UNIVERSITY OF HELSINKI

HUS

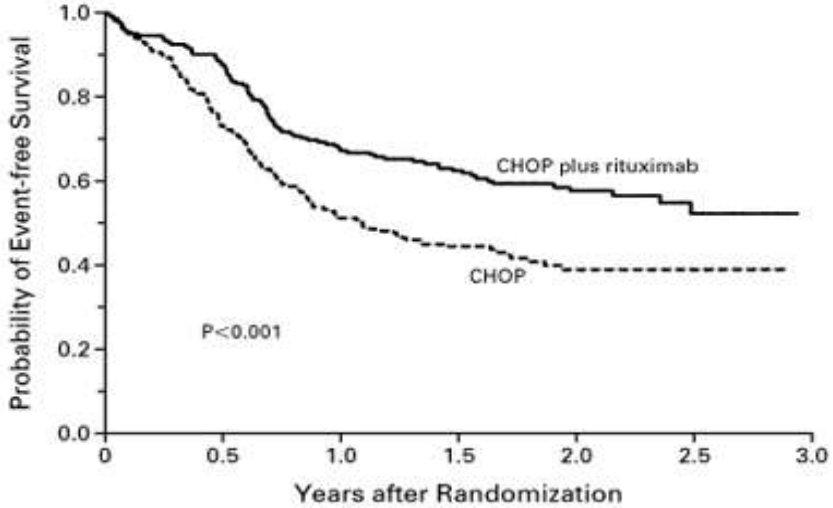
MITEN LYMFOOMIEN HOITOTULOKSIA VOITAISIIN PARANTAA?

Sirpa Leppä
HUS, Syöpätautien klinikka &
HY, Genomibiologian tutkimusohjelma

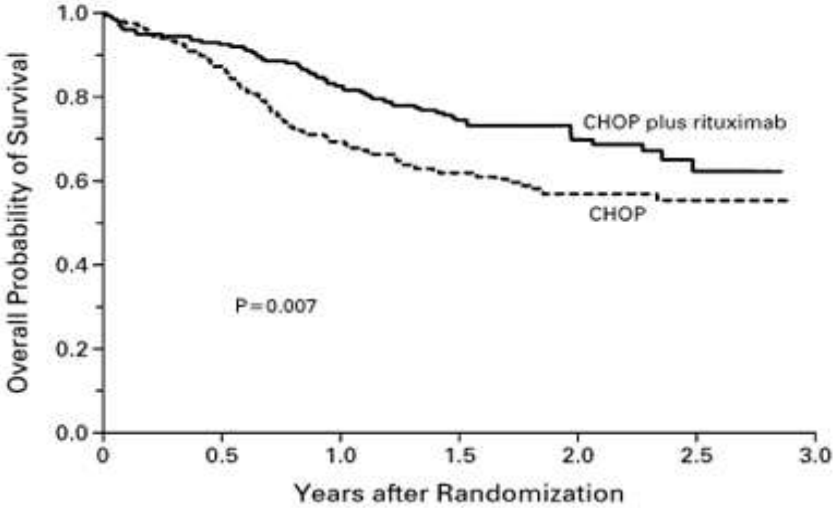
ONKOLOGIPÄIVÄT 30-31.8.2013

Hoitotulokset ovat parantuneet -70% DLBCL potilaista paranee

LNH-98.5: CHOP21 vs R-CHOP21 (>60v)



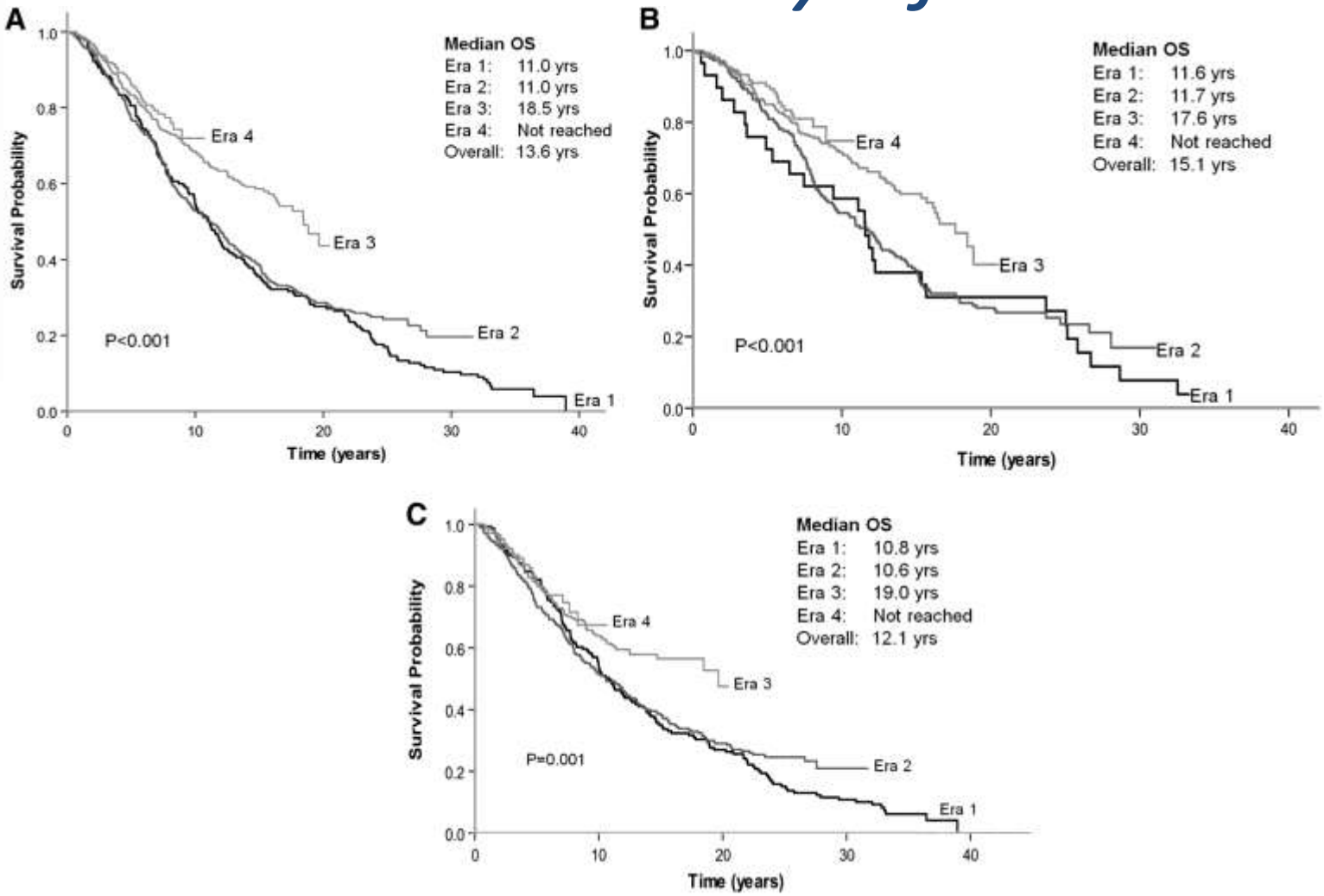
No. at Risk						
CHOP plus rituximab	202	177	137	108	63	19
CHOP	197	144	101	72	42	17



No. at Risk						
CHOP plus rituximab	202	187	167	118	64	21
CHOP	197	171	136	96	58	16

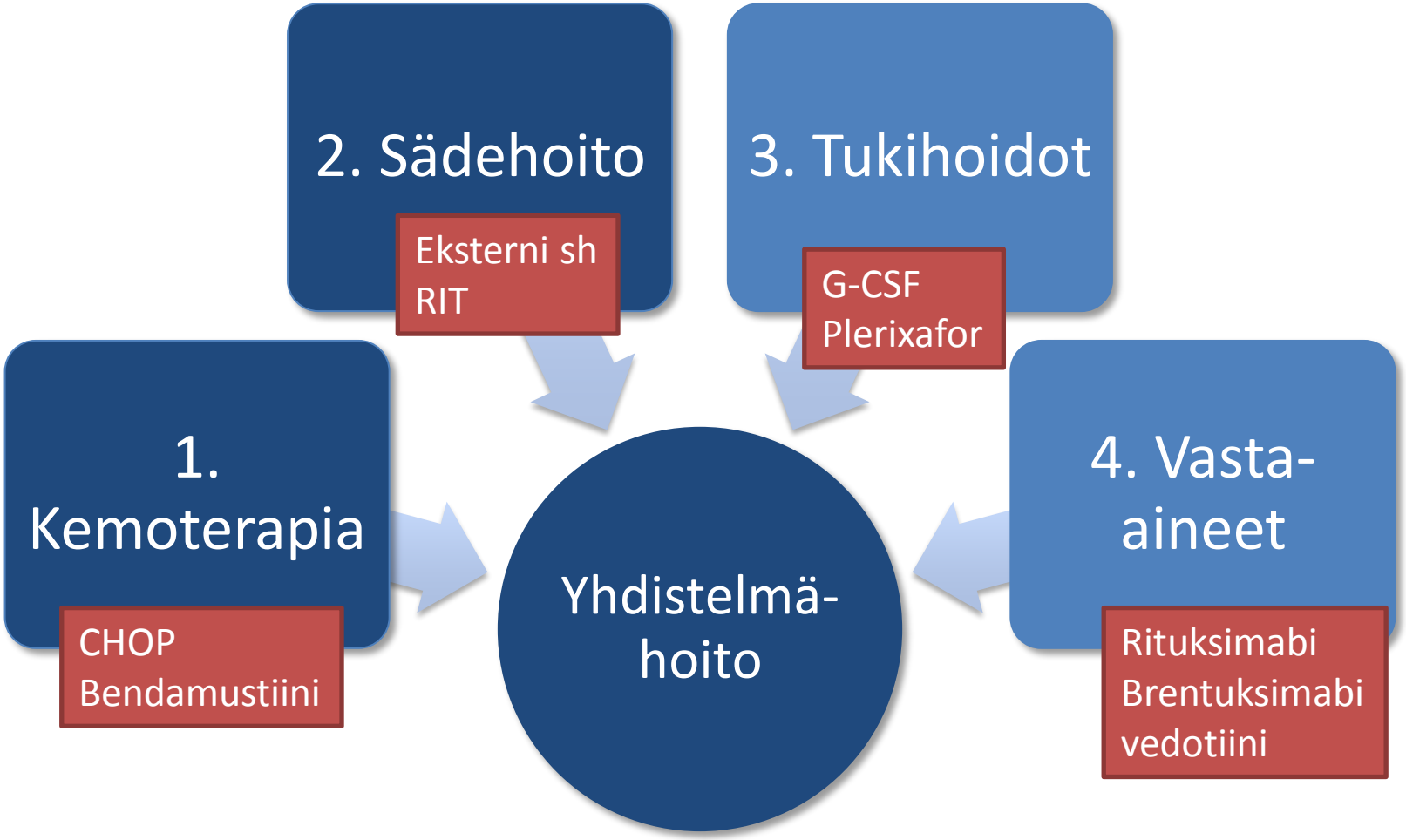
Coiffier et al., NEJM 2002& Feugier et al., JCO 2005

