

Australasian Leukaemia & Lymphoma Group

- > 350 clinician members
- > 70 sites
- 15-20 active trials

Professor Mark Hertzberg
Chair, Scientific Advisory Committee ALLG



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GROUP



Early Treatment Intensification with R-ICE Chemotherapy and Zevalin-BEAM Autologous SCT for Poor Prognosis Diffuse Large B-Cell Lymphoma as Identified by Interim PET/CT Performed After 4 Cycles of R-CHOP-14: ALLG NHL21 Phase II Trial

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**Supported in part by: Roche Products Australia Pty Ltd
Amgen Australia Pty Ltd, Bayer Pharmaceuticals Pty Ltd**

NHL21: Rationale

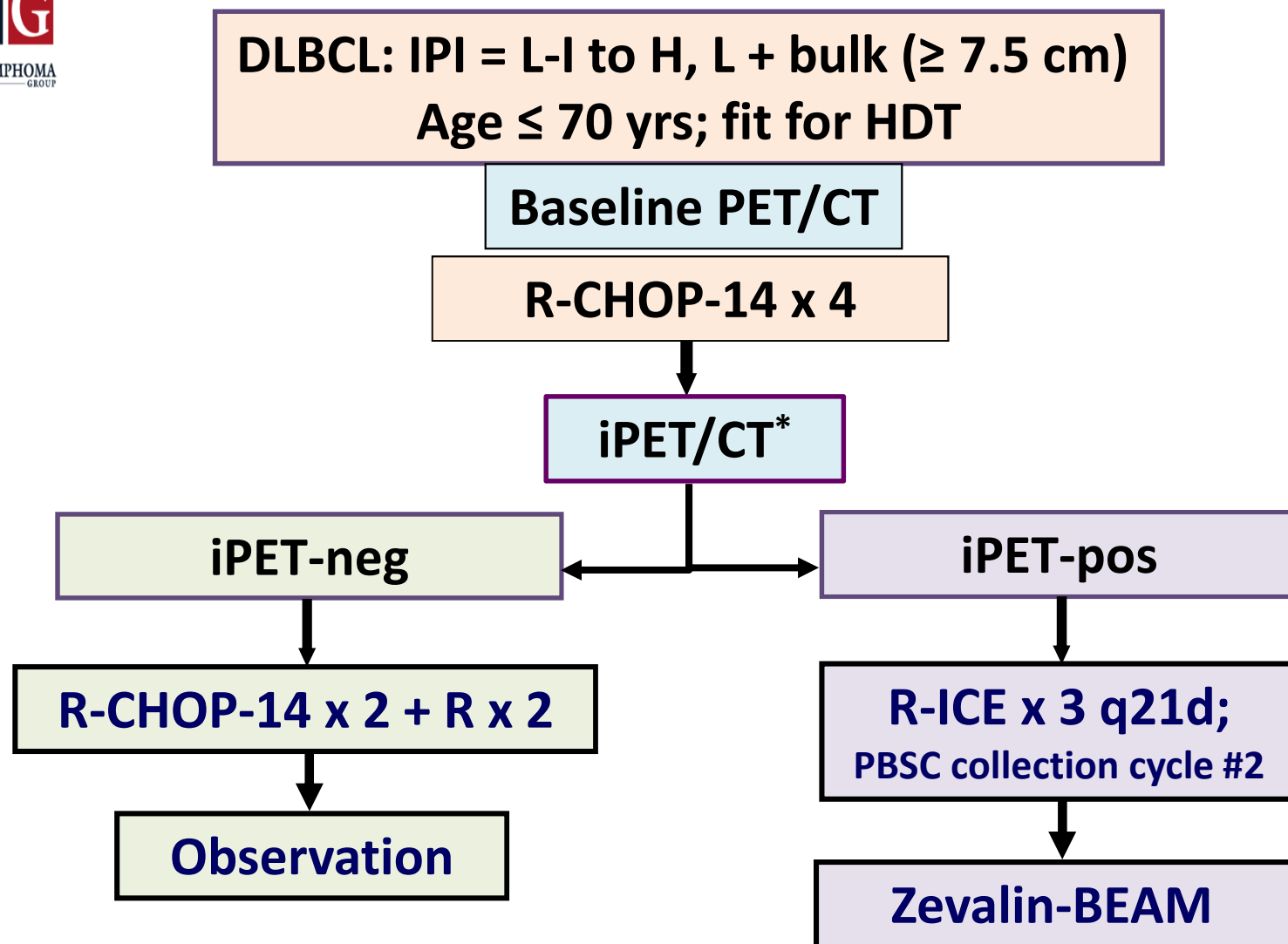
- **Interim PET after cycle 4 of R-chemotherapy has a higher PPV than after 2 cycles.**
- **A high PPV is desirable for selection of patients for treatment intensification.**
- **We chose to evaluate a change to high dose therapy (HDT) as the most widely accepted curative strategy for R-CHOP failures.**
- **Zevalin was combined with BEAM HDT:
potentially more effective than BEAM alone in relapsed DLBCL
without increased toxicity ^{1, 2}**

