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German Lymphoma Alliance

Welches Studiendesign benötigen wir, um Fortschritte bei der Therapie von DLBCL-Patienten zu erzielen?

Gerhard Held

Klinik für Innere Medizin 1

Westpfalz-Klinikum Kaiserslautern

Challenges

Negative Phase-III Trials:

- **Enzostaurin Maintenance**	***Crump, JCO, 2016.***
- **Lenalidomide Maintenance**	***Thieblemont, JCO, 2017***
- **B-ALL Protocol, PETAL**	***Dührsen, ASH, 2014***
- **DA-EPOCH-R**	***Wilson, ASH, 2016***
- **Obinutuzumab, GOYA**	***Vitolo, JCO, 2017***
- **Ibrutinib, PHOENIX**	***Jannsen, press release, 2018***
- **…**	

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Challenges

German Lymphoma Alliance

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The Algorithm

German Lymphoma Alliance

Declination in clinical sciences:

- **Phase-I**
- **Phase-II**
- **Phase-III**

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The Algorithm

German Lymphoma Alliance

Declination in clinical sciences:

- Phase-I
- **Phase-II**
- **Phase-III**

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Phase-II

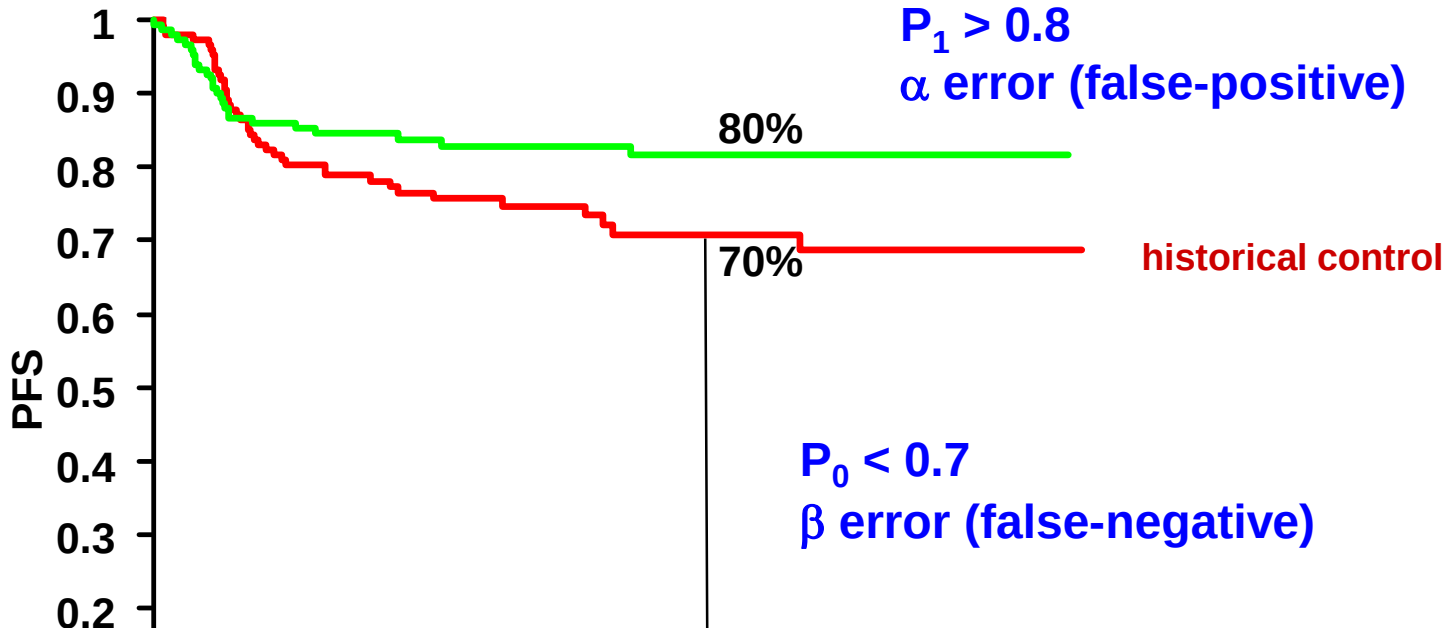
German Lymphoma Alliance

Estimation of efficacy

- **Minimization of false-negative conclusion**
- **Minimisation of false-positive conclusion**

Phase-II

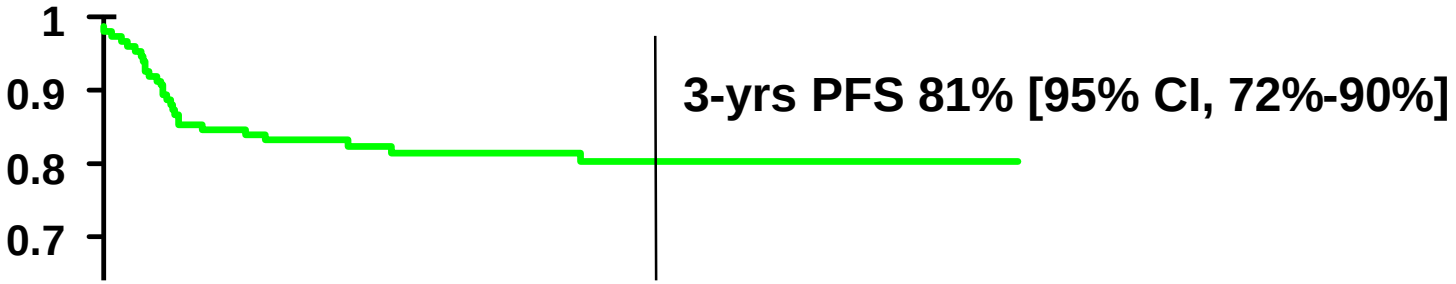
Assumption:



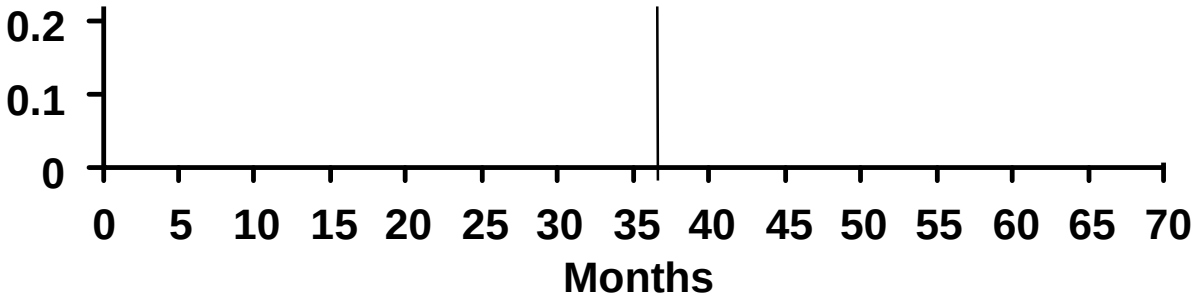
➡ **Sample size calculation**

Phase-II

Hypothetical result:



