The young side of

LYMPHOMA

gli under 40 a confronto

Milano, 14-15 aprile 2023

Linfomi cerebrali

Efficacia e sicurezza della radioterapia di consolidamento

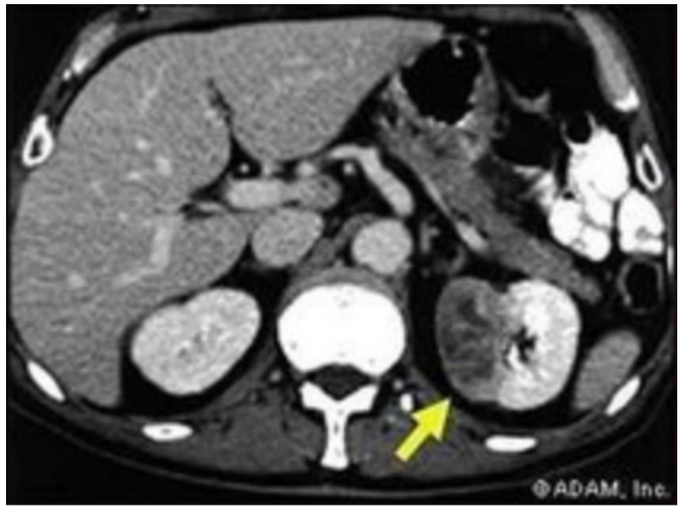
S. Bartoncini
A.O.U. Città della Salute e della Scienza di Torino – Radioterapia U.

Disclosures of Sara Bartoncini: none

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

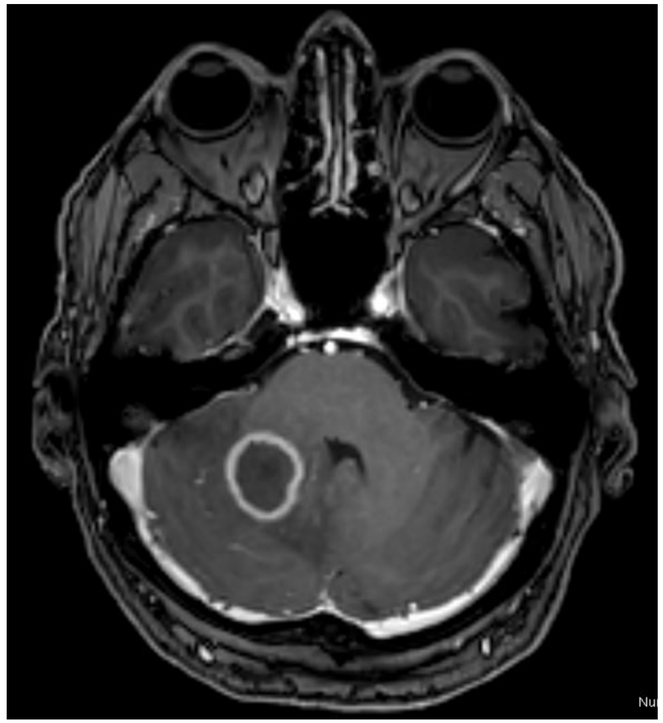
CLINICAL CASE

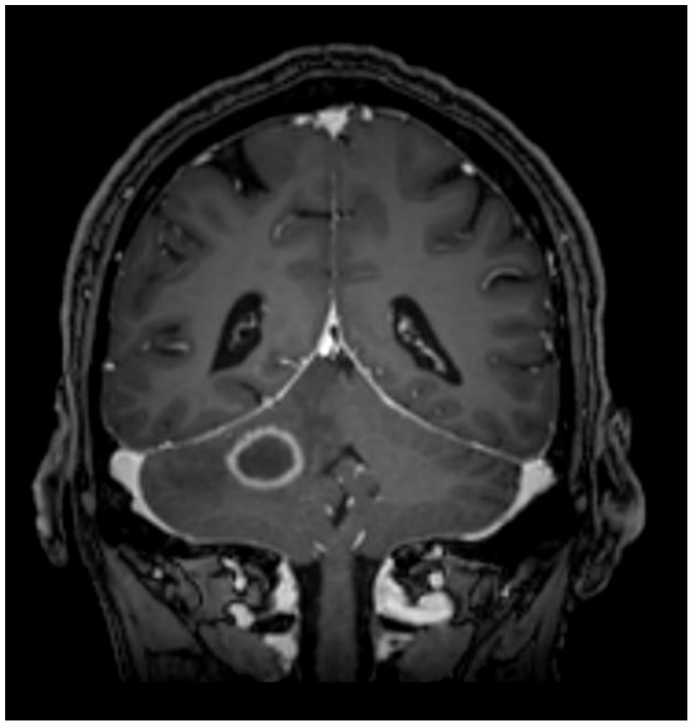
- 63 years, male
- Hypertension, diabetes, coronary heart disease (coronary angioplasty)
- April 2020: tiredness and loss weight
- **CT: exophytic left kidney neoformation**



CLINICAL CASE

- Headache and neurocognitive decline
- **MRI:** at right cerebellar hemisphere, expansive processs (25 mm) with peripheral enhancement and central necrotic component. Marked mass effect due to presence of edema





HOW WOULD YOU STAGING THIS PATIENT?

A. Stereotactic biopsy

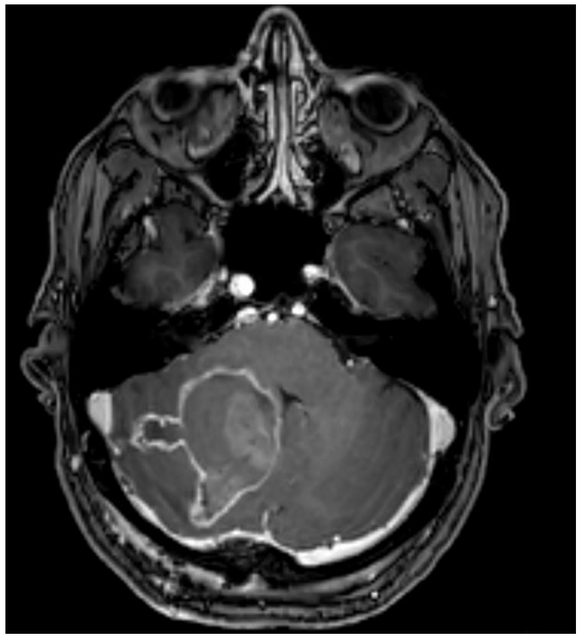
B. Neurosurgical exeresis

C. Other radiological imaging

D. Other strategy

CLINICAL CASE

- **Neurosurgical exeresis:** PCNSL, EBV+
- MRI: small area referable to further localization



- PET-CT and Bone Marrow Biopsy: no extracranial dissemination of lymphoma
- **Renal neoformation biospy: clear cell carcinoma**
- KPS: 70

HOW WOULD YOU TREAT THIS PATIENT?

A. High dose Methotrexate

B. High dose Methotrexate + ARA-C

C. High dose Methotrexate + ARA-C + Rituximab

D. High dose Methotrexate + ARA-C + Rituximab + Thiotepa

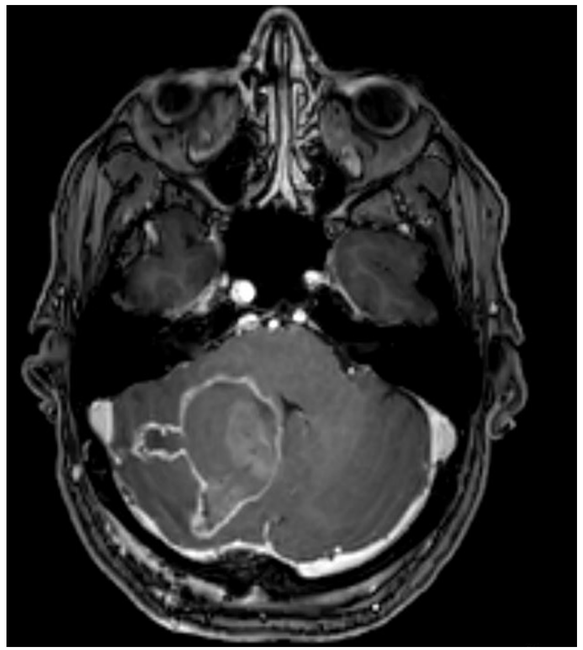
E. High dose Methotrexate + ARA-C+ Rituximab + Procarbazine + Vincristine

