

New developments in NHL: ASCO 2009

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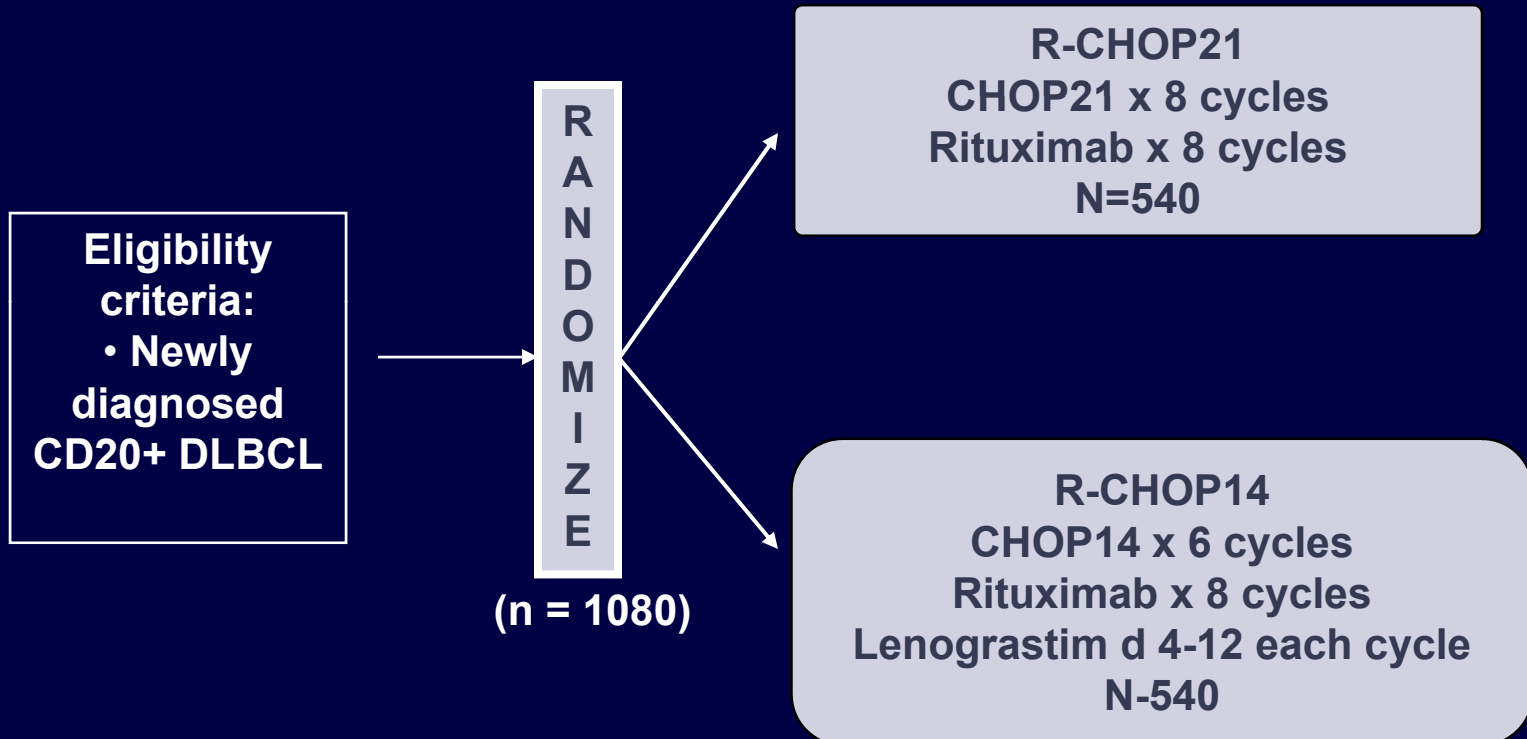
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Topics for Discussion

- **Non-Hodgkin Lymphoma**

- Upfront DLBCL – moving beyond R-CHOP
- Relapsed DLBCL – limited progress
- Indolent lymphoma
 - Vaccines
 - New Combinations and Novel Agents
- T-Cell Lymphoma

Phase III R-CHOP14 vs. R-CHOP21 regimen in newly diagnosed DLBCL



- Stratification:**
- IPI (0-1, 2, 3, 4-5)
 - Age <60 vs. ≥60 years
 - Treatment center

- **Primary: Overall Survival**
- **Secondary: Failure free survival**
 - Toxicity
 - Response

R-CHOP-21 vs R-CHOP-14 in DLBCL

Strengths

- 1000+ patients, 119 sites, 3.5 years
- All ages, mostly advanced stage, balanced IPI
- Powered for overall survival
- Waiting for sufficient followup for full presentation (current median f/u 17 months)

Weaknesses (debatable)

- 8 cycles of therapy
- GCSF in roughly 50% of R-CHOP-21, all R-CHOP-14

Toxicity during treatment

Toxicity grade ≥ 3	R-CHOP21 %	R-CHOP14 %
Neutropenia*	58	31
Thrombocytopenia*	4	9
Anaemia	1	2
Febrile neutropenia*	13 (2 deaths)	5
Infection	22 (1 death)	18 (2 deaths)
Cardiac	0.4	2
Neurological	7	11
Other grade 5 toxicities	n=4	n=4

* $p < 0.01$ (considered significant due to multiple testing)