➡ **Superior efficacy towards historical control**



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Phase-II

German Lymphoma Alliance

Historical controls -> treatment-by-time interactions:

Results of identical treatment improve over time

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Phase-II

German Lymphoma Alliance

Historical controls -> treatment-by-time interactions:

Results of identical treatment improve over time

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Phase III Randomized Study of R-CHOP vs. DA-EPOCH-R and Molecular Analysis of Untreated Large B-Cell Lymphoma: CALGB/Alliance 50303

Wyndham H. Wilson, Sin-Ho Jung, Brandelyn N. Pitcher, Eric D.Hsi, Jonathan Friedberg, Bruce Cheson, **Nancy L. Bartlett**, Scott Smith, Nii Wagner-Johnston, Brad S. Kahl, Louis M. Staudt, Kristie A. Blum, Jeremy Abramson, Oliver W. Press, Richard I. Fisher, Kristy L. Richards, Heiko Schoder, Julie E. Chang, Andrew D. Zelenetz, John P. Leonard

Abstract 469, American Society of Hematology, Dec 4, 2016

Wilson et al; ASH 2016, abstract 469

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Phase-II

German Lymphoma Alliance

Historical controls -> treatment-by-time interactions:

R-CHOP vs. DA-EPOCH-R

50303 Statistical Design

- Target sample size 478
- Assumptions
  - 3 yr EFS of **55%** in R-CHOP arm
  - HR of 1.53 for R-CHOP vs DA-EPOCH-R detectable with 90% power, 2-sided logrank α <0.05
  - 10% ineligibility rate
- Final Analysis planned after 242 events

- Target sample size increased to 523 for PET correlate
- Revised final analysis timing due to low event rate
  - DSMB review May 2015 158 events. Recommended analysis at 178 events expected in May 2016 (80% power, HR 1.53)
  - DSMB recommended release of data July 2016 with 167 events.

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Wilson et al; ASH 2016, abstract 469

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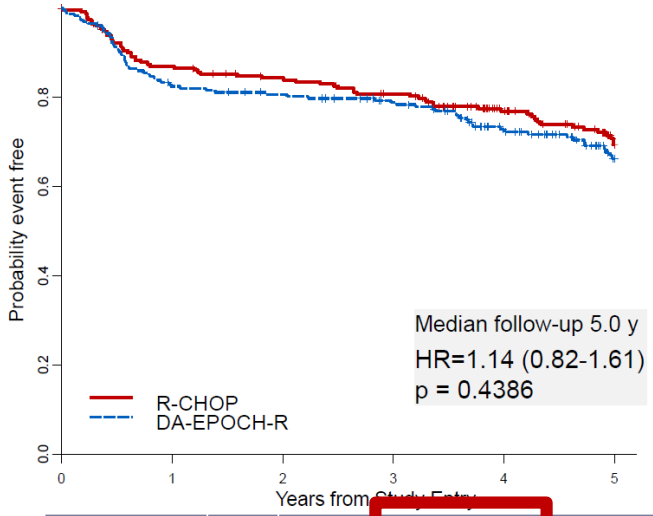
Phase-II

German Lymphoma Alliance

Historical controls -> treatment-by-time interactions:

R-CHOP vs. DA-EPOCH-R

50303 Event Free Survival



Arm	N	Events	3 Y (95% CI)	5 Y (95% CI)
R-CHOP	233	64	0.81 (0.75-0.85)	0.69 (0.62-0.75)
DA-EPOCH-R	232	70	0.79 (0.73-0.84)	0.66 (0.59-0.72)

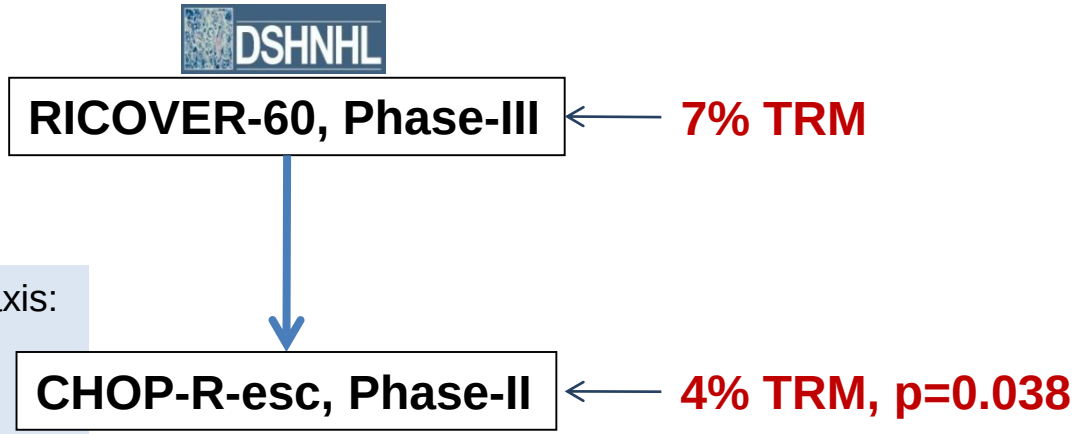
ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Wilson et al; ASH 2016, abstract 469

Phase-II

Historical controls -> treatment-by-time interactions:

Results of identical treatment improve over time



Mandatory anti-infective prophylaxis:

- Aciclovir
- Cotrimoxazol
- Fluorchinolon (neutropenia)

Zettl et al; submitted

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Phase-II

German Lymphoma Alliance

Levelling of prognostic factors?

- Indirect evidence of efficacy in subgroups?