Follikulaarinen lymfooma

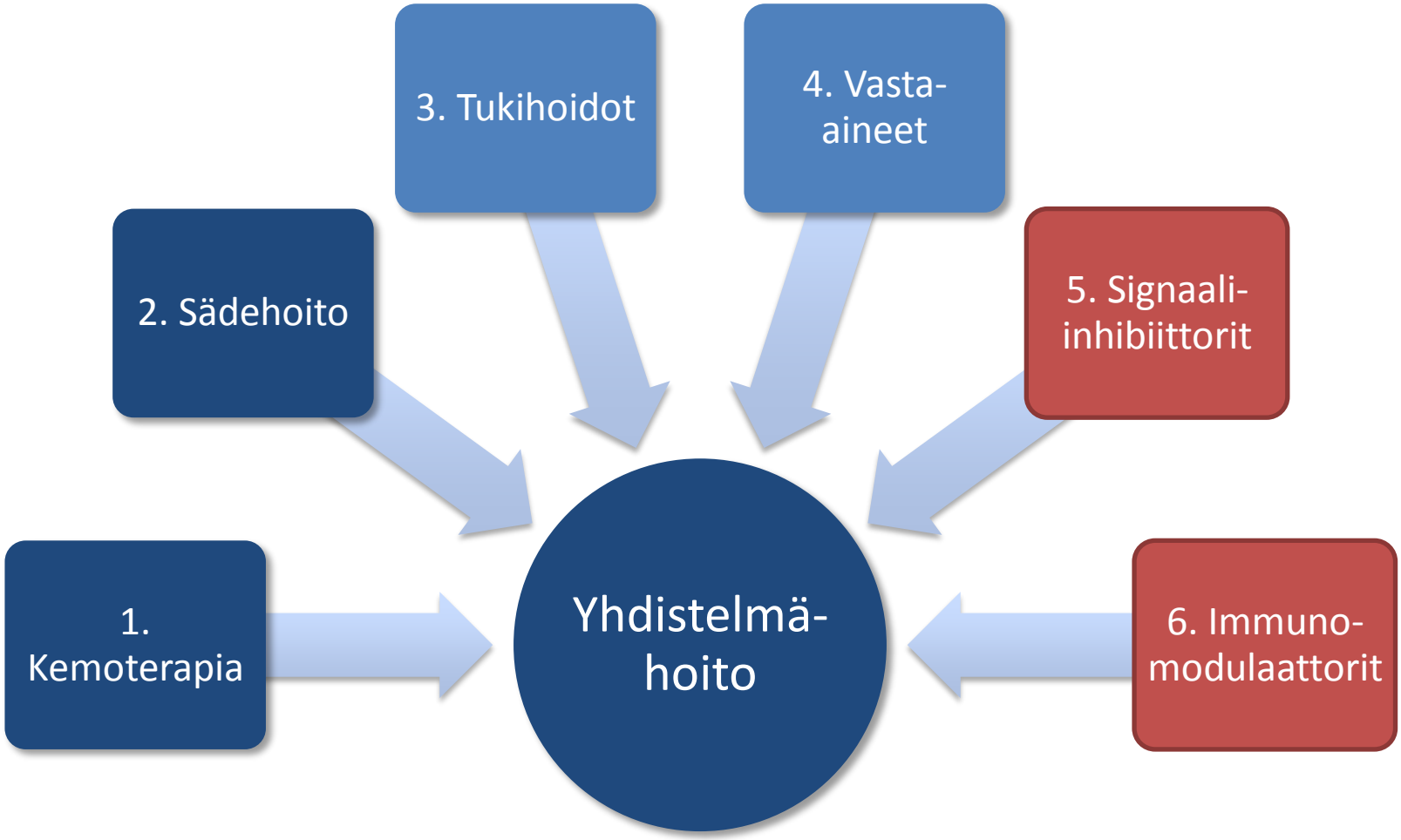


Tan D et al. Blood 2013;122:981-987

Lymfoomahoitojen kulmakivet

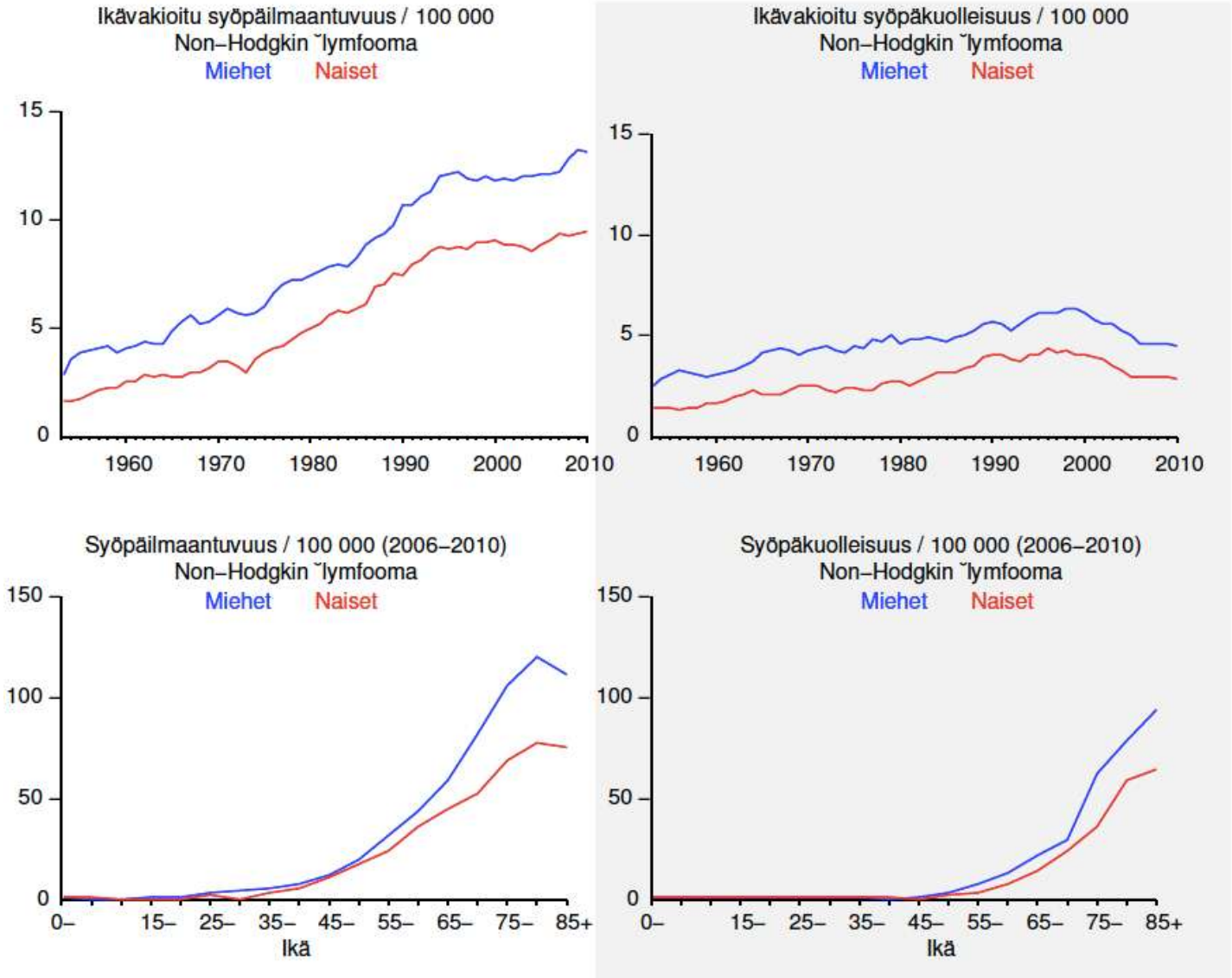


Lymfoomahoidot tulevaisuudessa



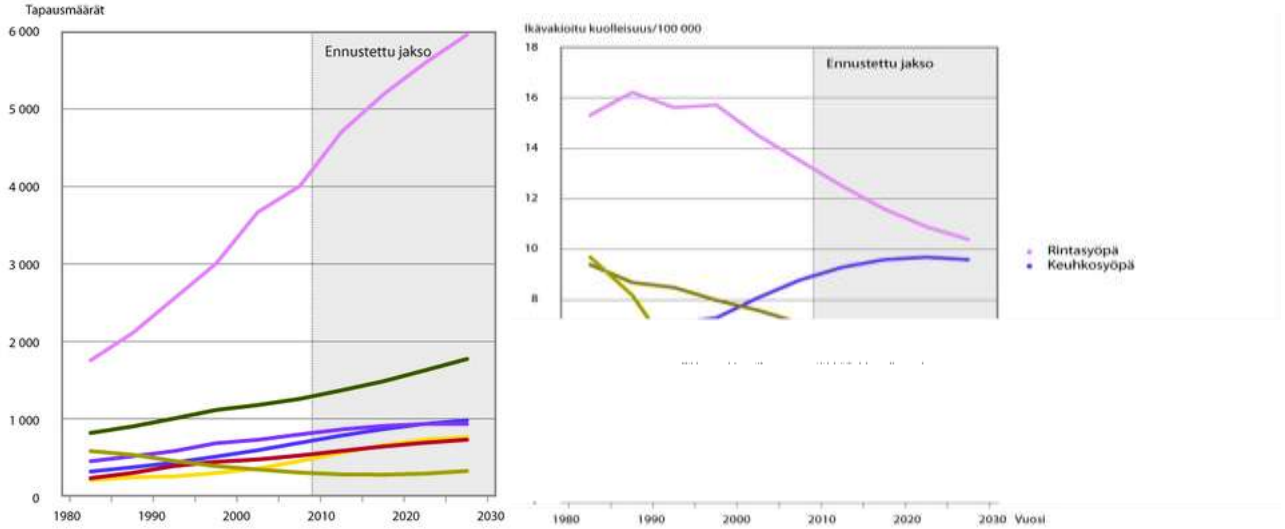
Non-Hodgkin lymfoomat-yleisyys

- 7./8. yleisin syöpä
- v. 2011 1184 uutta tapausta

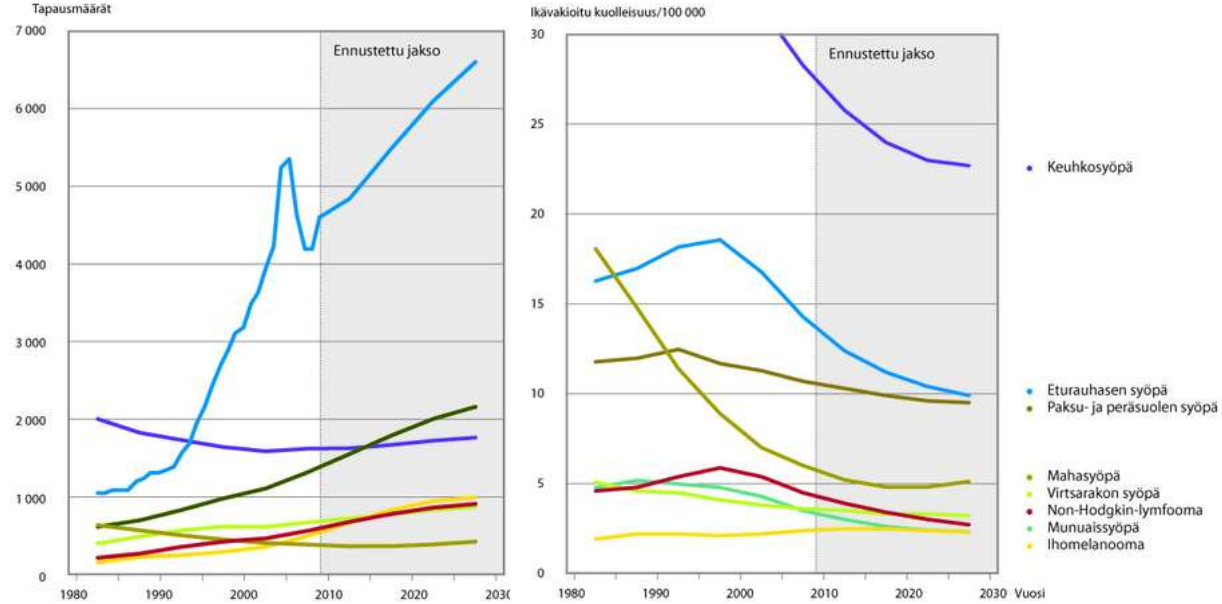


Ennustettu ilmaantuvuus ja kuolleisuus

Naiset



Miehet



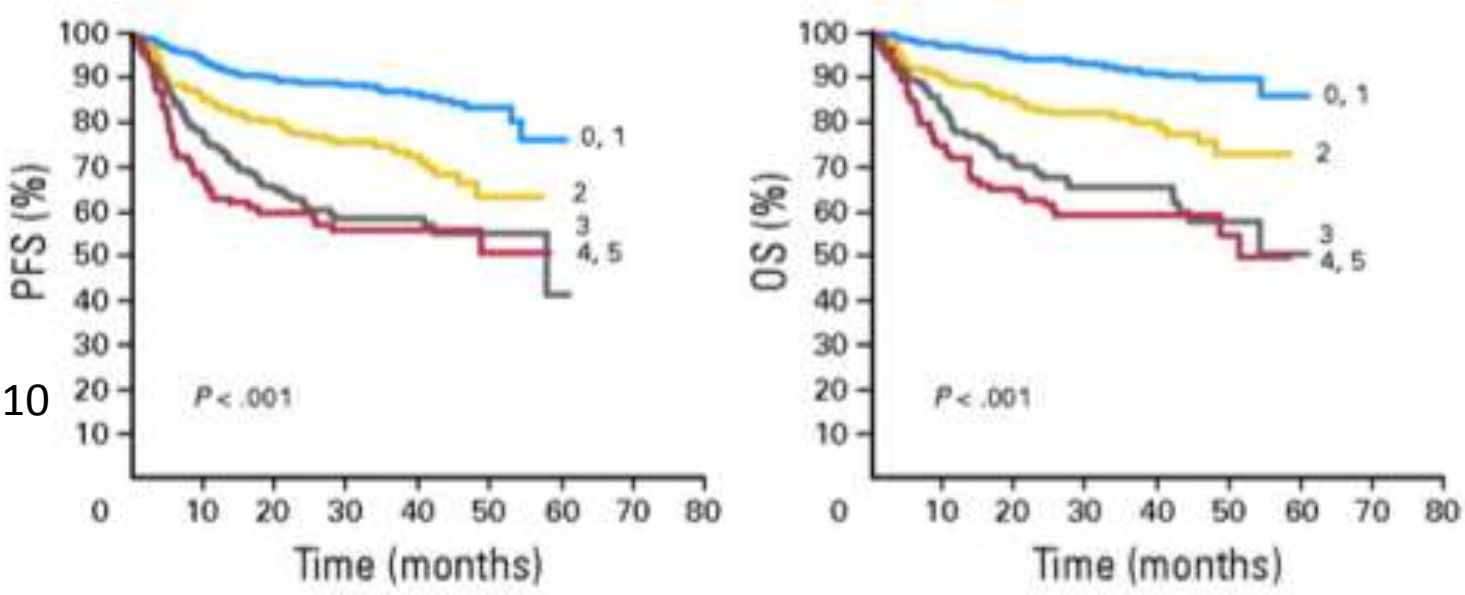
Pukkala ym., 2011

Haasteita

- Non-Hodgkin lymfoomien määrä lisääntyy
- Väestö ikääntyy
- 30-50% ei parane

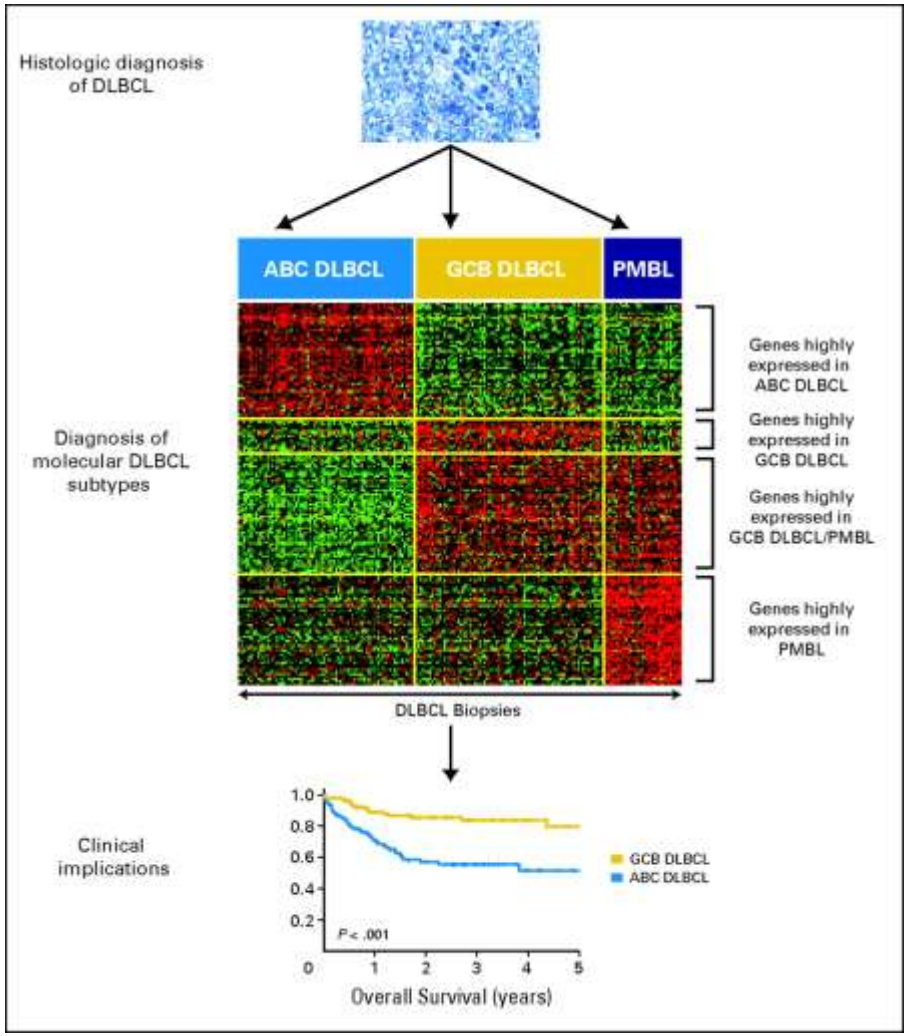
IPI-luokitus
R-aikakaudella

Ziepert et al., 2010