F. Whole Brain RT

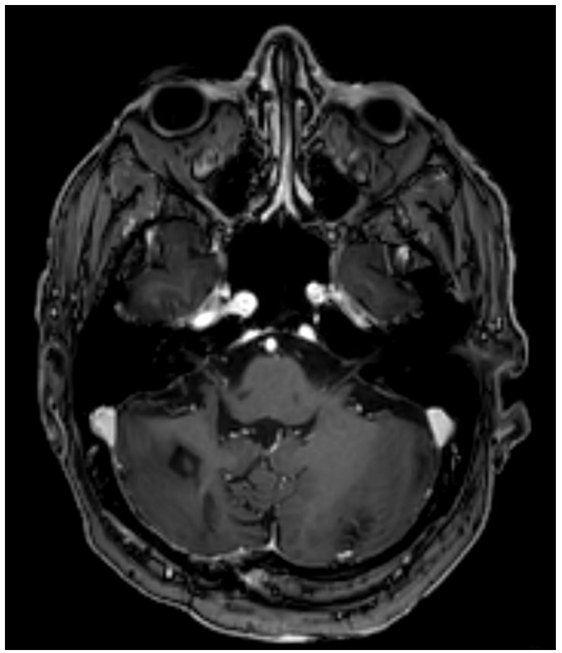
CLINICAL CASE

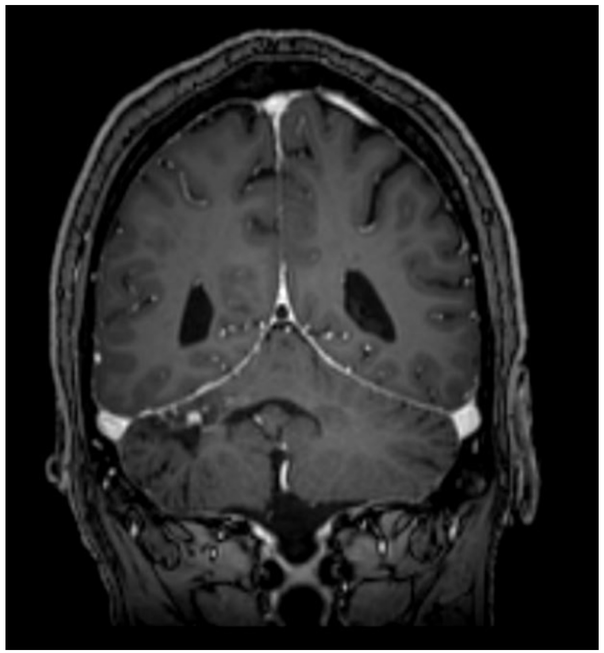
- The patient was treated according to HD-MTX regimen x 4
  (**M**ethotrexate + **A**RA-C + **Ri**tu**x**imab)
- Complete response after CT

Before CT



After CT





CONSOLIDATIVE TREATMENT?

A. No

B. Autologous stem cell transpantation

C. Whole Brain RT 30-36 Gy

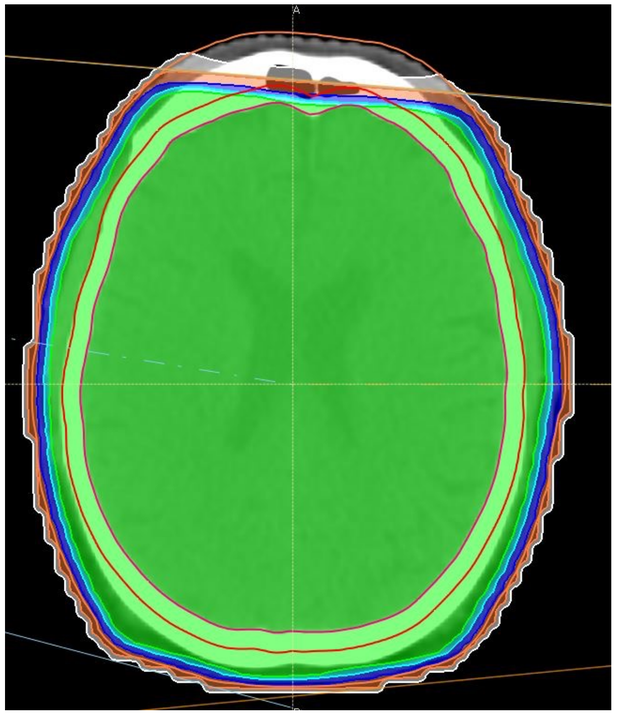
D. Whole Brain RT 40-45 Gy

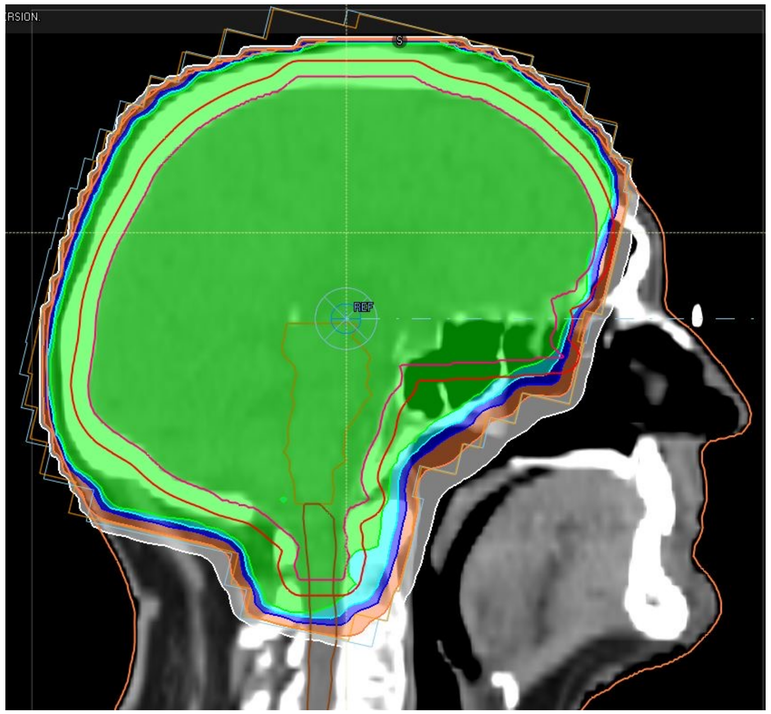
E. Whole Brain RT Reduced Dose (23.4 Gy)

WHOLE BRAIN RADIOTHERAPY:

RT fields for PCNSL

Total Dose 23,4 Gy/13 fractions





CONSOLIDATION TREAMENT

WBRT

Auto-HCT

Novel agents

NEUROTOXICITY

Cognitive functions in primary central nervous system lymphoma: literature review and assessment guidelines

D. D. Correa[1]*, L. Maron[2], H. Harder[3], M. Klein[4], C. L. Armstrong[5], P. Calabrese[6], J. E. C. Bromberg[3], L. E. Abrey[1], T. T. Batchelor[7] & D. Schiff[8]

Annals Oncol. 2007;18

Neuro-Oncology 14(1):101–108, 2012.
doi:10.1093/neuonc/nor186
Advance Access publication October 19, 2011

NEURO-ONCOLOGY

Cognitive functions in primary CNS lymphoma after single or combined modality regimens

Denise D. Correa, Weiji Shi, Lauren E. Abrey, Lisa M. DeAngelis, Antonio M. Omuro, Mariel B. Deutsch, and Howard T. Thaler

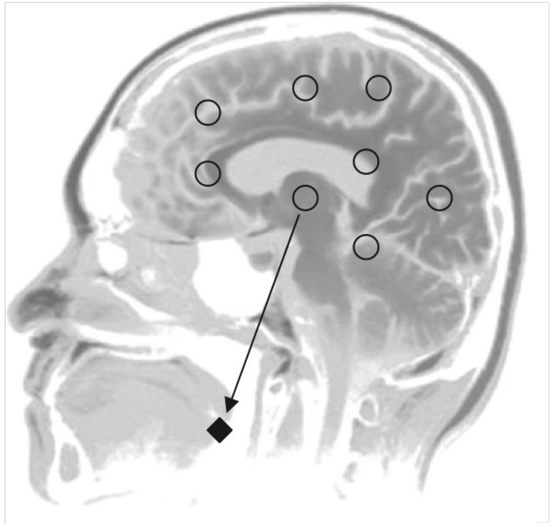
Departments of Neurology (D.D.C., L.E.A., L.M.D., A.M.O., M.B.D.); and Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY (W.S., H.T.T.)

