# Mitä uutta lymfoomien hoitokäytännöissä?

S. Jyrkkiö, TYKS

Onkologiapäivät 30.8.13

# Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

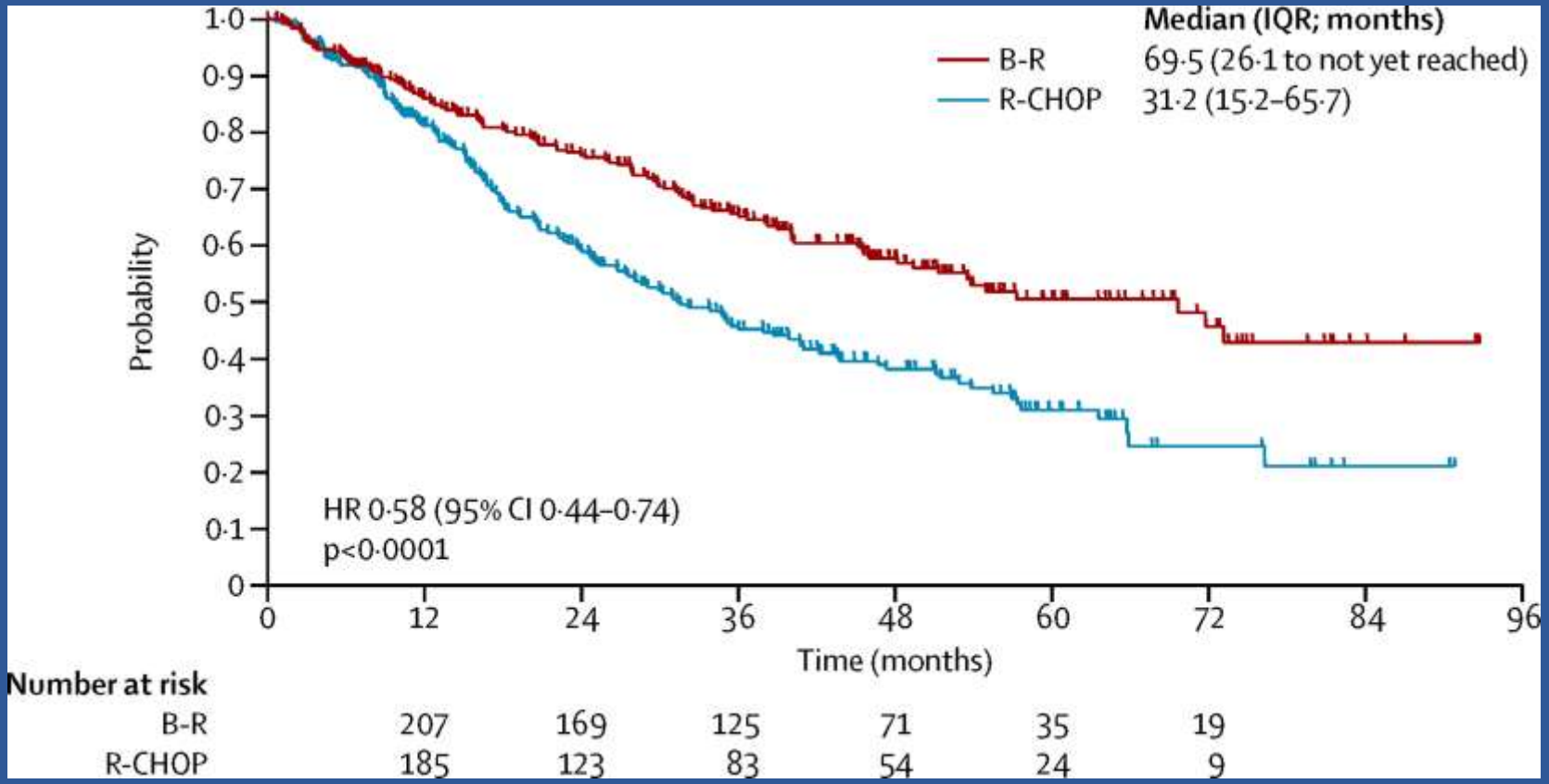
*Mathias J Rummel, Norbert Niederle, Georg Maschmeyer, G Andre Banat, Ulrich von Grünhagen, Christoph Losem, Dorothea Kofahl-Krause, Gerhard Heil, Manfred Welslau, Christina Balser, Ulrich Kaiser, Eckhart Weidmann, Heinz Dürk, Harald Ballo, Martina Stauch, Fritz Roller, Juergen Barth, Dieter Hoelzer, Axel Hinke, Wolfram Brugger, on behalf of the Study group indolent Lymphomas (StiL)*

Lancet 2013; 381: 1203–10

Published Online
February 20, 2013
http://dx.doi.org/10.1016/S0140-6736(12)61763-2

- N=549
- FU 45 kk
- PFS 69 vs 31 kk

| | R-B | R-CHOP |
|---|---|---|
| Alopecia | 0 % | 100 % |
| Hematol toksisuus | 30 | 68 |
| Infektiot | 37 | 50 |
| Neuropatia | 7 | 29 |
| Stomatiitti | 6 | 19 |
| Eryteema | 16 | 9 |




Progression-free survival

*Rummel et al. The Lancet Volume 381, 2013:1203 - 1210*

# Ylläpito R R-B:n jälkeen?

- MAINTAIN-tutkimuksessa ensin 6 x R-B, sitten => **R 2 kk välein 2 vs 4 vuotta**
- N=947, 6 x R-B
  - Lymfosyytit 1500 => 500 /µl
  - CD4 555 => 118
  - CD8 316 => 198
  - IgG 8,65 => 7,51 g/l
  - IgM 0,76 => 0,42
  - 17 infektiokuolemaa (1,4 %) (9 sepsistä, 4 PML, 3 pneumoniaa, 1 akt hepatiitti B)

*Abstr. #32 ICML, Lugano, June 19-22,2013*

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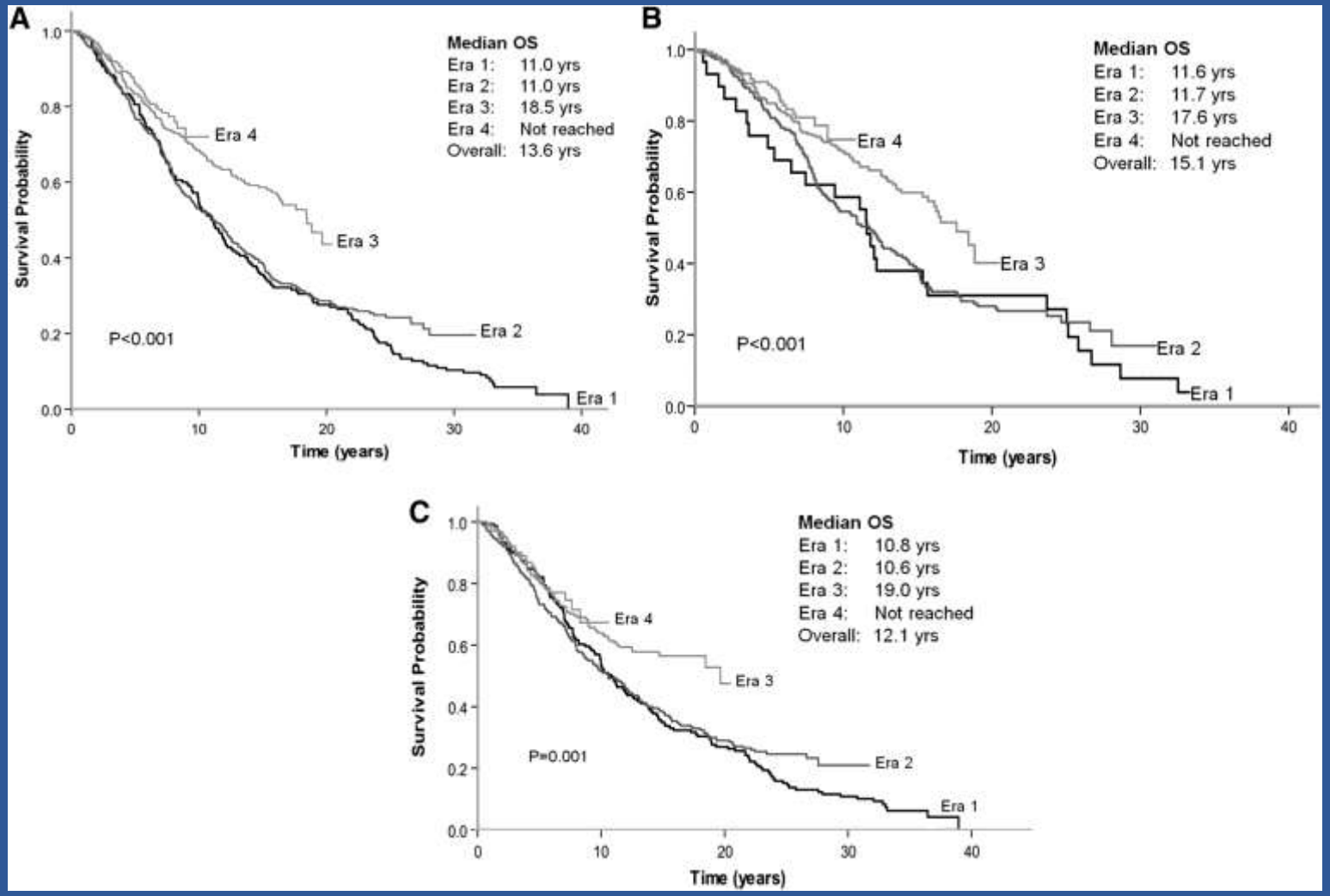
# Onko FL ennuste parantunut?