R-CHOP-21 vs R-CHOP-14 in DLBCL

Key points – dosing/toxicity

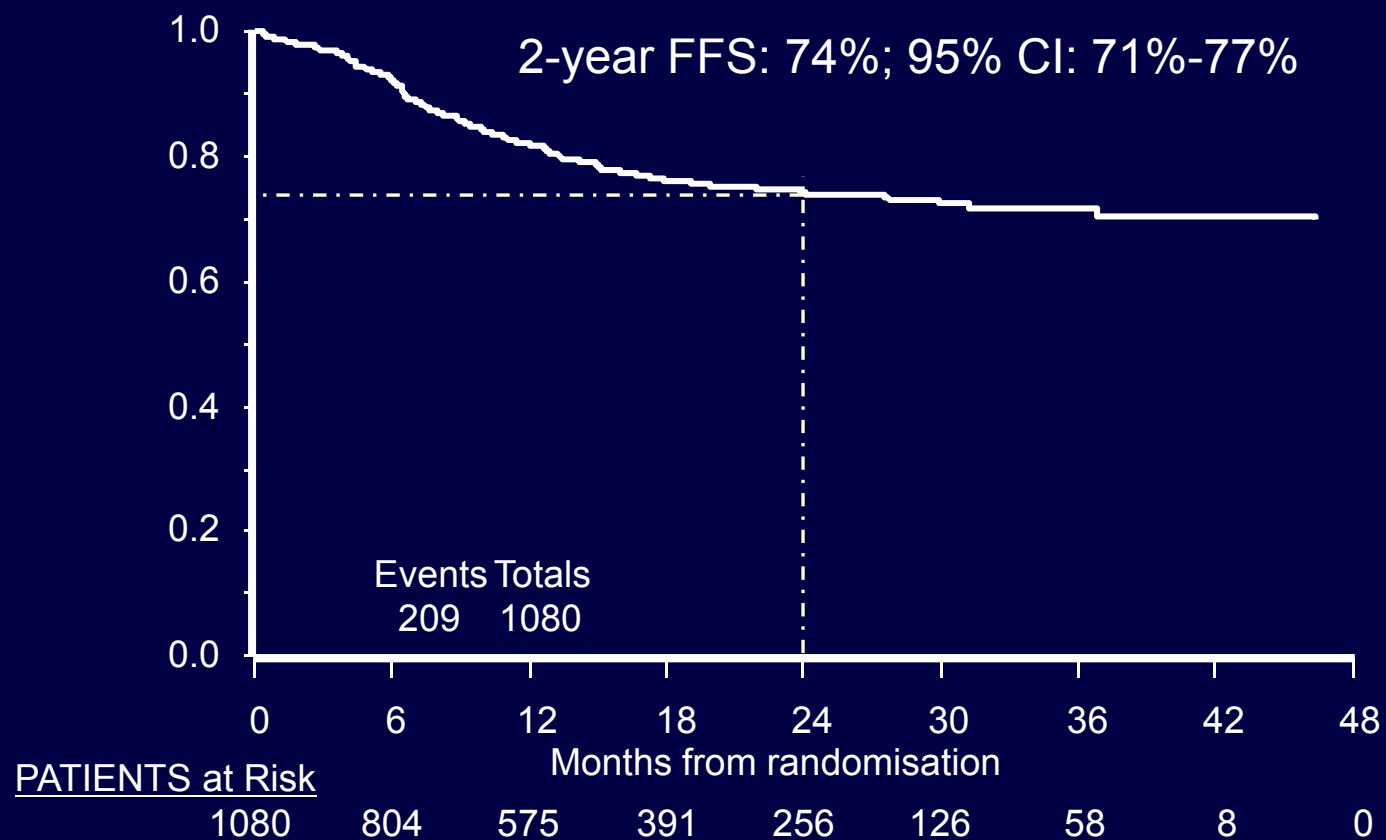
- More early stopping in R-CHOP-21
 - R-CHOP-21 19% stopped early (6% NR/PD/death)
 - R-CHOP-14 10% stopped early (2% NR/PD/death)
 - Importance vs artifact of regimen
 - 8 cycles, Shorter duration of therapy with 14d cycle, Less GCSF, MD choice
- Similar % dose delays
- More thrombocytopenia with R-CHOP-14
- More neutropenia, FN with R-CHOP-21 (less GCSF)

Overall response rates

Based on end of treatment scan n=831	R-CHOP21 n= 405 %	R-CHOP14 n=426 %
CR	49	40
CRu	14	18
PR	24	32
SD	6	5
PD/relapse	6	4
CR/CRu p=0.183	63	58
CR/CRu/PR p=0.139	88	91

249 patients not evaluable or data missing

Failure-free survival: Entire cohort



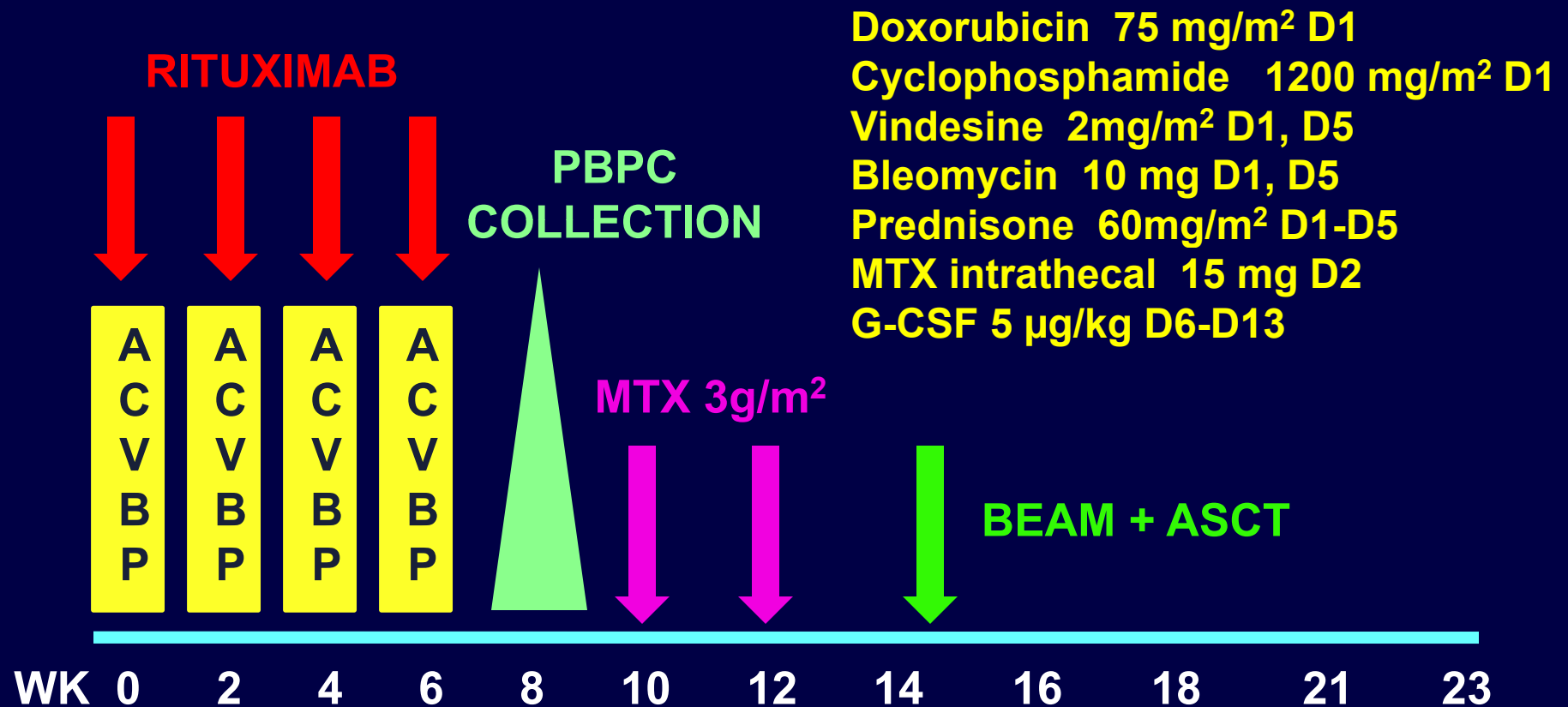
Cunningham et al. *J Clin Oncol* 2009; 27(suppl):435s (abstract 8506).