- ✓ Pts treated with **WBRT + HD-MTX**: diffuse cognitive impairments of sufficient severity to interfere with QoL; more cognitive impairment than CT alone
- ✓ Areas of attention, executive function, memory and psychomotor speed
- ✓ Relationship between disease control, treatment modality, survival, cognitive functions, and QoL in order to guide treament choice
- ✓ High incidence of neurotoxicity in **patients >60 years**

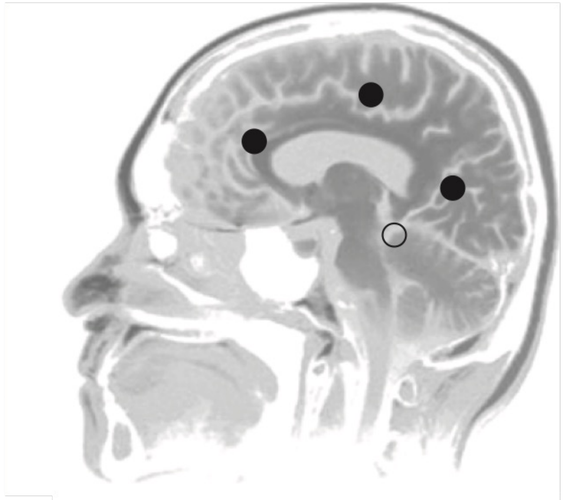
CLINICAL INVESTIGATION **Brain**

CONSOLIDATION RADIOTHERAPY IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMAS: IMPACT ON OUTCOME OF DIFFERENT FIELDS AND DOSES IN PATIENTS IN COMPLETE REMISSION AFTER UPFRONT CHEMOTHERAPY

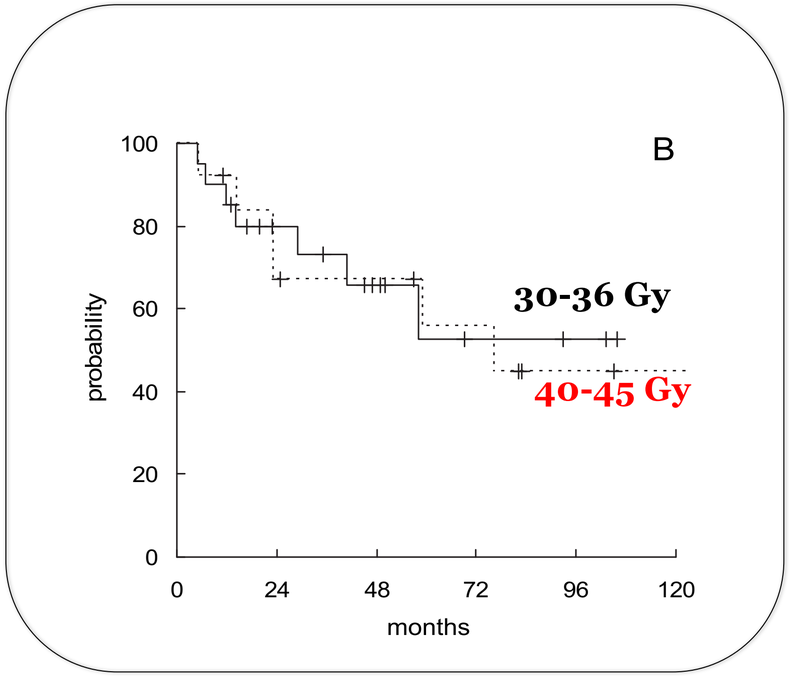
WB dose 30-36 Gy



WB dose 40-45 Gy



OS according to **WBRT dose**

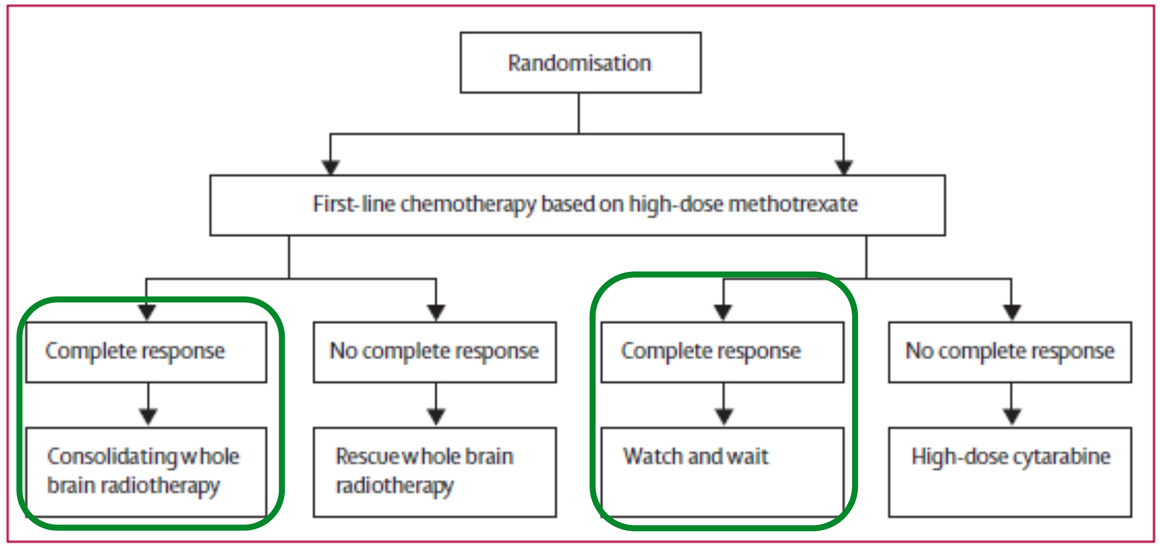


WBRT 30 to 36 Gy; higher doses are not advisable (not change outcome and could increas risk of severe neurotoxicity)

Ferreri AJ et al, IJROBP 2011; 80

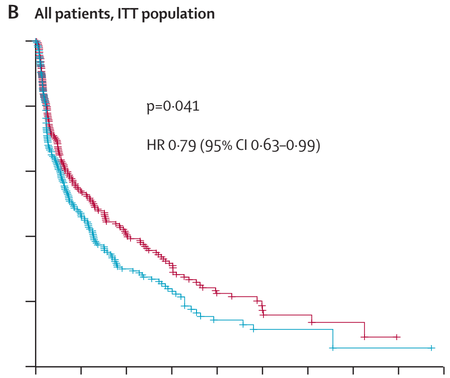
High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial

Eckhard Thiel, Agnieszka Korfel*, Peter Martus, Lothar Kanz, Frank Griesinger, Michael Rauch, Alexander Röth, Bernd Hertenstein, Theda von Toll, Thomas Hundsberger, Hans-Günther Mergenthaler, Malte Leithäuser, Tobias Birnbaum, Lars Fischer, Kristoph Jahnke, Ulrich Herrlinger, Ludwig Plasswilm, Thomas Nägele, Torsten Pietsch, Michael Bamberg, Michael Weller*

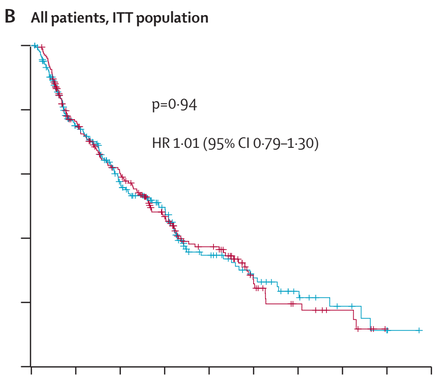


WBRT: 45 Gy/30 fr

PFS



OS



"Although whole brain radiotherapy has a role in disease control, the absence of a survival benefit in this study could justify its omission from first-line treatment in primary CNS lymphoma."