**A. All pts B. No initial therapy C. Pts receiving initial therapy**




1. 60-75
2. 76-86
3. 87-96
4. 97-03

*Tan D et al. Blood 2013;122:981-987*

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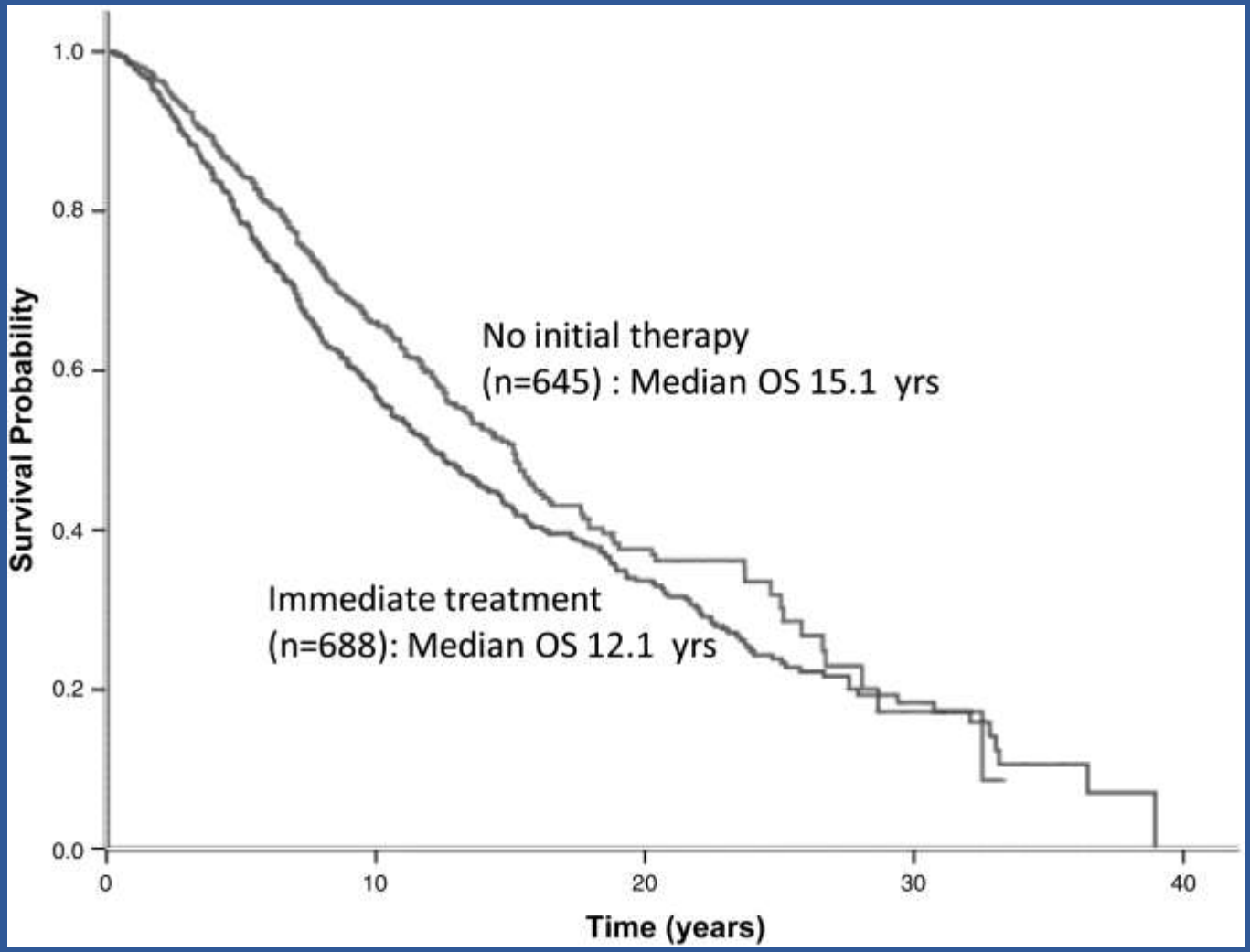
# Seuranta vai heti hoitoon?




*Tan D et al. Blood 2013;122:981-987*

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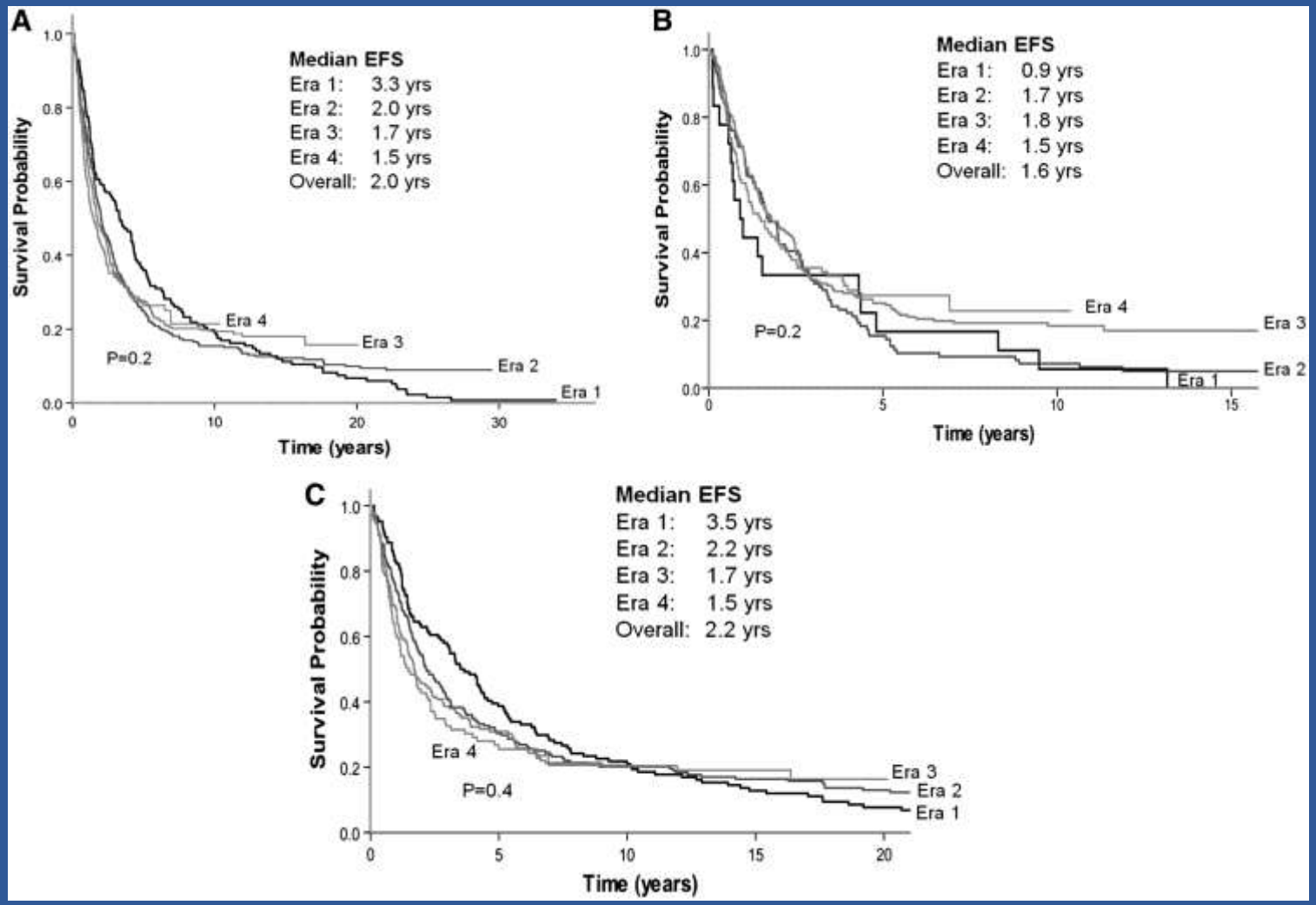
# EFS after first treatment course by era of diagnosis.