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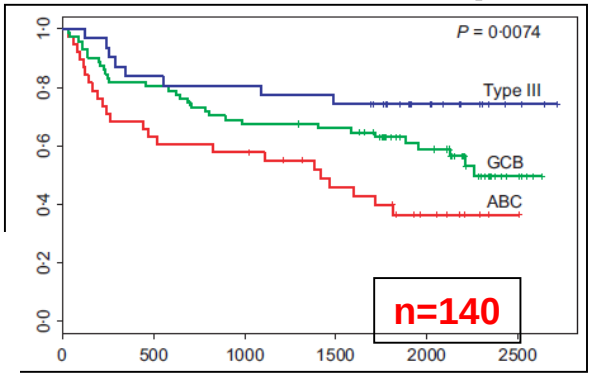
Phase-II

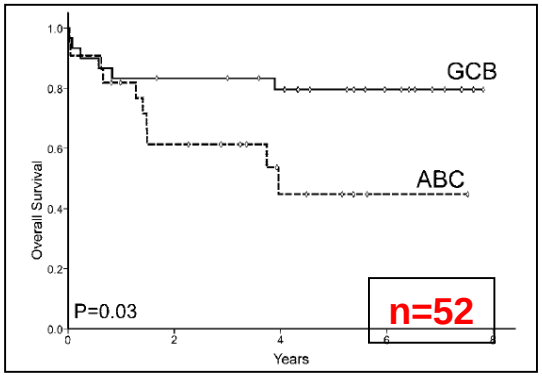
German Lymphoma Alliance

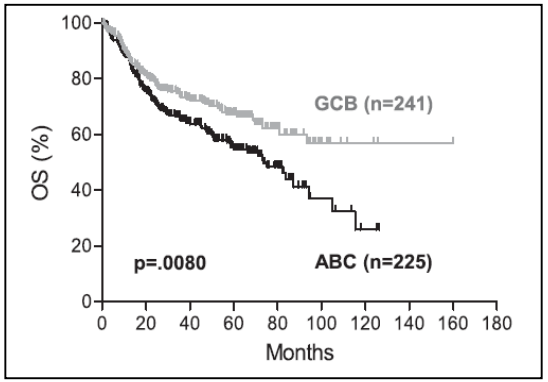
Levelling of prognostic factors?

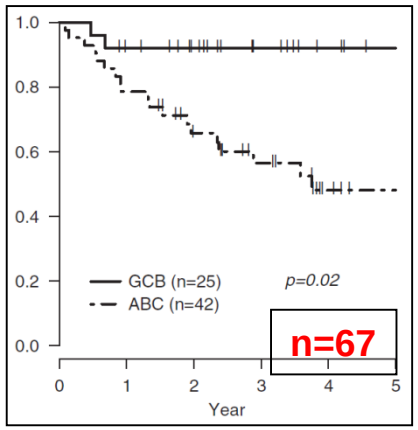
GBC vs. ABC, Gene-expression profiling (GEP):

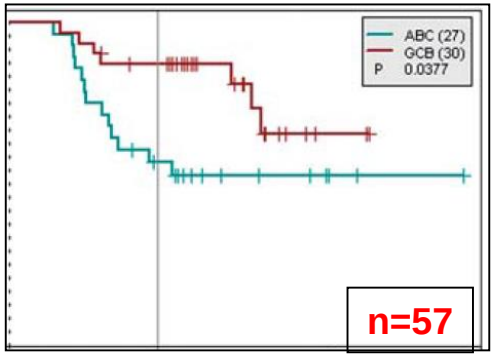
Überleben

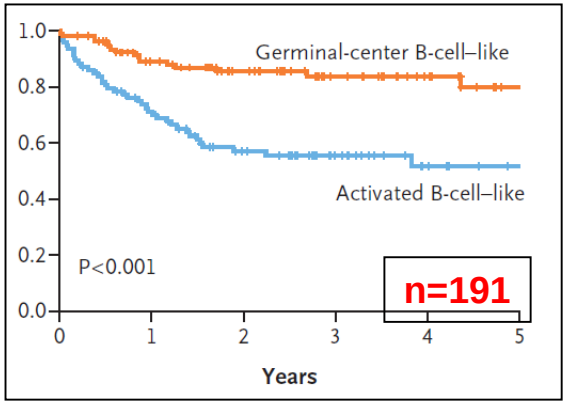










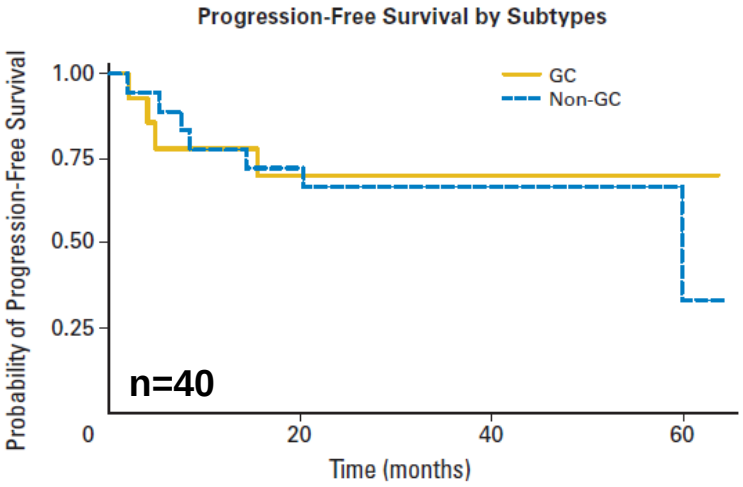


Barrans, BJH, 2012; Gutierrez-Garcia, Blood 2012; Hu, Blood 2103; Jais, Leukemia 2008; Lanic, Leuk Lymph 2011; Lenz, NEJM 2008.

Phase-II

Levelling of prognostic factors?

R-CHOP + Bortezomib



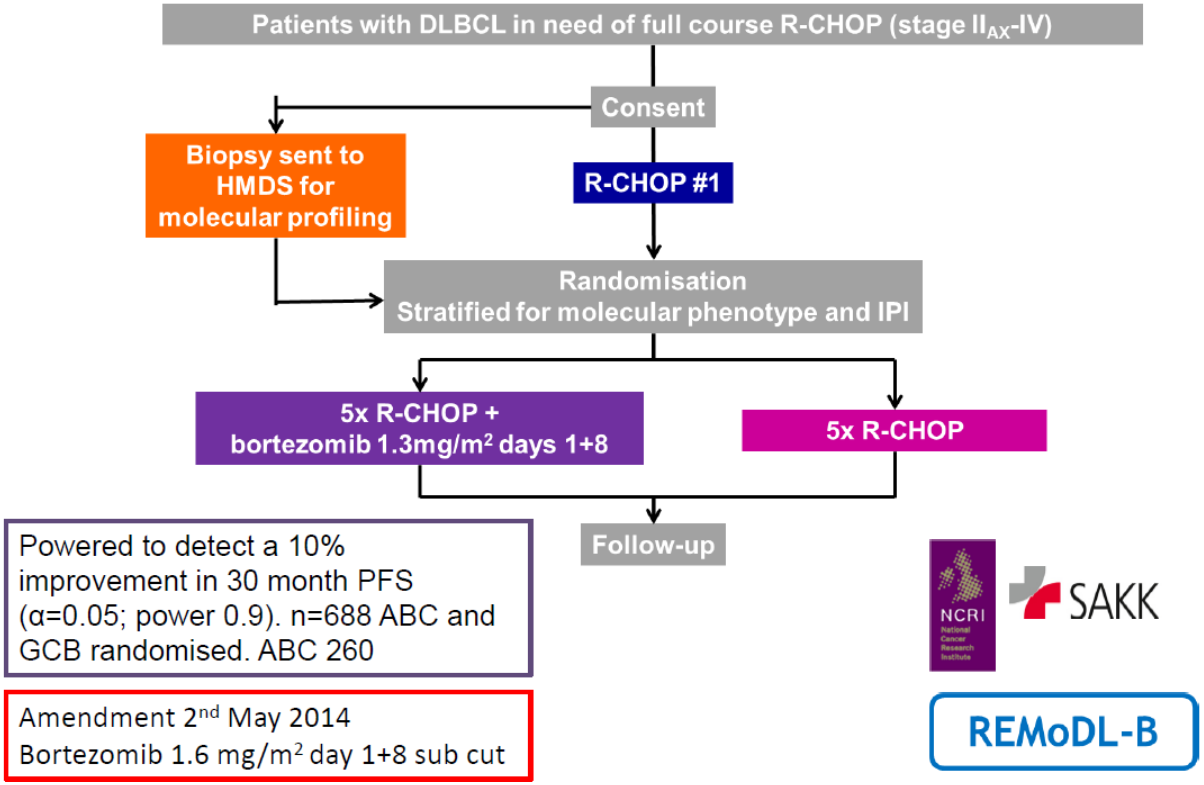
Hypothesis: Subgroup-specific activity of Bortezomib in ABC-like DLBCL