Thiel E. et al. Lancet Oncol 2010;11

Whole-brain radiotherapy in primary CNS lymphoma

Andrés J M Ferreri, Lisa DeAngelis, Gerald Illerhaus, Brian P O'Neill, Michele Reni, Carole Soussain, Joachim Yahalom*

- ✓ **Poor protocol adherence** (57.7%)
- ✓ **Randomisation caveats and low statistical power**
- ✓ **Long accrual period** (2000-2009, 75 centers)
- ✓ **Involvement of many centers with little experience in PCNSL** (high rates of erroneous response assessment, patients lost to follow-up, and toxic deaths).
- ✓ **Inconsistent data for iatrogenic neurotoxicity** (exclusively assessed by MRI)
- ✓ Positive effect of WBRT on PFS and not in OS suggest an unbalanced effect of salvage therapy

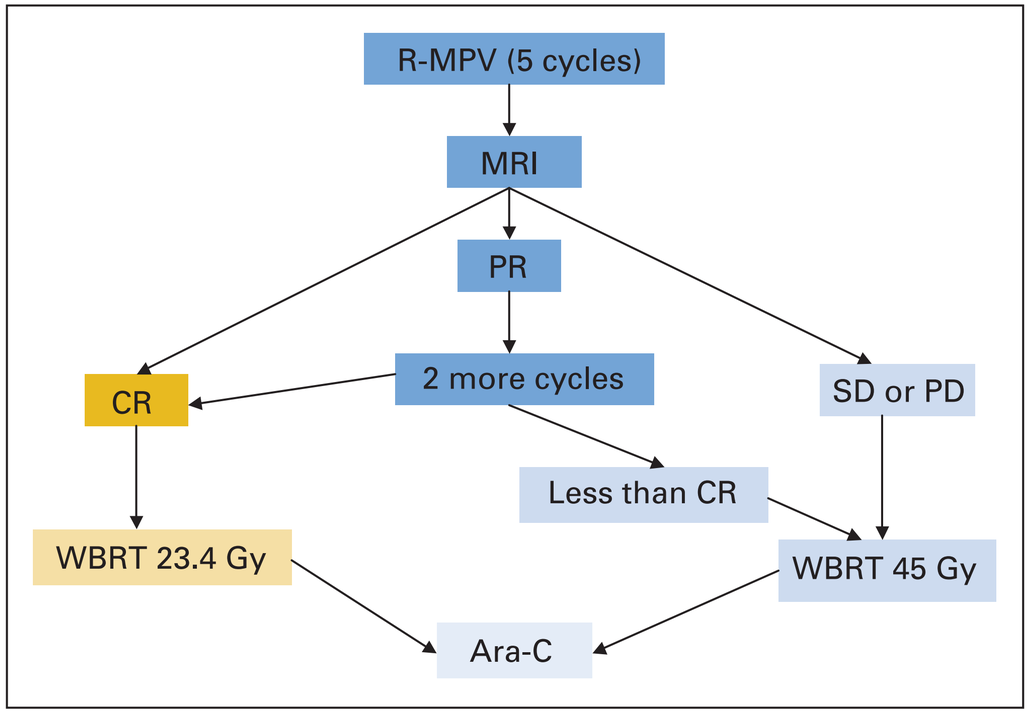
The G-PCNSL-SG-1 trial is compromised by several flaws and failed to prove its primary hypothesis.

Lancet 2011

JOURNAL OF CLINICAL ONCOLOGY

Combined Immunochemotherapy With Reduced Whole-Brain Radiotherapy for Newly Diagnosed Primary CNS Lymphoma

Reduced dose WBRT



- ✓ **Chemotherapy R-MVP**
  - Rituximab
  - Methotrexate
  - Vincristine
  - Procarbazine
- ✓ **WBRT**
  - rdWBRT (23.4 Gy/13 fr) if CR after chemo
  - WBRT (45 Gy/25 fr) if PR-SD-PD after chemo
- ✓ **Consolidative CT**
  - High dose ARA-Cx 2 cycles

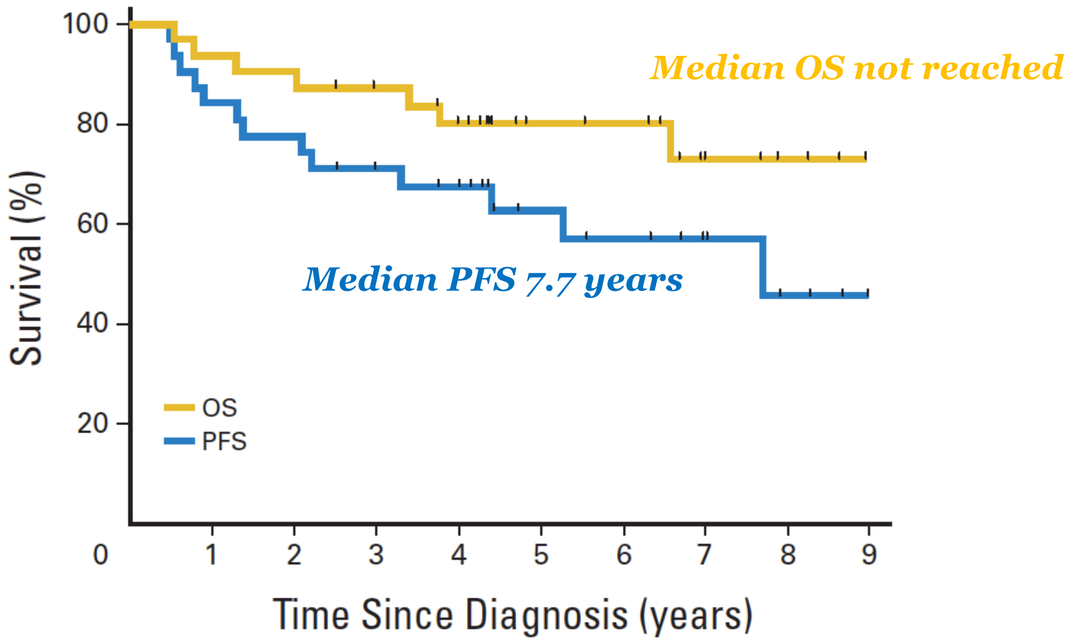
CR rate: 47%
ORR rate: 95%

Gaurav et al. 2007

VOLUME 31 · NUMBER 31 · NOVEMBER 1 2013
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Rituximab, Methotrexate, Procarbazine, and Vincristine Followed by Consolidation Reduced-Dose Whole-Brain Radiotherapy and Cytarabine in Newly Diagnosed Primary CNS Lymphoma: Final Results and Long-Term Outcome

Patrick G. Morris, Denise D. Correa, Joachim Yahalom, Jeffrey J. Raizer, David Schiff, Barbara Grant, Sean Grimm, Rose K. Lai, Anne S. Reiner, Kathy Panageas, Sasan Karimi, Richard Curry, Gaurav Shah, Lauren E. Abrey, Lisa M. DeAngelis, and Antonio Omuro



Reduced Dose WBRT

PFS:	OS:
1 year 84%	1 year 94%
2 year 77%	2 year 90%
3 year 71%	3 year 87%

Morris et al. 2013

VOLUME 31 · NUMBER 31 · NOVEMBER 1 2013
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Toxicity profile

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Patrick G. Morris, Denise D. Correa, Joachim Yahalom, Jeffrey J. Raizer, David Schiff, Barbara Grant, Sean Grimm, Rose K. Lai, Anne S. Reiner, Kathy Panageas, Sasan Karimi, Richard Curry, Gaurav Shah, Lauren E. Abrey, Lisa M. DeAngelis, and Antonio Omuro

Prospective comprehensive neuropsychological evaluations:

- ✓ At baseline
- ✓ After induction chemotherapy (before rdWBRT)
- ✓ At 6-months after completion of rdWBRT

Three cognitive domains were evaluated:

- ✓ Executive (Trail Making Test; Brief Test of Attention)
- ✓ Verbal memory (Hopkins Verbal Learning Test)
- ✓ Motor speed (Grooved Pegboard Test)

RESULTS

- ✓ **At baseline**, cognitive impairment was present in several domains.
- ✓ **After CT**, there was a significant improvement in executive ($P<0.01$) and verbal memory ($P<0.05$)
- ✓ There was ***no evidence of significant cognitive decline***, except for motor speed ($P<0.05$).
- ✓ Self-reported ***quality of life remained stable*** during the follow-up period

RTOG 1114

PHASE II RANDOMIZED STUDY OF RITUXIMAB, METHOTREXATE, PROCARBAZINE, VINCRISTINE, AND CYTARABINE WITH AND WITHOUT LOW-DOSE WHOLE-BRAIN RADIOTHERAPY FOR PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

SCHEMA

STRATIFY

RPA Class

Class 1: age ≤ 50

Class 2: age > 50 and KPS ≥ 70

Class 3: age >50 and KPS < 70

RANDOMIZE

Arm A (chemo only)	R-MPV Cycle 1	R-MPV Cycle 2	R-MP Cycle 3 (no vincristine)	R-MP Cycle 4 (no vincristine)		Ara-C Cycle 1	Ara-C Cycle 2
Arm B (chemo + low-dose WBRT)	R-MPV Cycle 1	R-MPV Cycle 2	R-MP Cycle 3 (no vincristine)	R-MP Cycle 4 (no vincristine)	Low-Dose WBRT (13 fx)	Ara-C Cycle 1	Ara-C Cycle 2

1 cycle = 28 days
(8 MTX doses total)

ENROLLMENT CLOSED

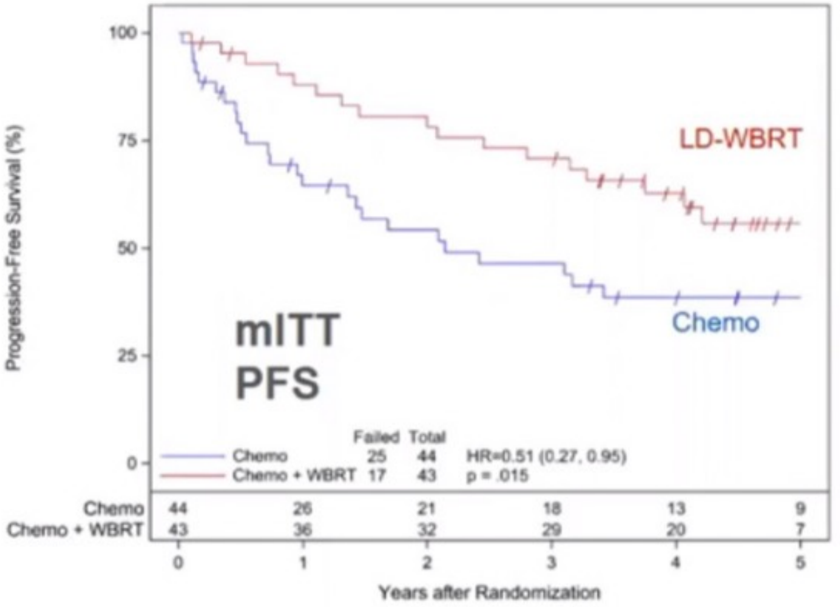
Meeting Abstract | 2020 ASCO Annual Meeting I

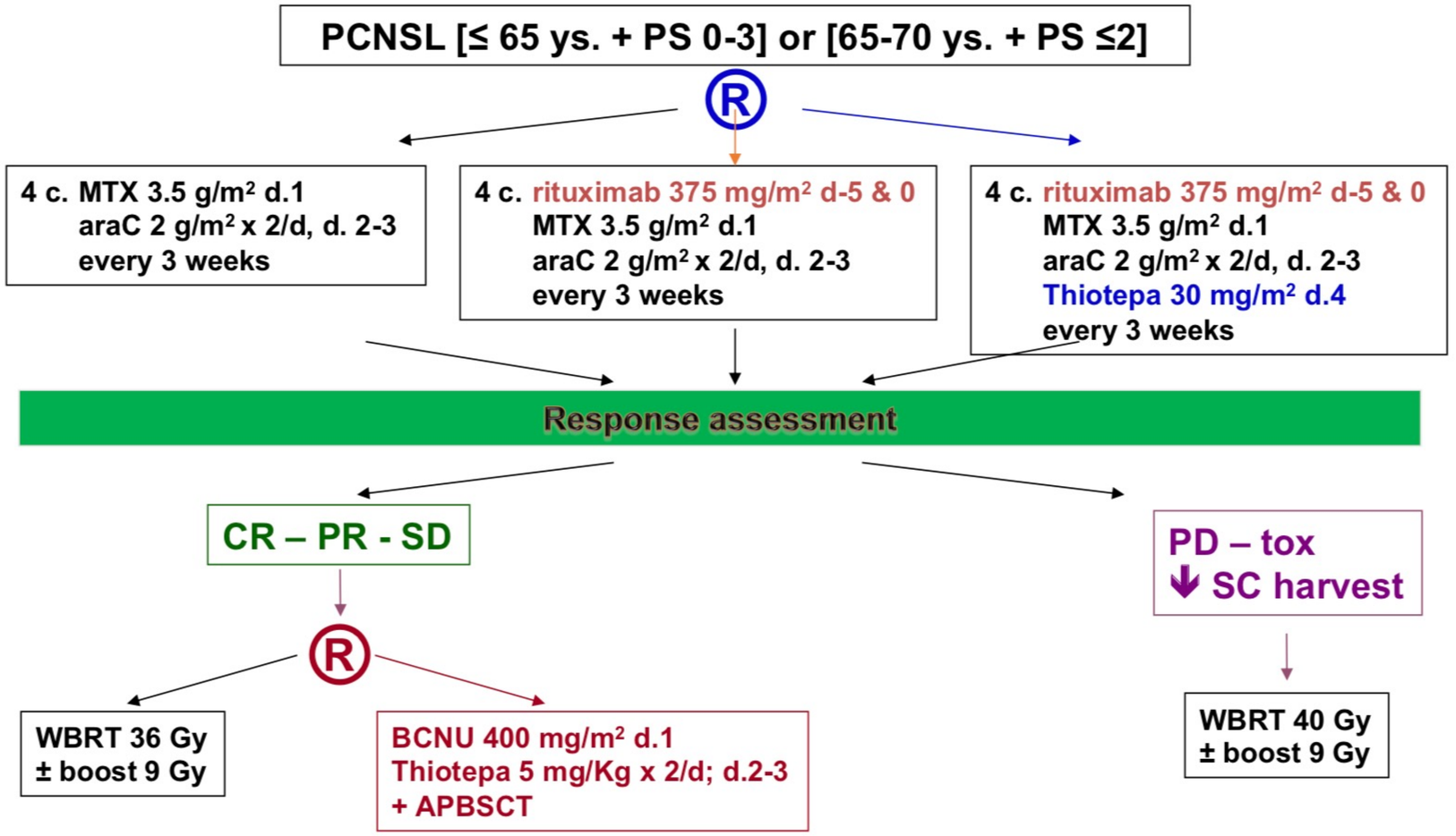
CENTRAL NERVOUS SYSTEM TUMORS

Randomized phase II study of rituximab, methotrexate (MTX), procarbazine, vincristine, and cytarabine (R-MPV-A) with and without low-dose whole-brain radiotherapy (LD-WBRT) for newly diagnosed primary CNS lymphoma (PCNSL).

