ESMO Clinical Practice Guidelines

Diffuse Large B-Cell Lymphoma Discussion

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SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

Disclosures

Dr Tam has received conference travel grants from Roche and Gilead

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v116–v125, 2015
doi:10.1093/annonc/mdv304

Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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ESMO DLBCL Guidelines : Pathology

- Diagnosis in reference Haematopathology lab
- Surgical excision is preferred mode of biopsy
- Immunophenotypic Ix (flow or IHC) should accompany morphology
- Specials: Cell of Origin, “Double-Hit”

ESMO DLBCL Guidelines : Clinical Workup

- PET/CT is Gold Standard; contrast enhanced CT may still add value
- Bone Marrow may be waived if PET shows bone or marrow involvement
- CNS – subject of this discussion
- Cardiac function, fertility preservation

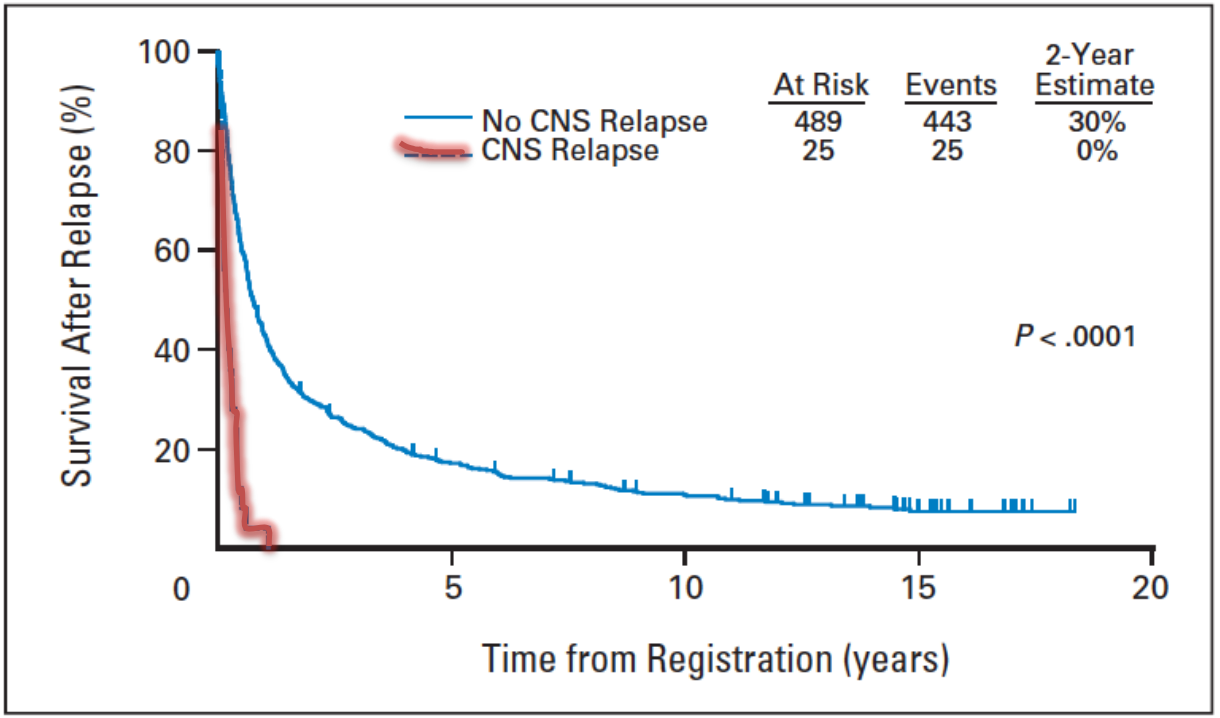
ESMO DLBCL Guidelines : Standard Frontline Therapy

- Fit Patients : R-CHOP-21 x 6
  - IF-RT on bulk
  - aaIPI 2 or 3 = consider 8 cycles, R-CHOEP, frontline auto
- > 80 years : R-miniCHOP-21 x 6
- Cardiac dysfunction : substitute doxorubicin for etoposide, gemcitabine or liposomal doxorubicin
- PET/CT for restaging (5 point scale)