NHL21: Endpoints and Statistics

- **Primary Endpoint: 2-yr PFS from iPET**
- **The expected 2-yr PFS rate for iPET-4-positive patients treated with R-CHOP based on historical data at study design was considered to be on average 40% (range, 36-47%)¹⁻⁵**
- **With a switch to early treatment intensification the aim was to increase the 2-yr PFS to 65%**
- **A one-stage design with 33 iPET-positive patients provided a probability of at least 90% to detect a difference in 2-yr PFS of 40% versus 65%; 2-sided alpha of 0.05.**

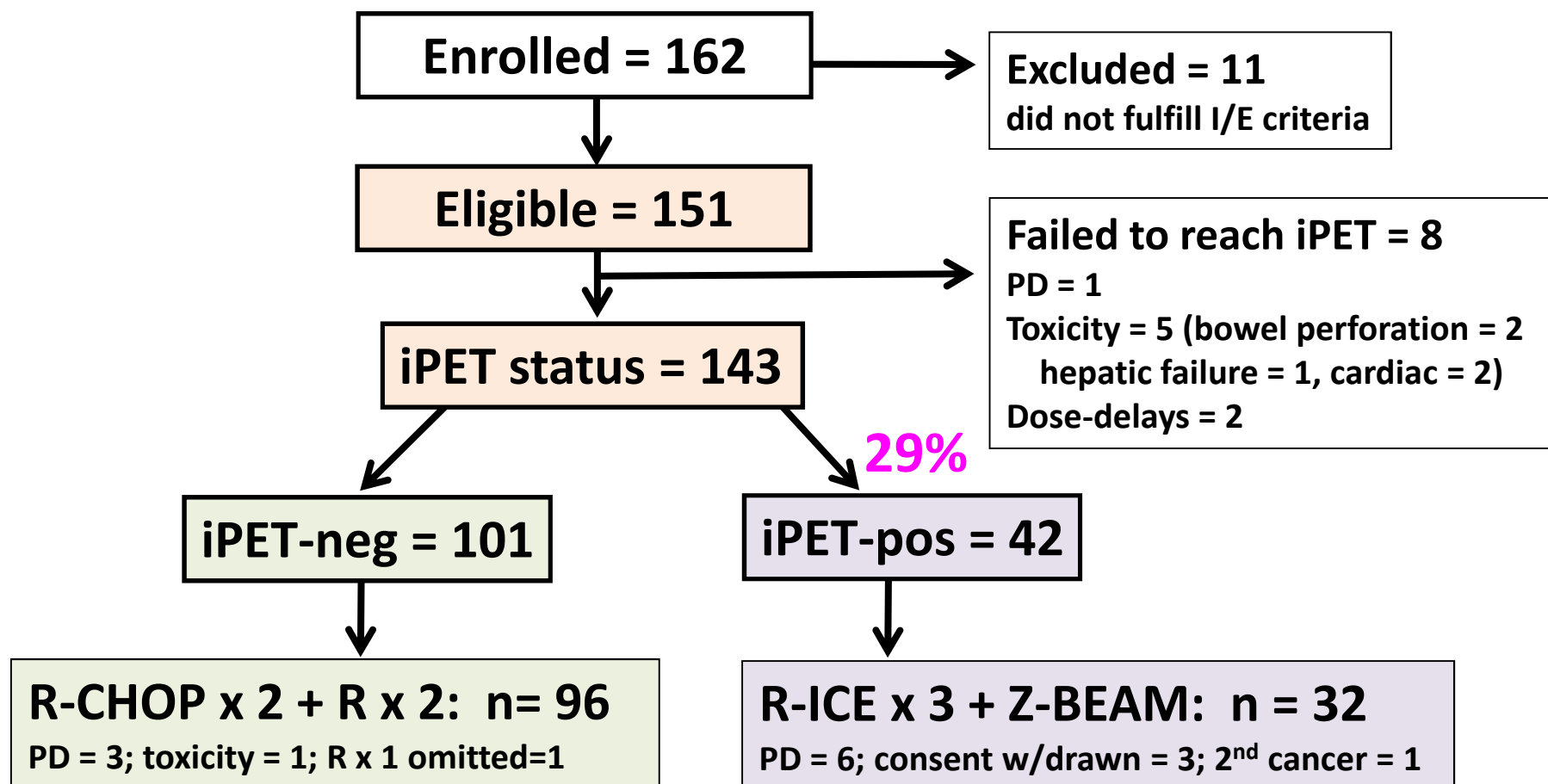
1. Haioun et al. Blood 2005;106:1376-81
2. Yang et al. Eur J Cancer 2011;47:1312-18
3. Itti et al. J Nucl Med 2009;50:527-533

4. Safar et al. J Clin Oncol 2012;30:184-90; 3-yr
5. Dupuis et al. Ann Oncol 2009;20:503-7; *5-yr



- *1. Delay #5 R-CHOP-14 x 7 days: iPET d17-20 of cycle #4.
- 2. Central PET consensus reporting by 2 PET physicians: IHP criteria

NHL21 Consort Diagram



	iPET-	iPET+	Total
IF-RT	5/101 (5%)	10/42 (24%)	15/143 (10%)

