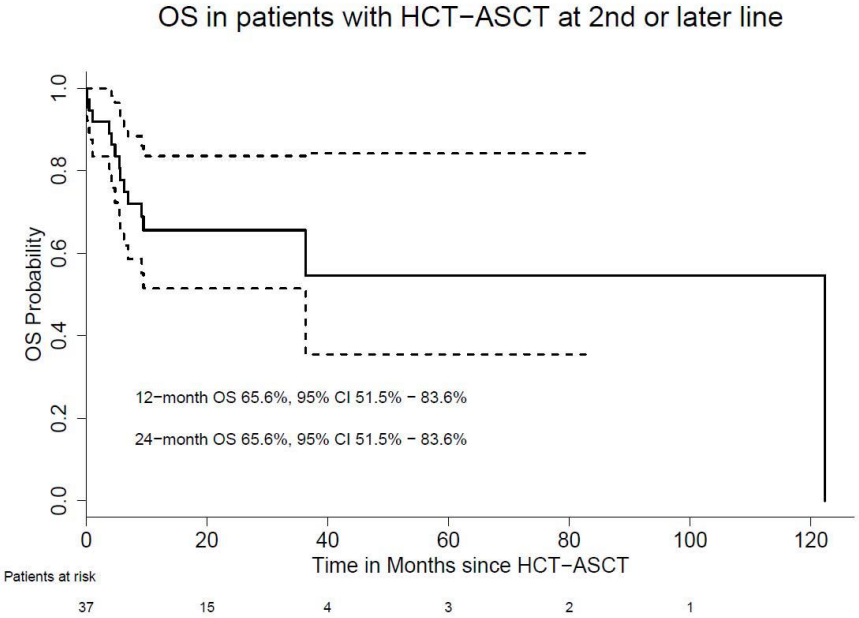




| | OS | | | | PFS | | | |
|---|---|---|---|---|---|---|---|---|
| | MULTIVARIATE ANALYSIS | | | | MULTIVARIATE ANALYSIS | | | |
| | P-value | HR | 95% HR Confidence Limits | | P-value | HR | 95% HR Confidence Limits | |
| **Line of treatment at IC-ASCT** | | | | | | | | |
| 1st line | - | 1 | | | - | 1 | | |
| 1st relapse | **<0.0001** | 3.4 | 1.9 | 6.2 | **<0.0001** | 3.2 | 1.7 | 5.6 |
| Beyond 1st relapse | **<0.0001** | 6.9 | 3.4 | 14.0 | **<0.0001** | 6.7 | 3.7 | 12.4 |
| **Type of IC-ASCT** | 0.3 | | | | | | | |
| TBC+TT-Bu | | | | | - | 1 | | |
| TT-BCNU | | | | | **0.05** | 1.2 | 0.7 | 1.9 |
| BEAM | | | | | **0.01** | 2.6 | 1.3 | 5.2 |

*Schenone et al. BMT 2022*

# ASCT in elderly (≤ 70) at relapse

**European study(TT-based)**

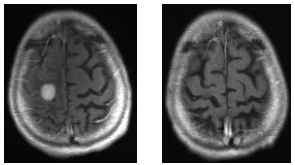



- N = 36
- Median age= 67 (66-70)
- 2-y PFS = 54 %
- 2y-OS = 66 %

*Schorb E, et al. Bone Marrow Transplant 2017;52:1113-19*

# TARGETED THERAPIES

| | Drug | Study | N | Results | Ref |
|---|---|---|---|---|---|
| iMiDs | Lena 25 mg + Ritux | Phase II | 50 | Best ORR = 67 % (18 CR: 40%)<br>ORR end of induction = 36 %<br>Median PFS = 7 months | *Ghesquières Annals of Oncol2019* |
| | Poma 3, 5, 7, 10 mg + Dex | Phase IB/II | 25 | ORR = 48 % (5 CR + uCR)<br>Median PFS = 5 months | *Tun Blood 2018* |