Ruan et al; JCO, 2011

Phase-II

Levelling of prognostic factors?

REMoDL-B: Study design

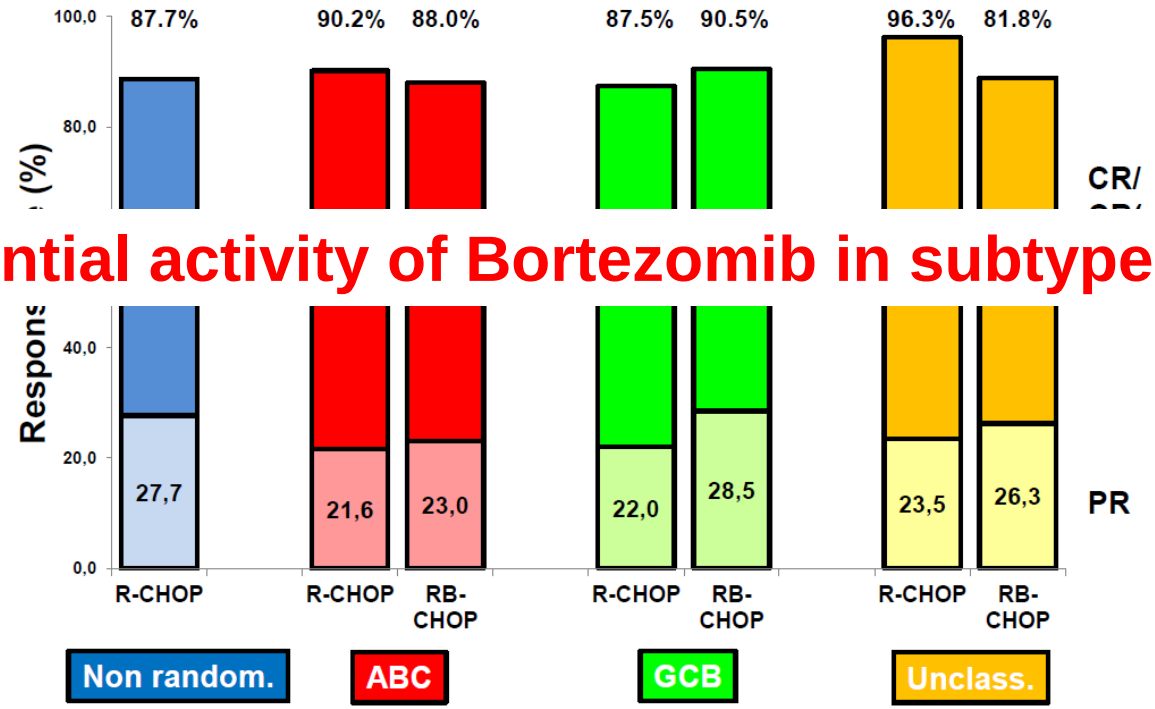


Davies, ASH; 2015

Phase-II

Levelling of prognostic factors?

REMoDL-B Response rate (%): Molecular profile and arm



No differential activity of Bortezomib in subtypes of DLBCL

Davies, ASH; 2015

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Phase-II

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Levelling of prognostic factors?

- Indirect evidence of efficacy in subgroups?

Phase-III

randomized controlled multicenter trials:

- **definitive assessment of efficacy, in comparison with current standard treatment.**

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Phase-III

German Lymphoma Alliance

Examples of negative Phase-III trials in DLBCL:

- **R-CHOP-21 vs. R-CHOP-14**
- **R-CHOP-21 vs. DA-EPOCH-R**
- **R-CHOP-21 vs. G-CHOP-21**

Cunningham, Lancet; 2013. Wilson et al; ASH 2016, abstract 469. Vitolo et al; JCO 2017

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Phase-III

German Lymphoma Alliance

Examples of negative Phase-III trials in DLBCL:

- **R-CHOP-21 vs. R-CHOP-14** — *OS: 70% -> 78%, power 90%, α=5%*
- **R-CHOP-21 vs. DA-EPOCH-R**
- **R-CHOP-21 vs. G-CHOP-21**