LD-WBRT dose: 23,4 Gy/13 fr

- ✓ Median follow up 55 months, **91 patients**
- ✓ **Response rate:** 83% (CT) vs 81% (CTRT)
- ✓ Median PFS: 25 months CT arm, not reached CTRT arm
- ✓ **2 year PFS 54% (CT) vs 78% (CTRT)**
- ✓ **Addiction of LD-WBRT to R-MPV-A improves PFS**
- ✓ Severe neurotoxicity rates were not statistically significantly increased





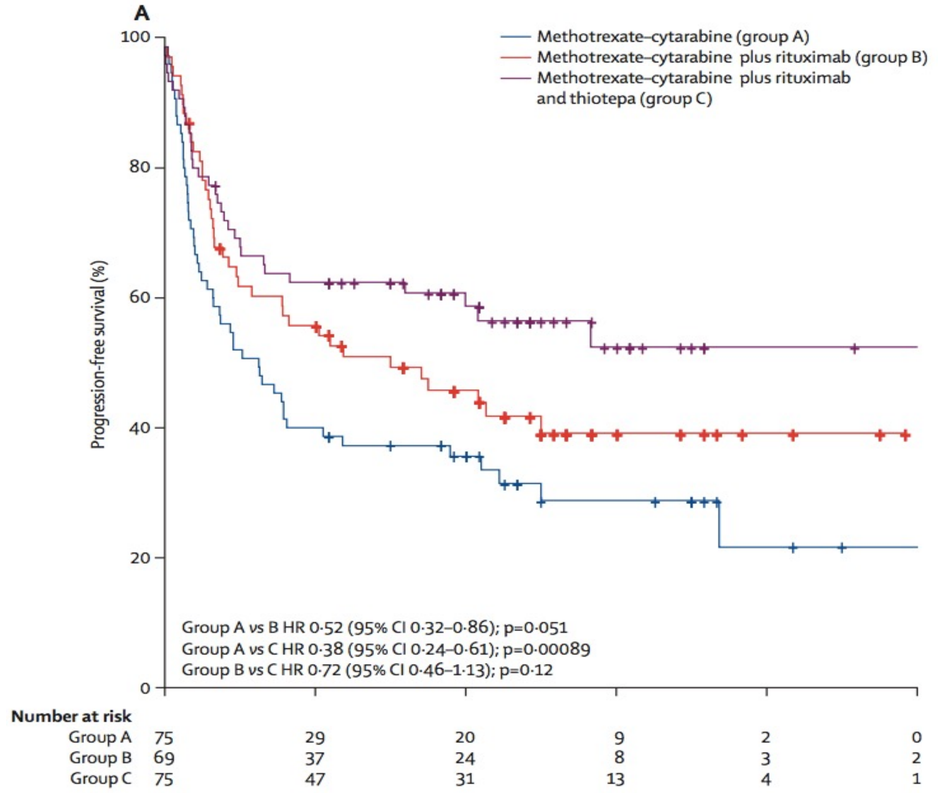
IELSG 32

219 pts (118 for second randomisation)

Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial

ORR:
Arm A: 53% (CR 23%)
Arm B: 74% (CR 30%)
Arm C: 87% (CR 49%)

OS @ 2 years:
Arm A: 40%
Arm B: 58%
Arm C: 66%



Ferreri AJM. et al. Lancet Hematol 2016;3

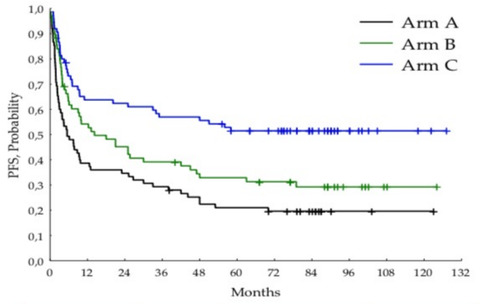
Randomized Controlled Trial > Leukemia. 2022 Jul;36(7):1870-1878.
doi: 10.1038/s41375-022-01582-5. Epub 2022 May 13.

Long-term efficacy, safety and neurotolerability of MATRix regimen followed by autologous transplant in primary CNS lymphoma: 7-year results of the IELSG32 randomized trial

Andrés J M Ferreri # 1, Kate Cwynarski # 2, Elisa Pulczynski 3, Christopher P Fox 4,

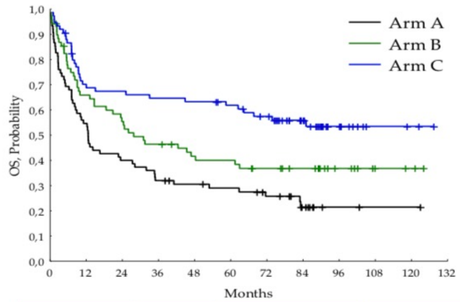
MATRix: Efficacy

MEDIAN FOLLOW-UP: 88 MONTHS (IQR 77-99)



	HR	95%CI	p
A vs. B	0·66	0·43 - 1·02	0·06
A vs. C	0·41	0·21 - 0·61	0·00001
B vs. C	0·63	0·42 - 0·92	0·01

Ferreri AJM et al. Leukemia 2022

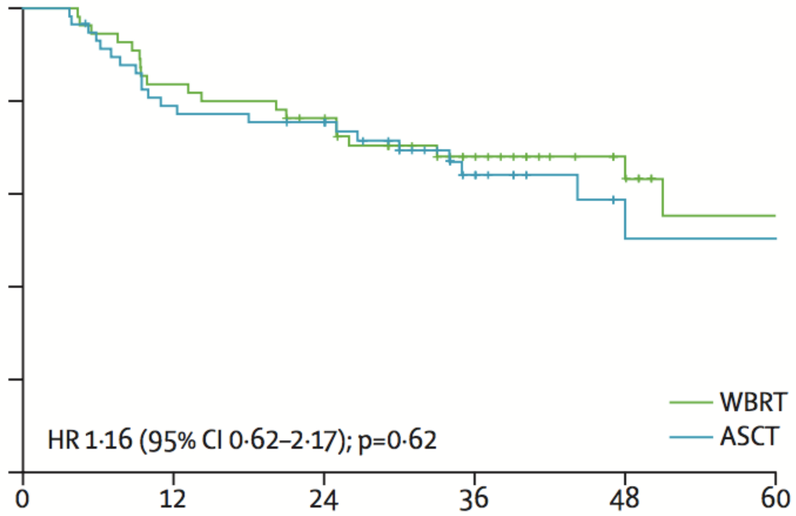


	HR	95%CI	p
A vs. B	0·64	0·41 - 0·99	0·049
A vs. C	0·42	0·24 - 0·64	0·00005
B vs. C	0·66	0·44 - 0·98	0·044

Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial

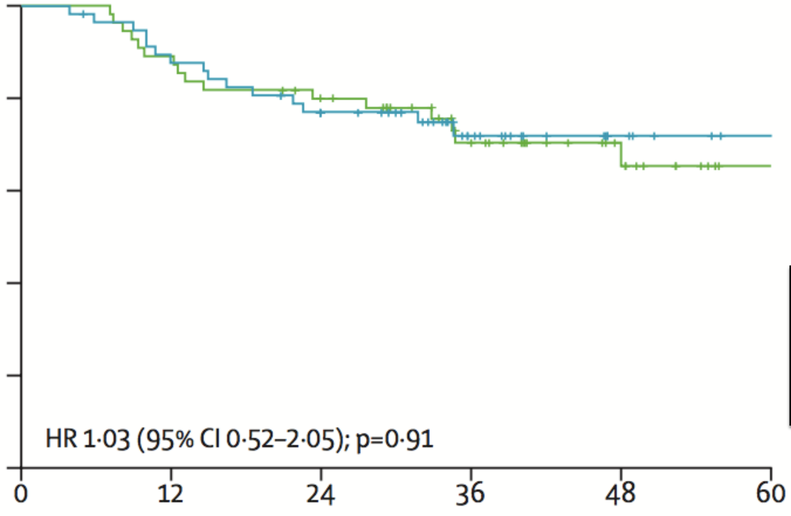
IELSG 32

PFS (per protocol)



WBRT	55	46	40	25	14	3
ASCT	58	45	43	21	7	3

OS (per protocol)



WBRT	55	49	42	27	15	3
ASCT	58	51	44	24	10	5

2 ys PFS 80% (WBRT) vs 69% (ASCT)

Ferreri AJM. et al. Lancet Haematol 2017

Randomized Controlled Trial > Leukemia. 2022 Jul;36(7):1870-1878.
doi: 10.1038/s41375-022-01582-5. Epub 2022 May 13.