Responses in the brain, the eyes and the CSF

# TARGETED THERAPIES

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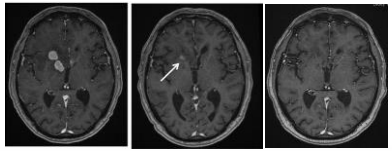
| | Poma 3, 5, 7, 10 mg + Dex | Phase IB/II | 25 | ORR = 48 % (5 CR + uCR)<br>Median PFS = 5 months | *Tun Blood 2018* |
| IBTK | Ibrutinib<br>560 mg/840 mg | Phase I<br>Phase II | PCNSL (n = 13)<br>PCNSL + sCNSL (n = 44) | Detectable CSF level<br>ORR = 70 %<br>Median PFS = 4.6 months | *Grommes Cancer Discovery 2017;* |
| | Ibrutinib<br>560 mg | Phase II | 52<br>(38 brain +) | Detectable CSF level<br>ORR = 52 % (10 CR) @ 2 months<br>Median PFS = 4.8 months | *Soussain Eur J Cancer 2019* |
| | Tirabrutinib | Phase I/II | 44 | ORR: 64%; CR = 34%<br>Median PFS = 2.9 months | *Narita NeuroOncol 2021* |

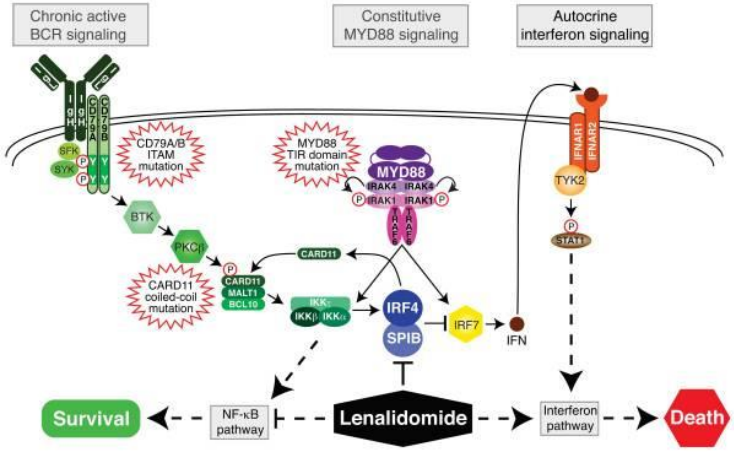


Before 2months 18 months

- ✓ Responses in the brain, the eyes and the CSF
- ✓ Response >12 months in 15 patients, (including 6 brain+)

# Ritux-Lenalidomide-Ibrutinib






*Yang et al, Cancer cell 2012*

CLINICAL/SCIENTIFIC NOTE

## Rituximab-Lenalidomide-Ibrutinib Combination for Relapsed/Refractory Primary CNS Lymphoma

### A Case Series of the LOC Network

Caroline Houillier, MD, Cecile Moluçon Chabrot, MD, Marie-Pierre Moles-Moreau, MD, Lise Willems, MD, Guido Ahle, MD, Agathe Waultier-Rascalou, MD, Luc-Matthieu Fornecker, MD, PhD, Khê Hoang-Xuan, MD, PhD, and Carole Soussain, MD, PhD

*Neurology 2021*

N = 14 R/R PCNSL (11 pts refractory to last treatment)
Response in 8 patients: 4 CR and 4 PR
Median time to response = 2.5 months

- Consolidation in 3: 2 WBRT ; 1 ASCT
- Bridge to CART-cell in one patient

1-y OS = 53%

On going US study NCT03703167

| | DLBCL | | EBV⁻ PCNSL |
|---|---|---|---|
| **PD-1 Ligand Deregulation** | | | |
| 9p24.1/*PD-L1*$^{gain}$ and/or *PD-L2*$^{gain}$ | 6% (11/180)[a] | 7% (4/55)[a] | 52% (33/63)[p] |
| *PD-L1* or *PDL-2* translocation | NA | NA | 6% (4/66)[q] |