Discussion Points for This Case

- How to assess CNS risk
- What CNS prophylaxis is ideal
- How to treat CNS relapse

The outlook for patients who develop CNS relapse is dismal



Bernstein *et al*, JCO 2009;27:114

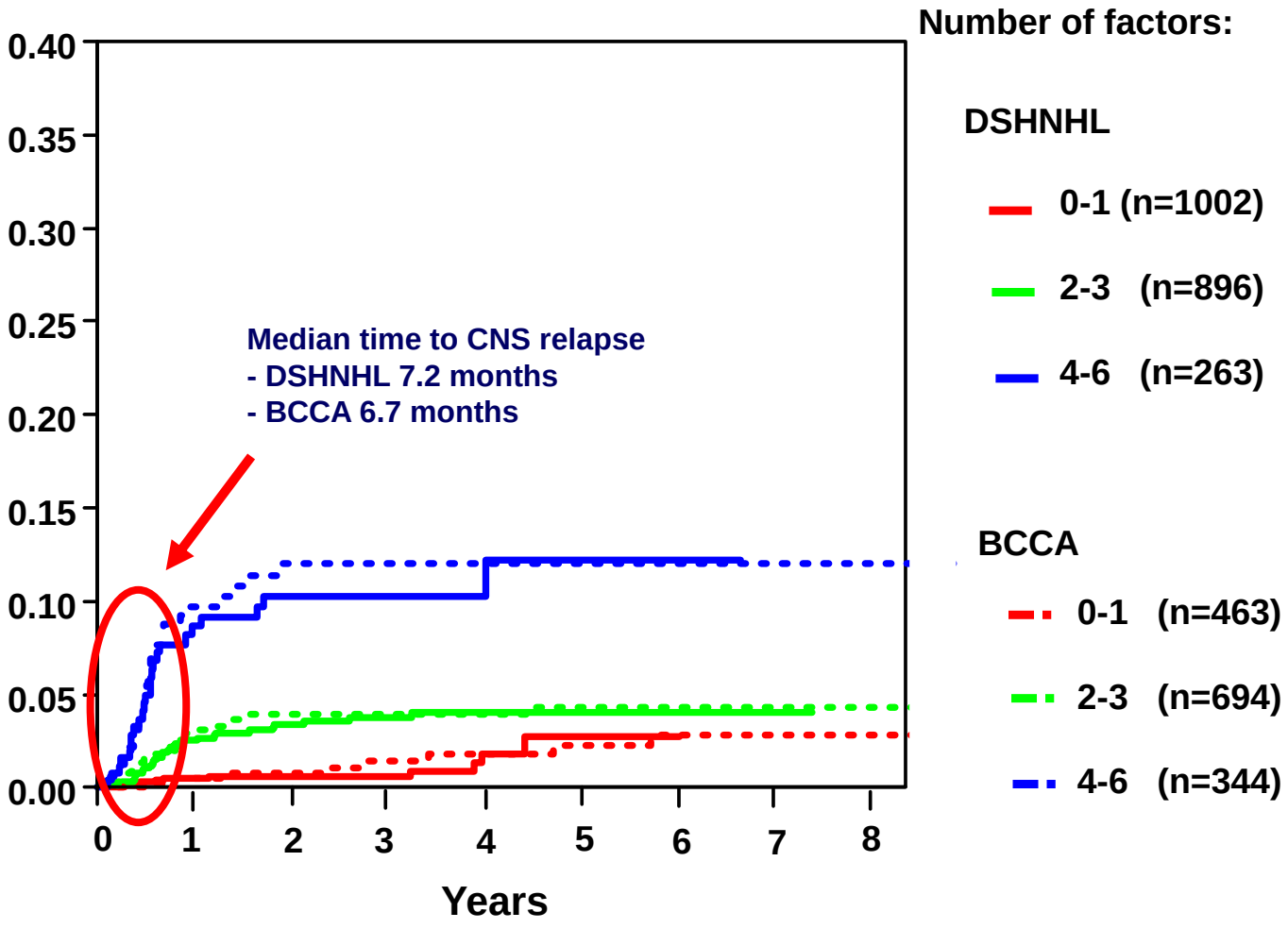
ESMO Guidelines on CNS Risk Assessment in DLBCL

