Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

14.–17. Juni 2018

KML-Experten berichten vom EHA 2018 in Stockholm

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Lymphom Kompetenz KOMPAKT EHA Stockholm 14.–17. Juni 2018

Prof. Dr. med. Dr. h.c. Andreas Engert

Hodgkin Lymphom

Lt. Oberarzt der Klinik I für Innere Medizin der Uniklinik Köln |
Leiter Deutsche Hodgkin Studiengruppe (GHSG) |
Vorstandsmitglied Kompetenznetz Maligne Lymphome e.V.

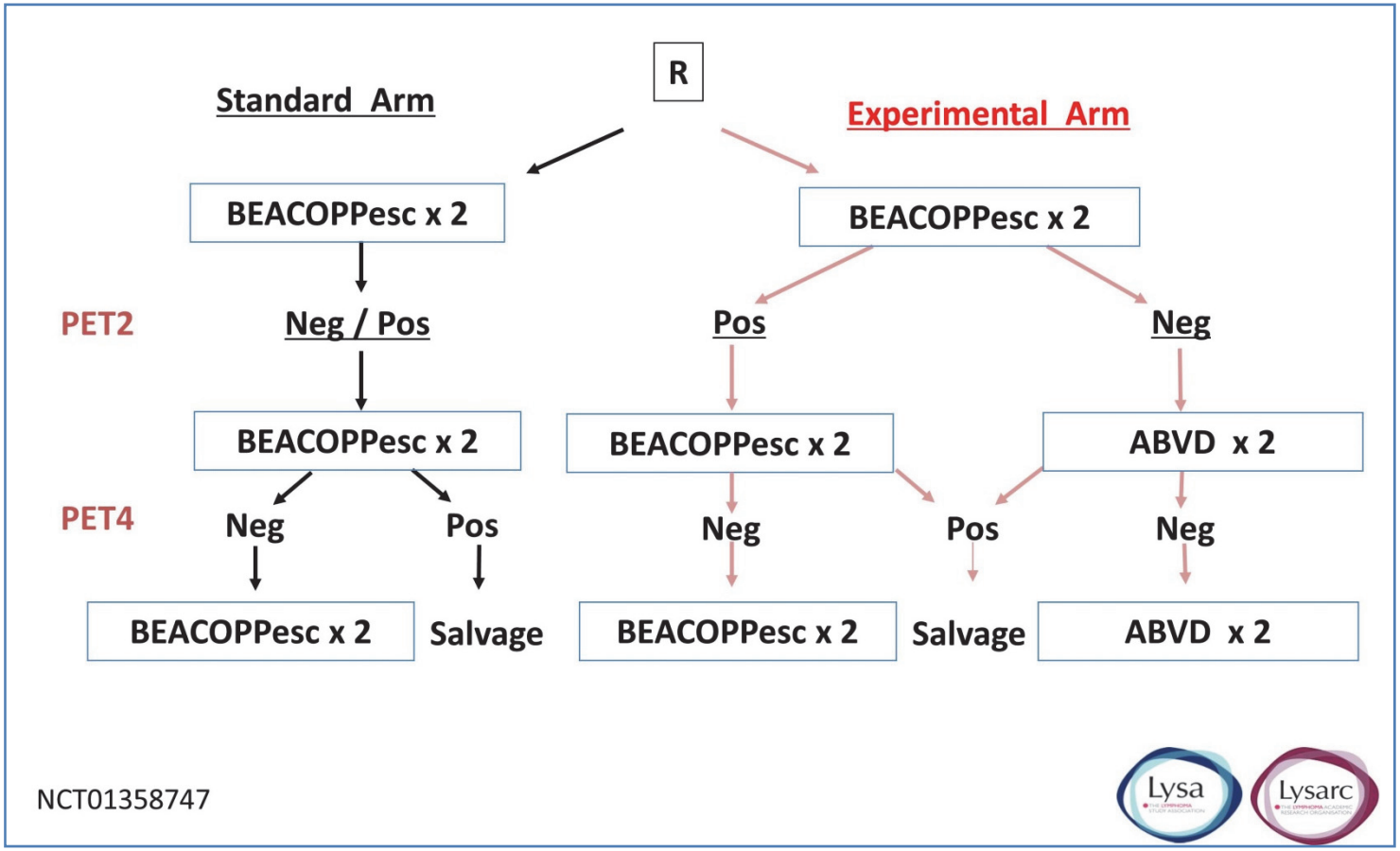
(S577) Randomized phase III study comparing an early PET driven treatment de-escalation to a not PET-monitored strategy in patients with advanced stages Hodgkin lymphoma - Interim analysis of the AHL2011 LYSA study