*Chapuy et al, Nat Med 2018*

# First results of the AcSé Pembrolizumab Phase II in the Primary CNS Lymphoma (PCNSL) cohort

Khe Hoang-Xuan, Roch Houot, Carole Soussain,, Marie Blonski, Anna Schmitt, Vincent Delwail, Gandhi Laurent Damaj, Herve Ghesquieres, Frédéric Peyrade, Adrian Tempescul, Julie Abraham, Philippe Agape, Guido Ahle, Nathalie Baize, Pierre Bories, Chantal Campello, Emmanuel Gyan, Fabrice Jardin, Philippe Rey, Sylvain Choquet, Caroline Houillier, Nathalie Cassoux, Valerie Touitou, Nadine Martin-Duverneuil, Frederic Legrand, Assia Lamrani-Ghaouti, Ophelie Querel, Natalie Hoog Labouret, Clotilde Simon, Sylvie Chevret, and Christophe Massard.

*Blood (2020) 136 (Supplement 1) : 15*

unicancer LOC

# Anti-PD1



From July 2017 to October 2019: N = 50 patients from 17 centers, including 9 PVRL

Patient Characteristics:

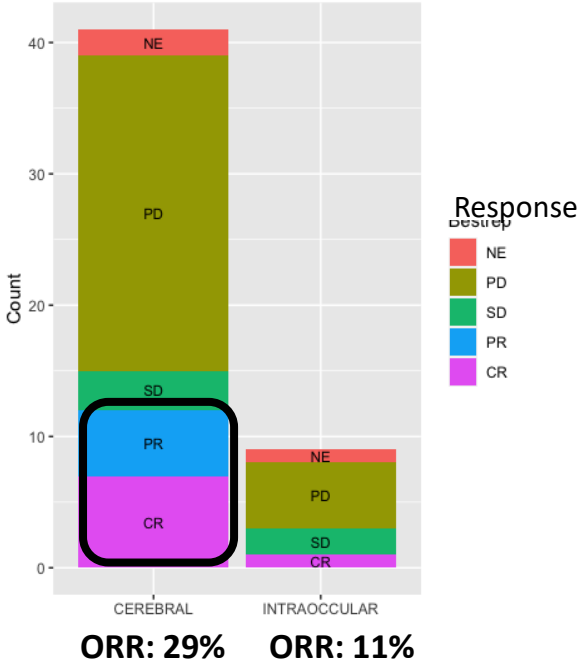
Age Median: 72 years (range 43 – 83 )

Previous line of treatment Median : 3 (1 - 9)

- Median number of cycles = 4 (range 1-35)

| **Best ORR** | **13** | **(26%)** |
|---|---|---|
| CR | 8 | (16%) |
| PR | 5 | (10%) |
| SD | 5 | (10%) |
| PD | 29 | (58%) |
| NE | 3 | (6%) |

**In responders:** Median duration of response = 10 months




**ORR: 29%** **ORR: 11%**

# CART-cells

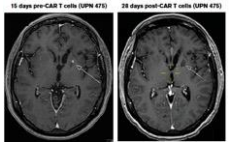


STIMULUS REPORT

blood advances

CD19-directed CAR T-cell therapy for treatment of primary CNS lymphoma

N = 5
CR: 3/5



Encouraging preliminary results:
- Faisability of CART-cells in PCNSL
- Neurotoxicity not increased
- Signal of efficacy

*Siddiqi et al, Blood Adv 2021*

blood
Letter to Blood

December 2021

TO THE EDITOR:

# CAR T-cell therapy in primary central nervous system lymphoma: the clinical experience of the French LOC network

Marion Alcantara,[1,2] Caroline Houillier,[3] Marie Blonski,[4] Marie-Thérèse Rubio,[5,6] Lise Willems,[7] Agathe Waultier Rascalou,[8] Magali Le Garff-Tavernier,[9] Karim Maloum,[9] Clotilde Bravetti,[9] Laetitia Souchet,[10] Damien Roos-Weil,[10] Véronique Morel,[10] Madalina Uzunov,[10] Carole Metz,[11] Meriem Dhib-Charfi,[11] Stéphanie Nguyen,[10] Natalia Shor,[12] Dimitri Psimaras,[3] Nicolas Weiss,[13] Nathalie Jacque,[10] Silvia Solorzano,[10] Nicolas Gauthier,[10] Marie Le Cann,[10] Françoise Norol,[10] Carole Soussain,[1,2] and Sylvain Choquet[10]