## A. All pts B. No initial therapy C. Pts receiving initial therapy




*Tan D et al. Blood 2013;122:981-987*

# Vai pitääkö alkaa hoitaa heti??

- N=631 FL prospektiivinen seuranta (dg:t v. 02-09)
- FU 60 kk
- Transformaatioita 10,7 % 5 v kuluessa => 2%/v
- Kohonnut LD korreloi transformaatioriskiin
- Korkein transformaatioriski niillä, joita aluksi vain seurattiin 14,4 % vs R-hoidetut 3,2 %
- Jos transformaatio > 18 kk dg:sta, OS parempi (5 v OS 66 vs 22 %)

*Link et al. J Clin Oncol 2013, prepub July 29*

# Brentuximab vedotin

## NPP experiences

- Indikaatio: refraktaari HL tai relapsi ASCT:n jälkeen
- Responssit 3-4 kuurin jälkeen

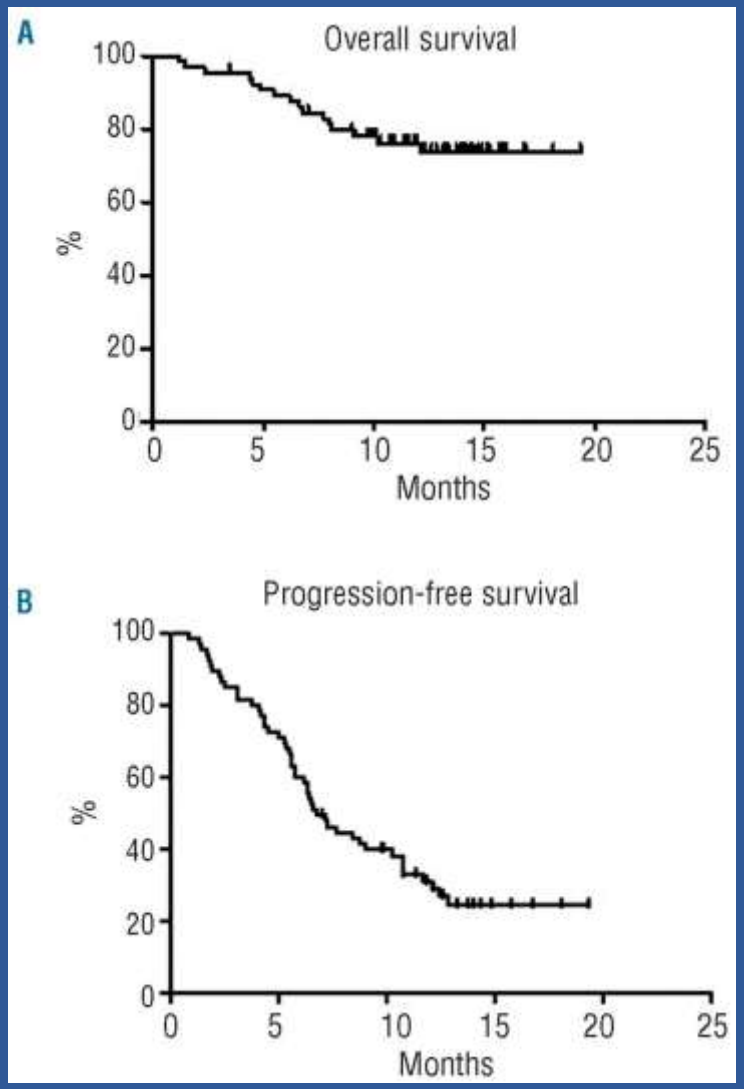
| Study | N. pts | ORR% | CR% |
|---|---|---|---|
| Pivotal[11] | 102 | 73 | 32 |
| German NPP[14] | 45 | 60 | 22 |
| UK NPP[15] | 18 | 72 | 17 |
| Italian NPP | 65 | 70.7 | 21.5 |

*NPP: Named Patient Program; pts: patients; ORR, overall response rate; CR: complete response.*

- Neuropatia: 21 %

*Zinzani et al. Haematologica 2013;98:1232*

# (A) Overall survival and (B) progression-free survival.




*Zinzani P L et al. Haematologica 2013;98:1232-1236*

# Treatment for early-stage Hodgkin lymphoma: has radiotherapy had its day?

Radford J. J Clin Oncol 2012;30:3783-3785

Illidge T. Hematol Oncol 2013;31 (s.1):92-95

# Onko pelkkä ABVD riittävä hoito?

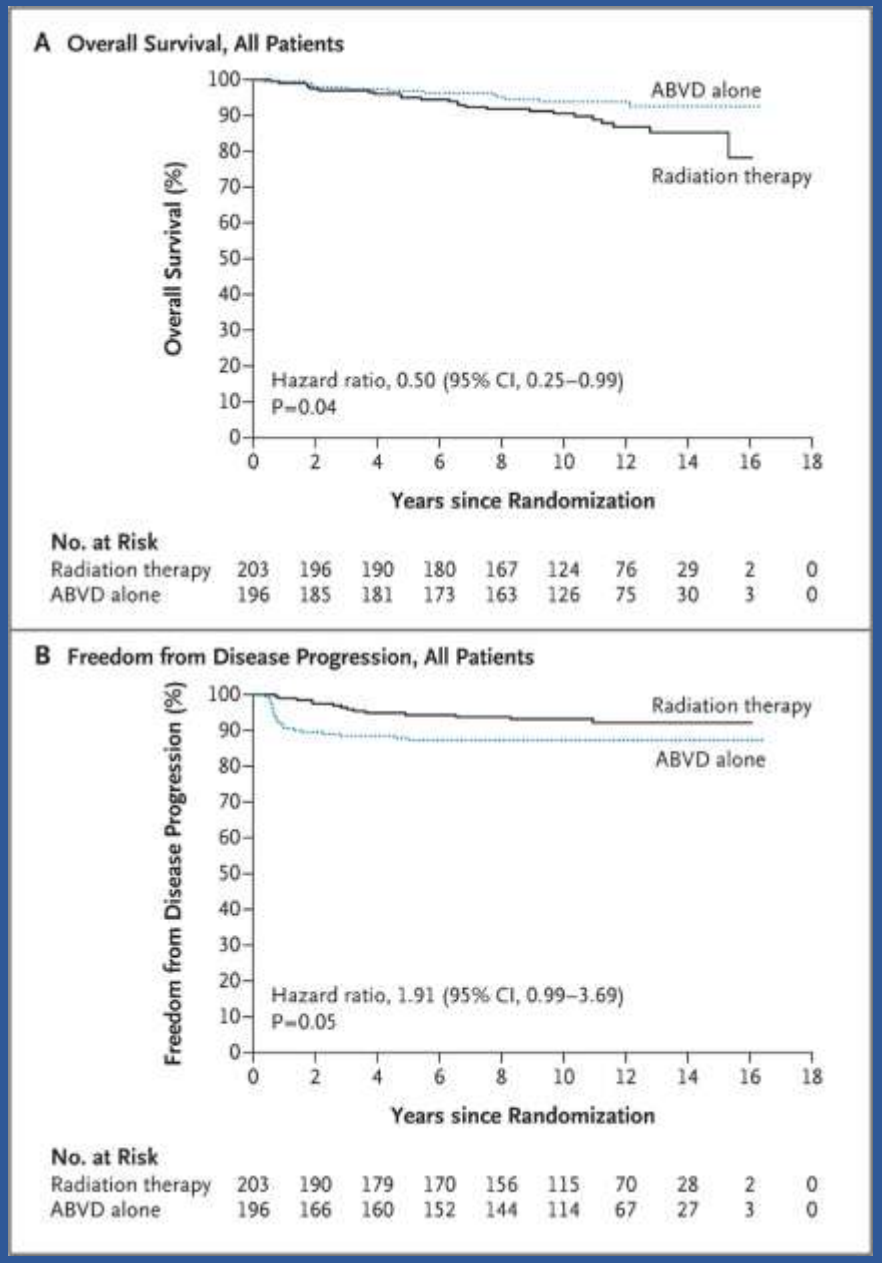
- N=405
- STI-IIA non-bulky HL
- ABVDx4-6 vs RT or ABVDx2 + RT