Presenter: Olivier Casasnovas, *Dijon, Frankreich*

Author(s): Olivier Casasnovas, Pauline Brice, Reda Bouabdallah, Gilles Salles, Aspasia Stamatoulas, Jehan Dupuis, Oumedaly Reman, Thomas Gastinne, Bertrand Joly, Krimo Bouabdallah, Emmanuelle Nicolas-Virelizier, Serge Bologna, Franck Morschhauser, Richard Delarue, Hassan Farhat, Philippe Quittet, Alina Berriolo-Riedinger, Adrian Tempescul, Véronique Edeline, Hervé Maisonneuve, Jean Claude Eisenmann, Alexandra Traverse-Glehen, Marc André, Nicolas Mounier, Michel Meignan, Christophe Fermé

AHL 2011: Study design

O. Casasnovas et al., Abstract S577



AHL2011: Adverse events ≥ grade 3

O. Casasnovas et al., Abstract S577

Safety set	BEACOPPesc n = 444		BEACOPPesc + ABVD n = 334		p
Patients with AE	444	100%	334	100%	NS
Patients with AE Grade ≥3	433	98%	324	97%	NS
AE grade ≥ 3					
Anemia	55	**11%**	7	**2%**	**< 0.000001**
Leukopenia	378	**85%**	243	**72%**	**0.00003**
Neutropenia	372	84%	286	85%	NS
Febrile neutropenia	26	**6%**	9	**3%**	**<0.04**
Thrombocytopenia	197	**44%**	42	**13%**	**< 0.000001**
Sepsis	29	6.5%	13	3.9%	NS
Mucositis	7	1.6%	5	1.5%	NS

AHL2011: PET2 results (central review)

O. Casasnovas et al., Abstract S577

		Treatment arm: Standard n = 401		Experimental n = 381		All n = 782	
PET2							
	Evaluable	386	96%	368	97%	754	96%
	Negative	**338**	**88%**	**319**	**87%**	657	87%
	Positive	48	12%	49	13%	97	**13%**
PET4							
	Evaluable	373	93%	348	92%	721	92%
	Negative	**347**	**93%**	**332**	**95%**	679	94%
	Positive	26	7%	16	5%	42	**6%**

84% of patients received 2 x BEACOPPesc + 4 x ABVD in the experimental arm

AHL 2011: PFS according to PET2 result

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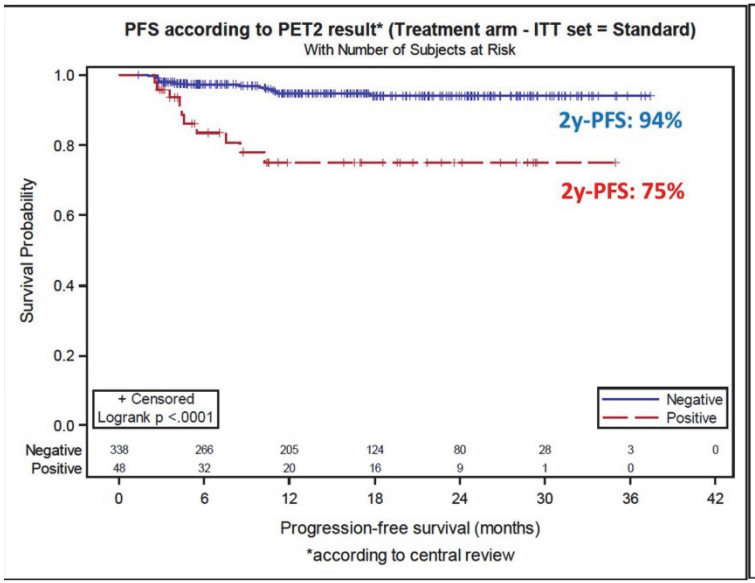