| | LCP N = 9 |
|---|---|
| **Age, median (min – max)** | **67 (48 – 75)** |
| male | 3 (33%) |
| **ECOG médian (min – max)** | **1 (0 – 4)** |
| **N (median) previous line (min – max)** | **3 (2 – 5)** |
| Previous MTX HD | 9 (100%) |
| **Previous ASCT** | **7 (78%)** |
| Previous WBRT | 1 (eye) |
| **Bridge therapy** | **8 (89%)** |
| **PD at time of CART-cells infusion** | **4 (44%)** |
| T-cell depletion : FC | 9 (100%) |
| Tisa-cel<br>Axi-cel | 7 (78%)<br>2 (22%) |

blood® Letter to *Blood*

*December 2021*

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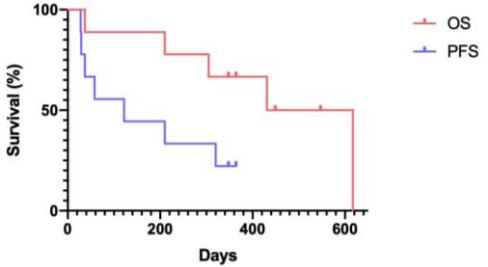
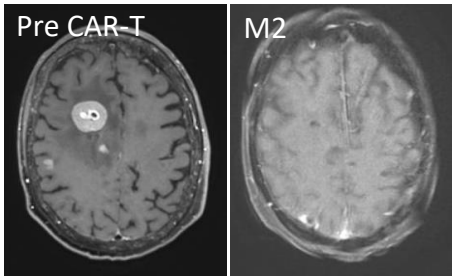
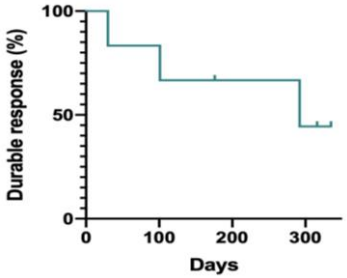



- Median FU: 15 months
- IPCG criteria
- Centralized review

| | LCP; N = 9 |
|---|---|
| **Response at M1** | |
| ORR | 6 (67%) |
| CR | 3 (33%) |
| PD | 2 (22%) |
| **Response at M3** | |
| ORR | 6 (67%) |
| CR | 5 (56%) |
| PD | 2 (22%) |
| **Best response** | |
| **CR** | **5 (56%)** |
| **PR** | **1 (11%)** |

- 12 months-OS : 67%: median OS : 17 months
- 12 months-PFS : 22%
- Median PFS in Responder : 9 months
  - Median DoR : 10 months



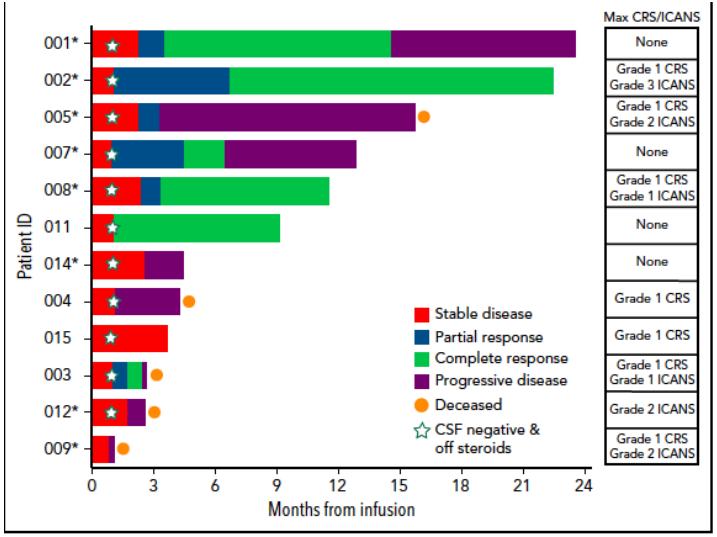
blood® Regular Article

CLINICAL TRIALS AND OBSERVATIONS

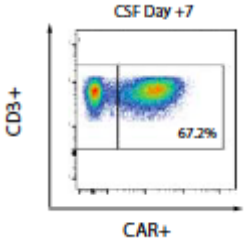
# Safety and efficacy of tisagenlecleucel in primary CNS lymphoma: a phase 1/2 clinical trial