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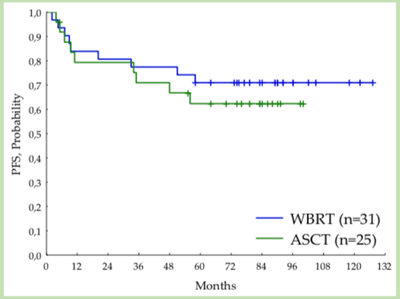
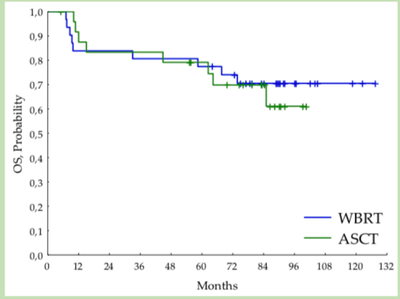
Andrés J M Ferreri # 1, Kate Cwynarski # 2, Elisa Pulczynski 3, Christopher P Fox 4,

IELSG32

Patients treated with MATRIX + consolidation had a 7-year OS of 70%, without a difference between WBRT and BCNU-TT conditioned ASCT





Ferreri AJM et al. Leukemia 2022

Received: 3 April 2022 | Revised: 18 August 2022 | Accepted: 17 September 2022

DOI: 10.1002/hon.3083

ORIGINAL ARTICLE

WILEY

Autologous hematopoietic cell transplantation versus whole-brain radiotherapy consolidation in primary central nervous system lymphoma: A systematic review and meta-analysis

Narendranath Epperla[1] | Tea Reljic[2] | Sayan Mullick Chowdhury[3] | Andrés J. M. Ferreri[4] | Ambuj Kumar[2] | Mehdi Hamadani[5]

Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial

Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients 60 Years of Age and Younger: Results of the Intergroup ANOCEF-GOELAMS Randomized Phase II PRECIS Study

Houillier C et al JCO 2019

- ✓ **No significative difference** in OS, PFS, ORR, CR rate, relapse rate
- ✓ **Neuropsychological tests** were different and inconsistently reported in the two studies
- ✓ A trend toward lower tretament related mortality in WBRT arm compared to auto-HCT arm (not significant)
- ✓ Both studies showed a significant decline in attention/executive function in WBRT compared to auto-HCT

Received: 3 April 2022 | Revised: 18 August 2022 | Accepted: 17 September 2022

DOI: 10.1002/hon.3083

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Narendranath Epperla[1] | Tea Reljic[2] | Sayan Mullick Chowdhury[3] | Andrés J. M. Ferreri[4] | Ambuj Kumar[2] | Mehdi Hamadani[5]

- ✓ **NO superiority of auto-HCT or WBRT** consolidation therapies, but more neurocognitive decline associated with WBRT
- ✓ **Decision is individualized** based on age, frailty, and co-morbidities.
- ✓ One of the **main goals is to improve efficacy while minimizing toxicity**
- ✓ **Ongoing clinical trials with novel agents** as maintenance strategies can provide similar outcomes with better toxicity profile

clinical trial updates

Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients Age 60 Years and Younger: Long-Term Results of the Randomized Phase II PRECIS Study

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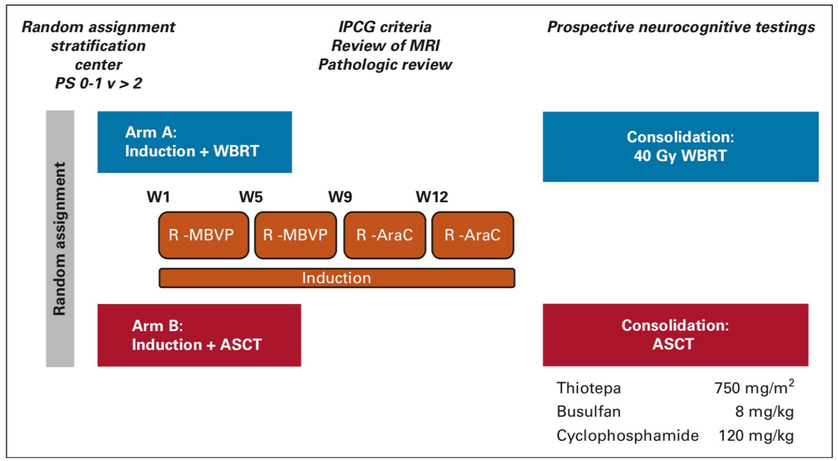

R-MBVP (rituximab, HD-MTX, etoposide, carmustine, prednisone)

- ✓ **Median follow-up 8 years**
- ✓ 53 and 44 pts: induction CT followed by WBRT or ASCT, respectively

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Irradiation or Autograft in First-Line Treatment of PCNSL

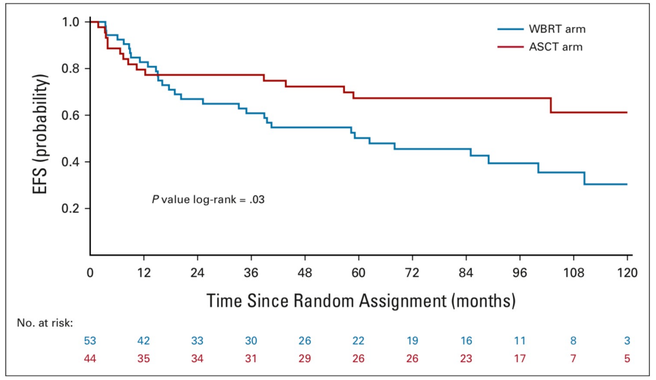

FIG 1. The long-term EFS from random assignment in the PP population. ASCT, autologous stem-cell transplantation; EFS, event-free survival; PP, per-protocol; WBRT, whole-brain radiotherapy.

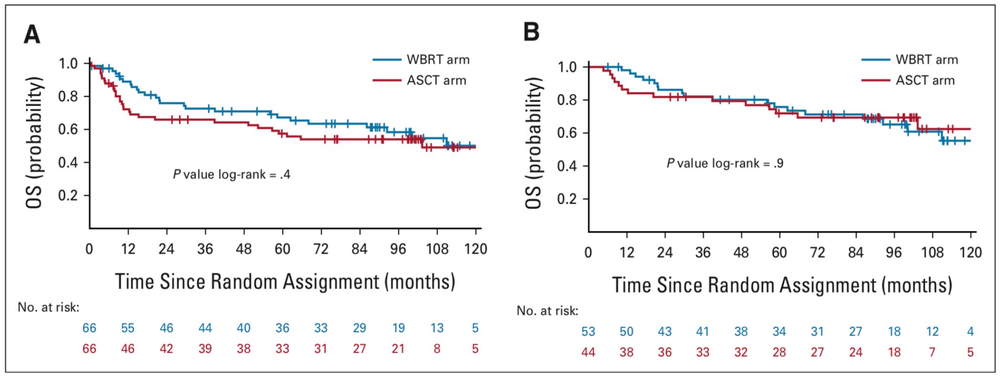

FIG A3. (A) The long-term OS from random assignment in the ITT population. (B) The long-term OS from random assignment in the PP population. ASCT, autologous stem-cell transplantation; OS, overall survival; ITT, intent-to-treat; PP, per-protocol; WBRT, whole-brain radiotherapy.