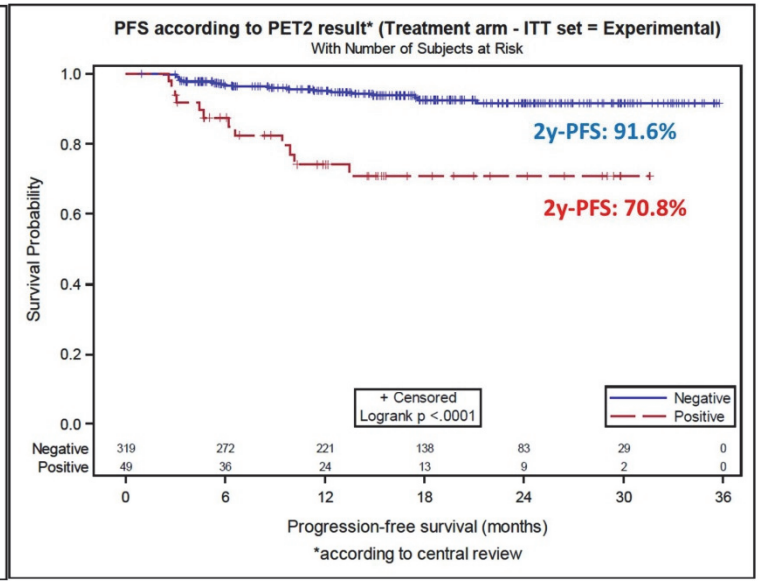

Standard arm

Experimental arm

AHL 2011: PFS according to the PET driven strategy

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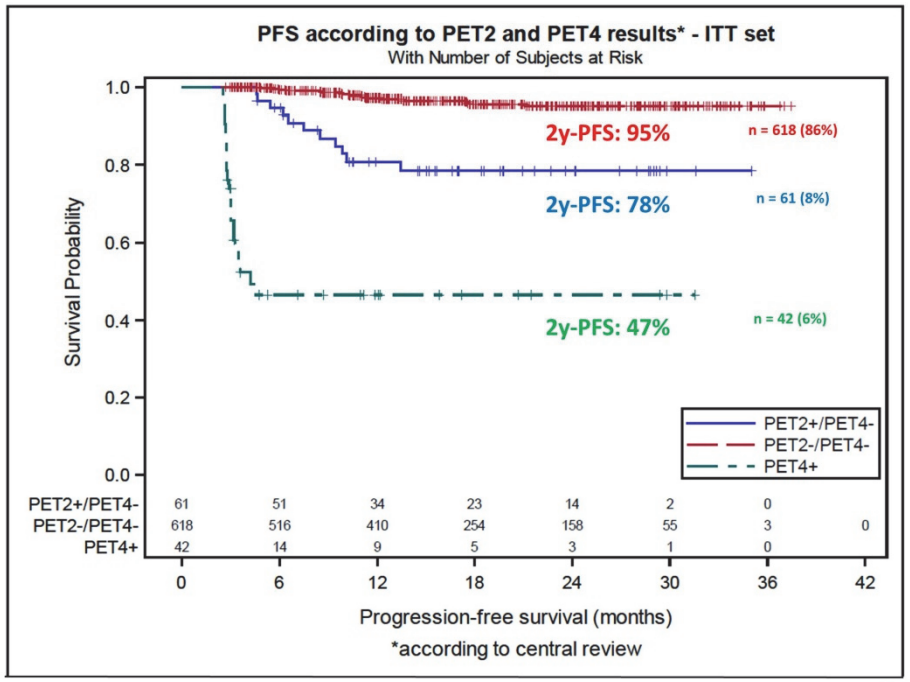