- Heterogeeninen tautiryhmä, >70 alatyyppiä

Application of gene expression profiling allows the distinction of histologically undistinguishable molecular subtypes.

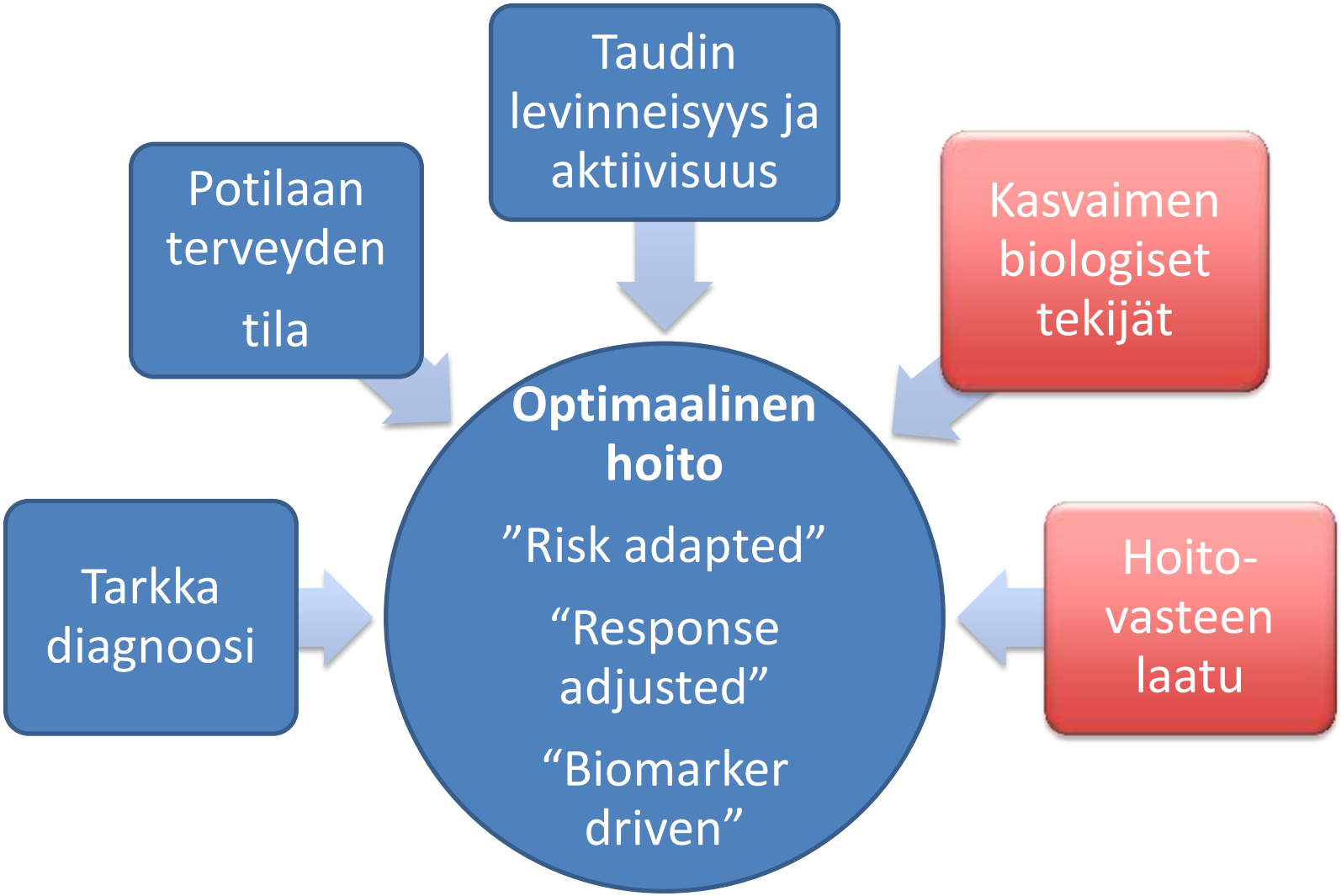


Nogai H et al. JCO 2011;29:1803-1811

Ajankohtaisia kysymyksiä

- Miten keventää hoitoa uusimisriskin ollessa pieni?
- Miten parantaa agressiivisten B-ja T-solulymfooma ja HL potilaiden hoitotuloksia?
  - primäärihoidolle refräktäärit
  - primäärihoidon jälkeen uusiutuneet
  - iäkkäät
- Miten määritellä korkean riskin potilaat?
- Miten estää lymfooman eteneminen keskushermostoon?

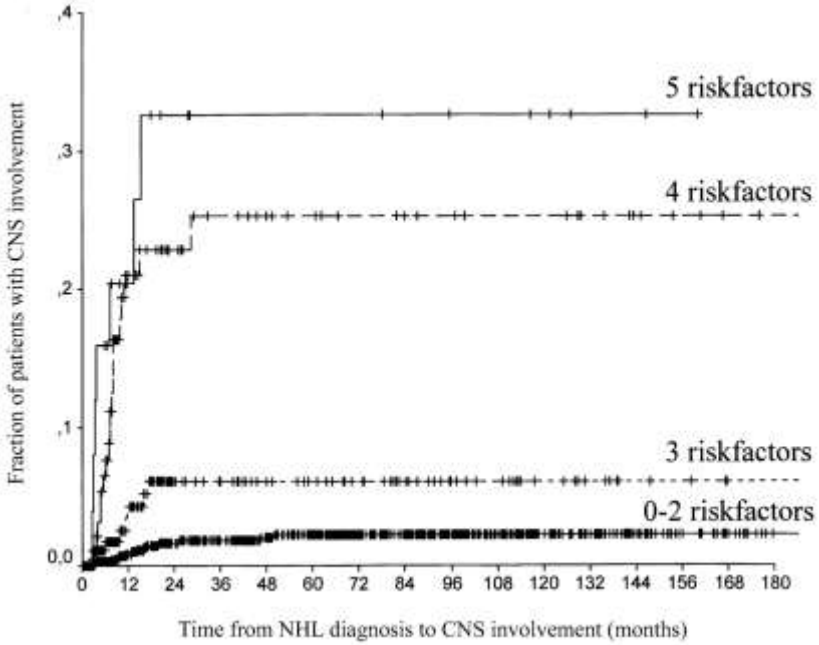
Hoidon suunnittelu-Mitä pitää huomioida?