R-CHOP-21 vs R-CHOP-14 in DLBCL

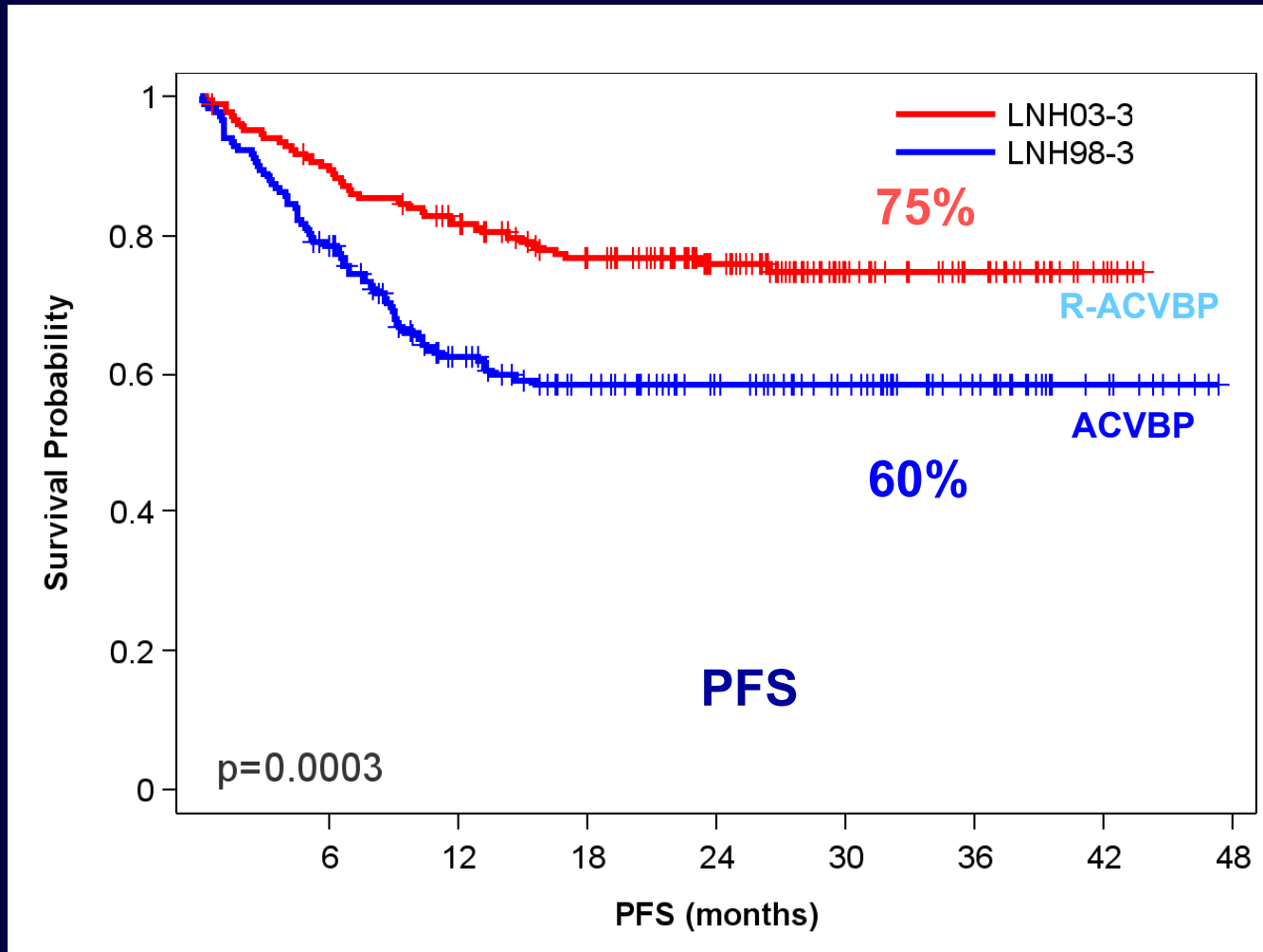
Key points – efficacy

- End of treatment ORR and CR rates similar
- 2 year FFS – 74% (seems good for “all comers”)
- Bottom line
 - More time will tell (? late 2010)
 - R-CHOP-21 remains current standard

Phase II trial of R-ACVBP with up-front autotransplantation in patients with poor risk DLBCL NHL : LNH 2003-3



Progression free survival



	study	N	Median	Min	Max
Follow-up(mo)	LNH03-3	181	27	0	44
Follow-up (mo)	LNH98-3	181	26	0	47

R-ACVBP + AuSCT in DLBCL

• Strengths

- Multicenter study, 200+ pts (2 years)
- 75% received AuSCT
- aalPI 2 or 3 (targeting high risk)

• Weaknesses

- Phase II, with historical comparison
- Under age 60 only

R-ACVBP + AuSCT in DLBCL

Key points

- 75% PFS, 81% OS (at 3 years f/u)
- PFS 15% better than non-rituximab similar regimen (historical comparison)
- Bottom line
 - Effective regimen for high risk, younger patients
 - Needs comparative study
 - Do you need the SCT?
 - Do you need the ACVBP (vs CHOP)?

Epratuzumab (anti-CD22) + R-CHOP-21 in DLBCL

• Strengths

- Multicenter study
- Representative by age, IPI
- Definitions and reporting of both EFS and PFS