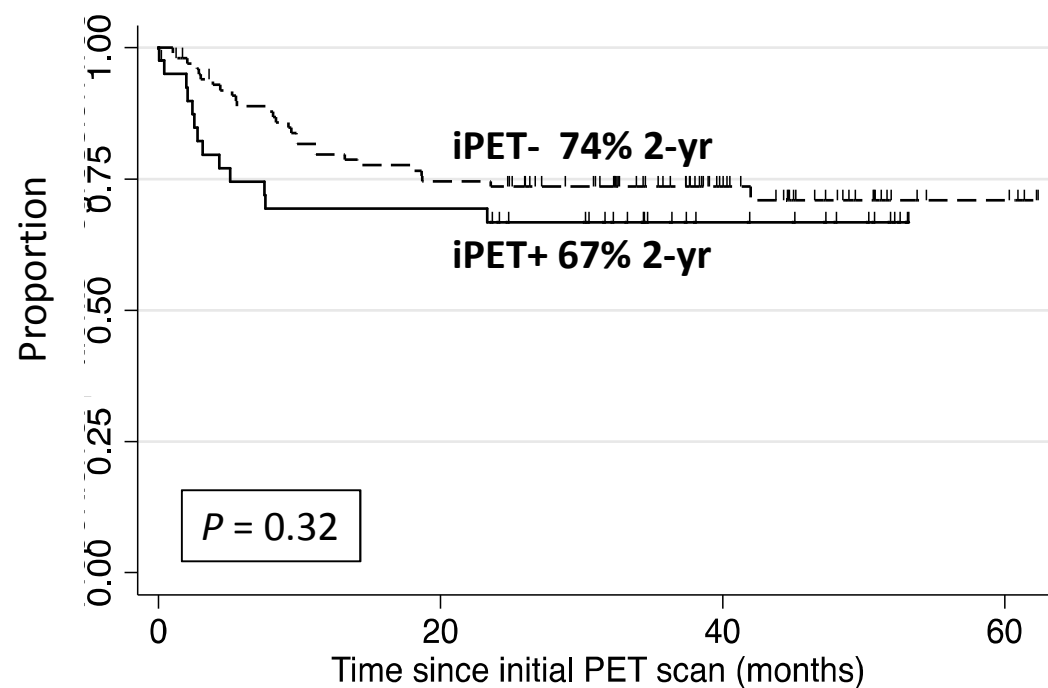
Patient Characteristics (n=151)

Characteristic	No. (%)	Characteristic	No. (%)
Median age yrs	57 (21-69)	BM involvement	25 (17%)
Age > 60 yrs	61 (40%)	Extranodal sites > 1	72 (48%)
Age ≤ 60 yrs	90 (60%)	Bulky dis. ≥ 7.5 cm	81 (54%)
Males	94 (62%)	IPI 0,1	30 (20%)
Stages 3 or 4	119 (79%)	IPI 2	40 (27%)
ECOG PS > 1	20 (13%)	IPI 3	47 (31%)
Elevated LDH	118 (78%)	IPI 4,5	34 (23%)
B symptoms	76 (50%)	aaIPI 2-3	83 (55%)