“Risk adapted” approaches

- Kliininen riskiluokka
  - IPI
  - FLIPI
  - MIPI
  - IPS
- CNS riski-> profylaksia
- Biologiset riskitekijät
  - GCB vs ABC fenotyyppi
  - MYC/BCL2 “double hit”

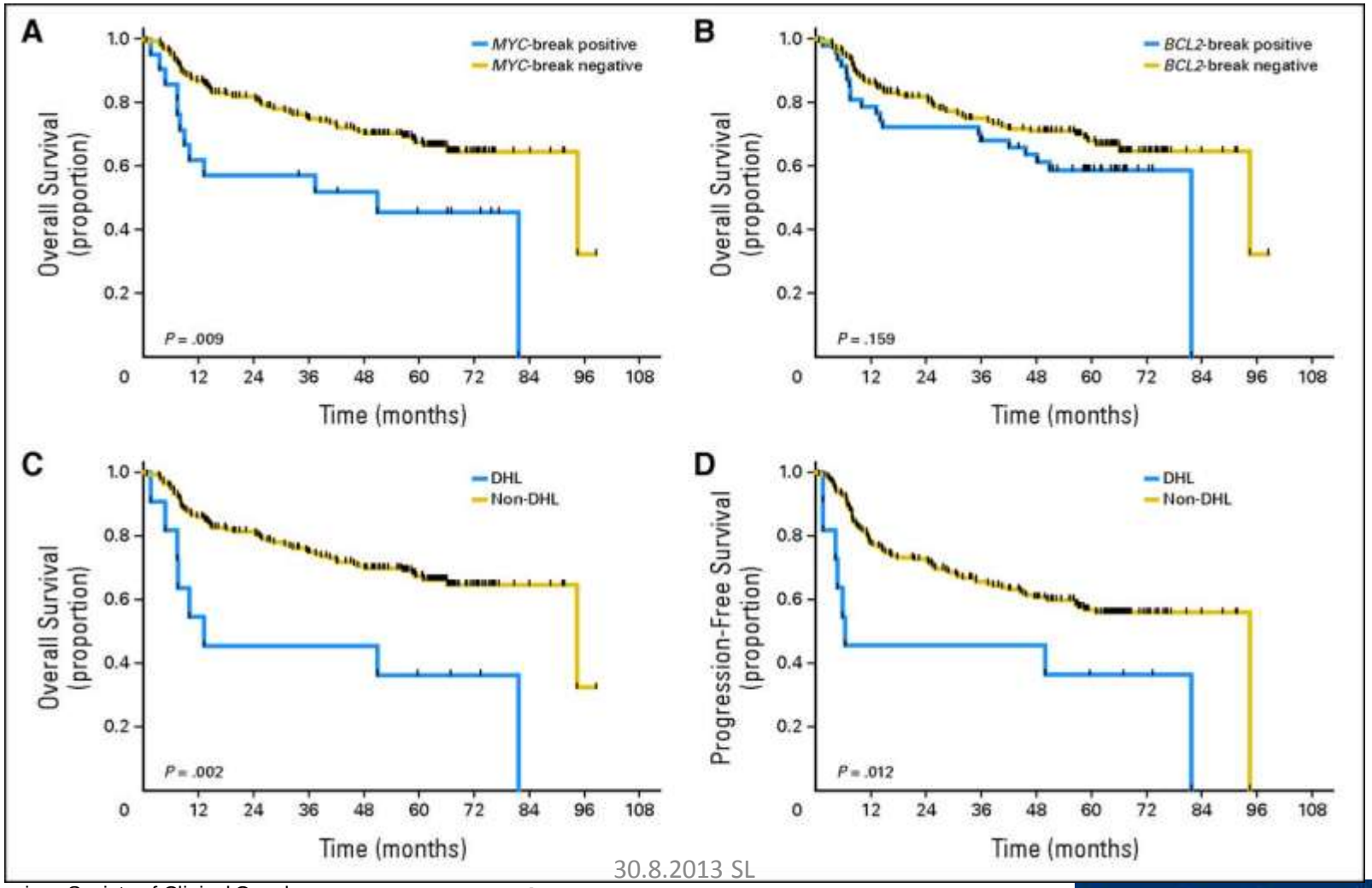
Probability for CNS relapse according to the number of risk factors



Hollender A et al. Ann Oncol 2002;13:1099-1107

Biologiset riskitekijät- myc/bcl2

Overall survival (OS) and progression-free survival (PFS) after treatment with rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone in patients with diffuse large B-cell lymphoma (DLBCL) harboring gene breaks in MYC, BCL2, or both.

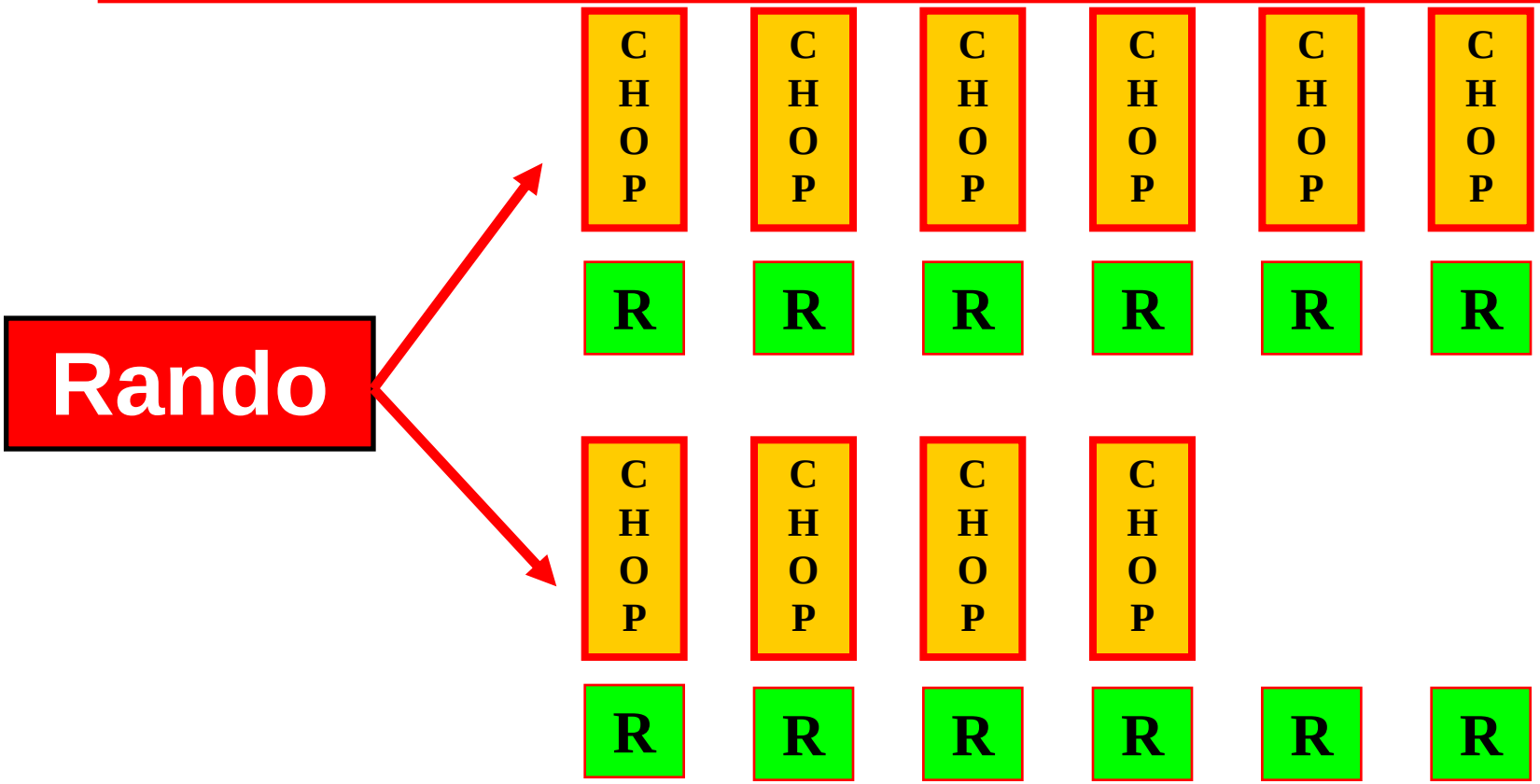


Green T M et al. JCO 2012;30:3460-3467

Miten keventää?

Treatment for IPI=0 and „No Bulk“

FLYER (6-6/6-4) STUDY DESIGN



Miten estää eteneminen keskushermostoon?

CHIC-Study

Nordic approach to intensive CNS directed therapy for high risk DLBCL patients

(aaIPI 2-3, or other risk factors for CNS progression)

CHIC Schedule

Dxm + vincristine + R prephase

↓

HD MTX+R-CHOP14x2 and R-CHOEP14

CR, CRu, PR → SD, PD → second line, followed for survival

↓

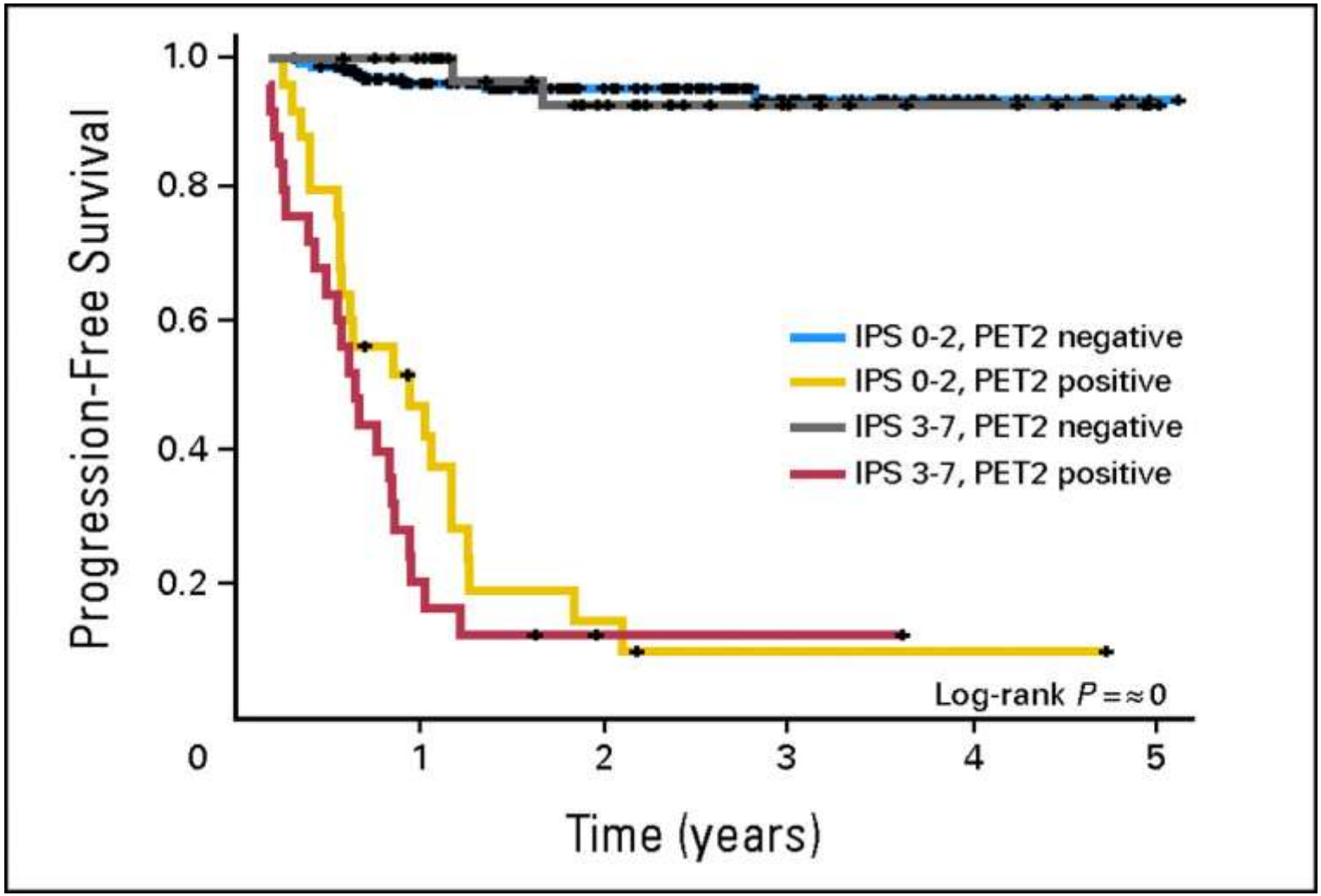
3xR-CHOEP14 →R-Cytarabine 12 g/m^2

→ SD, PD → second line, followed for survival
→ PR → viable tumor tissue second line, followed for survival