- High-intermediate and High Risk IPI (score 3 – 5)
  - Especially those with >1 extranodal site or high LDH
- Additional Risk Factors – testes, renal and adrenal, MYC
- CNS Prophylaxis recommended in these cases (II, A)
- Assessment of CSF should include flow cytometry

Tilly Ann Oncol 2015, 26(s5):v116-125

IPI-Based Risk Score (DSHNHL with Validation by BCCA)

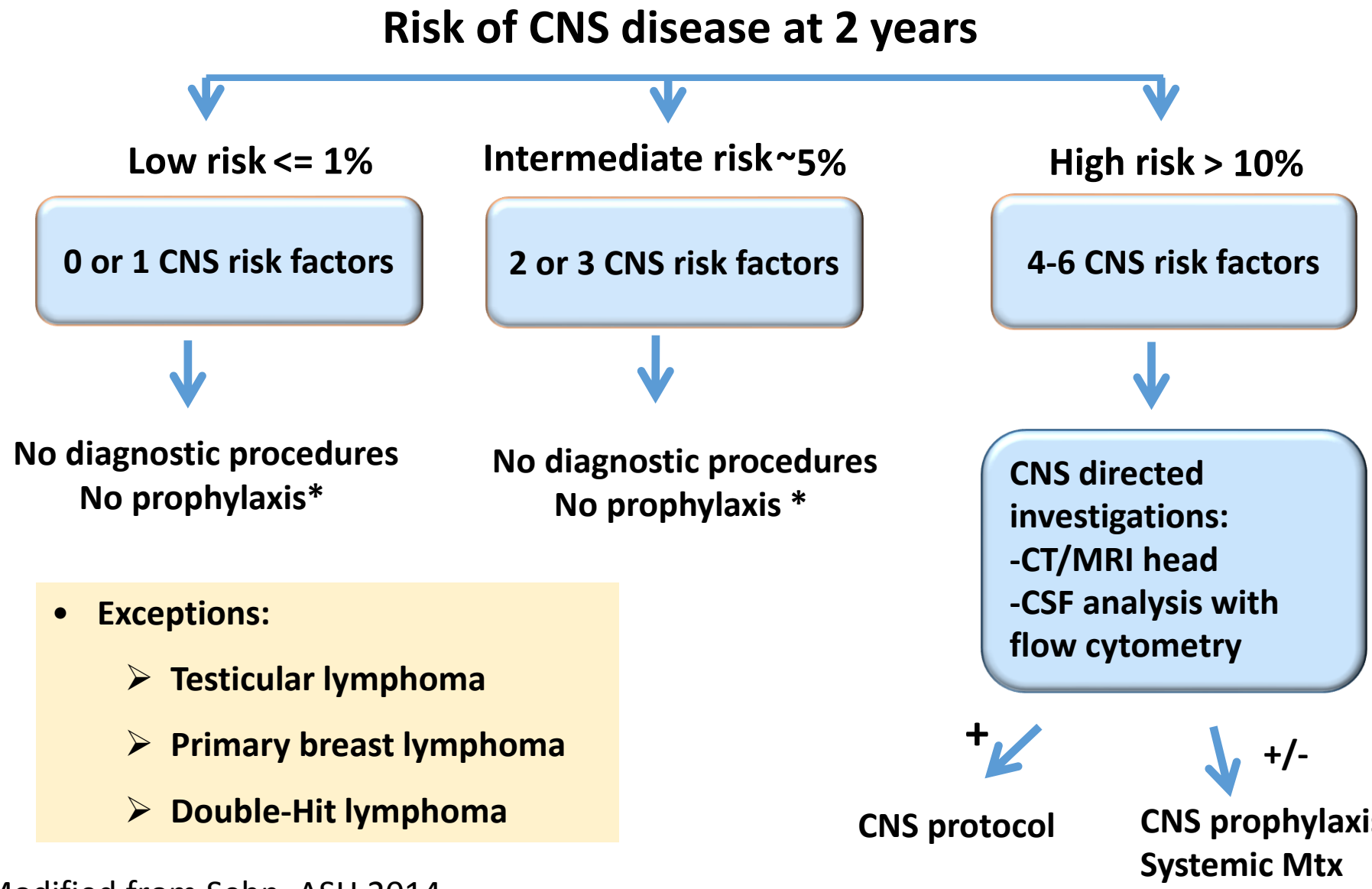
FACTORS
Age > 60
Stage 3 / 4
High LDH
ECOG 2+
2+ extranodal
Kidney / Adrenal