54%

PFS is equivalent: iPET- vs. iPET+

n=143: Median follow up = 35 m

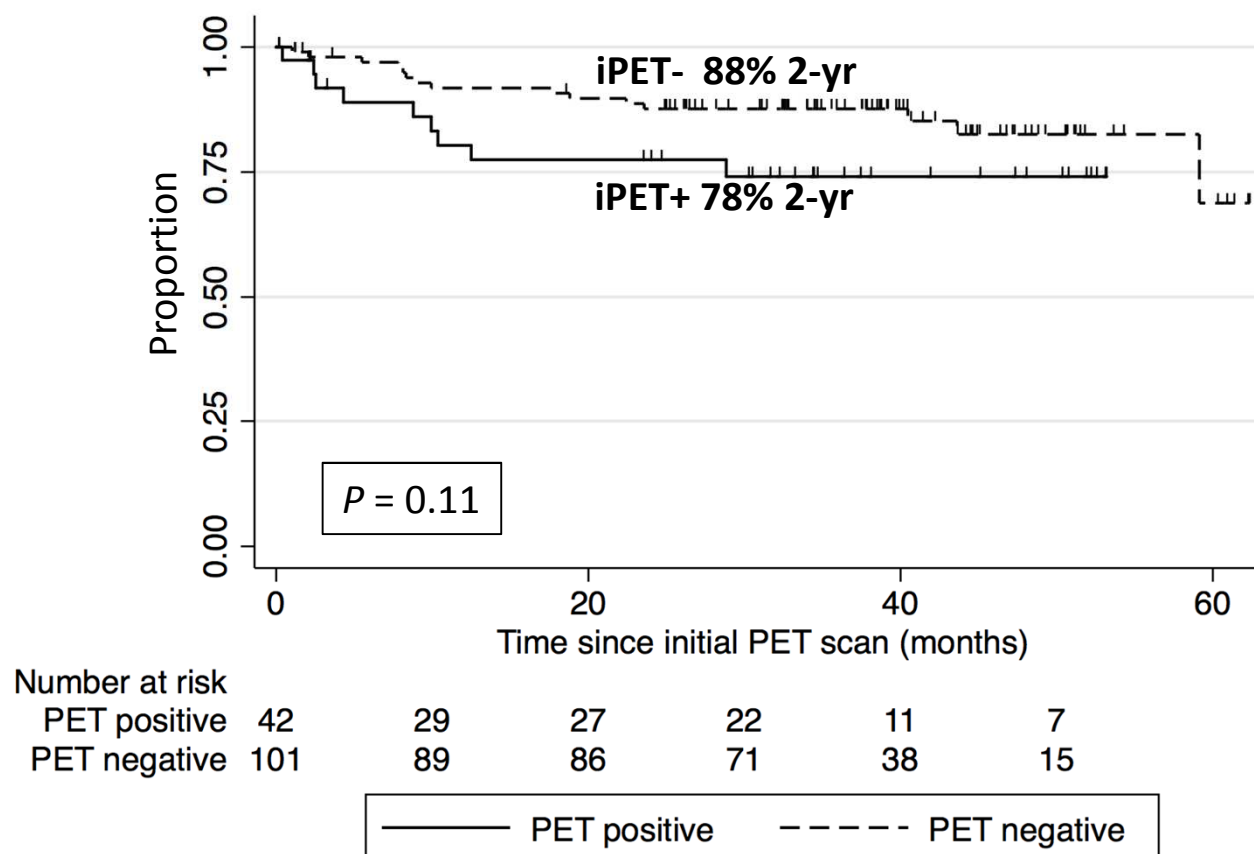


Number at risk				
PETstatus = PET +ve	42	27	11	0
PETstatus = PET -ve	101	73	32	5

— PETstatus = PET +ve - - - - PETstatus = PET -ve

OS is equivalent: iPET- vs. iPET+

n=143: Median follow up = 35 m



Adverse Events

Gde 3-4 > 5%: R-CHOP / R-ICE	iPET- (n = 101)	iPET+ (n = 42)
Any grade 3-4 event	58/101 (58%)	34/42 (76%)
Neutropenia	28%	44%
Febrile neutropenia	10%	46%
Thrombocytopenia	7%	49%

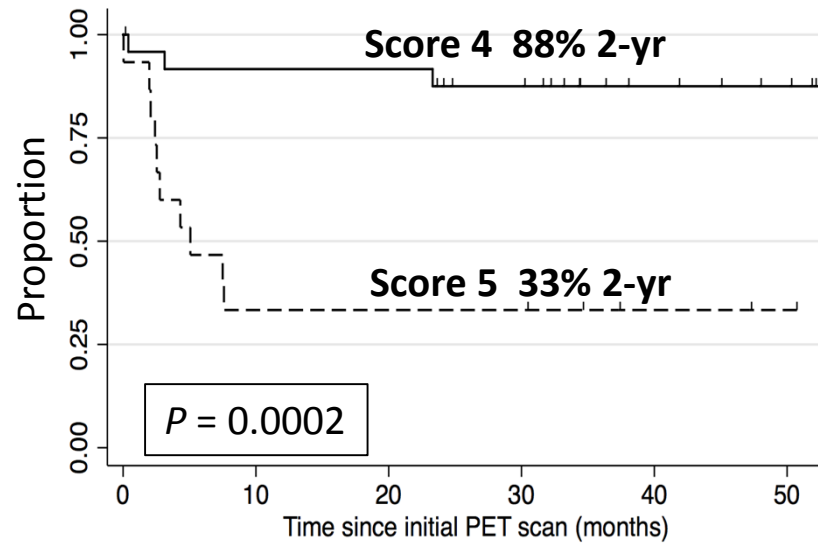
Zevalin-BEAM (n = 32)	Median (range)
Gde 3-4 mucositis	30%
Days to neutrophils > 1.0 x 10⁹/L	11 days (9-104)
Days to platelets > 50 x 10⁹/L	16 days¹ (12-505)
Death	2.4%²

¹ Four patients had delayed platelet engraftment beyond 30 days

² One patient died d+33 ASCT from hypoxic respiratory failure + viral pneumonitis