↓

CR, PR+PET- without viable tumor tissue → Regular follow-up

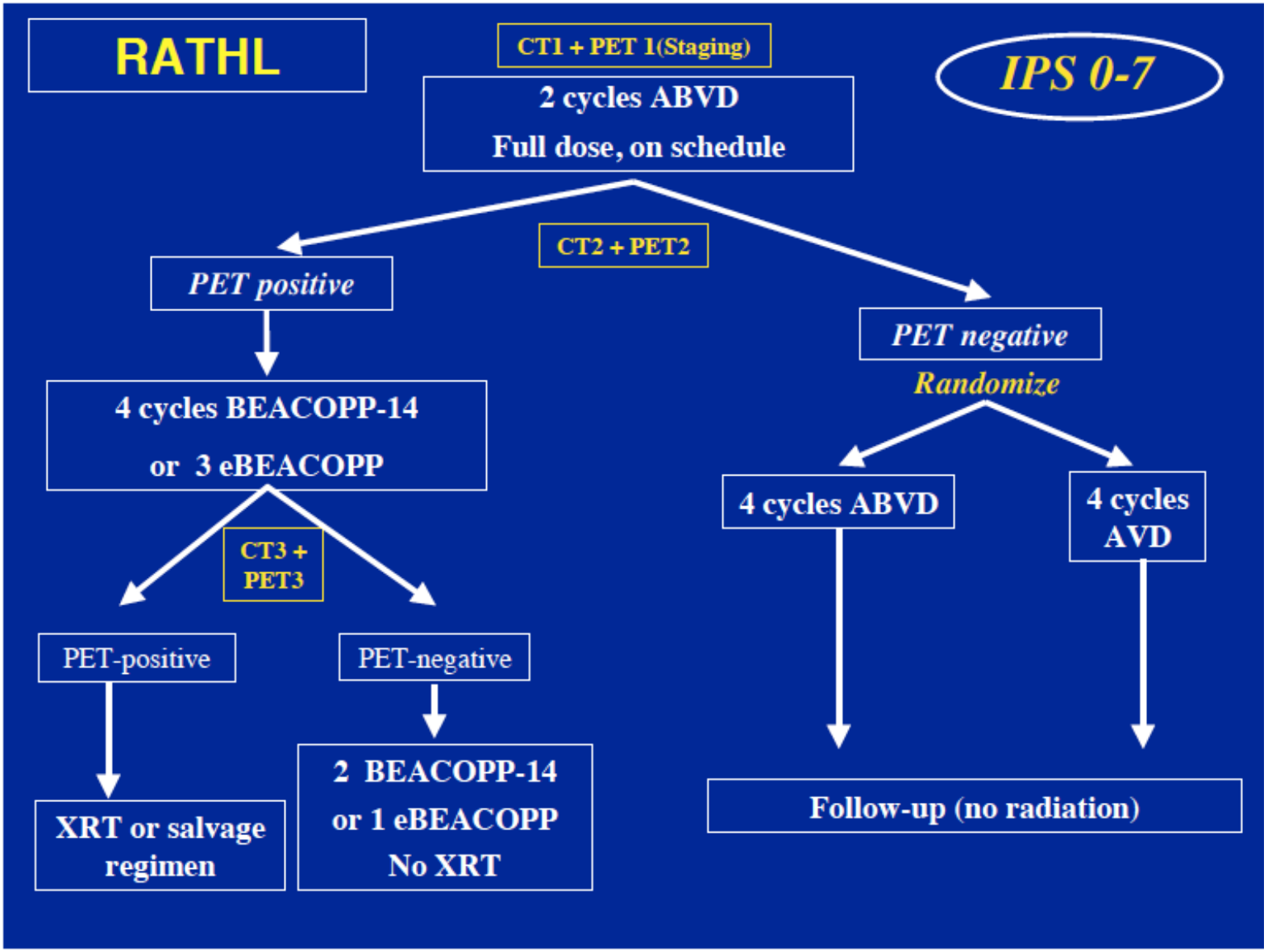
Response adjusted therapy- HL



Gallamini A et al. JCO 2007;25:3746-3752

JOURNAL OF CLINICAL ONCOLOGY ASCO

Response adjusted therapy in HL (RATHL)



Targeted/biomarker driven therapy

- Vasta-aineet
- Signaali-inhibiittorit

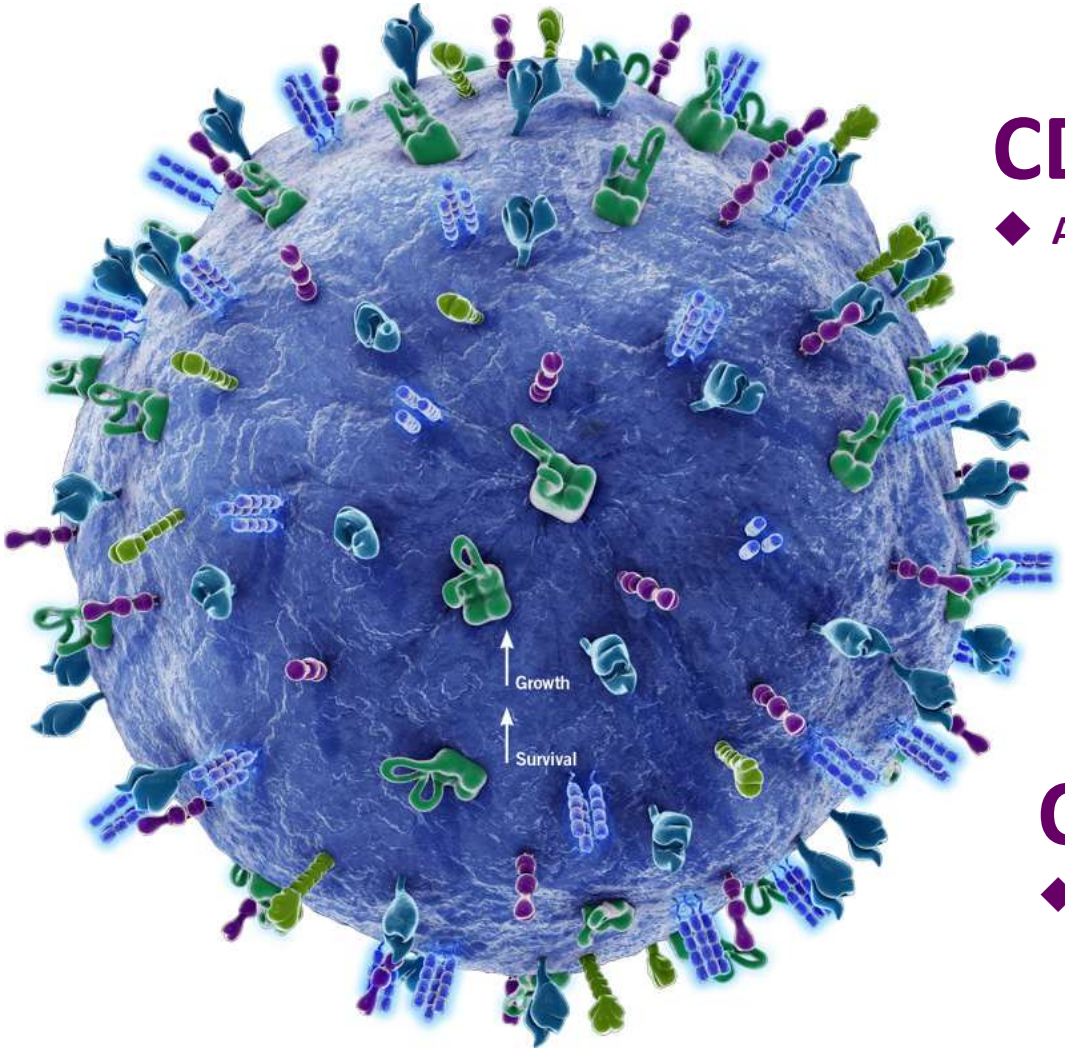
B & T-cell surface antigens as therapeutic targets in lymphomas

CD20

- Rituximab (iv&sc)
- Ofatumumab
- Obinutuzumab

CD20*

- ^{90}Y-Ibritumomab -tiuxetan
- ^{131}I-Tositumomab



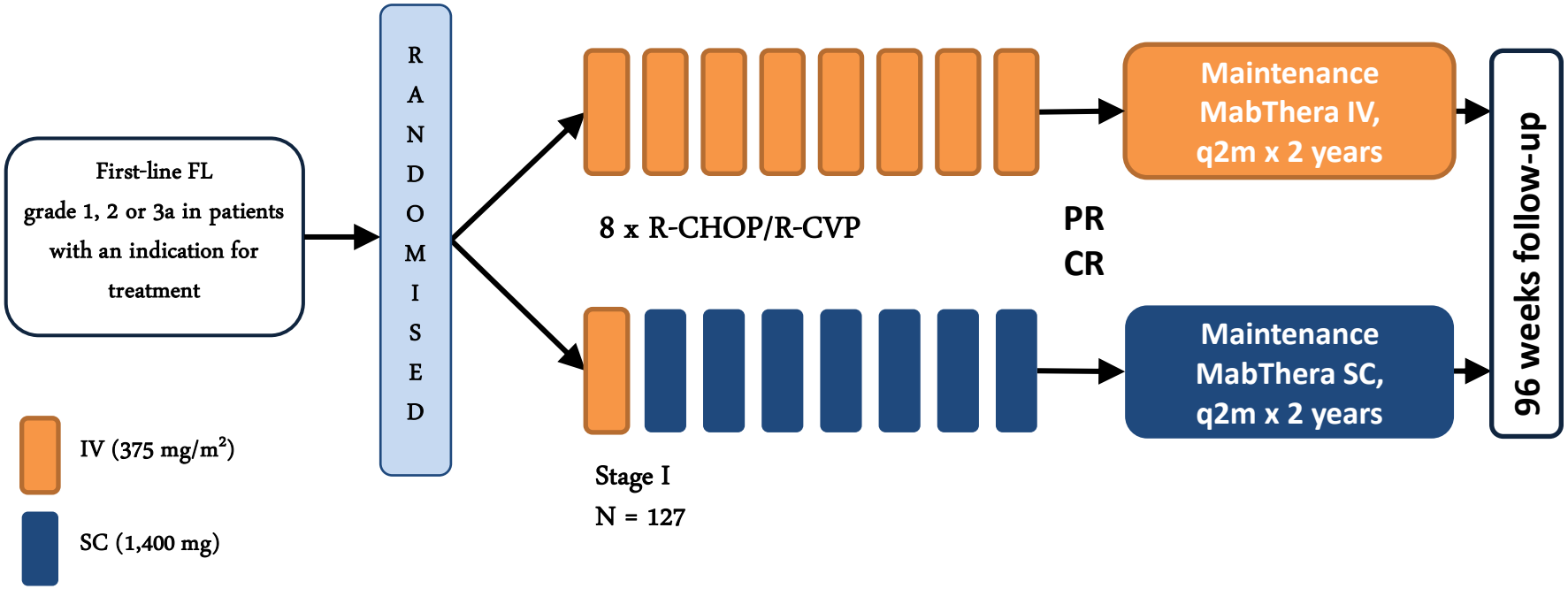
CD52

- Alemtutsumab

CD30

- Brentuximab vedotin

Rituximab sc in FL: SABRINA (BO22334) study design



- Stage 1 primary endpoint: MabThera SC:IV C_{trough} ratio at Cycle 7 of induction (comparison of serum levels of MabThera SC compared with IV)
- Stage 1 secondary endpoints: MabThera SC:IV AUC ratio during induction, efficacy (ORR/CR) and safety

- Davies A, *et al.* ASH 2012; Abstract 1629 (poster).