LYSA AHL2011 Study

O. Casasnovas et al., Abstract S577

- 823 patients randomised to either
  - 6 x BEACOPPesc (standard arm)
  - PET-driven approach where patients PET-negative after 2 x BEACOPPesc continued with 4 x ABVD
- 88% of patients in the exp.arm were PET2 negative
- Median f/u 16 months
- 2-year PFS 91.6% vs. 88.3%

Conclusions: It looks safe to reduce treatment intensity in patients who are PET-negative after 2 x BEACOPPesc

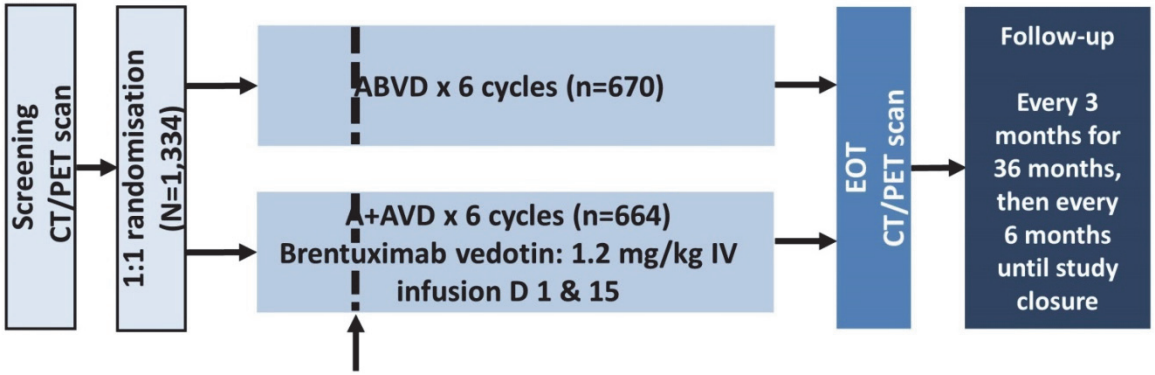
(S112) Brentuximab vedotin plus chemotherapy in high-risk, advanced-stage classical Hodgkin lymphoma patients: Results of pre-specified sub-group analyses from the ECHELON-1 study

Presenter: M. Hutchings, *Kopenhagen, Dänemark*

Author(s): Martin Hutchings, John Radford, Andrea Gallamini, Arpad Illes, Anna Sureda, Joseph M. Connors, Alice Sykorova, Hirohiko Shibayama, Jeremy S. Abramson, Neil Chua, Jonathan W. Friedberg, Jan Koren, Ann Steward LaCasce, Lysiane Molina, Neil Josephson, Eric Song, Hina Jolin, Rachael Liu, Ashish Gautam, Stephen Ansell

ECHELON-1: Open-label, global, randomised, phase 3 study of frontline A+AVD vs ABVD in advanced cHL

M. Hutchings et al., Abstract S112



- Inclusion criteria
  - cHL stage III or IV
  - ECOG PS 0, 1 or 2
  - Age ≥18 years
  - Measurable disease
  - Adequate liver and renal function

cHL, classic Hodgkin lymphoma; CT, computerised tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end-of-treatment; PET, positron emission tomography