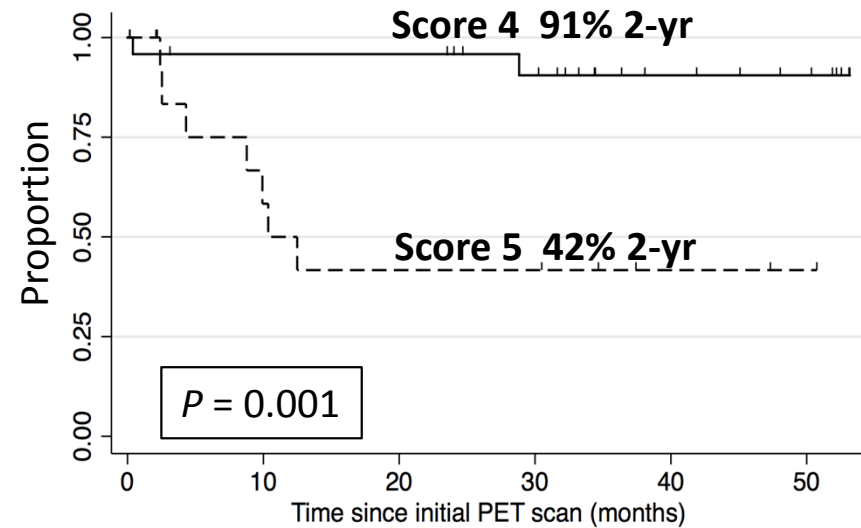
iPET-pos Deauville Score 4 vs. 5

PFS



Number at risk						
Deauville = 4	27	22	22	17	9	6
Deauville = 5	15	5	5	5	2	1

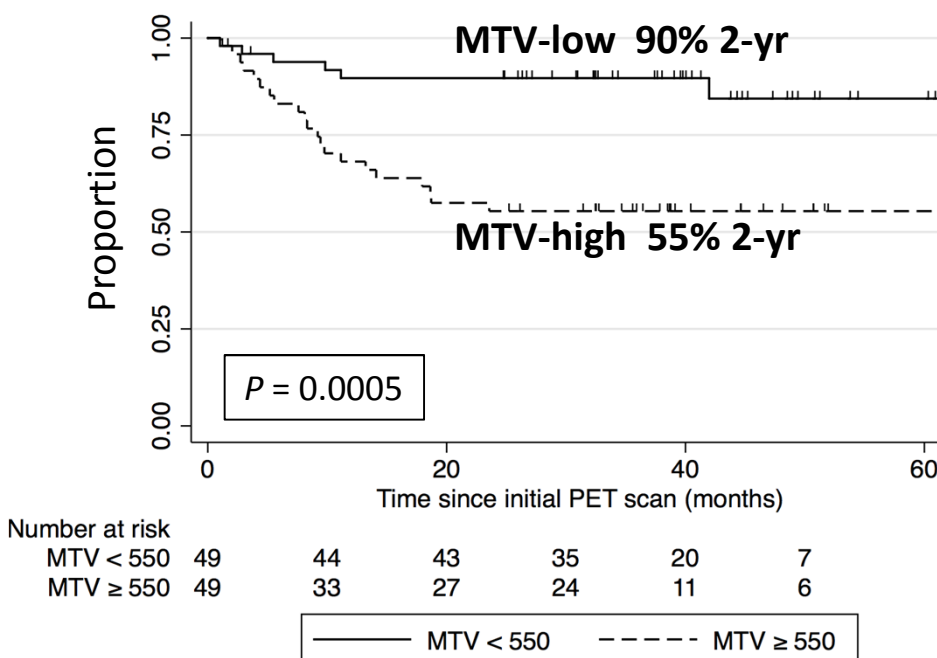
OS



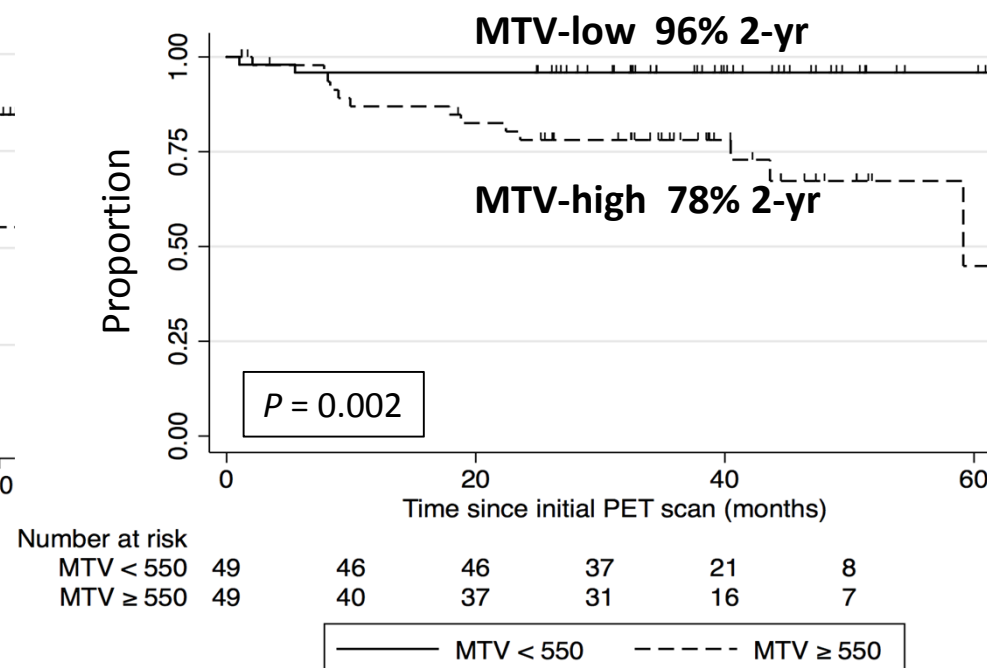
Number at risk						
Deauville = 4	27	22	22	17	9	6
Deauville = 5	15	7	5	5	2	1