**Kritiikkiä:**
Manttelisädehoito 35 Gy

| | CT | CT+RT |
|---|---|---|
| Kuolemat | 12 | 24 |
| HL tai tox | 6 | 4 |
| Muu syy | 6* | 20 ** |

*4 toinen ca, 2 sydän
** 10 toinen ca, 2 sydän, 3 infektiota, **5 muuta (mitä??)**

*Meyer et al. NEJM 2012;366:399-408*



# Hodgkinin lymfooman hoitosuositus

- STIA-IIA ilman riskitekijöitä ABVDx2 + RT 20 gy
- STI-II riskitekijät +  ABVDx4 + RT 30 Gy
- ST>IIA ABVD x 6-8

**Saksan lymfoomaryhmän HL ST I-II riskitekijät**

- Bulk tuumori (> 0.33 thoraxin leveydestä)
- Perna-affisio
- Ekstranodaaliaffisio
- La > 50 mm/t tai B-oireet ja La >30 mm/t
- > 2 affisoitunutta imusolmukealuetta

ARTICLE IN PRESS

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Critical Review

# Modern Radiation Therapy for Hodgkin Lymphoma: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group (ILROG)

Lena Specht, MD, PhD,* Joachim Yahalom, MD,† Tim Illidge, MD, PhD,‡ Anne Kiil Berthelsen, MD,§ Louis S. Constine, MD,|| Hans Theodor Eich, MD, PhD,¶ Theodore Girinsky, MD,# Richard T. Hoppe, MD,** Peter Mauch, MD,†† N. George Mikhaeel, MD,‡‡ and Andrea Ng, MD, MPH††, on behalf of ILROG

# Involved site radiation therapy

- Huomioidaan prim tuumori ja jätetuumori
- Marg 5-15 mm
- Minimoidaan norm kudosten sädehoitamista

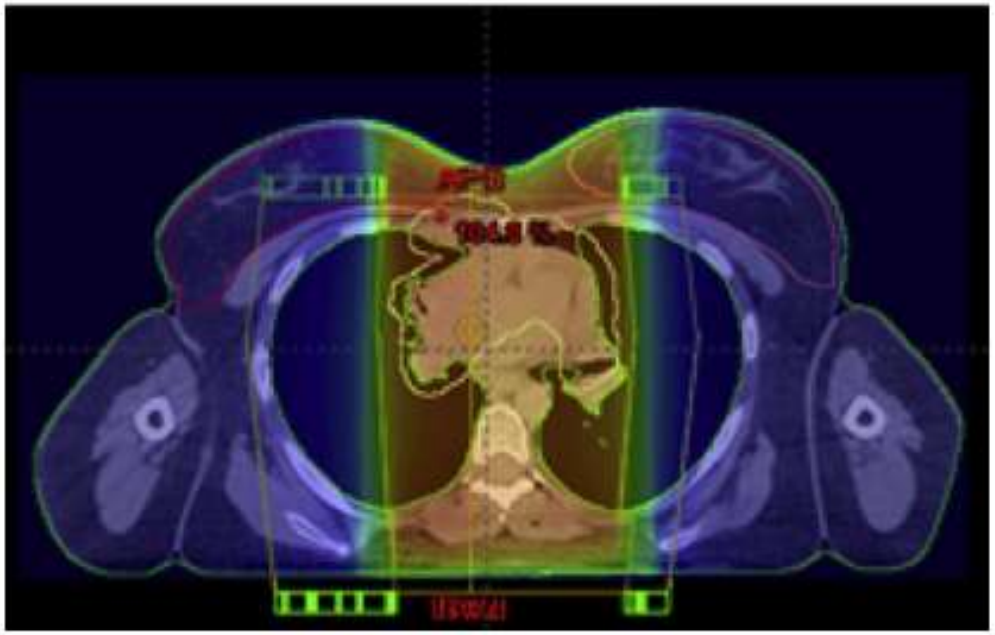


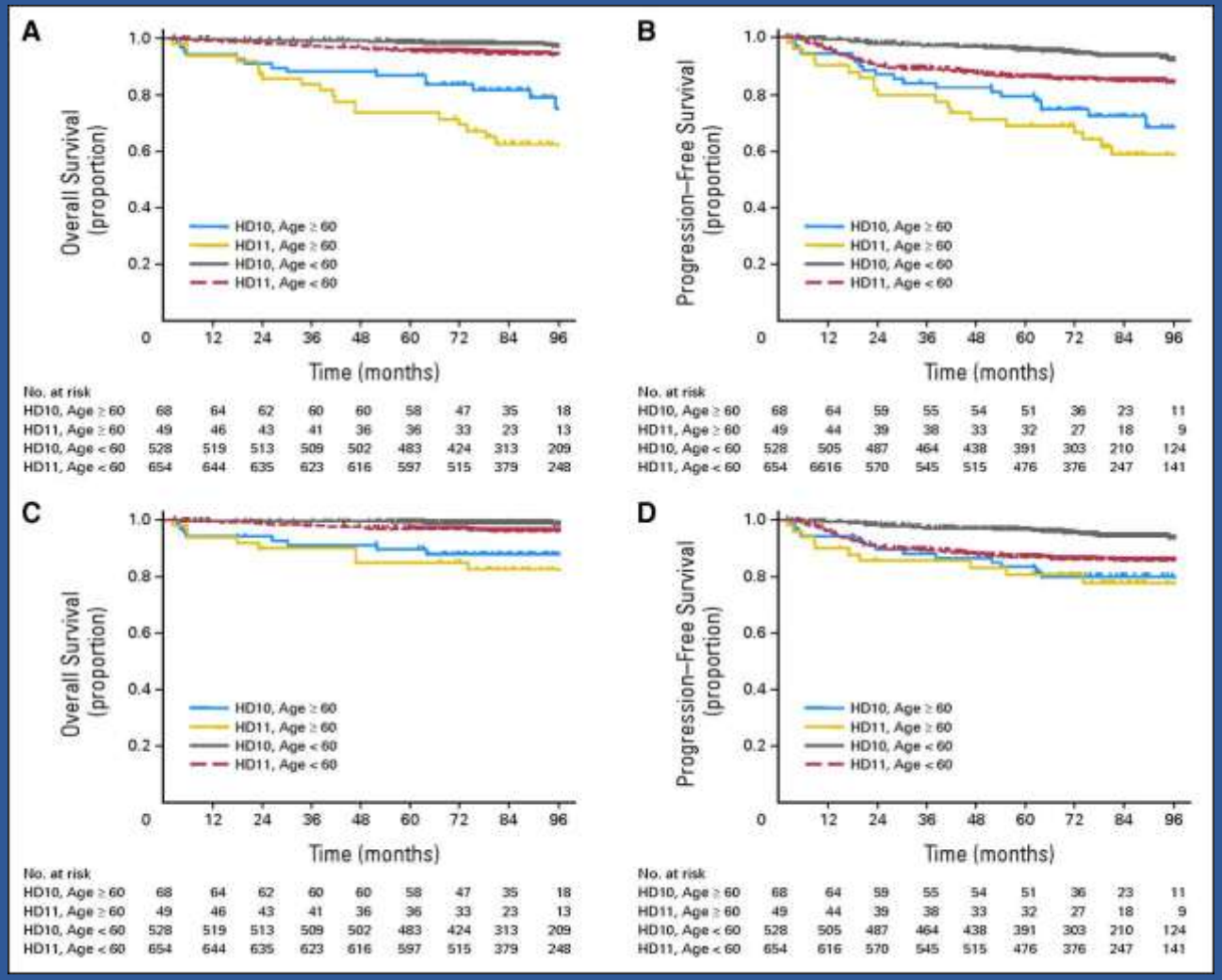
**Fig. 2.** Involved site radiation therapy with anteroposterior-posteroanterior technique, field (*above*) and dose distribution (*below*).