Schmitz, ICML 2013

Sehn, ASH 2014

IPI-Based Risk Score and Management

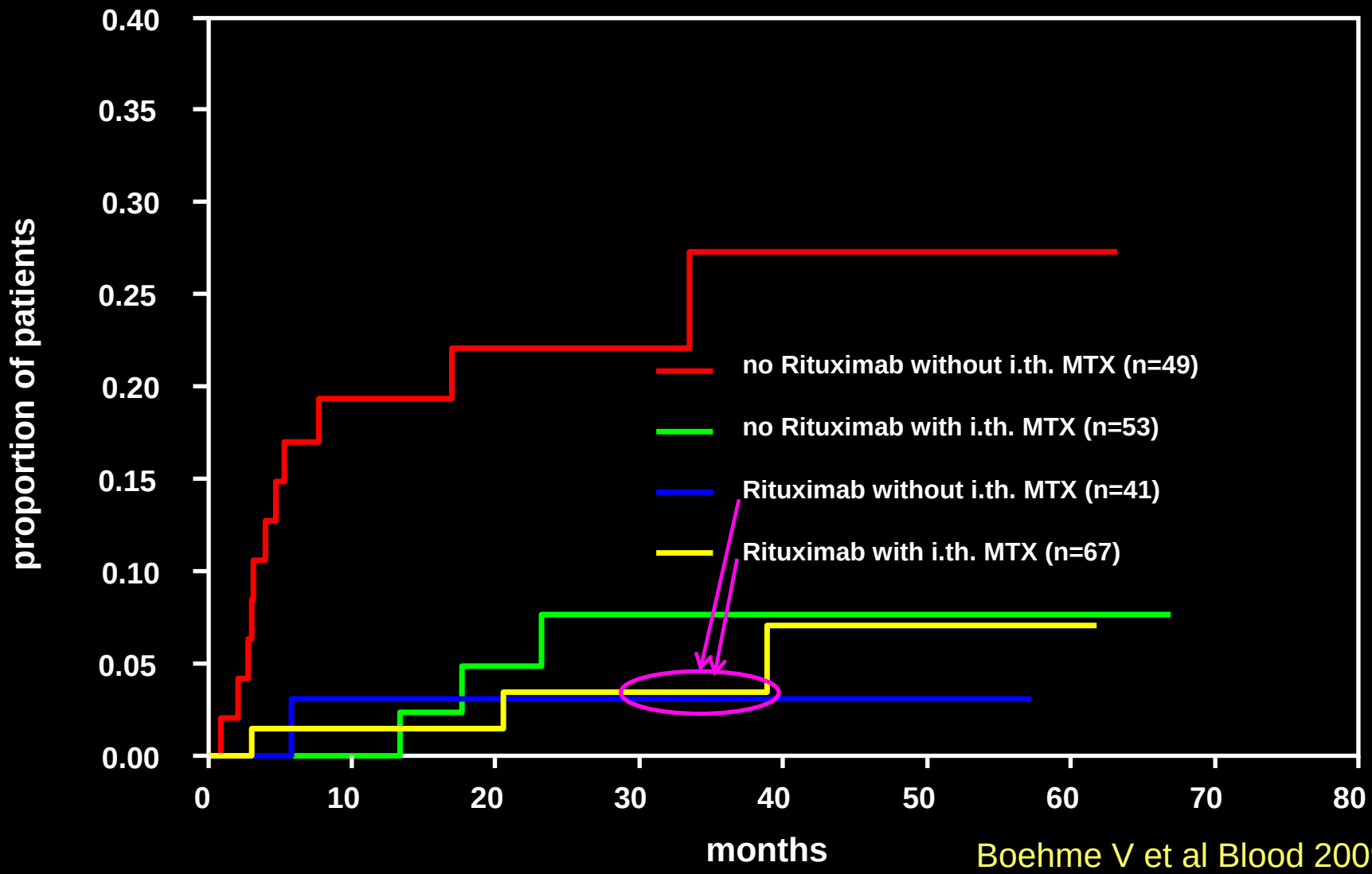


- **Exceptions:**
  - **Testicular lymphoma**
  - **Primary breast lymphoma**
  - **Double-Hit lymphoma**