Baseline TMTV < 550 cm³ (low) vs. ≥ 550 cm³ (high) iPET-neg*

PFS



OS

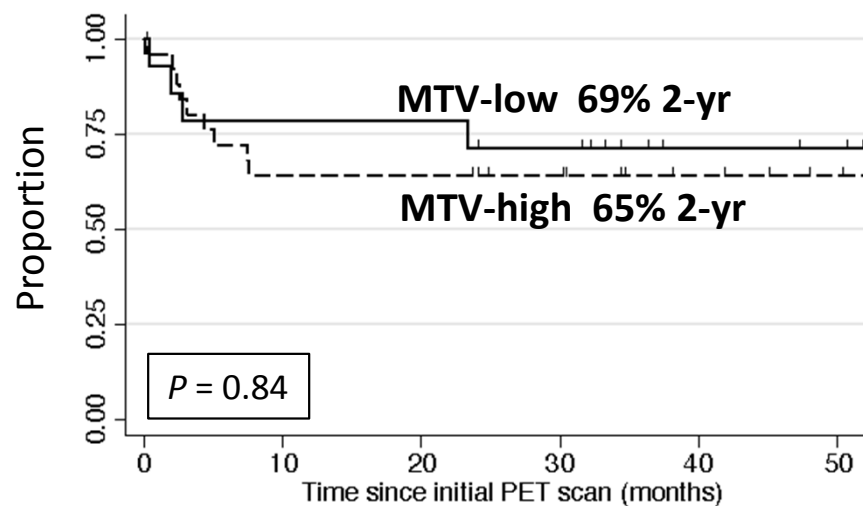


*ROC analysis of the data indicated maximum sensitivity and specificity at TMTV = 560 cm³

Baseline TMTV < 550 cm³ (low) vs. ≥ 550 cm³ (high) iPET-pos

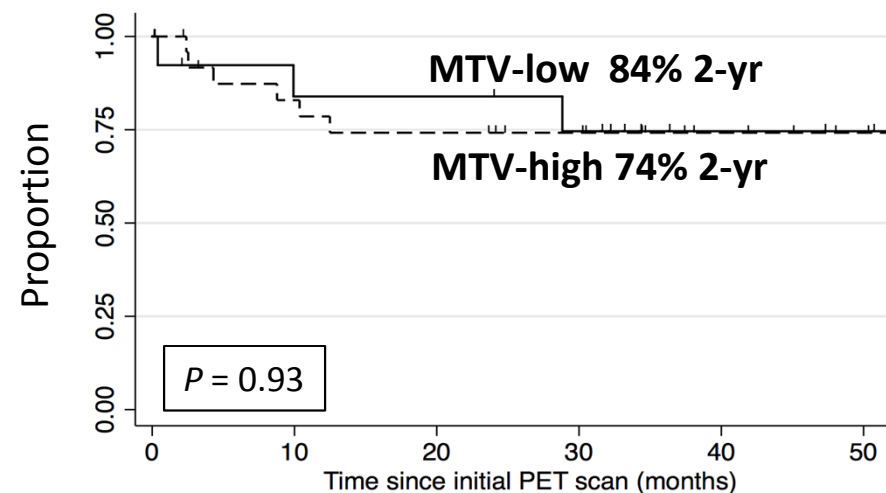
PFS

OS



Number at risk						
MTV < 550	15	11	11	9	3	2
MTV ≥ 550	27	16	16	13	8	5

— MTV < 550 - - - - MTV ≥ 550



Number at risk						
MTV < 550	15	10	10	8	3	2
MTV ≥ 550	27	19	17	14	8	5

— MTV < 550 - - - - MTV ≥ 550

PFS: Multivariate Analysis*

	HR	95% CI	<i>P</i>
Stage III/IV	1.7	1.1-2.8	0.027
B symptoms	1.6	1.3-2.4	0.020
Baseline MTV ≥ 550 cm ³	2.3	1.1-4.8	0.022

OS: Multivariate Analysis*

	HR	95% CI	<i>P</i>
Age > 60 yrs	2.4	1.1-5.5	0.035
ECOG PS > 1	3.4	1.3-8.6	0.011
BM involvement	5.6	2.2-14.3	< 0.001
Deauville Score 5	2.6	1.5-4.4	< 0.001

*Cox proportional hazards regression

Conclusions (I)

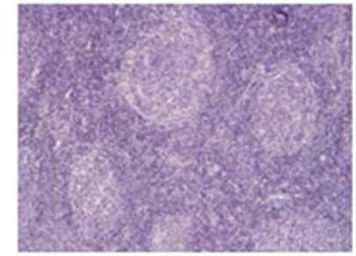
- In iPET-positive DLBCL patients after 4 cycles of R-CHOP-14, R-ICE followed by Z-BEAM HDT results in 2-yr PFS comparable to iPET-negative patients treated with R-CHOP-14 alone.
- iPET-positive DLBCL patients with Deauville Score 4 displayed highly favorable outcomes following treatment intensification.
- In contrast, patients with Deauville Score 5 derived less clear cut benefit indicating this group may represent an unmet need.