# Iäkkään potilaan HL

- STI-II HD10 ja HD11 trialit
- N=1299, > 60 v N=117
- > 60 vuotiailla:
  - Aggressiivisempi HL
  - Hoidon annosintensiteetti huonompi
  - G3-4 toksisuus 68 %; TRM 5 %
  - CR 89 % vs 96 %
  - 5 v OS 90 vs 97 %

*Böll ym. J Clin Oncol 2013;31:1522-9*

**Kaplan-Meier plots of (A) overall survival, (B) progression-free survival, (C) time to HL-related death, and (D) time to HL-related failure according to stage and age group.**




**Böll B et al. JCO 2013;31:1522-1529**

# Iäkkään potilaan HL

- Iäkkäille tarvitaan uusia tutkimuksia/hoito-ohjelmia
- Hoidon toksisuutta pitäisi keventää
- Prognostinen tekijä ”loss of activity in daily living”
- NLG protokolla tulossa

bjh state of the art review

# Modern management of lymphocyte predominant Hodgkin lymphoma

Katharine H. Xing[1] and Kerry J. Savage[1,2]

[1]Department of Medical Oncology, British Columbia Cancer Agency, and [2]Centre for Lymphoid Cancer, British Columbia Cancer Agency, Vancouver, BC, Canada

- ST IA RT / WW postoper
- ST > I => kuten klassinen HL, lapsilla ilman RT
- CD20 + => R voi käyttää
- 20-25 % advanced disease, ABVD/RCHOP?
- ASCT asema epäselvä

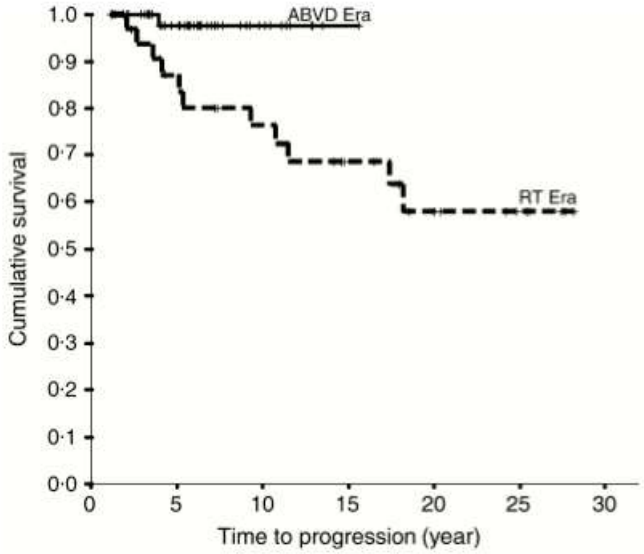


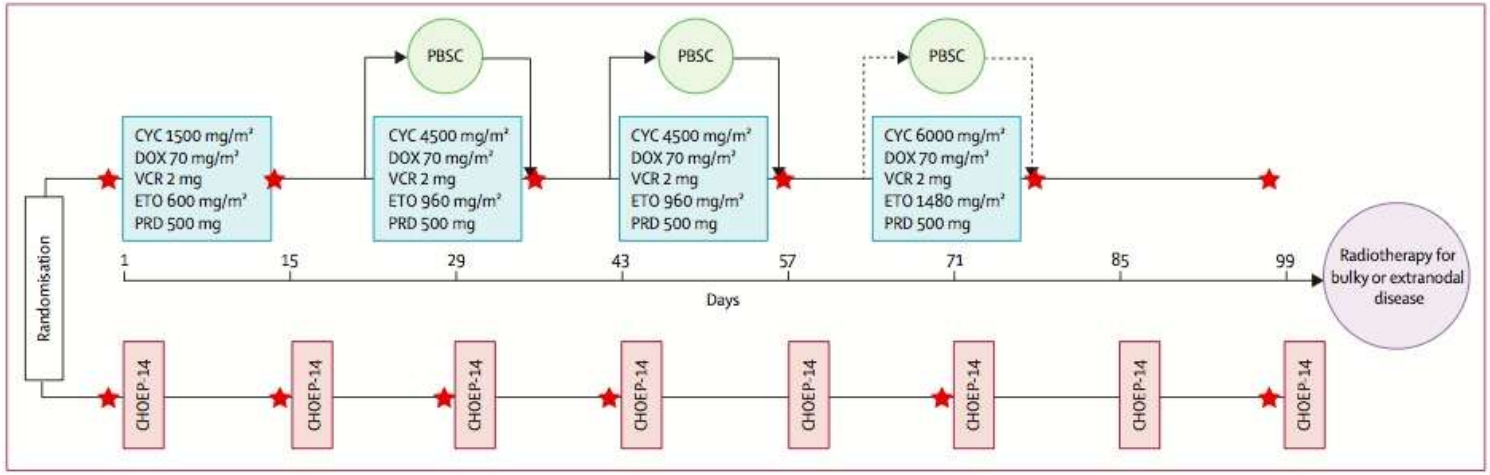

Fig 2. Era to era comparison of TTP of limited stage NLPHL treated with RT or ABVD +/− RT. This research was original published in *Blood*. Savage *et al* (2011). ©American Society of Hematology. Reproduced with permission. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; RT, radiotherapy.

*BJH 2013;161:316-329*

# DLBCL:
# ONKO ANNOSINTENSITEETILLÄ MERKITYSTÄ?

# Conventional chemotherapy (CHOEP-14) with rituximab or high-dose chemotherapy (MegaCHOEP) with rituximab for young, high-risk patients with aggressive B-cell lymphoma: an open-label, randomised, phase 3 trial (DSHNHL 2002-1)

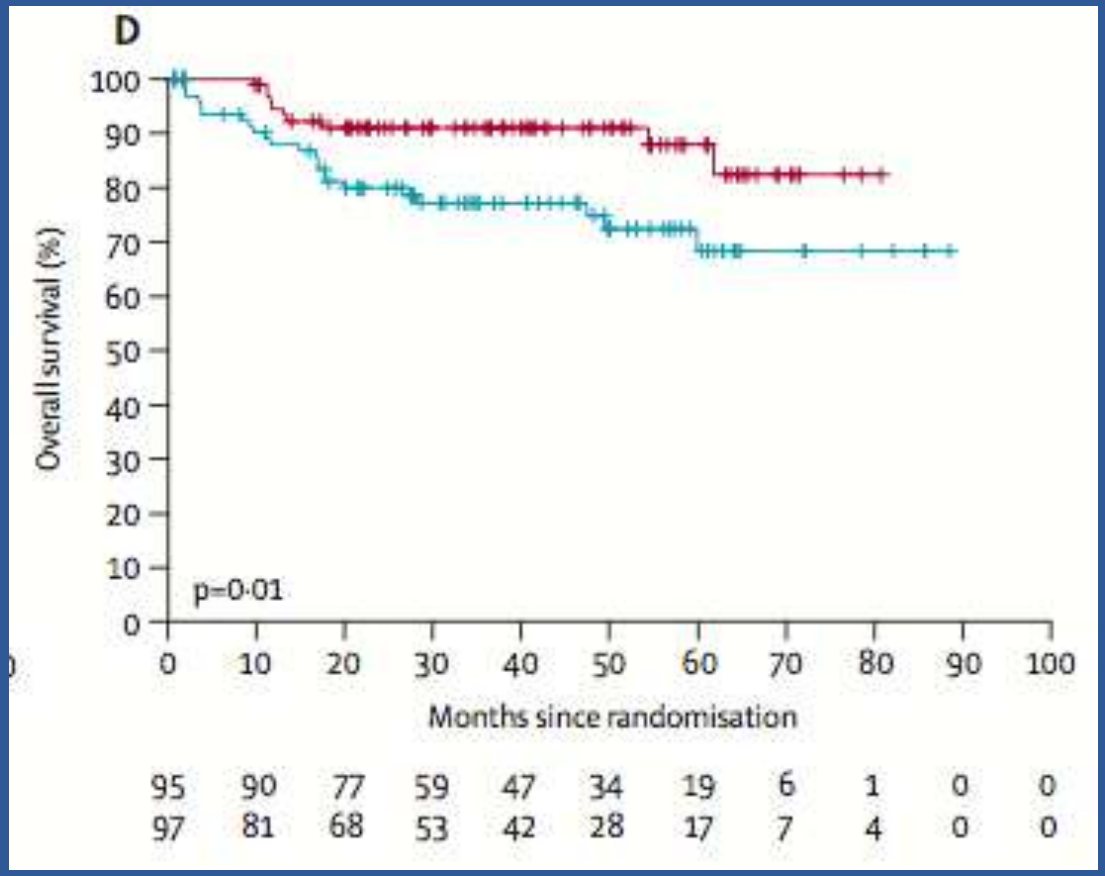
*Norbert Schmitz, Maike Nickelsen, Marita Ziepert, Mathias Haenel, Peter Borchmann, Christian Schmidt, Andreas Viardot, Martin Bentz, Norma Peter, Gerhard Ehninger, Gottfried Doelken, Christian Ruebe, Lorenz Truemper, Andreas Rosenwald, Michael Pfreundschuh, Markus Loeffler*, Bertram Glass*, for the German High-Grade Lymphoma Study Group (DSHNHL)†*