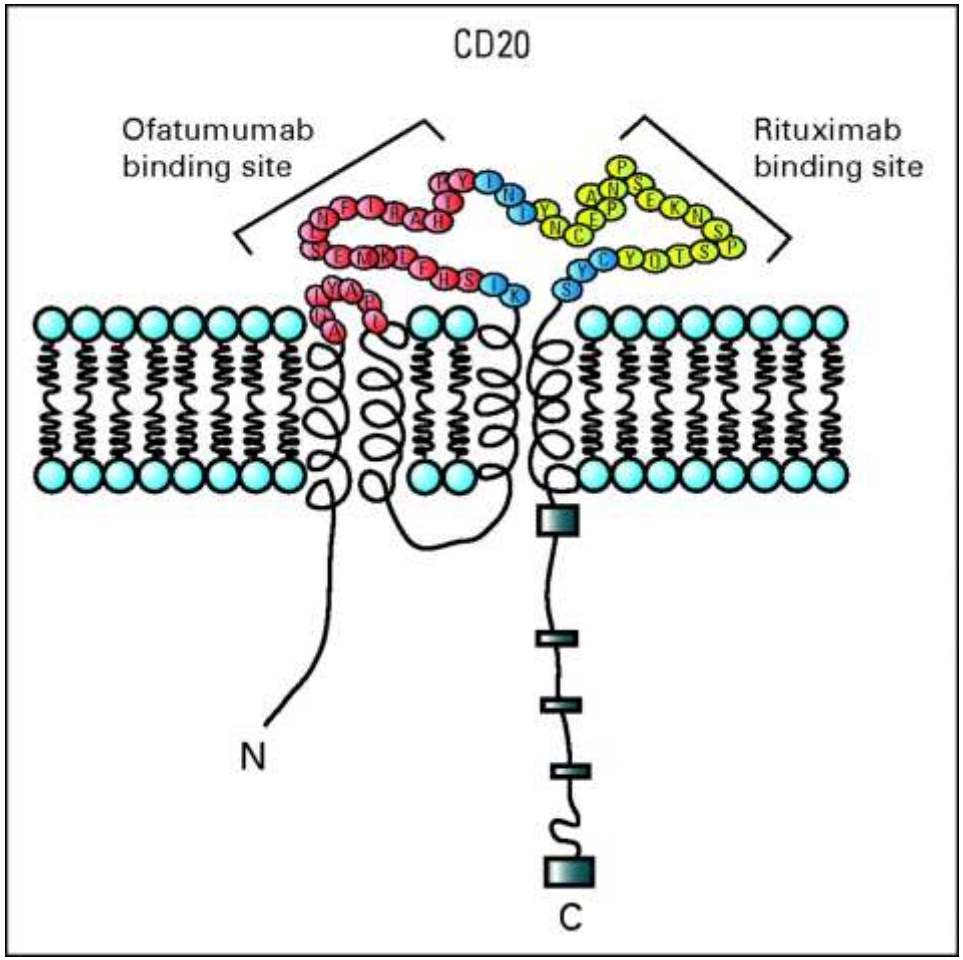
SC route of administration delivers comparable efficacy to IV administration

	MabThera	
	IV (n = 64)	SC (n = 63)
Overall response rate	84.4% [95% CI: 73.1–92.2]	90.5% [95% CI: 80.4–96.4]
CR/CRu	29.7% [95% CI: 18.9–42.4]	46.0% [95% CI: 33.4–59.1]
PR	54.7% [95% CI: 41.7–67.2]	44.4% [95% CI: 31.9–57.5]

ORR and CRR indicate that switching to the SC route of administration does not impair MabThera's anti-lymphoma activity

Davies A, *et al.* ASH 2012; Abstract 1629 (poster).

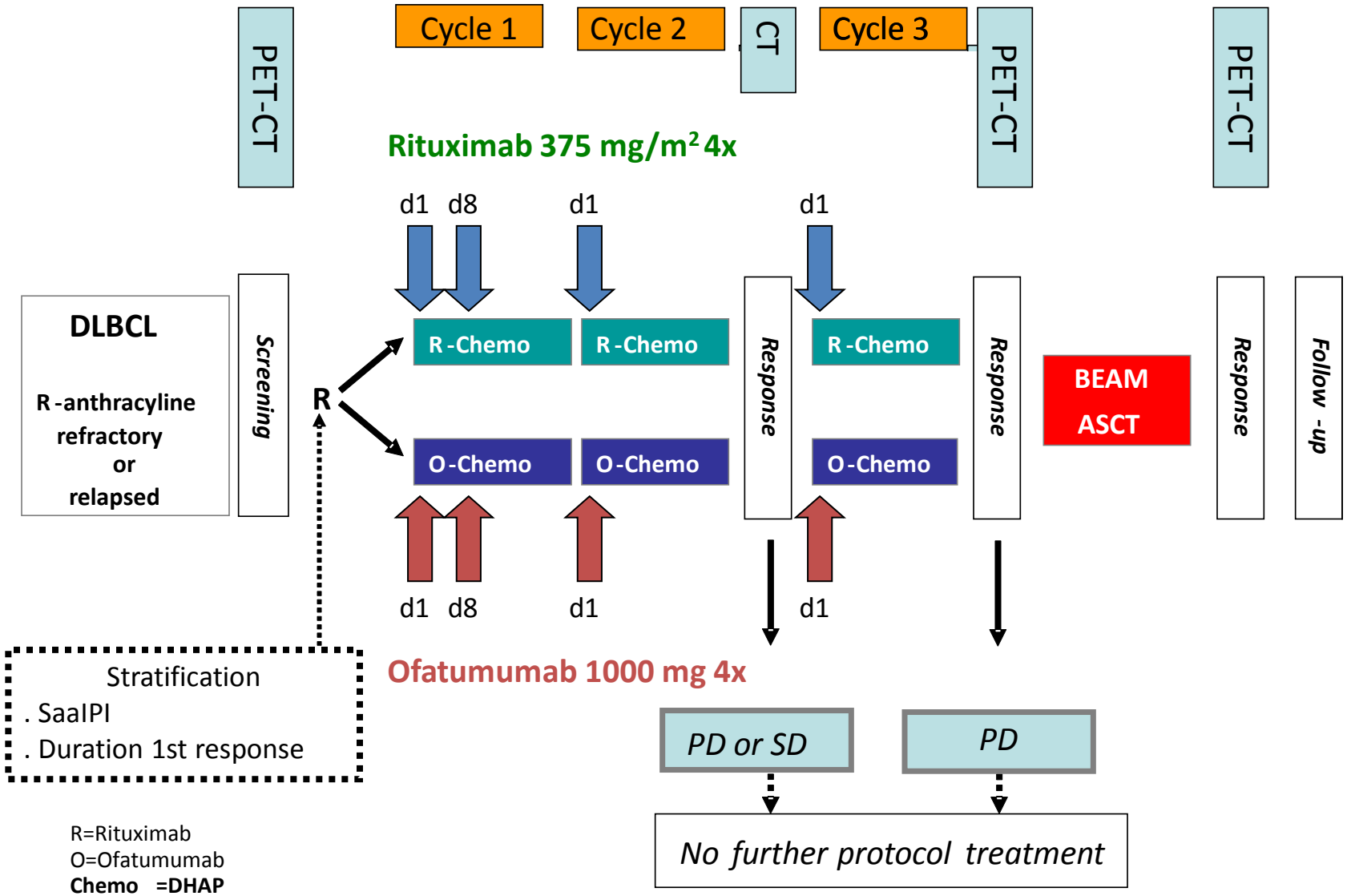
Ofatumumab binds to an epitope on CD20 that is distinct from rituximab



Cheson B D JCO 2010;28:3525-3530

[1]Polyak M, et al. Blood 2002; **99**: 3256–62; [2]Teeling JL, et al. J Immunol 2006: **177**: 362–371;
[3]Du J, et al. Mol Immunol 2009; **46**: 2419–2423. Figure: Du J, et al. Structure of the Fab fragment of therapeutic antibody ofatumumab provides insights into the recognition mechanism with CD20. Mol Immunol 2009; **46**: 2419–2423 © Elsevier, Ltd.

HOVON98/GSK ORCHARRD Study Design Ofatumumab versus Rituximab salvage Chemoimmunotherapy followed by ASCT in Relapsed or Refractory DLBCL



R=Rituximab
O=Ofatumumab
Chemo =DHAP
Cycle =21 days

GA101: A unique, glycoengineered, Type II anti-CD20 monoclonal antibody

- The first Type II, glycoengineered, humanised anti-CD20 mAb[1–3]
  - Designed to provide an advancement in antibody technology[1,3]
- In preclinical studies comparing it with rituximab, GA101 showed:
  - Increased direct cell death induction[1,3]
  - Enhanced ADCC[1]
- GA101 is being evaluated in an extensive clinical trial programme in B-cell malignancies

ADCC, antibody-dependent cell-mediated cytotoxicity; mAb, monoclonal antibody

1. Mössner E, *et al. Blood* 2010; 115:4393–4402; 2. Niederfellner G, *et al. Blood* 2011; 118:358–367;
3. Alduaij W, *et al. Blood* 2011; 117:4519–4529.

GALLIUM (BO21223) Phase III in FL: Study design

First-line iNHL
(N = 1,400*)

- Age ≥ 18 years
- FL (grades 1–3a), splenic MZL, nodal/extranodal MZL
- Stage III or IV, or stage II bulky disease (d ≥ 7 cm), requiring treatment
- ECOG ≤ 2

Randomise

Induction	Maintenance
GA101 x 8 cycles + CHOP x 6 or GA101 x 8 cycles + CVP x 8 or GA101 x 6 cycles + benda. x 6	GA101 q2mo x 2 years
Rituximab x 8 cycles + CHOP x 6 or rituximab x 8 cycles + CVP x 8 or rituximab x 6 cycles + benda. x 6	Rituximab q2mo x 2 years

CR, PR†

GA101: 1,000 mg d1, d8, d15, cycle 1; d1, cycles 2–6 (28-day cycles) or 2–8 (21-day cycles); maintenance 1,000 mg q2mo
Rituximab IV induction: 375 mg/m^2 d1, cycles 1–6 (28-day cycles) or 1–8 (21-day cycles); maintenance: 375 mg/m^2 q2mo
Bendamustine: cycles 1–6 (28-day cycles); CVP: cycles 1–8 (21-day cycles); CHOP: cycles 1–6 (21-day cycles)

Primary endpoint

- PFS in FL

Secondary endpoints

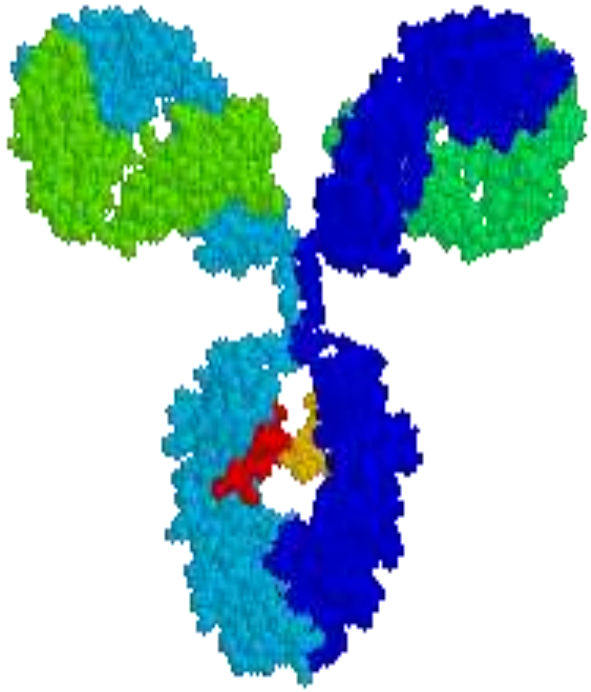
- PFS (in overall population)
- PFS (assessed by IRC)
- ORR and CR
- ORR and CR (assessed by IRC)
- Overall survival
- Event-free survival
- Disease-free survival
- Response duration
- Time to next lymphoma treatment
- Safety
- Patient-reported outcomes
- Medical resource utilisation

This trial is currently recruiting

This trial is being conducted in collaboration with the **UK National Cancer Research Institute (NCRI)** and the **German Low-grade Lymphoma Study Group (GLSG)**

* 1,200 patients with FL and 200 patients with other iNHL;
† Patients with SD enter observation phase for up to 2 years
CR, complete response; FL, follicular lymphoma; iNHL, indolent NHL; IRC, Independent Review Committee; MZL, marginal zone lymphoma; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SD, stable disease
www.clinicaltrials.gov NCT01332968 (May 2012).