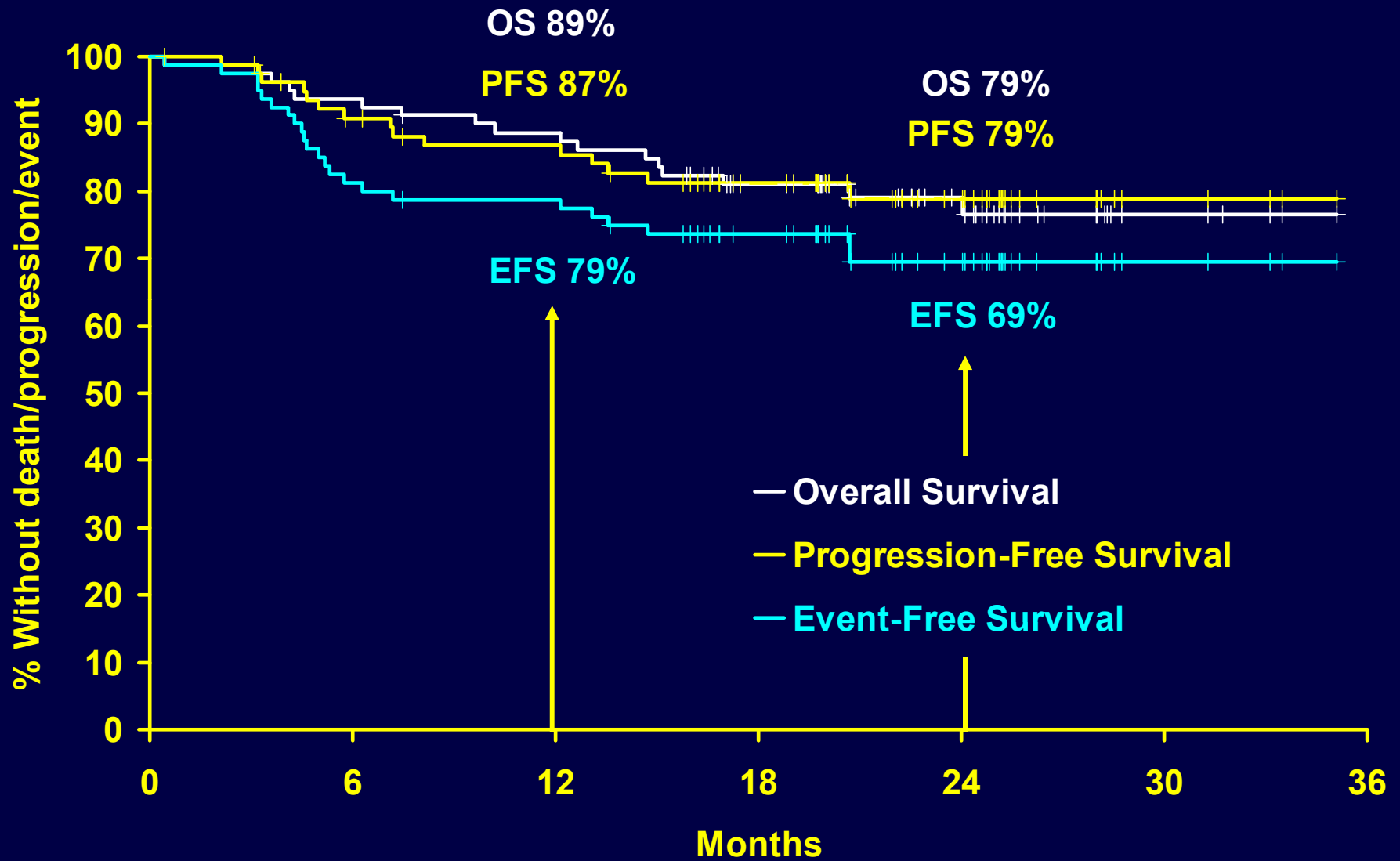
• Weaknesses

- Phase II, comparisons to other groups
- 80 eligible patients (107 enrolled)

Phase II Trial of Anti-CD22 MoAb Epratuzumab Plus R-CHOP in Previously Untreated DLBCL: Response

Response	Patients
Response by CT (n = 80)	
Overall Response Rate	94%
CR/CRu	71%
PR	23%
PET Response (n=77)	
Overall Response Rate	96%
CR/CRu	87%
PR	9%
EFS at 12 months (n = 80)	79%
PFS at 12 months (n = 80)	87%
OS at 12 months (n = 80)	89%

OS / PFS / EFS



Micallef. et al. *J Clin Oncol* 2009; 27(suppl):436s (abstract 8508).

Epratuzumab (anti-CD22) + R-CHOP-21 in DLBCL

Key points

- Toxicity similar to R-CHOP except 70% gr 4 neutropenia, 17% FN
 - Use of GCSF
- Efficacy
 - 94% ORR (71% CR/CRU), 87% PET negative
 - 2 year PFS 79%, OS 79%
 - IPI 3-5 2 year PFS 78%
- Bottom line
 - Compares favorably, randomized study needed

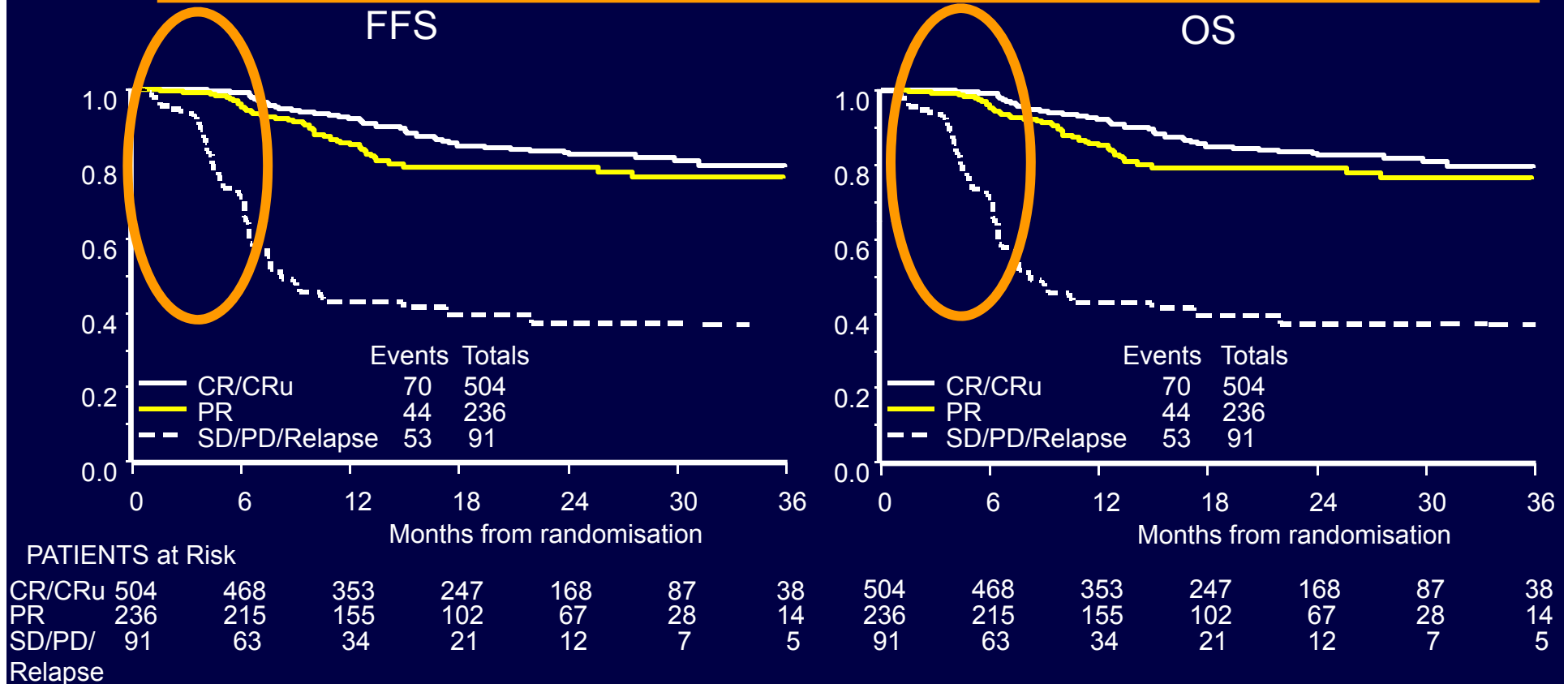
Lining up these 3 studies w/ respect to “higher risk” patients (apples to oranges to plums)

- CHOP-R (21 or 14)
 - 2 year FFS - IPI 2-3 72%, IPI 4-5 60%
- R-ACVBP + AuSCT
 - 3 year PFS - aaIPI 2-3 75%
- CHOP-E-R
 - 2 year PFS – IPI 3-5 78%
 - 2 year FFS – IPI 3-5 67%
- Bottom line – cautious optimism

R-CHOP-21 or 14

FFS and OS by response*

50 % of failures and deaths occur within 6 months



*Based on end of treatment scan (n=831)

Cunningham et al. *J Clin Oncol* 2009; 27(suppl):435s (abstract 8506).