Lancet Oncol 2012; 13: 1250–59

aaIPI 2-3
Rituksimabi ★

# Raskas hoito, huonompi hoitotulos




R-CHOEP-14
R-MegaCHOEP

# Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial

*Richard Delarue, Hervé Tilly, Nicolas Mounier, Tony Petrella, Gilles Salles, Catherine Thieblemont, Serge Bologna, Hervé Ghesquières, Maya Hacini, Christophe Fruchart, Loïc Ysebaert, Christophe Fermé, Olivier Casasnovas, Achiel Van Hoof, Antoine Thyss, Alain Delmer, Olivier Fitoussi, Thierry Jo Molina, Corinne Haioun, André Bosly*

| | R-CHOP14 (n=106) | R-CHOP21 (n=109) |
|---|---|---|
| Lymphoma | 54 (51%) | 57 (52%) |
| Toxic effects of study treatment | 14 (13%) | 14 (13%) |
| Concurrent illness | 20 (19%) | 13 (12%) |
| Other cancer | 9 (8%) | 14 (13%) |
| Toxic effects of additional treatment | 2 (2%) | 5 (5%) |
| Other reason, or reason unknown | 7 (7%) | 6 (6%) |

*Table 5:* **Causes of death**

*Lancet Oncol* 2013; 14: 525–33

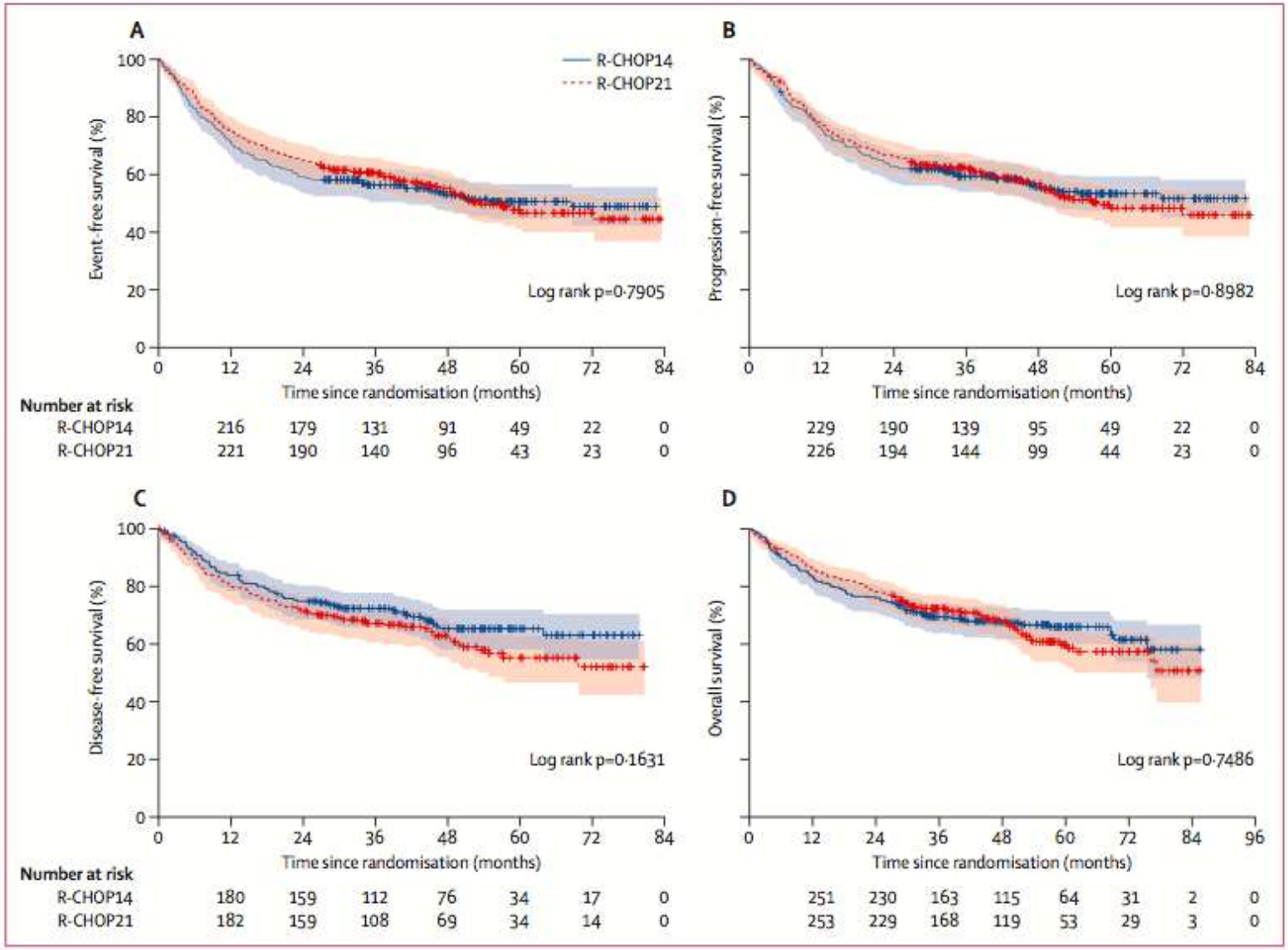



***Figure 2:*** **Survival endpoints**
(A) Event-free survival. (B) Progression-free survival. (C) Disease-free survival. (D) Overall survival. Shaded areas show 95% CIs.

# DLBCL: TARVITAANKO SÄDEHOITOA?

# Unfolder Study

- IPI 1 or IPI 0 with bulk ≥ 7,5 cm, ST I-IV
- Age 18-60 y

  - RCHOP21x6 => CR => +/- RT (bulk or extranodal)
  - RCHOP14x6 => CR => +/- RT (bulk or extranodal)

- Interim analysis, unpublished, suggested better OS with RT. **Treatment arm without RT prematurely closed.**
- Estimated primary completion date April 2015
- Target N=1072

*www.lymphome.de*

Clinical Investigation: Lymphoma

# Patterns of Failure in Advanced Stage Diffuse Large B-Cell Lymphoma Patients After Complete Response to R-CHOP Immunochemotherapy and the Emerging Role of Consolidative Radiation Therapy

Zheng Shi, MD, PhD,*,† Satya Das, BA,‡ Derick Okwan-Duodu, PhD,‡ Natia Esiashvili, MD,*,† Christopher Flowers, MD,†,§ Zhengjia Chen, PhD,†,‖ Xiaojing Wang, MPH,†,‖ Kun Jiang, MD, PhD,¶ Loretta J. Nastoupil, MD,†,§ and Mohammad K. Khan, MD, PhD*,†