Matthew J. Frigault,[1,2,*] Jorg Dietrich,[3,*] Kathleen Gallagher,[2] Mark Roschewski,[4] Justin T. Jordan,[3] Deborah Forst,[3] Scott R. Plotkin,[3] Daniella Cook,[1,2] Keagan S. Casey,[1,2] Kevin A. Lindell,[1,2] Gabriel D. Depinho,[1,2] Katelin Katsis,[2] Eva Lynn Elder,[2] Mark B. Leick,[1,2] Bryan Choi,[2,5] Nora Horick,[2] Frederic Preffer,[6] Meredith Saylor,[1] Steven McAfee,[1] Paul V. O'Donnell,[1] Thomas R. Spitzer,[1] Bimalangshu Dey,[1] Zachariah DeFilipp,[1] Areej El-Jawahri,[1] Tracy T. Batchelor,[7] Marcela V. Maus,[1,2,*] and Yi-Bin Chen[1,*]

N = 12
ORR: 7 (58%)
CR : 6 (50 %)




| Characteristics | Patients (n = 12) |
|---|---|
| Median age (range), y | 63 (34-81) |
| Male:female | 7:5 |
| Infused/enrolled | 12/13 |
| **ECOG performance status, no. %** | |
| 0-1 | 7/12 |
| 2+ | 5/12 |
| **Disease location** | |
| Parenchymal | 11/12 |
| Leptomeningeal enhancement/CSF+ | 2/12 |
| **Cell of origin** | |
| Germinal center B-cell type | 1/12 |
| Nongerminal center B-cell type | 11/12 |
| Median no. of previous lines of antineoplastic therapy (range) | 4 (2-9) |
| **Prior methotrexate-based regimen** | |
| Yes | 12/12 |
| No | 0/12 |
| **Prior thiotepa-based ASCT** | |
| Yes | 3/12 |
| No | 9/12 |
| **BTKi refractory** | |
| Yes | 12/12 |
| No | 0/12 |
| **IMiD refractory*** | |
| Yes | 4/12 |
| No | 8/12 |
| **TEDDI-R refractory** | |
| Yes | 6/12 |
| No | 6/12 |
| **Prior radiotherapy** | |
| Yes | 4/12 |
| No | 8/12 |
| **Bridging therapy (including high-dose steroids)** | |
| Yes | 12/12 |
| No | 0/12 |
| Median vein-to-vein time, d | 33 (27-37) |

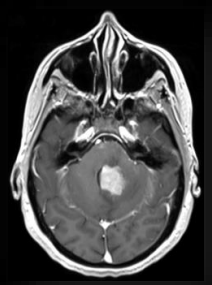


# CLINICAL CASES

# DF (date of birth: 01/11/1959)

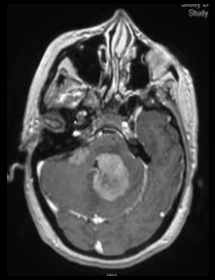


Feb 2013: DLBCL-PCNSL



R-MBVP

PD with hydrocephalus



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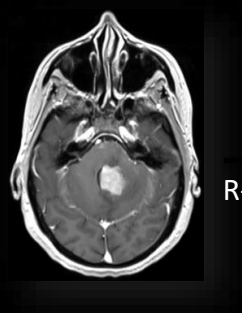
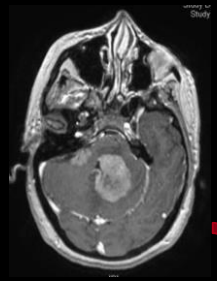
Feb 2013: DLBCL-PCNSL