Conclusions (II)

- **Baseline TMTV was strongly correlated with outcomes among iPET-negative patients, suggesting that TMTV may be an important prognostic determinant at diagnosis.**
- **These results lend support to ongoing evaluation in DLBCL patients of**
 - i. the role of iPET-adapted therapy, and**
 - ii. the prognostic impact of baseline TMTV.**

Currently Planned Exploratory Analyses

- **Objective:** Since baseline TMTV was strongly correlated with outcomes among iPET-negative patients, the plan is to correlate TMTV with patterns of treatment failure, that is, at initial or distant sites
- **Hypothesis:** that quantitative measures of disease distribution are predictive of the likelihood of local failure, and, that some patterns of failure might have been prevented by irradiating initial sites of high baseline TMTV



NHL26: R² consolidation in PET Positive patients after treatment of relapsed Follicular Lymphoma (RePLy)

PI Judith Trotman

Co-PIs: Michael Fulham (PET), Anna Johnston

NHL26: Hypothesis

That, after completion of R-chemotherapy for relapsed FL, Lenalidomide consolidation added to Rituximab maintenance therapy can convert patients remaining PET+ to PET-, with an acceptable toxicity profile.

Key Inclusion criteria

- Relapsed FL: Stage III or IV, or Stage II bulky disease ≥ 7 cm treated with R-chemo
- Achieved “conventional” (1999 criteria) SD, PR, CRu/CR (4-6 weeks) after re-induction therapy. (i.e. no PD)

Primary objective

To measure the % converting from PET+ after reinduction to PET- after 6mo of commencing Lenalidomide consolidation.

i.e. early primary endpoint in this pilot study

Secondary Objectives include:

- Toxicity / tolerability of Lenalidomide-Rituximab
- PET conversion rate after 12 months Lenalidomide-Rituximab
- PFS, OS
- HRQOL

NHL26 / RePLy Study Protocol

- Reinduction with combined rituximab-chemotherapy.
Physician's choice. ASCT permitted
- CT response assessment (4-6/52 post D1 last cycle)
 - If CR/PR/SD **NHL26 registration** followed by:
- Per-protocol PET-CT for all patients within 4-8/52 of D1 last cycle
- Standardised scanning criteria at accredited centres:
(RHH, PMCC, RPAH, PAH)
- PET+ defined as cut-off score ≥ 3 using 5PS
 - Scored by one local and two central PET physicians (RPAH)
 - 3rd reviewer to arbitrate in event of discordant central scoring
 - Central score defines PET status

NHL26/RePLy recruitment

- Very slow recruitment: 18 patients to date
Challenge: competing bendamustine, PI3Ki, BTKi, ABT199 studies
- Yet 8/18 (44%) have been PET+
- Shouldn't need to recruit many more patients:
est. ~18 to obtain a total of 16 evaluable PET+ patients.

16 patients provides 80% power with Type I error of 5%, assuming a conversion rate of at least 50% as worthy of further evaluation and 20% or lower as unacceptable.

NHL26: RePLy Key Points

- The first study of PET-adapted therapy in relapsed FL, using Rituximab & Lenalidomide as *consolidation* therapy.
- Patients reassurance of post-induction PET-negative scans
- Potential benefit to PET+ patients with a poor prognosis
- Need accelerated recruitment to answer early 1^o EP in this pilot

- Safety and efficacy of lenalidomide in combination with rituximab in recurrent indolent non-follicular lymphoma: final results of a phase II study conducted by the Fondazione Italiana Linfomi
- Stefano Sacchi, Raffaella Marcheselli, Alessia Bari, Gabriele Buda, Anna Lia Molinari, Luca Baldini, Daniele Vallisa, Marina Cesaretti, Pellegrino Musto, Sonia Ronconi, Giorgina Specchia, Franco Silvestris, Luciano Guardigni, Angela Ferrari, Annalisa Chiappella, Angelo Michele Carella, Armando Santoro, Francesco Di Raimondo, Luigi Marcheselli, Samantha Pozzi

SPARE SLIDES

Acknowledgements

- Supported by: Roche Products Australia Pty Ltd
Amgen Australia Pty Ltd
Bayer Pharmaceuticals Pty Ltd
- Jason Callahan, Michael Hofman: Peter MacCallum Cancer Centre
Nuclear Medicine Dept
- Colm Keane and Pauline Crooks: Univ Queensland Diamantina Inst.
- Lyn Griffiths: Queensland University of Technology
- Michael Green: University of Nebraska
- Ruth Columbus, Christine Vergara, Suzanne Cake: ALLG Trial Centre

Rationale

- **Prospective multi-center phase 2 study**
- **Sought to establish whether treatment intensification with R-ICE followed by ^{90}Y -ibritumomab tiuxetan (Zevalin)-BEAM for high risk DLBCL patients who are positive on interim PET (iPET) scan after 4 cycles of R-CHOP-14, can improve 2-year progression-free survival (PFS) from an historically unfavorable rate of 40% (range, 36-47%)¹⁻⁵ to a rate of 65%.**

1. Haioun et al. Blood 2005;106:1376-81
2. Yang et al. Eur J Cancer 2011;47:1312-18
3. Itti et al. J Nucl Med 2009;50:527-533

4. Safar et al. J Clin Oncol 2012;30:184-90; 3-yr
5. Dupuis et al. Ann Oncol 2009;20:503-7; *5-yr

Background

- **FDG-PET/CT performed after 2-4 cycles of R-chemotherapy has been shown to be predictive of outcome in DLBCL.**
- **However, methodological diversity has led to wide variations in negative and positive predictive values (PPV).**
- **Interim PET after cycle 4 of R-chemotherapy has a higher PPV than after 2 cycles.**
- **A high PPV is desirable for selection of patients for treatment intensification.**