International Journal of Radiation Oncology biology • physics

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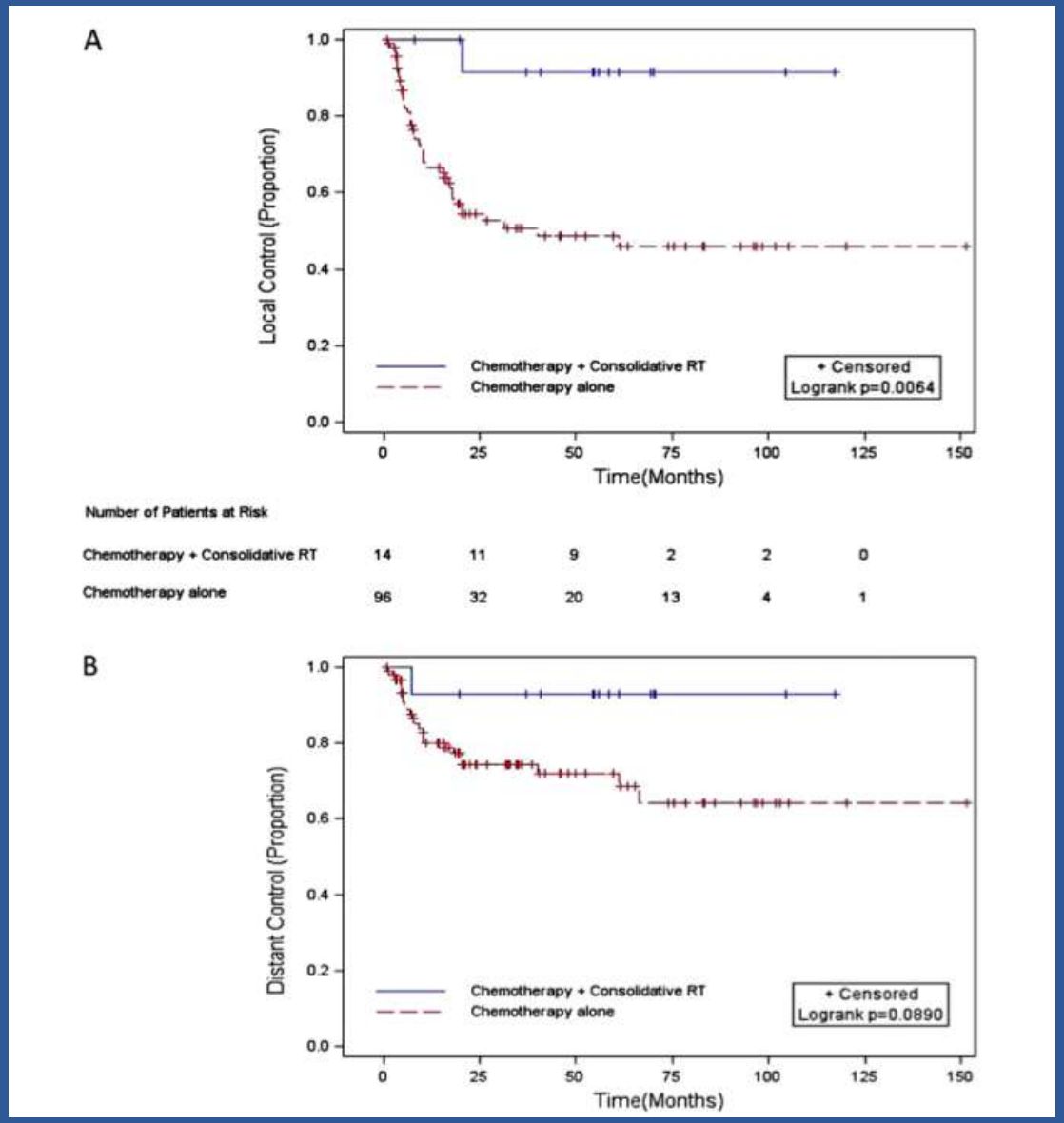
- Sädehoidon asema ST III-IV DLBCL hoidossa epäselvä
- Yhden keskuksen kokemus N=163
- RCHOPx6 => CR 67 % (N=110)
- Sädehoitoa annettiin näistä 14 potilaalle
- FU 33 kk
- Vain RCHOP => lokaali resid 44 %
- + RT => 7 %

Int J Radiation Oncol Biol Phys, Vol. 86, No. 3, pp. 569–577, 2013
0360-3016/$ - see front matter 
http://dx.doi.org/10.1016/j.ijrobp.2013.02.007

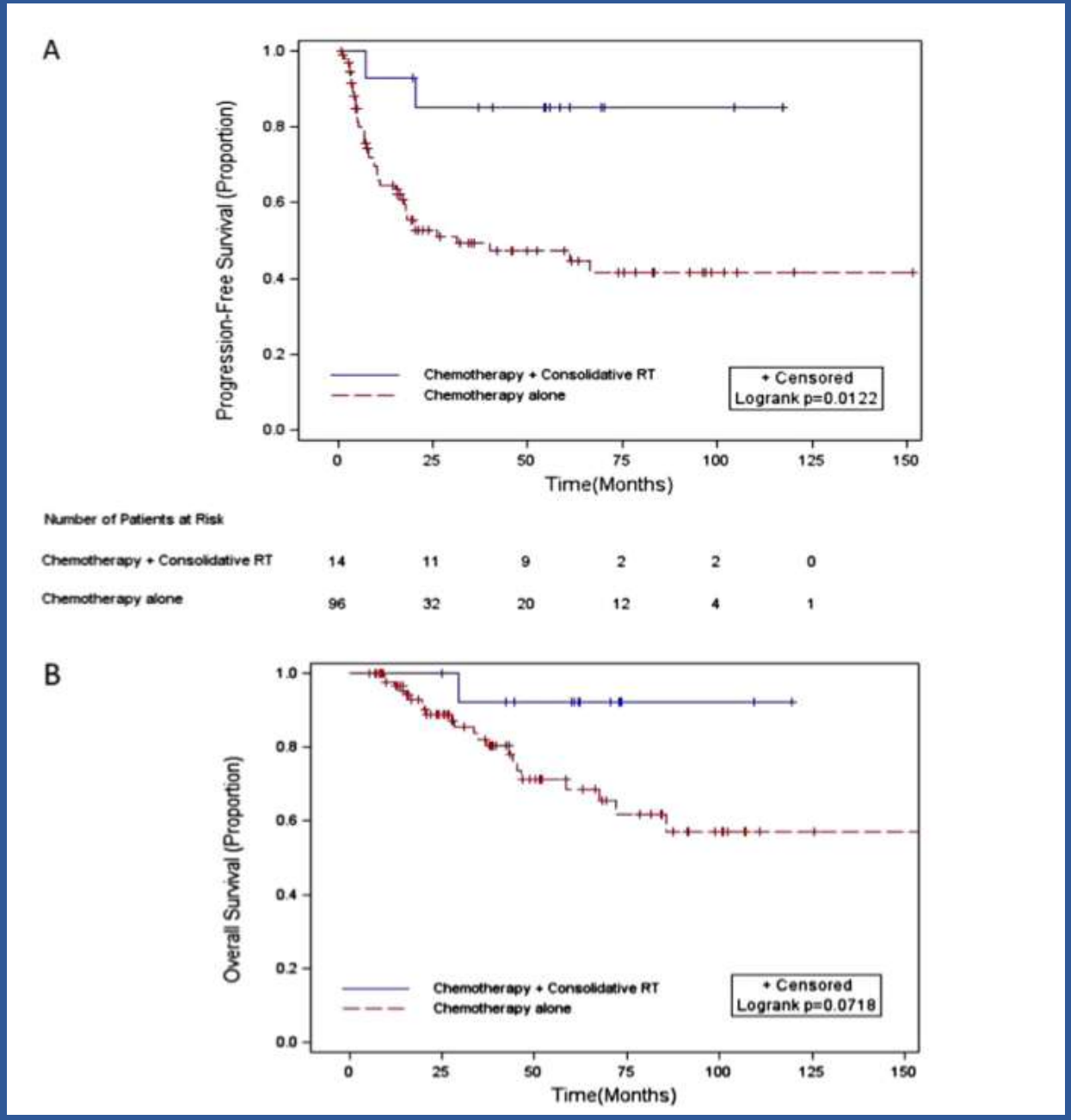
Lokaali kontrolli

Uusi tautipaikka



PFS

OS


A
Progression-Free Survival (Proportion)
1.0
0.8
0.6
0.4
0.2
0.0
Chemotherapy + Consolidative RT
Chemotherapy alone
+ Censored
Logrank p=0.0122
0
25
50
75
100
125
150
Time(Months)
Number of Patients at Risk
Chemotherapy + Consolidative RT 14 11 9 2 2 0
Chemotherapy alone 96 32 20 12 4 1
B
Overall Survival (Proportion)
1.0
0.8
0.6
0.4
0.2
0.0
Chemotherapy + Consolidative RT
Chemotherapy alone
+ Censored
Logrank p=0.0718
0
25
50
75
100
125
150
Time(Months)

# Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma

- N=51
- Faasi II
- Ikä 19-52 v
- FU 63 kk
- EFS 93 %
- OS 97 %
- Kaksi progredioi seuranta-aikana
- Ei sydänongelmia