Modified from Sehn, ASH 2014

CNS events in the RICOVER-60 trial

"high-risk" patients with/without i.th. MTX and with/without Rituximab



Boehme V et al Blood 2009

ESMO Guidelines on CNS Prophylaxis

- Intrathecal injections are not optimal
- Intravenous methotrexate reported to be efficient in preventing CNS relapse, and is preferred (IV, C)

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High Dose IV Methotrexate

- ≥3g/m^2 iv over 2 to 3 hours to maximise peak
- In reality: limited by age and renal function
- In Australia: ≥1g/m^2 (eg hyper-CVAD) considered adequate

Joerger and Ferreri Leuk& Lymph 2012

Treatment of Secondary Central Nervous System Lymphoma with Intrathecal Rituximab, High Dose Methotrexate and R-DHAP, Followed by Autologous Stem Cell Transplantation. A Phase II HOVON Study

ASH 2012: Abstract 306

15 of 34 patients completed treatment per protocol

1 year PFS = 21% (OS 22%)

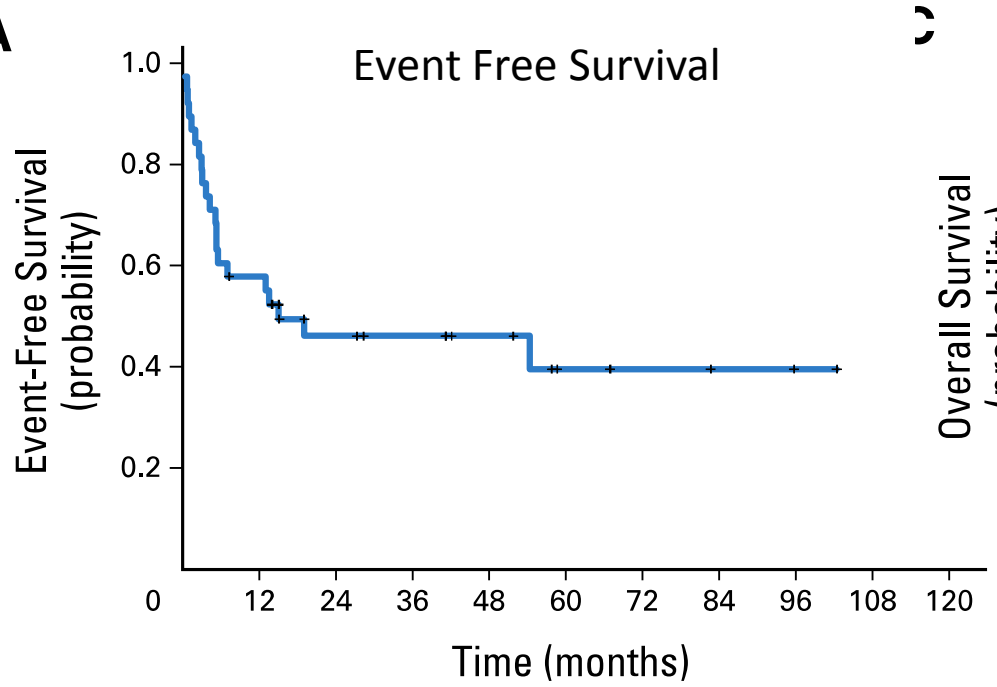
Italian Phase II Protocol (JCO 2015)