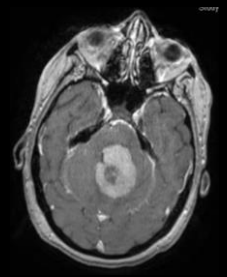


R-MBVP

PD with hydrocephalus



Ventricules shunt
and
R-DHAP



**PD**

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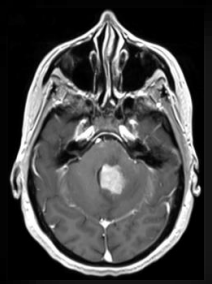
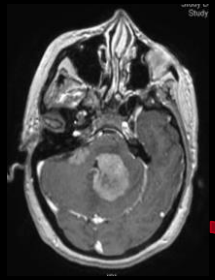


R-MBVP

PD with hydrocephalus



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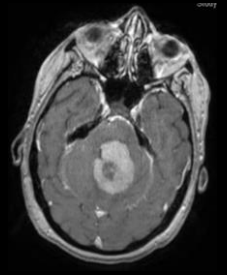
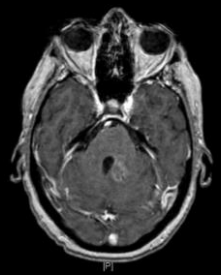
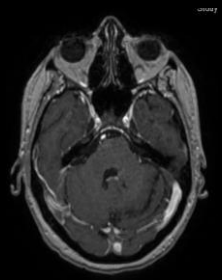


**PD**

R-ICE



After C1 R-ICE



After C4 R-ICE

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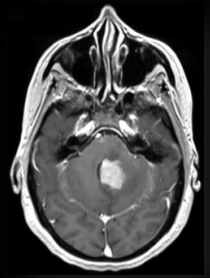
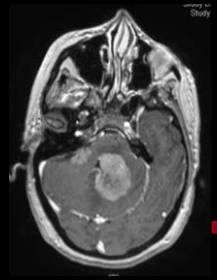
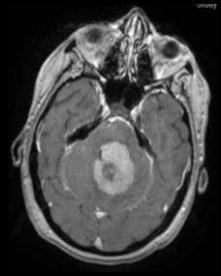


R-MBVP

PD with hydrocephalus

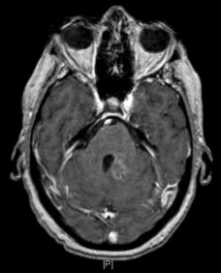


Ventricules shunt
and
R-DHAP

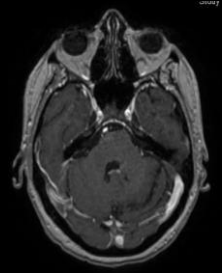


**PD**

R-ICE



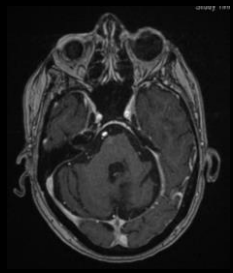
After C1 R-ICE



After C4 R-ICE

25.06.13
TBC + ASCT

31.07.2013
**CR**

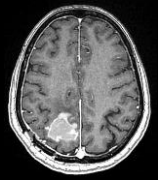


22.10.2021
CR

# MY (31/01/1955)

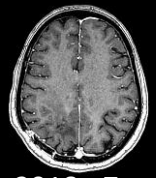


Feb 2017:
DLBCL-PCNSL



4 RMPV +
1 R-AraC

June 2017: CR



July 2017 -Jan 2018 : 7 maintenance R-MT

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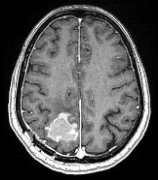

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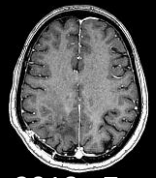
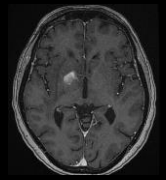


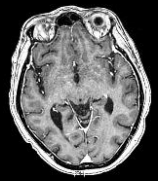
July 2017 -Jan 2018 : 7 maintenance R-MT