**To make progress beyond R-CHOP-21,
new approaches need to be used
earlier**

- New strategies need to be implemented at or near the start of therapy in order to reduce progression within the first 6 months

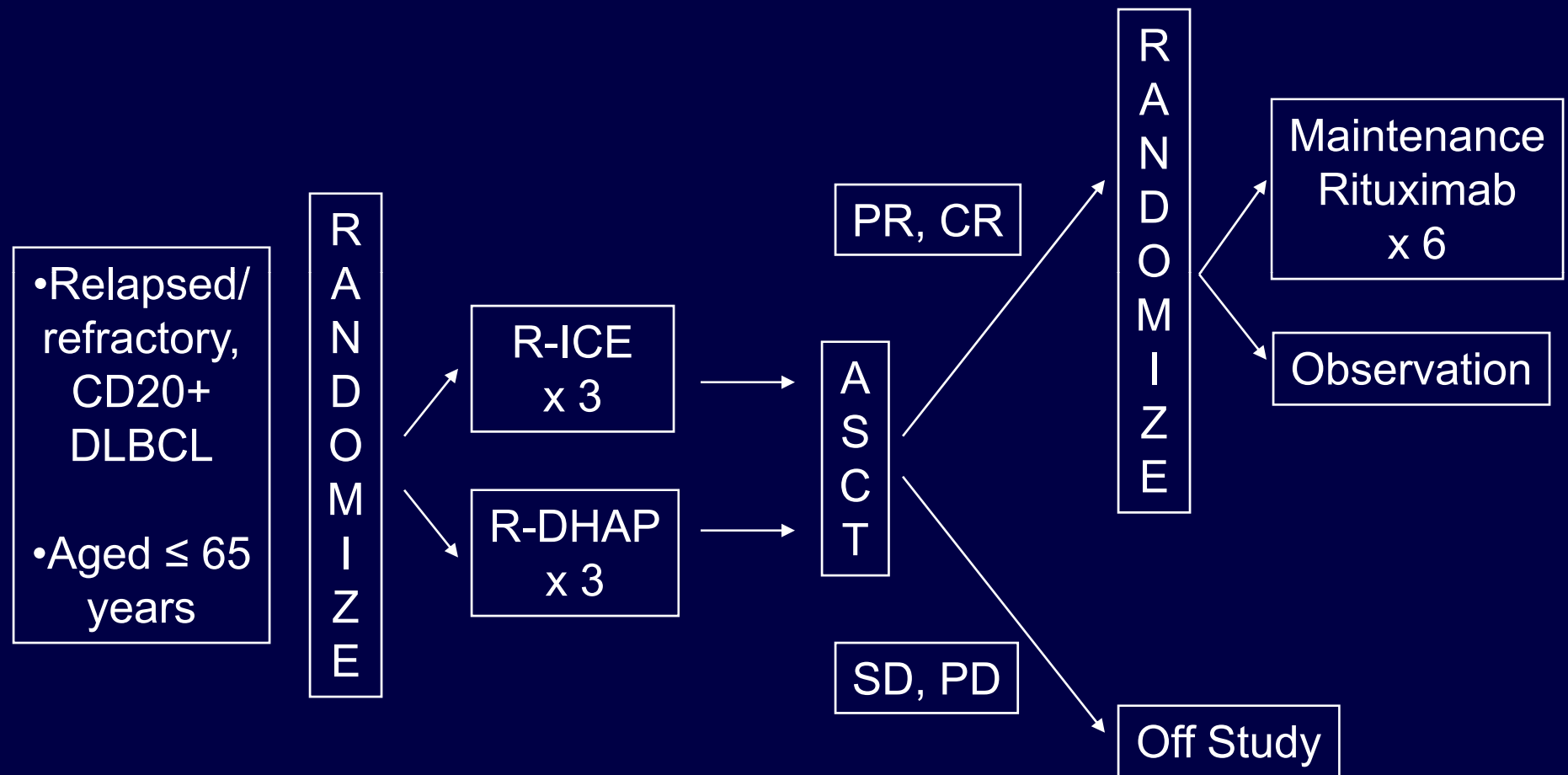
Possible new strategies beyond R-CHOP-21 in DLBCL

- New chemotherapy regimen from day 1
 - Different agents, dose, schedule
 - DA-EPOCH-R vs CHOP-R, CALGB 50303
- Addition of novel agents from day 1
- Changing regimens midstream (PET)
- AutoSCT or other “consolidation” in first remission
- “Maintenance therapies” after R-CHOP

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- Changing regimens midstream (PET) ??????
- AutoSCT or other ~~“consolidation”~~ in first remission
- ~~“Maintenance therapies”~~ after R-CHOP

R-ICE vs. R-DHAP Followed by ASCT and Maintenance Rituximab or Observation in Relapsed DLBCL (CORAL): Study Design

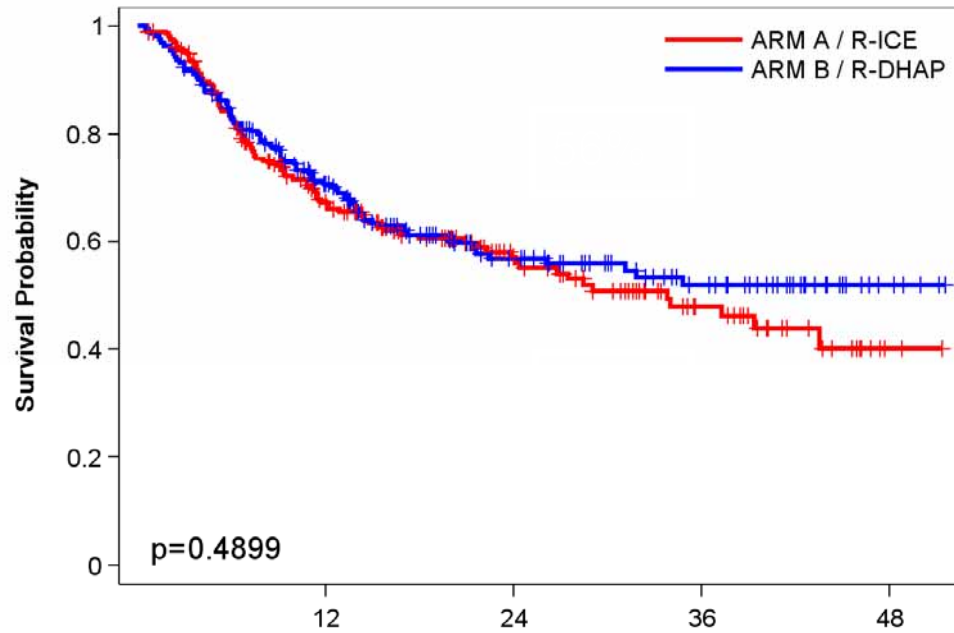


R-ICE Versus R-DHAP Followed by ASCT and Maintenance Rituximab or Observation in Relapsed DLBCL (CORAL): Grade 3/4 Adverse Events