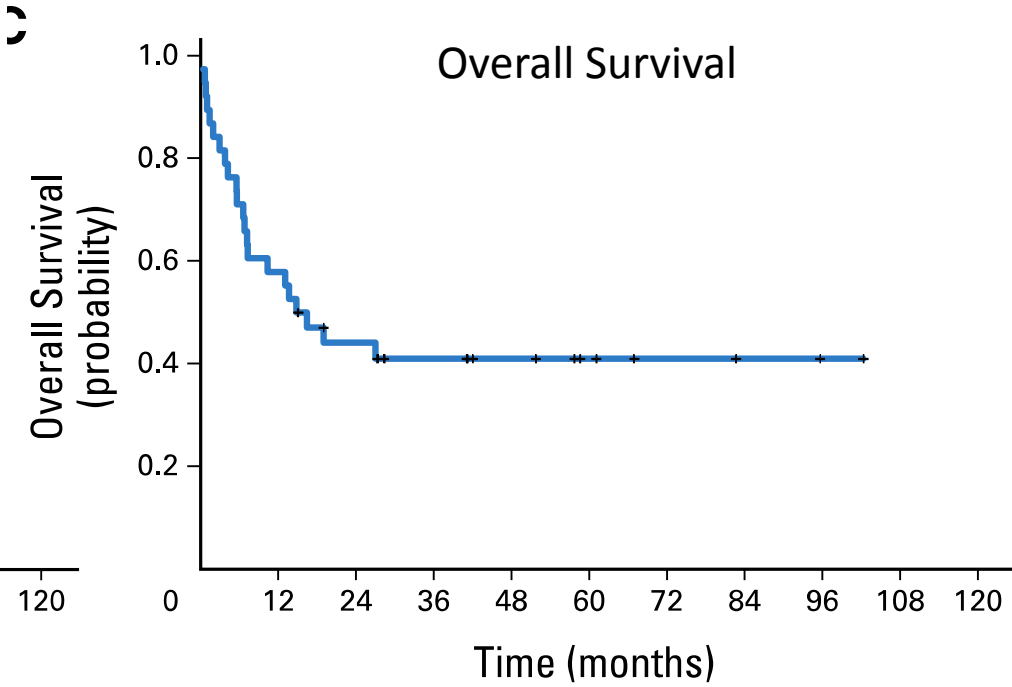
Regimen	Drug	Dose	Route
Debulking prephase			
Day 1	Rituximab	375 mg/m^2	Conventional infusion
Day 1	Cyclophosphamide	750 mg/m^2	IV bolus
Day 1	Doxorubicin	50 mg/m^2	IV bolus
Day 1	Vincristine	2 mg/dose	IV bolus
Days 1 to 5	Prednisone	45 mg/m^2 per day	Oral route
Induction phase*			
Day 1	Methotrexate	3.5 g/m^2	15-minute bolus + 3-hour infusion
Days 2 and 3	Cytarabine	2 g/m^2	Every 12 hours, 3-hour infusion
Days 3 and 11	Rituximab	375 mg/m^2	Conventional infusion
Day 6	Liposomal cytarabine	50 mg	Intrathecal route
Intensification phase†			
High-dose cyclophosphamide			
Day 1	Cyclophosphamide	7 g/m^2	4-hour infusion + mesna
Days 3 and 11	Rituximab	375 mg/m^2	Conventional infusion
Day 6	Liposomal cytarabine	50 mg	Intrathecal route
High-dose cytarabine‡			
Days 1 to 4	Cytarabine	2 g/m^2	Every 12 hours, 3-hour infusion
Days 5 and 12	Rituximab	375 mg/m^2	Conventional infusion
Day 5	Reinfusion of 1.5×10^6 CD34$^+$ cells/kg		
High-dose etoposide			
Day 1	Etoposide	2 g/m^2	6-hour infusion
Day 4	Liposomal cytarabine	50 mg	Intrathecal route
Consolidation phase: conditioning and autotransplantation			
Day −6	BCNU	400 mg/m^2	1-hour infusion
Days −5 and −4	Thiotepa	5 mg/kg	2-hour infusion
Day 0	Reinfusion of $\geq 5 \times 10^6$ CD34$^+$ cells/kg		

Ferreri, JCO 2015

Secondary CNS Involvement is Salvageable

Of 38 patients, 28 responded to induction, and 20 were autografted





Ferreri, JCO 2015

Conclusions

- How to assess CNS risk
  - 5 IPI Factors + Adrenal / Kidney
  - Exceptions: testicular, breast, double-hit
- What CNS prophylaxis is ideal
  - Limited effect of intrathecal injections
  - High-dose iv methotrexate
- How to treat CNS relapse
  - Anti-metabolite based salvage
  - Thiotepa based autograft