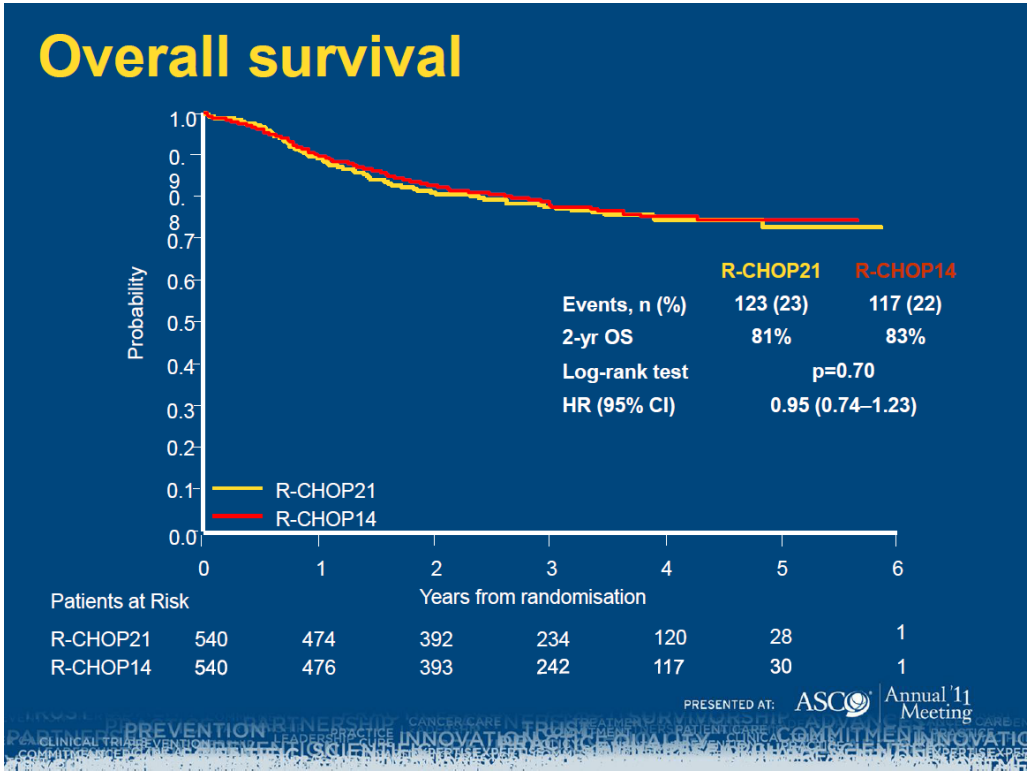
Cunningham, Lancet; 2013. Wilson et al; ASH 2016, abstract 469. Vitolo et al; JCO 2017

Phase-III

Examples of negative Phase-III trials in DLBCL:

R-CHOP-21 vs. R-CHOP-14

CD20⁺ DLBCL
>18 years
Stages II-IV,
I with bulk



Cunningham, Lancet; 2013

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Phase-III

German Lymphoma Alliance

Examples of negative Phase-III trials in DLBCL:

- **R-CHOP-21 vs. R-CHOP-14** — *OS: 70% -> 78%, power 90%, α=5%*
- **R-CHOP-21 vs. DA-EPOCH-R**
- **R-CHOP-21 vs. G-CHOP-21**

Cunningham, Lancet; 2013. Wilson et al; ASH 2016, abstract 469. Vitolo et al; JCO 2017

Phase-III

Examples of negative Phase-III trials in DLBCL:

- **R-CHOP-21 vs. R-CHOP-14** — *OS: 70% -> 78%, power 90%, α=5%*
- **R-CHOP-21 vs. DA-EPOCH-R** — *3-yrs EFS 55% -> 70%, power 90%, α=5%*
- **R-CHOP-21 vs. G-CHOP-21**

Cunningham, Lancet; 2013. Wilson et al; ASH 2016, abstract 469. Vitolo et al; JCO 2017

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Phase-III

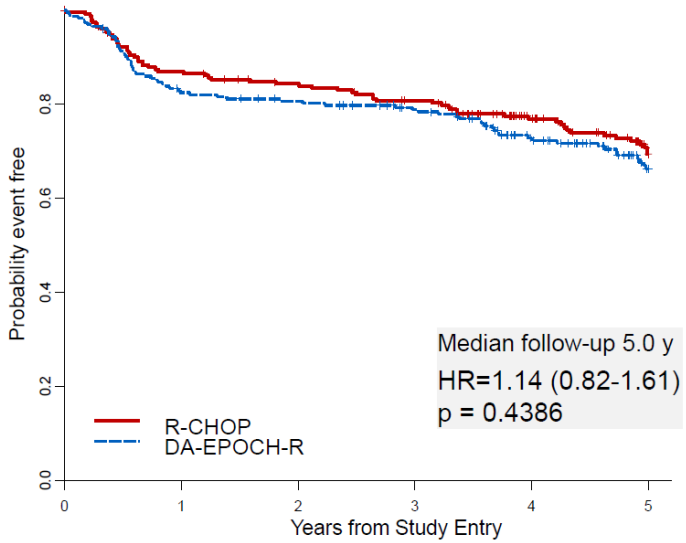
German Lymphoma Alliance

Examples of negative Phase-III trials in DLBCL:

R-CHOP-21 vs. DA-EPOCH-R

50303 Event Free Survival

CD20⁺ DLBCL
>18 years
Stages II-IV,
Stage I PMBCL



Arm	N	Events	3 Y (95% CI)	5 Y (95% CI)
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DA-EPOCH-R	232	70	0.79 (0.73-0.84)	0.66 (0.59-0.72)

3-yrs EFS 81% (95%CI 0.75-0.85)

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Wilson et al; ASH 2016, abstract 469

Phase-III

Examples of negative Phase-III trials in DLBCL:

- **R-CHOP-21 vs. R-CHOP-14** — *OS: 70% -> 78%, power 90%, α=5%*
- **R-CHOP-21 vs. DA-EPOCH-R** — *3-yrs EFS 55% -> 70%, power 90%, α=5%*
- **R-CHOP-21 vs. G-CHOP-21**

Cunningham, Lancet; 2013. Wilson et al; ASH 2016, abstract 469. Vitolo et al; JCO 2017

Phase-III

Examples of negative Phase-III trials in DLBCL:

- **R-CHOP-21 vs. R-CHOP-14** — *OS: 70% -> 78%, power 90%, α=5%*
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- **R-CHOP-21 vs. G-CHOP-21** — *3-yrs PFS 60%->68%, power 80%, α=5%*

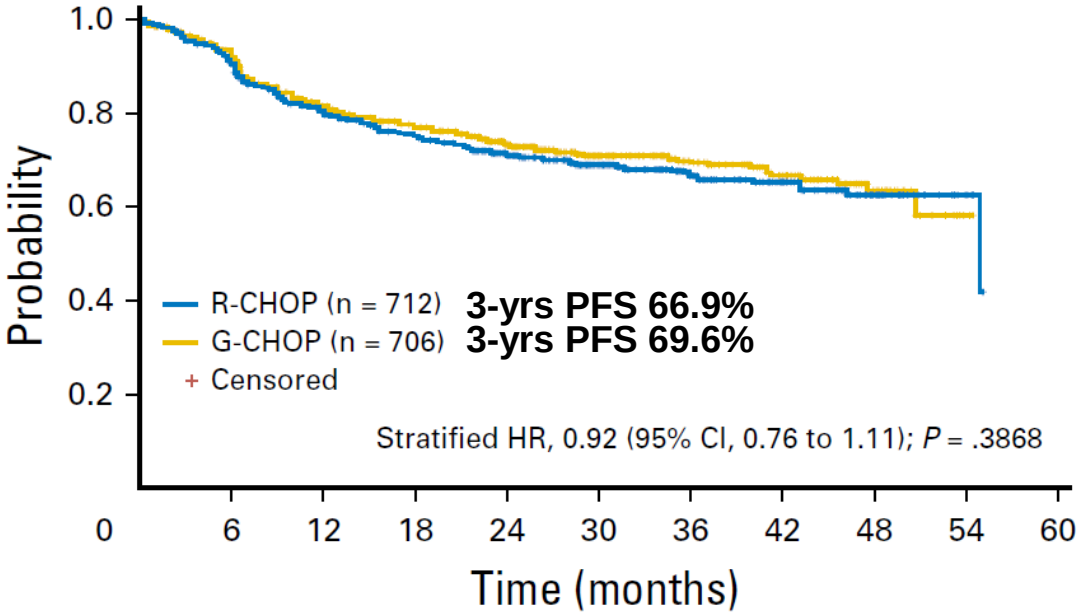
Cunningham, Lancet; 2013. Wilson et al; ASH 2016, abstract 469. Vitolo et al; JCO 2017