May 2019: relapse



3 R-ICE

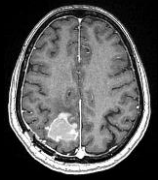
Aug 2019: CR



# MY (31/01/1955)



Feb 2017:
DLBCL-PCNSL



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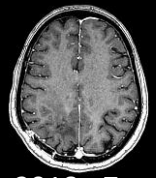

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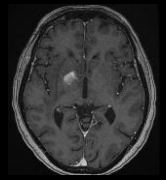

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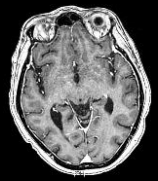
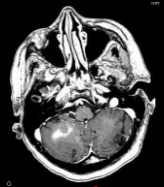
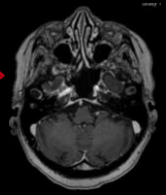


Sep 2019: relapse



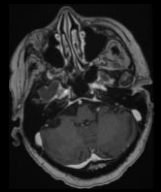
R2-Ibru

Nov 2019: CR



TT-BCNU + ASCT

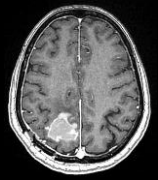
28.01.2020: CR



# MY (31/01/1955)



Feb 2017:
DLBCL-PCNSL



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1 R-AraC

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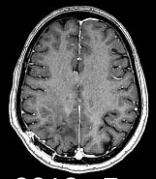

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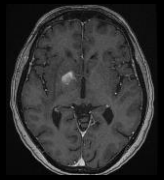
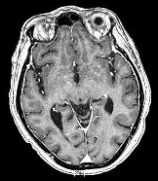


3 R-ICE

Aug 2019: CR



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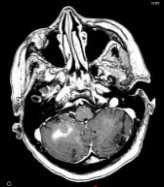
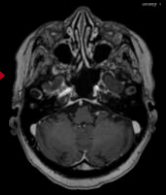


R2-Ibru

Nov 2019: CR



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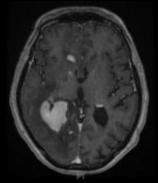
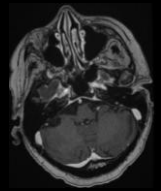
Nov 2020: relapse



28.01.2020: CR



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Feb 2017:
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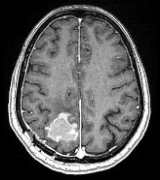

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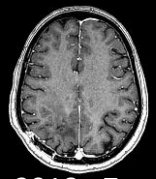
1 R-AraC

June 2017: CR



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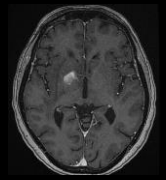
May 2019: relapse



3 R-ICE

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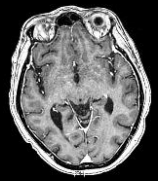

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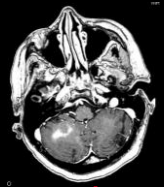

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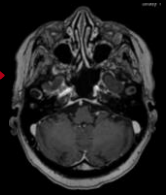

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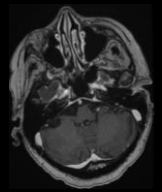
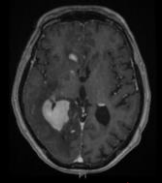
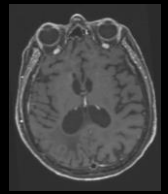


R-MTX + CART-cells

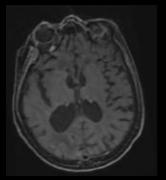
Nov 2020: relapse



Feb 2021:
M1 post CART-cell



April 2022



# CONCLUSION - PERSPECTIVES



- ✓ R/R : challenging issues
  - ➢ Decrease the incidence of R/R PCSNL by improving 1rst line treatment
  - ➢ Robust biomarkers are needed to assess MRD

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- ✓ Some activity of antiPD1

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- ✓ Encouraging results of CART-cells
- ✓ Some activity of antiPD1
  - ➢ Improve the efficacy of immunotherapies:
    - ❑ CART-cells earlier in the course of the disease, in combination with drugs able to modulate the immune brain microenvironment
    - ❑ anti-PD1 in combination, in maintenance?