*Dunleavy ym. NEJM 2013;368:1408-16*

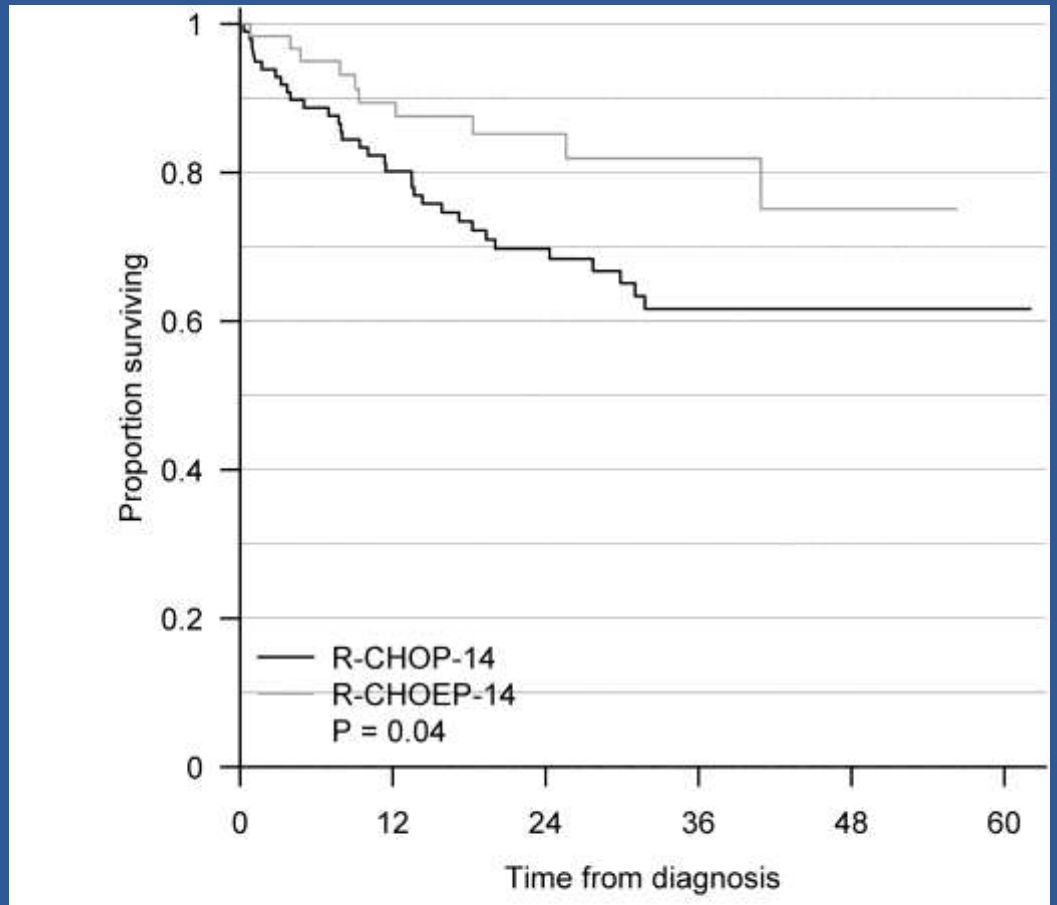
# DA-EPOCH

1. Etoposide 50 mg/m$^2$/day CIV 1, 2, 3, 4 (96 h)
2. Doxorubicin 10 mg/m$^2$/day CIV 1, 2, 3, 4 (96 h)
3. Vincristine 0.4 mg/m$^2$/day CIV 1, 2, 3, 4 (96 h)
4. Cyclophosphamide 750 mg/m$^2$/day IV day 5
5. Prednisone 60 mg/m$^2$/bid Oral day 1, 2, 3, 4, 5

Annostaso riippuu nadir-arvoista. Sykli 21 vrk

***Wilson W ym. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. Blood 2002;99;2685-93.***

## Overall survival (Kaplan–Meier plot) for the 159 patients assigned to chemotherapy with R-CHOP-14 or R-CHOEP-14.




| Number at risk | | | | | | |
|---|---|---|---|---|---|---|
| R-CHOP-14 | 98 | 75 | 52 | 27 | 12 | 4 |
| R-CHOEP-14 | 61 | 48 | 27 | 14 | 3 | 0 |

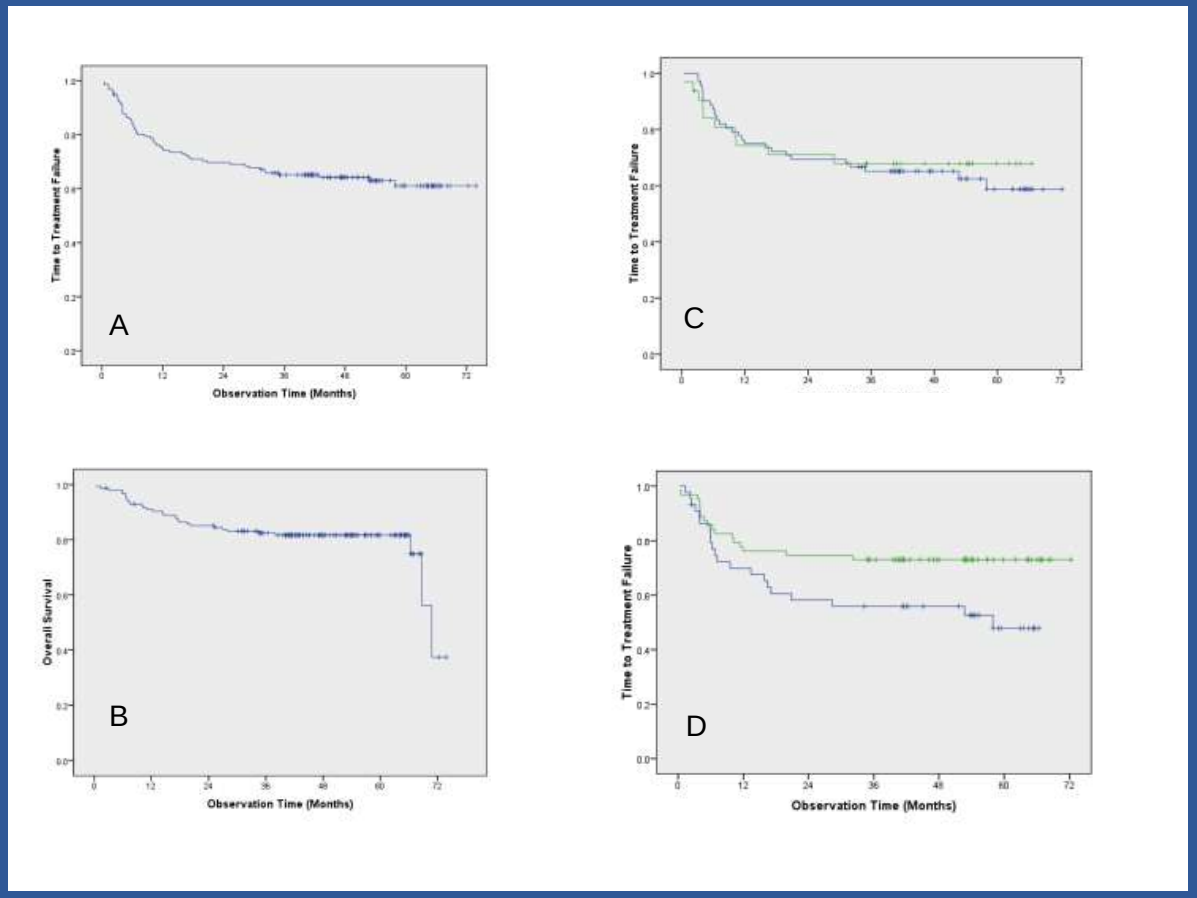
**Gang A O et al. Ann Oncol 2012;23:147-153**



Annals of Oncology

# R-CHOEP-14 x 6 Followed by Systemic CNS Prophylaxis for Patient less than 65 years with Diffuse Large B-Cell Lymphoma /Follicular Lymphoma Grade 3 with Age Adjusted IPI Score 2-3. Holte H et al. Ann Oncol 2013.

1 A. Time to treatment failure, 1B. Overall survival,. 1C. Effect of % positive Ki67 tumor cells on Time to Treatment Failure. Green line: Ki67 like or above median, n = 63, blue line: Ki67 below median value, n = 44. P = 0.035. Figure 1D. Effect of immunohistochemically defined DLBCL subgroup on Time to Treatment Failure. Green line: non-GC phenotype, n = 32, blue line: GC phenotype, n = 72. P = 0.753



# Kiitos!