Phase-III

Examples of negative Phase-III trials in DLBCL:

R-CHOP-21 vs. G-CHOP-21

CD20⁺ DLBCL
>18 years
IPI ≥ 2
IPI=1 + age<60
IPI=0 + bulk



No. at risk:

R-CHOP	712	616	527	488	413	227	142	96	41	6
G-CHOP	706	622	540	502	425	240	158	102	39	2

Vitolo, JCO; 2017

Phase-III

Examples of negative Phase-III trials in DLBCL:

- **R-CHOP-21 vs. R-CHOP-14** — *OS: 70% -> 78%, power 90%, α=5%*
- **R-CHOP-21 vs. DA-EPOCH-R** — *3-yrs EFS 55% -> 70%, power 90%, α=5%*
- **R-CHOP-21 vs. G-CHOP-21** — *3-yrs PFS 60%->68%, power 80%, α=5%*

Cunningham, Lancet; 2013. Wilson et al; ASH 2016, abstract 469. Vitolo et al; JCO 2017

Phase-III

Lessons from negative Phase-III trials in DLBCL:

- **R-CHOP-21 is more effective than assumed,**
- **we are reaching a plateau of efficacy,**
- **in an unselected population improvement of the primary endpoint by >7% is NOT realistic any more.**

Consequences:

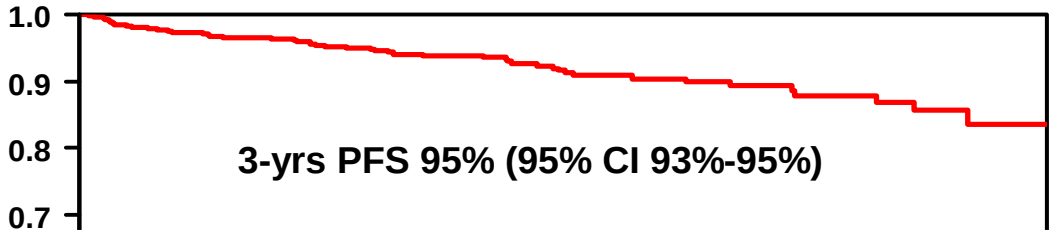
- **Larger trials?**
- **Trials in subgroups defined by biology or risk?**

Phase-III

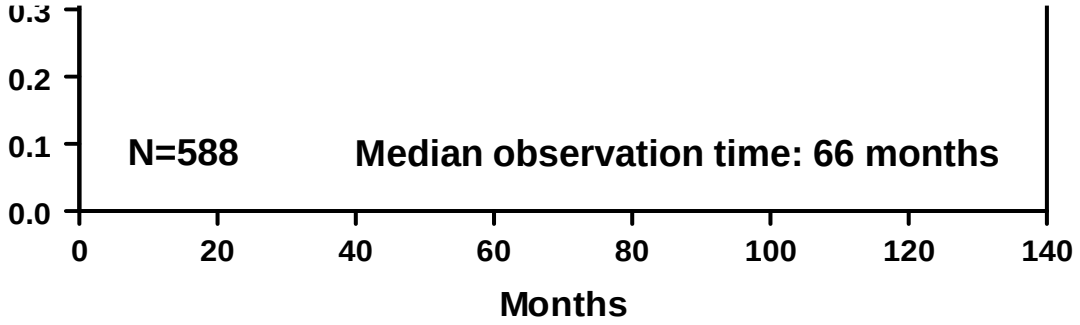
Subgroups defined by risk:

International Prognostic Index, low-risk:

FLYER:



➡ **Improvement of any survival-endpoint is NOT realistic!**



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Phase-III

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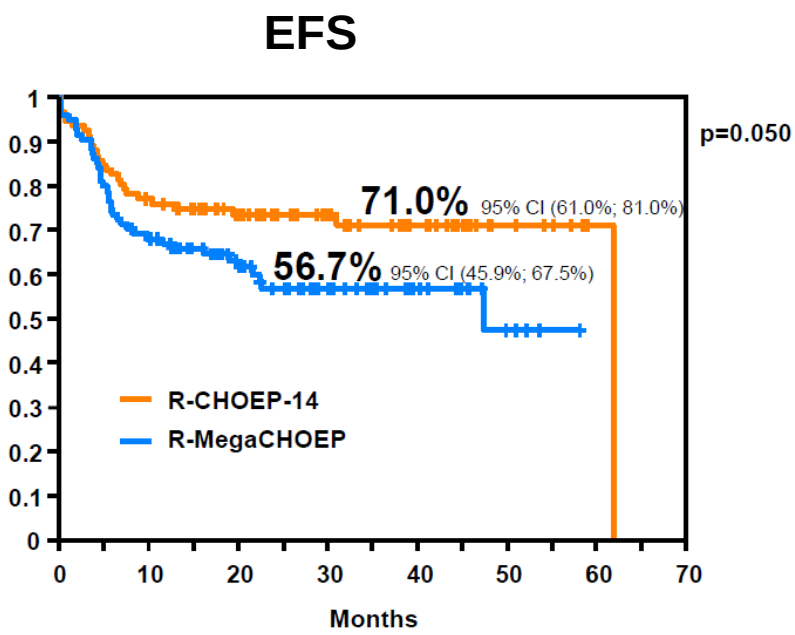
Subgroups defined by risk:

International Prognostic Index, high-risk:

Mega-CHOEP:

CD20⁺ DLBCL
18-60 years
IPI≥2



➡ **Internal Validation**

Schmitz et al, Lancet Oncol; 2012.