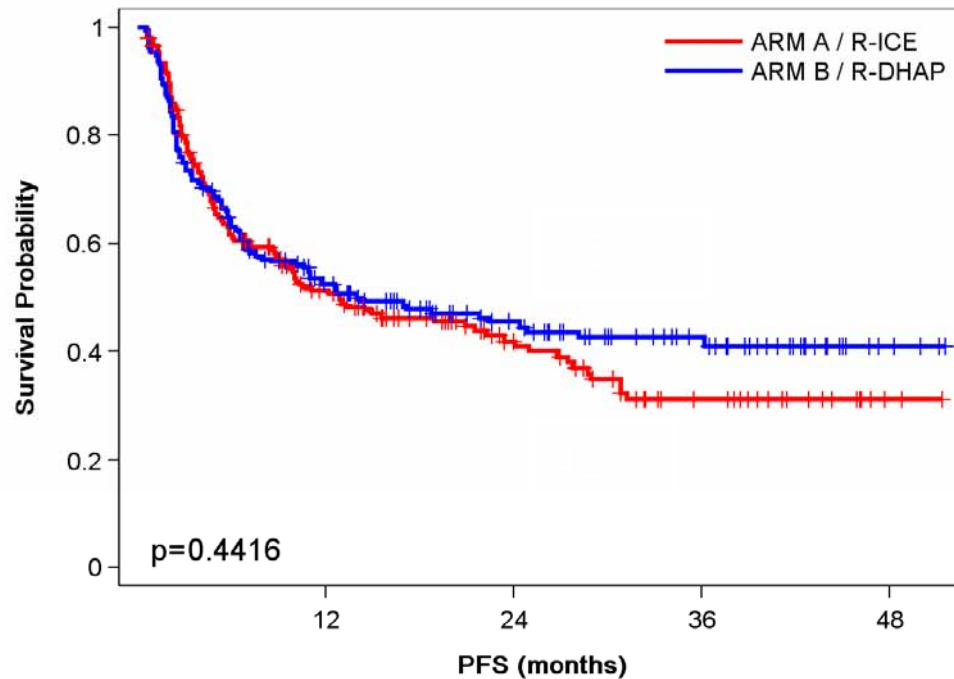
Grade 3/4 AE	R-ICE	R-DHAP
Infection		
With neutropenia	33 (17%)	31 (16%)
Without neutropenia	11 (6%)	15 (8%)
Renal Toxicity	2 (1%)	11 (6%)
Platelets transfusions	35%	57%

R-ICE Versus R-DHAP Followed By ASCT and Maintenance R or Obs in DLBCL (CORAL): Efficacy

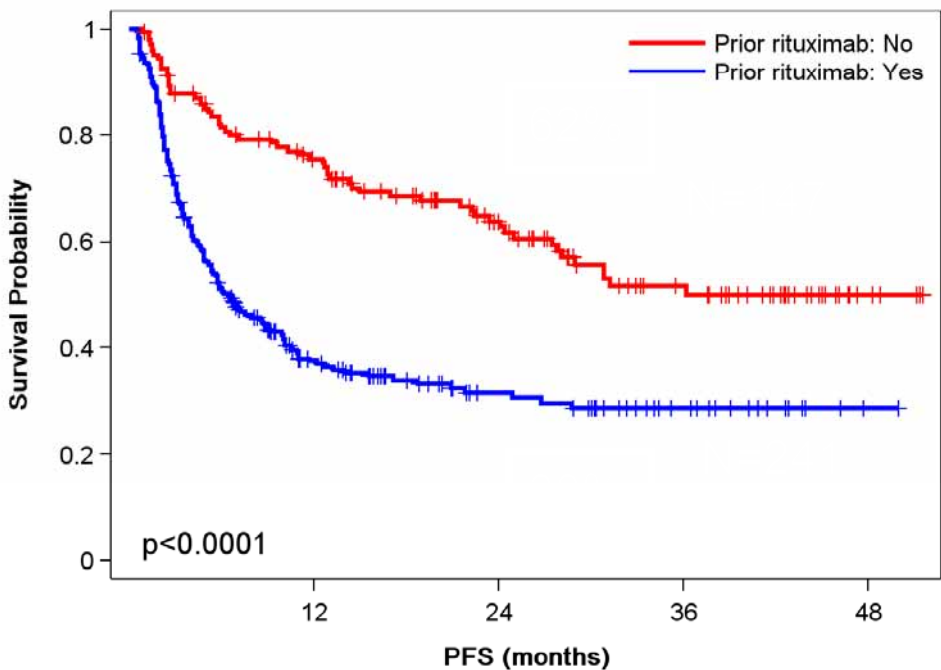
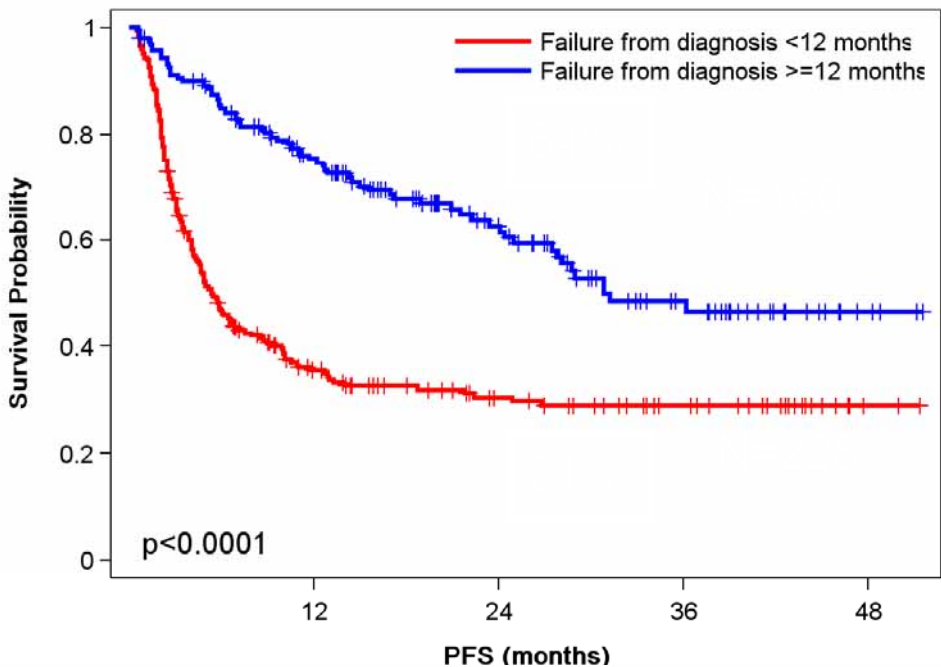
ORR	%	P Value
All Patients (n = 388)	63%	-
CR/CRu	38%	
R-ICE (n=197)	63.5%	-
R-DHAP (n=191)	63%	
No Prior Rituximab (n = 122)	83%	< .0001
Prior Rituximab (n = 124)	51%	
Relapsed > 12 mo (n = 140)	88%	< .0001
Refractory < 12 mo (n = 106)	46%	
sIPI 0-1 (n = 160)	71%	< .0002
sIPI 2-3 (n = 76)	52%	