NHL21 Endpoints

- **Primary Endpoint: 2-yr PFS from iPET**
- **The expected 2-yr PFS rate for iPET-4-positive patients treated with R-CHOP based on historical data was considered to be 40% (range, 36-47%)¹⁻⁵**
- **By switching these patients to early treatment intensification the aim was to increase the 2-yr PFS to 65%.**
- **A one-stage design with 33 iPET-positive patients provided a probability of $\geq 90\%$ to detect a difference in 2-yr PFS of 40% vs. 65% with a 2-sided alpha of 0.05. Since it was expected that at least 20% would be iPET-positive, the planned accrual was 165.**

1. Haioun et al. Blood 2005;106:1376-81
2. Yang et al. Eur J Cancer 2011;47:1312-18
3. Itti et al. J Nucl Med 2009;50:527-533

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Conclusions (I)

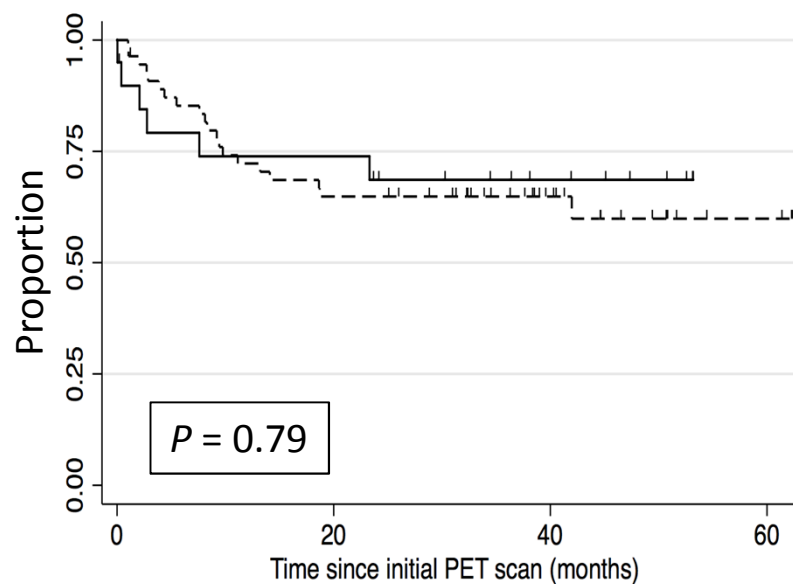
- In iPET-positive DLBCL patients after 4 cycles of R-CHOP-14, R-ICE followed by Z-BEAM HDT results in 2-yr PFS comparable to iPET-negative patients treated with R-CHOP-14 alone.
- Delaying cycle #5 R-CHOP-14 by 7 days and undertaking interim PET with central review, can be readily achieved.

Conclusions (II)

- **iPET-positive DLBCL patients with Deauville Score 4 displayed highly favorable outcomes following treatment intensification.**
- **In contrast, patients with Deauville Score 5 derived less clear cut benefit indicating this group may represent an unmet need.**

IPI 3-5: PFS and OS are equivalent

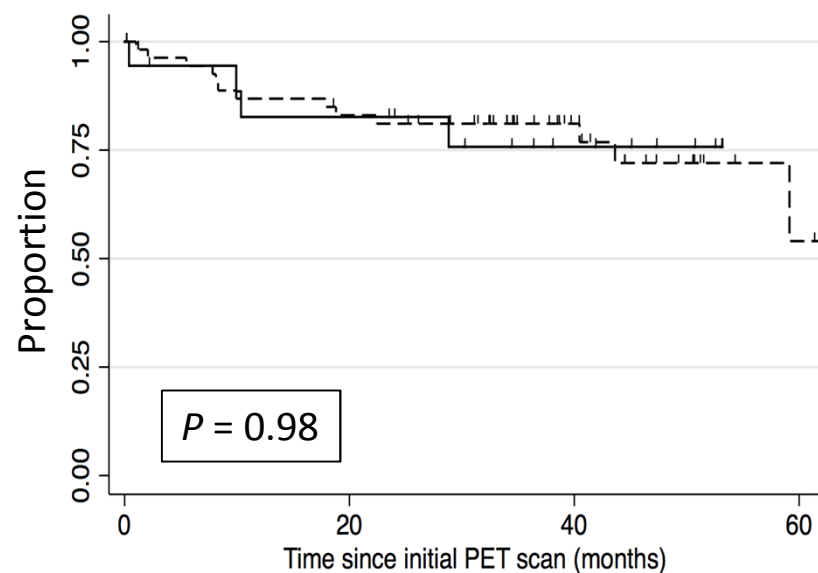
PFS:
iPET- vs. iPET+



Number at risk						
PET positive	20	14	14	11	7	4
PET negative	55	40	35	31	16	8

— PET positive - - - - PET negative

OS:
iPET- vs. iPET+



Number at risk						
PET positive	20	15	14	11	7	4
PET negative	55	46	43	38	20	10

— PET positive - - - - PET negative

NHL21: Other Endpoints

- **Secondary Endpoint: 2-yr OS from iPET**
- **Subsequent exploratory analyses:**
 - **iPET: Deauville 5-point score**
 - **Baseline PET: Total Metabolic Tumour Volume**