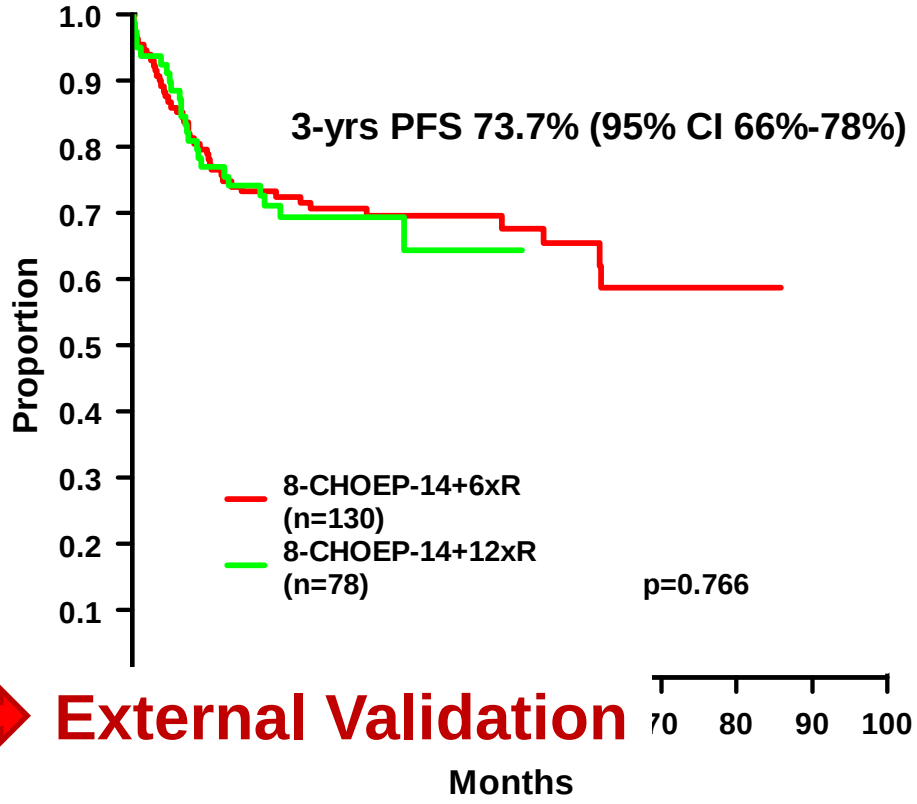
Phase-III

Subgroups defined by risk:

International Prognostic Index, high-risk:

Mega-CHOEP:

CD20⁺ DLBCL
18-60 years
IPI≥2



➡ **External Validation**

Schmitz et al, Lancet Oncol; 2013. Schmitz et al., ASH 2015, abstract 473

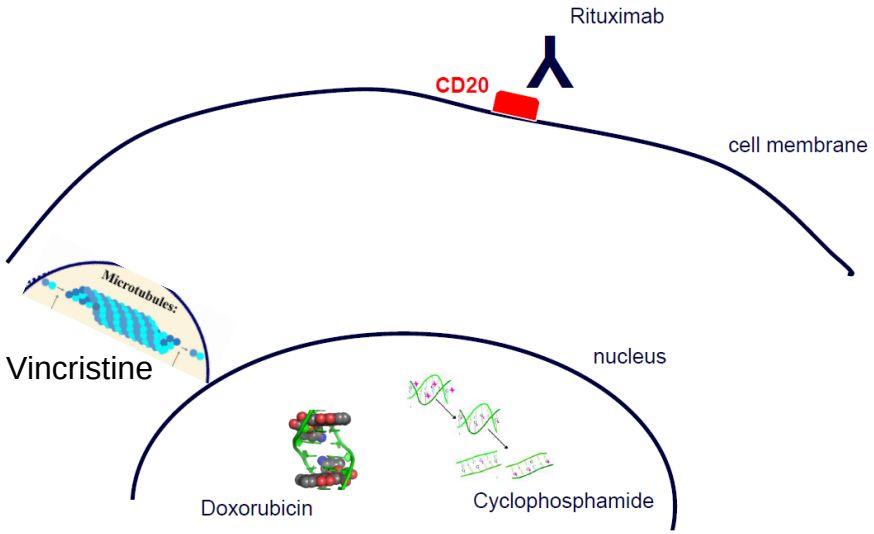
Phase-III

Hypothetical trial:

Improvement of R-CHOP by R-CHOEP in IPI≥2 patients:

Rationale:

The principle R-CHOP

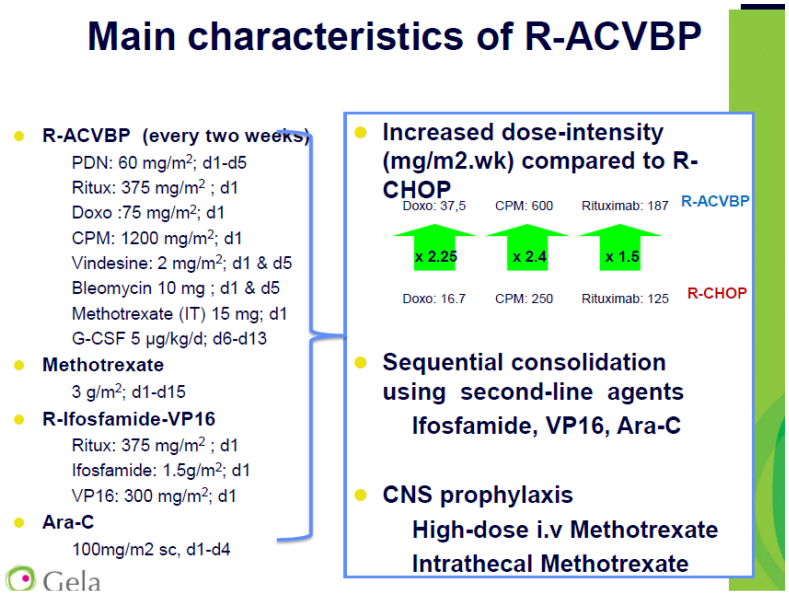


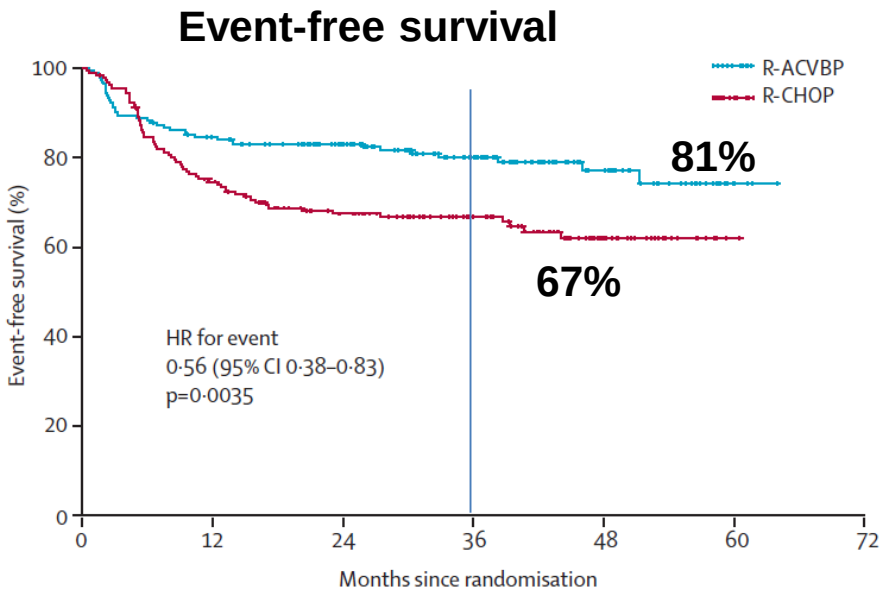
Phase-III

Hypothetical trial:

Improvement of results by direct DNA interaction:

LNH03-2B:
18-60 years, aaIPI=1





Recher Lancet ; 2011

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Phase-III

German Lymphoma Alliance

Hypothetical trial:

Improvement of results by direct DNA interaction:

CALGB-50303:

50303 5-yr EFS by IPI and age

	% of Pts	ALL	R-CHOP	DA-EPOCH-R	P-value
Age					0.073
≤ 60	59	71%	73%	70%	
> 60	41	63%	65%	61%	
IPI					<0.001
0-1	27	82%	90%	72%	
2	38	70%	72%	68%	
3	25	55%	50%	61%	
4-5	10	53%	40%	60%	

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Wilson et al; ASH 2016, abstract 469

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Phase-III

German Lymphoma Alliance

Hypothetical trial:

Improvement of R-CHOP by R-CHOEP in aaIPI≥2 patients:

Statistical assumption:

- **R-CHOP-21 -> 2-yrs PFS = 64%,**
- **R-CHOEP-21 improves 2-yrs PFS by 7%,**
- **R-CHOEP-14 improves 2-yrs PFS of R-CHOEP-21 by 4%**

➡ **2-yrs PFS of R-CHOEP-14 = 75%**

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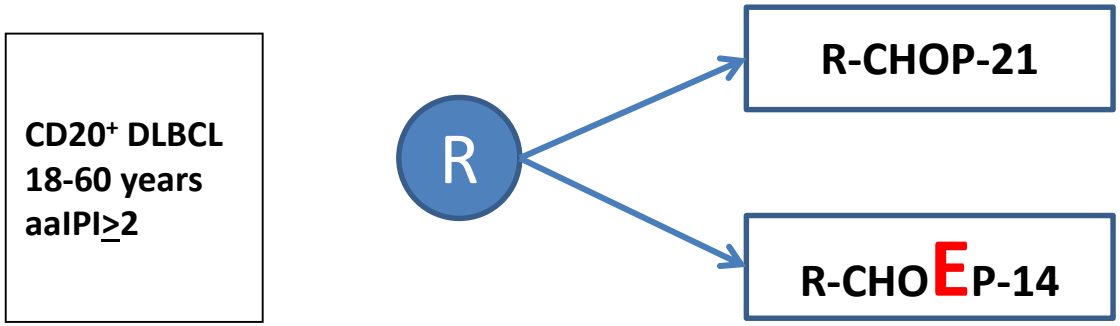
Phase-III

German Lymphoma Alliance

Hypothetical trial:

Improvement of R-CHOP by R-CHOEP in aaIPI≥2 patients:

Statistical analysis:



➡ 2-yrs PFS improved from 64% to 73%, 80% power, α=0.05 (two-sided)

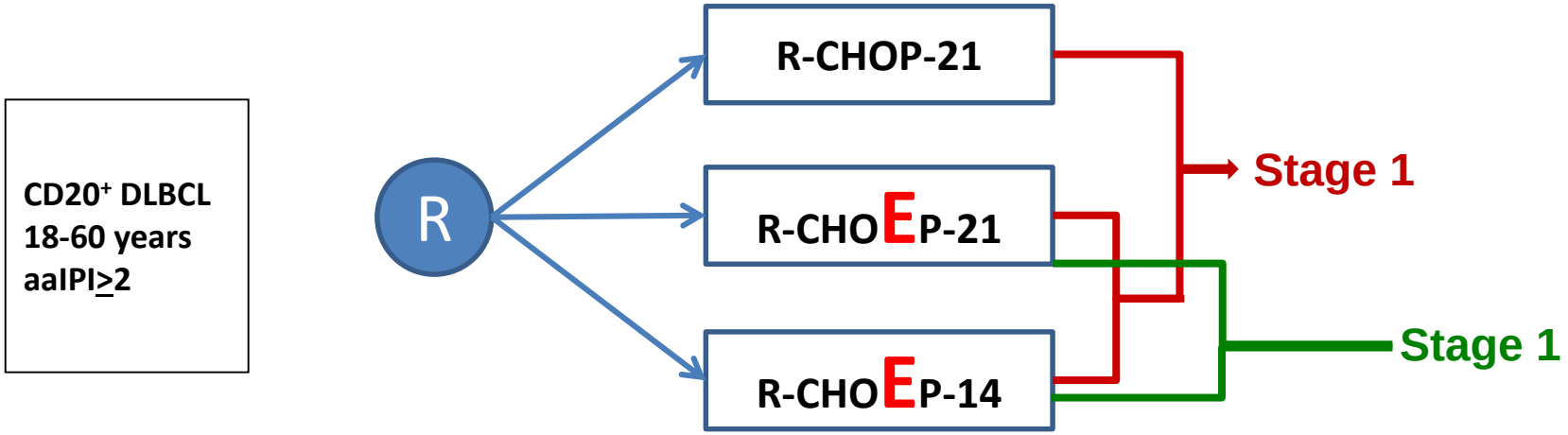
➡ Sample size: n=834 (417/417)

Phase-III

Hypothetical trial:

Improvement of R-CHOP by R-CHOEP in aaIPI≥2 patients:

Adaptive design - Sample size reestimation:



➡ Stage 1: R-CHOP-21 vs. R-CHOEP-14/21

➡ Stage 2: sample size reestimation R-CHOEP-14 vs. R-CHOEP-21 based on observed Hazard ratios using prespecified boundaries

Bhatt & Mehta, NEJM 2016

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Phase-III

German Lymphoma Alliance

Hypothetical trial:

Improvement of R-CHOP by R-CHOEP in aaIPI≥2 patients:

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Conclusion

German Lymphoma Alliance

Trials in DLBCL:

- Textbook of methods in clinical trials is valid
  - algorithm phase-I -> phase II -> phase III
- R-CHOP is more effective than assumed,
- We are reaching a plateau of efficacy,
- Do not overestimate efficacy of the experimental therapy

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Acknowledgement

German Lymphoma Alliance

Studiensekretariat Homburg / Saar:

Michael Pfreundschuh, Viola Pöschel…

UKS Universitätsklinikum des Saarlandes

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