**OVERALL SURVIVAL
ACCORDING TO TREATMENT
ARM (INDUCTION ITT)**



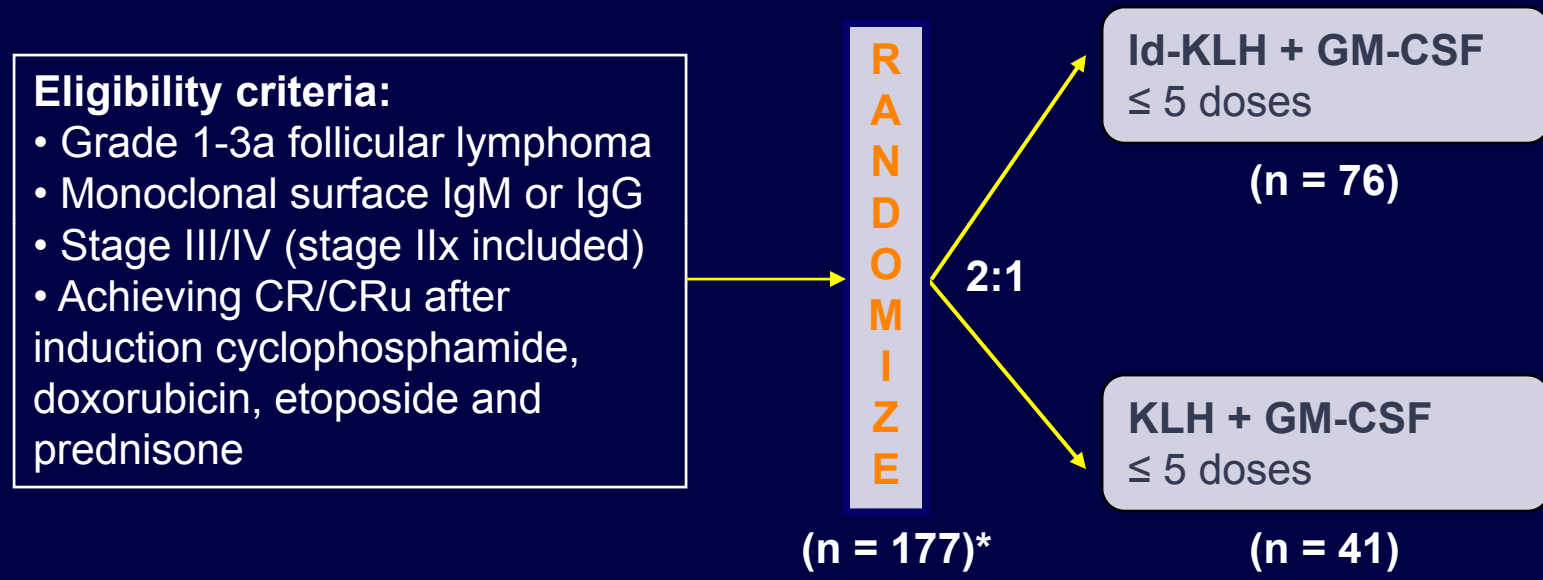
**PROGRESSION-FREE
SURVIVAL ACCORDING TO
TREATMENT ARM
(INDUCTION ITT)**



**PROGRESSION-FREE
SURVIVAL
ACCORDING TO FAILURE
FROM DIAGNOSIS
(INDUCTION ITT)**

**PROGRESSION-FREE
SURVIVAL ACCORDING TO
PRIOR RITUXIMAB
(INDUCTION ITT)**

Phase III BV301 Trial of Idiotypic Vaccine (Id-KLH) in Follicular Lymphoma in First CR



* A total of 60 patients failed to maintain CR/CRu and did not receive the study drug.

- **Primary endpoint: disease-free survival**
- **Secondary endpoints: safety, overall survival, immunologic and molecular responses**

Schuster et al. *J Clin Oncol* 2009; 27(suppl):793s (abstract 2).

Results

Enrollment

Assessed for eligibility
(n=234)

Excluded from Randomization
(n=57)
Did not receive induction therapy (n=6)
Achieved CR (n=2)
Achieved CRu (n=2)
Achieved PD (n=11)
Achieved SD (n=31)
Unknown/Not assessed (n=5)

Stratify / Randomize

Randomized (n=177)

Allocated to Id-KLH
(BiovaxID) (n=118)

Allocated to KLH
(Control) (n=59)

ITT
(n=177)

Post-Induction
Recovery
Period
(6-12 months)

Failed to Maintain
CR/CRu (n=42)

Failed to Maintain
CR/CRu (n=18)

PD,
no vax
(n=60)