- ✓ **Event free survival:** 67% and 39% in ASCT and WBRT respectively (significantly lower risk of relapse after ASCT, p<0,001)
- ✓ **OS:** 69% and 65% in ASCT and WBRT respectively (not significant)
- ✓ Balance (52% vs 10%) and neurocognition (64% vs 13%) significantly **deteriorated after WBRT** compared with ASCT

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REGULAR ARTICLE

blood advances

Reduced-dose WBRT as consolidation treatment for patients with primary CNS lymphoma: an LOC network study

- ✓ **Retrospective data in patients <60 years** inCR after HD-MTD
- ✓ 2013-2018, 29 pts
- ✓ **Neuropsychological follow up:** maintenance or improvements their baseline conditions

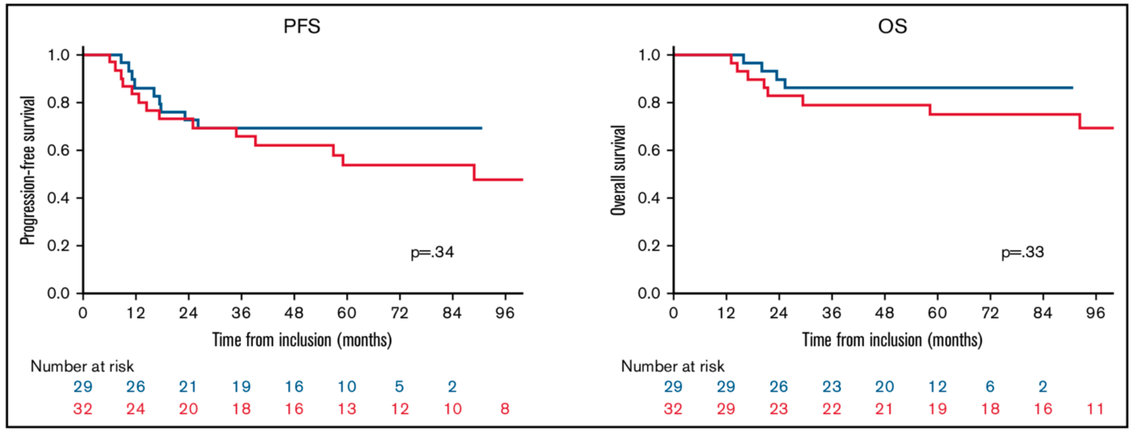

Figure 2. Comparison of outcomes between the rdWBRT cohort (blue curve) and WBRT cohort in the PRECIS trial (red curve).

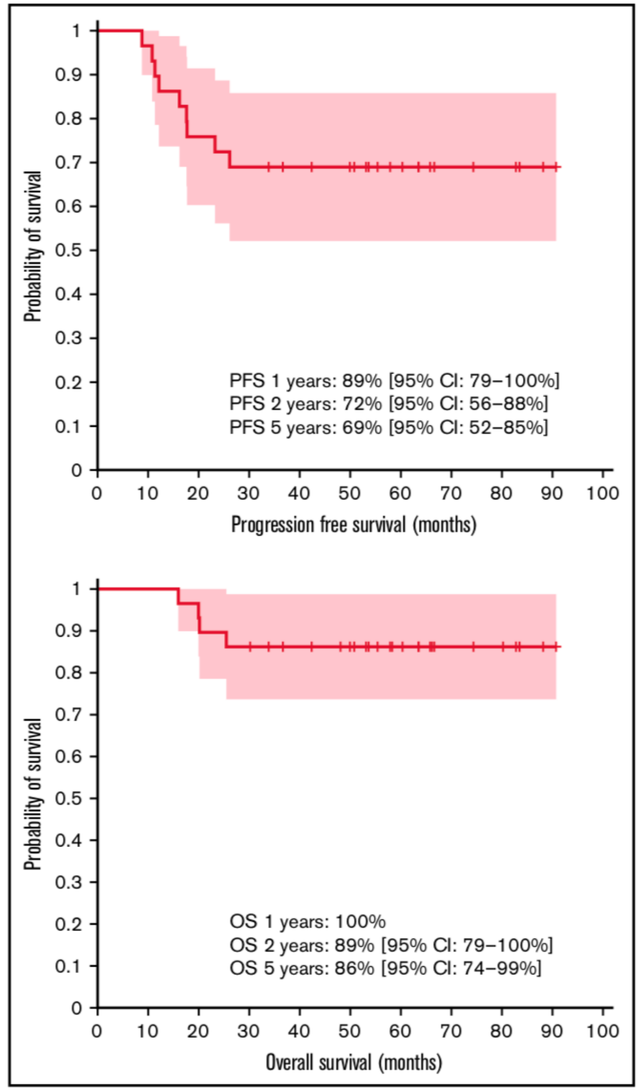

Figure 1. OS and PFS after diagnosis.

Blood Advances 2022

Journal of Neuro-Oncology (2019) 144:553–562
https://doi.org/10.1007/s11060-019-03257-1

CLINICAL STUDY

Check for updates

Longitudinal cognitive assessment in patients with primary CNS lymphoma treated with induction chemotherapy followed by reduced-dose whole-brain radiotherapy or autologous stem cell transplantation

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- ✓ Statistically significant **improvement from baseline up to year 3** in attention/executive functions, graphomotor speed, and memory in both groups
- ✓ **Decline** in attention/ececutive functions and memory after year 3 in both groups and increase in brain structure abnormalities
- ✓ **No difference in cognitive performance or QoL**

ORIGINAL ARTICLE

High-dose methotrexate-based immuno-chemotherapy for elderly primary CNS lymphoma patients (PRIMAIN study)

K Fritsch[1,26], B Kasenda[2,3,26], E Schorb[1], P Hau[4], J Bloehdorn[5], R Möhle[6], S Löw[7], M Binder[8], J Atta[9], U Keller[10], H-H Wolf[11], SW Krause[12], G Heß[13], R Naumann[14], S Sasse[15], C Hirt[16], M Lamprecht[17], U Martens[18], A Morgner[19], J Panse[20], N Frickhofen[21], A Röth[22], C Hader[23], M Deckert[24], H Fricker[1], G Ihorst[25], J Finke[1,26] and G Illerhaus[1,2,26]

Successful change of treatment strategy in elderly patients with primary central nervous system lymphoma by de-escalating induction and introducing temozolomide maintenance: results from a phase II study by the Nordic Lymphoma Group

Elisa J Pulczynski [1], Outi Kuittinen [2], Martin Erlanson [3], Hans Hagberg [4], Alexander Fosså [5], Mikael Eriksson [6], Marie Nordstrøm [7], Bjørn Østenstad [8], Øystein Fluge [9], Sirpa Leppä [10], Bente Fiirgaard [11], Hanne Bersvendsen [12], Unn-Merete Fagerli [13]

› Br J Haematol. 2019 Jul;186(1):180-183. doi: 10.1111/bjh.15787. Epub 2019 Feb 3.

Low-dose lenalidomide maintenance after induction therapy in older patients with primary central nervous system lymphoma

Khoan Vu [1], Gabriel Mannis [1 2], Jimmy Hwang [2 3], Huimin Geng [2 4], James L Rubenstein [1 2 5]

Clinical Trial › Blood. 2019 Jan 31;133(5):436-445. doi: 10.1182/blood-2018-09-875732. Epub 2018 Dec 19.

Phase 1b trial of an ibrutinib-based combination therapy in recurrent/refractory CNS lymphoma

Christian Grommes [1 2 3], Sarah S Tang [2], Julia Wolfe [1], Thomas J Kaley [1 3], Mariza Daras [1 3], Elena I Pentsova [1 3], Anna F Piotrowski [1 3], Jacqueline Stone [1 3], Andrew Lin [1 3], Craig P Nolan [1 3], Malbora Manne [1], Paolo Codega [2], Carl Campos [2], Agnes Viale [4], Alissa A Thomas [1], Michael F Berger [4 5 6], Vaios Hatzoglou [7], Anne S Reiner [8], Katherine S Panageas [8], Lisa M DeAngelis [1 3], Ingo K Mellinghoff [1 2 3 9]

ONGOING TRIALS on the role of maintenance therapy

CONCLUSIONS

Multidisciplinary Team

- ✓ **A Consolidative therapy is strongly recommended** after induction chemotherapy for PCNSL

- ✓ **WBRT and ASCT are both effective**, as consolidation therapies after high-dose-methotrexate-based chemoimmunotherapy with a 95% CR rate, and 75-80% progression-free survivors at 2 years

- ✓ **The best consolidative approach** should be individualized based on age, frailty and co-morbidities within a multidisciplinary tumor board, taking into account the toxicity profile of each strategy.

Keith Haring - Wallpaper