Anti-CD52 antibody: alemtuzumab



Alemtuzumab
(MabCampath®)

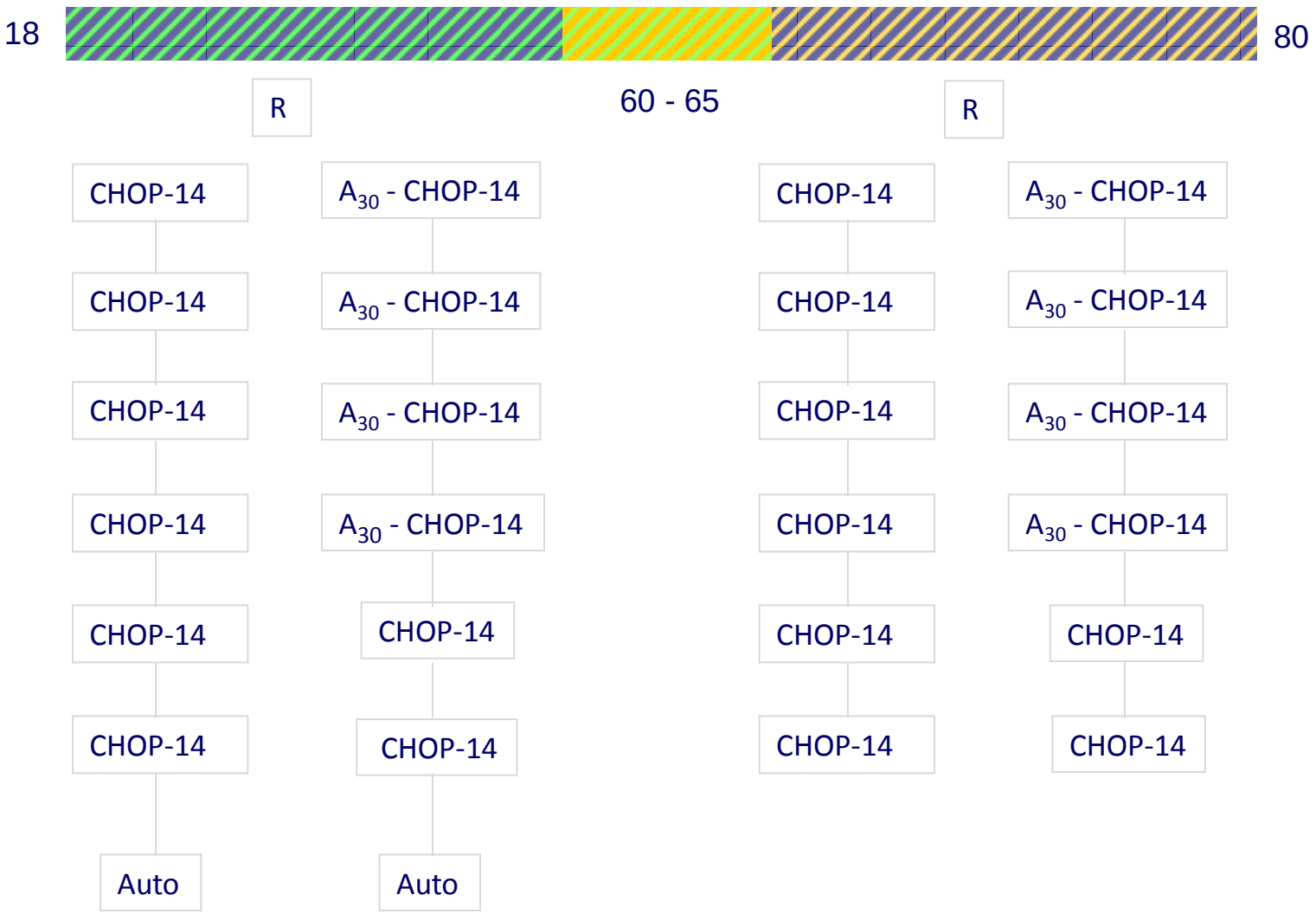
- Genetically reshaped, humanised (CDR grafted) IgG1 kappa monoclonal antibody (low immunogenicity)
- Anti-CD52: the first therapeutic humanised monoclonal antibody that targets the CD52 antigen

NORDIC LYMPHOMA GROUP

The ACT trials

AFTER the dose/age amendments

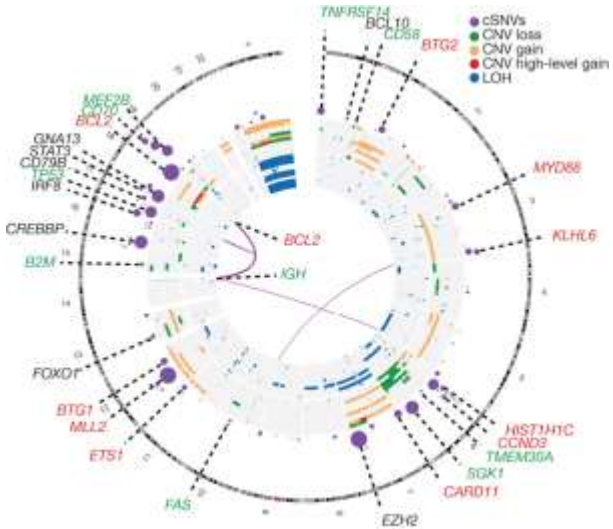
GERMAN HIGH GRADE NON-HODGKIN'S LYMPHOMA STUDY GROUP



Genomiikka ja molekyläriset ennustetekijät

Editysaskeleita

- On tunnistettu useita lymfoomiin assosioituvia somaattisia mutaatioita *(esim MLL2, MEF3C, CREBBP/EP300),* ja signaalireittejä



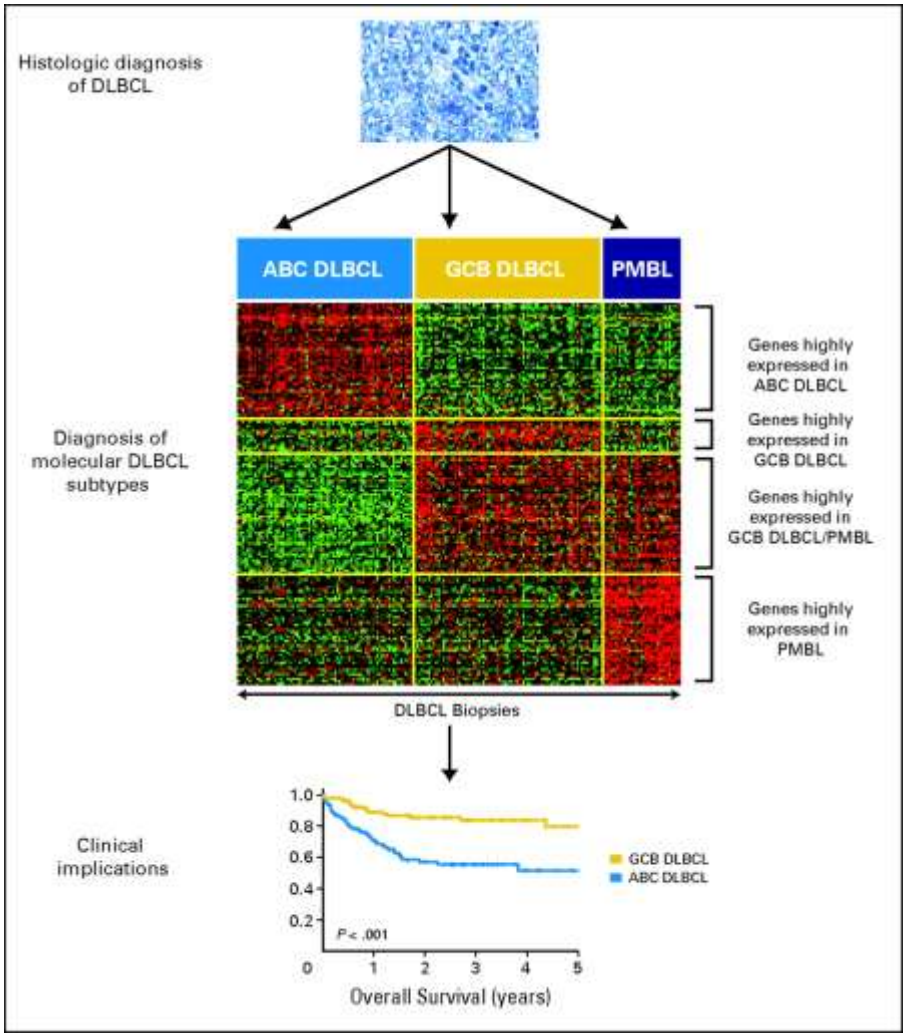
Genome-wide visualization of somatic mutation targets in NHL.

RD Morin *et al*. *Nature* **000**, 1-6 (2011) doi:10.1038/nature10351

Molekyläariset alaryhmät

Editysaskeleita

- On tunnistettu molekyläärisiä alaryhmiä (esim. GCB, ABC ja PMBCL)

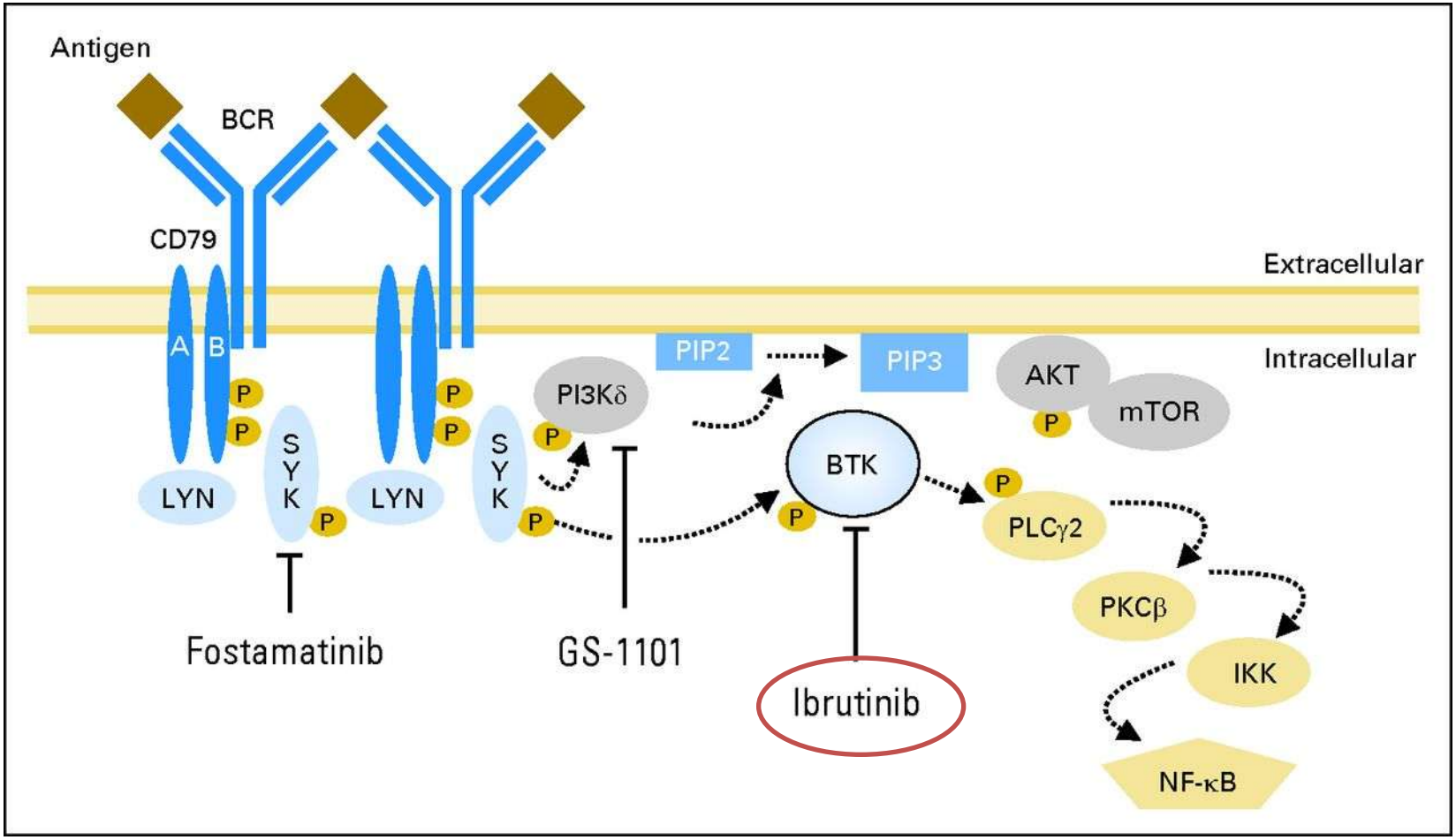


Nogai H et al. JCO 2011;29:1803-1811

Miten hyödyntää molekylääristä tietoa käytännössä?