Vaccination

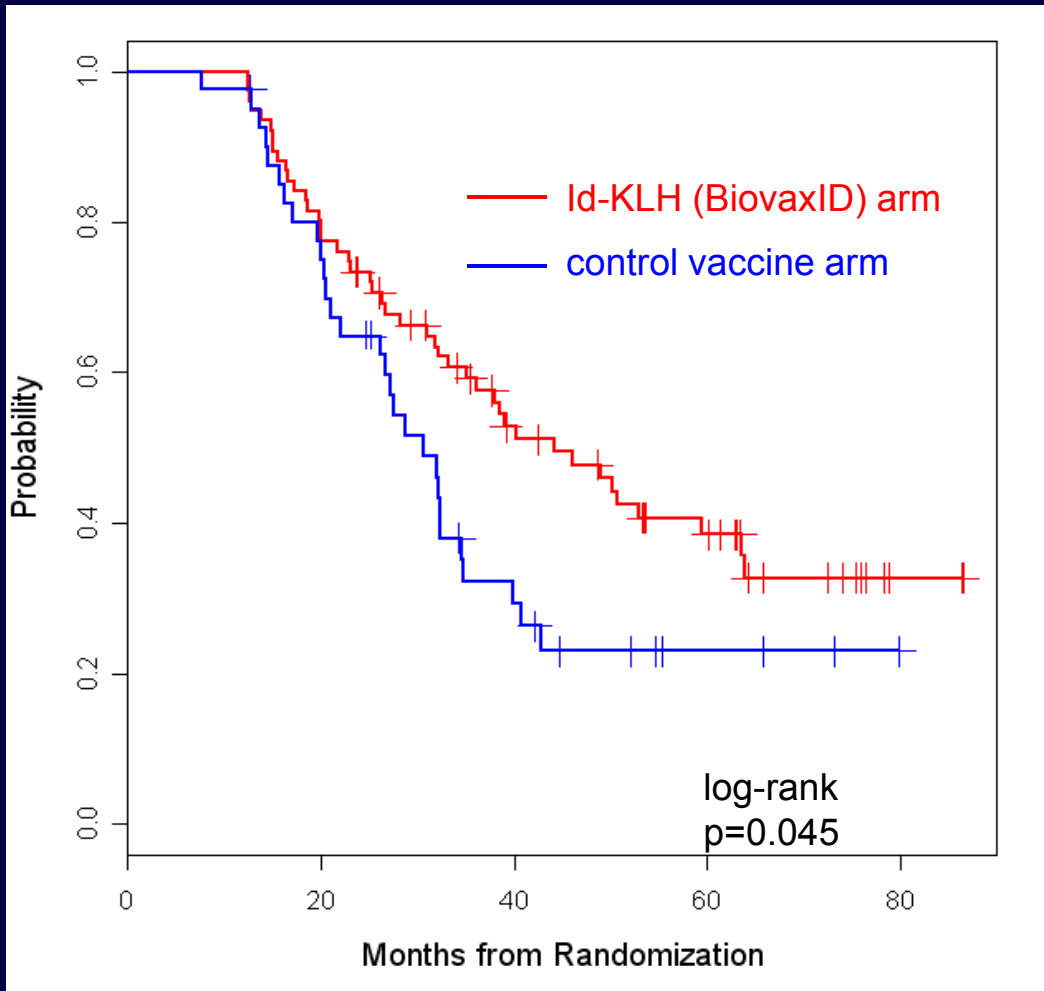
Vaccinated with
Id-KLH + GM-CSF (n=76)
Rec'd 5 immunizations (n=72)
Rec'd 4 immunizations (n=2)
Rec'd 3 immunization (n=2)

Vaccinated with
KLH + GM-CSF (n=41)
Rec'd 5 immunizations (n=39)
Rec'd 4 immunizations (n=1)
Rec'd 2 immunization (n=1)

modified
ITT
(n=117)

Schuster et al. *J Clin Oncol* 2009; 27(suppl):793s (abstract 2).

Disease Free Survival from Randomization for Id-KLH (BiovaxID) vs. Control Arms (mITT)



Median Follow-up
56.6 mo (range 12.6 – 89.3)

Median DFS
Id-KLH (BiovaxID) = 44.2 mo
Control vaccine = 30.6 mo

N = 117
Id-KLH (BiovaxID) N = 76
Control vaccine N = 41

Events
Id-KLH (BiovaxID) = 44
Control vaccine = 29

Cox PH Model
HR = 0.62; [95% CI: 0.39,0.99]
(p=0.047)

Schuster et al. *J Clin Oncol* 2009; 27(suppl):793s (abstract 2).

Bortezomib/bendamustine/rituximab (VBR) in rel/ref FL: VERTICAL study

- Bortezomib 1.6 mg/m² days 1, 8, 15, 22 x 5 cycles
- Bendamustine 50, 70, 90 mg/m²/d days 1, 2
- Rituximab 375 mg/m² Days 1, 8, 15, 22 (cycle 1), day 1 thereafter

Bendamustine dose level	N (%) (n = 15)		
	ORR	CR	PR
50 mg/m ² (n=3)	3 (100%)	2 (67%)	1 (33%)
70 mg/m ² (n=6)	3 (50%)	2 (33%)	1 (17%)
90 mg/m ² (n=6)	6 (100%)	4 (67%)	2 (33%)

Bortezomib/bendamustine/rituximab (VBR) in rel/ref FL: VERTICAL study

Grade 3/4 AE	N (%) (n = 16)
Neutropenia	4 (25%)
Fatigue	4 (25%)
Diarrhea	5 (31%)

**Bendamustine DLT,
70 mg/m² = Gr 4 Dermatitis
90 mg/m² = Gr 3 Thrombocytopenia**

Peripheral Neuropathy (all grades) = 7 (44%)

Phase I Trial of SGN-35 in Relapsed/Refractory Hodgkin Lymphoma or Systemic ALCL

- SGN-35: anti-CD30 Ab-drug conjugate (auristatin)
- Previous phase I trial evaluated every 3-week dosing
 - MTD 1.8 mg/kg
 - DLTs at 2.7 mg/kg: febrile neutropenia, hyperglycemia
 - ORR 15/28 (54%); CR 9/28 (32%)
 - Median PFS > 6 months
- Current study evaluating weekly SGN-35
 - DLTs
 - 1/6 patients at 1.0 mg/kg: grade 3 diarrhea
 - 2/6 patients at 1.4 mg/kg: grade 4 hyperglycemia, grade 3 GI
 - Best clinical response
 - All patients (n=27): ORR 48% (13); CR 37% (10)
 - Hodgkin's Lymphoma (n=22): ORR 41% (9); CR 27% (6)

PROPEL: Pralatrexate in Patients With Relapsed/Refractory PTCL

- PDX 30 mg/m²/week I.V., 6 of 7 weeks + vitamin B₁₂ and folic acid supplementation
- Median of 3 prior systemic regimens (range, 1-12)

Efficacy (by Central Review, IWC)	All Patients (n = 109)
ORR	30 (28%)
CR	8 (7%)
CRu	2 (2%)
PR	20 (18%)
SD	23 (21%)
Median duration of response	9.4 months
Median PFS	108 days
Median OS	14.7 months

PROPEL: Pralatrexate in Patients With Relapsed/Refractory PTCL

Grade 3/4 Adverse Events	Patients (n = 111)	
	Grade 3	Grade 4
Mucositis	20 (18%)	4 (4%)
Fatigue	5 (5%)	2 (2%)
Thrombocytopenia	15 (14%)	21 (19%)
Anemia	17 (15%)	2 (2%)
Neutropenia	14 (13%)	8 (7%)
Hypokalemia	4 (4%)	1 (1%)

Interim phase II study results of Lenalidomide in recurrent T cell lymphoma

Efficacy	Number of Patients (%) (n = 23)
Best Response	
ORR	7 (30%)
CR	0 (0%)
PR	7 (30%)
SD ≥ 3 months	2 (9%)
Median PFS	96 days
Median OS	241 days

Toxicities,

Gr. 4 thrombocytopenia = 33%

Gr. 3 neutropenia = 21%

Gr. 3 febrile neutropenia = 17%

Pain NOS = 17%

Conclusions

- CHOP-R-21 remains current standard for DLBCL
- Relapsed DLBCL remains challenging, particularly for those with short first remission
- Vaccines may improve DFS in FL upfront in certain settings, but overall impact debatable
- Numerous novel agents/regimens under evaluation in various lymphoma subtypes