- **REMoDLB**
  - A randomised evaluation of molecular guided therapy for diffuse large B-cell lymphoma with bortezomib
- **Phoenix**
  - A randomized study of the Bruton's tyrosine kinase (BTK) Inhibitor, PCI-32765 (Ibrutinib), in combination with R-CHOP in subjects with newly diagnosed non-germinal center B-cell subtype of diffuse large B-cell lymphoma

Antigen-dependent B-cell receptor (BCR) signaling and its targeting by small-molecule inhibitors



Wiestner A JCO 2013;31:128-130

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 8, 2013 VOL. 369 NO. 6

Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma

Michael L. Wang, M.D., Simon Rule, M.D., Peter Martin, M.D., Andre Goy, M.D., Rebecca Auer, M.D., Ph.D., Brad S. Kahl, M.D., Wojciech Jurczak, M.D., Ph.D., Ranjana H. Advani, M.D., Jorge E. Romaguera, M.D., Michael E. Williams, M.D., Jacqueline C. Barrientos, M.D., Ewa Chmielowska, M.D., John Radford, M.D., Stephan Stilgenbauer, M.D., Martin Dreyling, M.D., Wieslaw Wiktor Jedrzejczak, M.D., Peter Johnson, M.D., Stephen E. Spurgeon, M.D., Lei Li, Ph.D., Liang Zhang, M.D., Ph.D., Kate Newberry, Ph.D., Zhishuo Ou, M.D., Nancy Cheng, M.S., Bingliang Fang, Ph.D., Jesse McGreivy, M.D., Fong Clow, Sc.D., Joseph J. Buggy, Ph.D., Betty Y. Chang, Ph.D., Darrin M. Beaupre, M.D., Ph.D., Lori A. Kunkel, M.D., and Kristie A. Blum, M.D.

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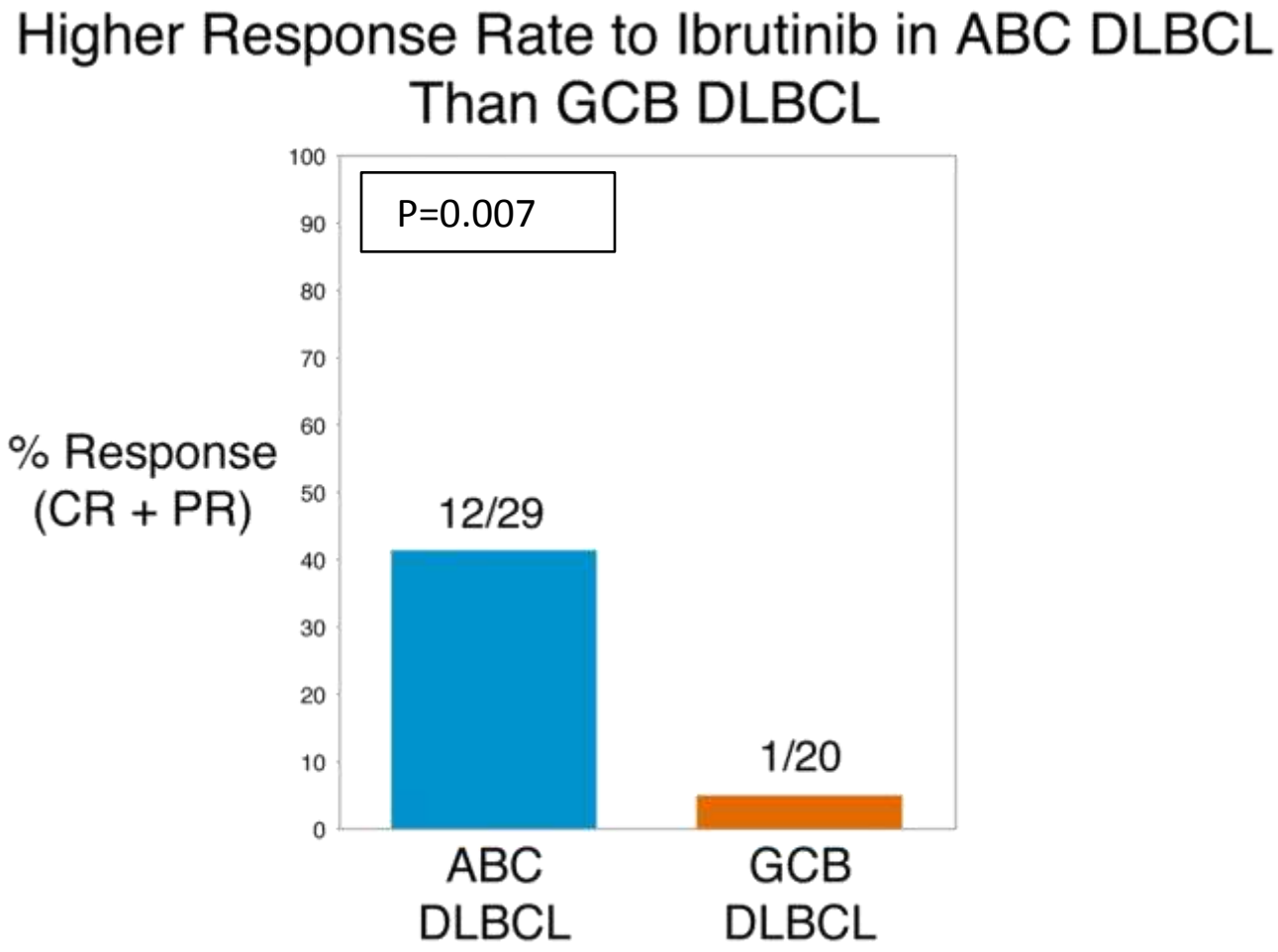
OF CLINICAL ONCOLOGY

ORIGINAL REP

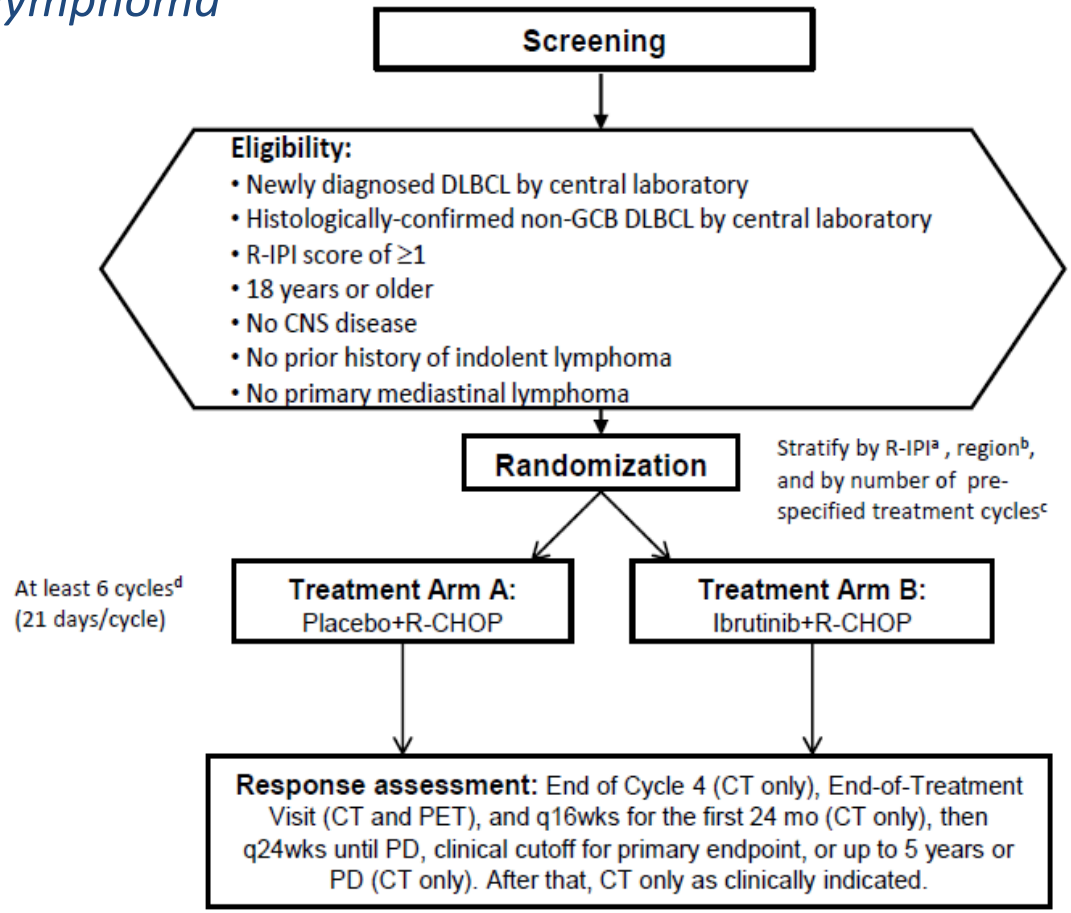
Bruton Tyrosine Kinase Inhibitor Ibrutinib (PCI Has Significant Activity in Patients With Relapsed/Refractory B-Cell Malignancies

Ranjana H. Advani, Joseph J. Buggy, Jeff P. Sharman, Sonali M. Smith, Thomas E. Boyd, Kathryn S. Kolibaba, Richard R. Furman, Sara Rodriguez, Betty Y. Chang, Juthamas Suk Raquel Izumi, Ahmed Hamdy, Eric Hedrick, and Nathan H. Fowler

Response in ABC and GCB DLBCL



Phoenix: A randomized study of the BTK Inhibitor, ibrutinib, in combination with R-CHOP in newly diagnosed non-germinal center B-cell subtype of diffuse large B-cell lymphoma



CT=computed tomography; CNS=central nervous system; DLBCL=diffuse large B-cell lymphoma; GCB=germinal center B-like cell; IHC=immunohistochemistry; mo=months; PD=progressive disease; PET=positron emission tomography; q=every; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-IPI=revised international prognostic index; wks=weeks

[a] R-IPI score of 1-2 versus 3-5.

[b] U.S./Western Europe vs. Rest of World.

[c] Six versus 8 cycles.

[d] Sites will pre-specify 6 or 8 cycles prior to study start (no adjustment permitted once pre-specified).

R-CHOP:

- At least 6 cycles (6 vs 8 cycles)
- (21 days per cycle)

- **Cyclophosphamide 750 mg/m^2 day 1**
- **Doxorubicin 50mg/m^2 day 1**
- **Vincristine 1.4mg/m2 (max 2mg) day 1**
- **Prednisolone 100mg/m^2 days 1-5**
- **Rituximab 375mg/m^2 day 1**

Muita faasi III vaiheessa olevia lääkkeitä tai tutkimusaiheita

- Entsastauriini
- Everolimuusi
- Lenalidomidi
- Bortetsomibi
- Rituksimabin optimaalisempi annostelu
- Brentuksimabi vedotiini ensilinjassa

…Tulevaisuudessa…

- Alaryhmät tarkentuvat
- Biologisia ennustetekijöitä otetaan osaksi hoidonsuunnittelua
- PET ohjaa hoidon valintaa
- Uusien biologisten lääkkeiden asema ja annostelu osana hoitoa on selkiytynyt
- Genomilaajuisen profiloinnin avulla löydetään potilaille tautispefisisiä hoitokohteita

Miten lymfoomien hoitotuloksia voidaan parantaa?