1. Connors JM, *et al*. N Engl J Med 2018;378:331–44.

ECHELON-1: Results from primary analyses

M. Hutchings et al., Abstract S112

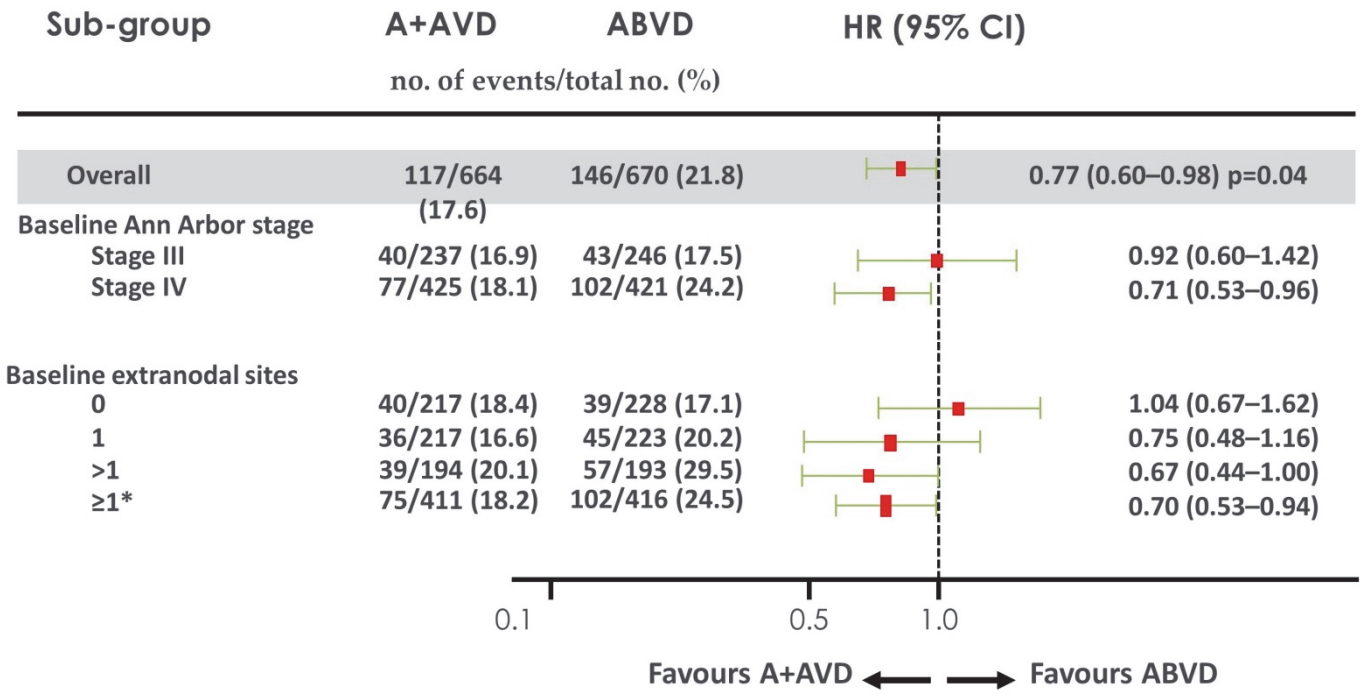
- Primary endpoint was mPFS
  - Defined as time to progression, death, or evidence of non-complete response after completion of frontline therapy followed by subsequent anticancer therapy
- Primary endpoint was met – significant reduction in mPFS for A+AVD vs ABVD (HR=0.77 [95% CI: 0.60, 0.98]; p=0.035)
  - 2-year mPFS rates were 82% (A+AVD) and 77% (ABVD)
- Key secondary endpoint: OS
  - Median not reached
  - Interim OS HR=0.73 (95% CI: 0.45, 1.18; p=0.20)

CI, confidence interval; HR, hazard ratio; mPFS, modified progression-free survival;
OS, overall survival

1. Connors JM, *et al*. N Engl J Med 2018;378:331–44.

Summary of mPFS per IRF: High-risk sub-groups

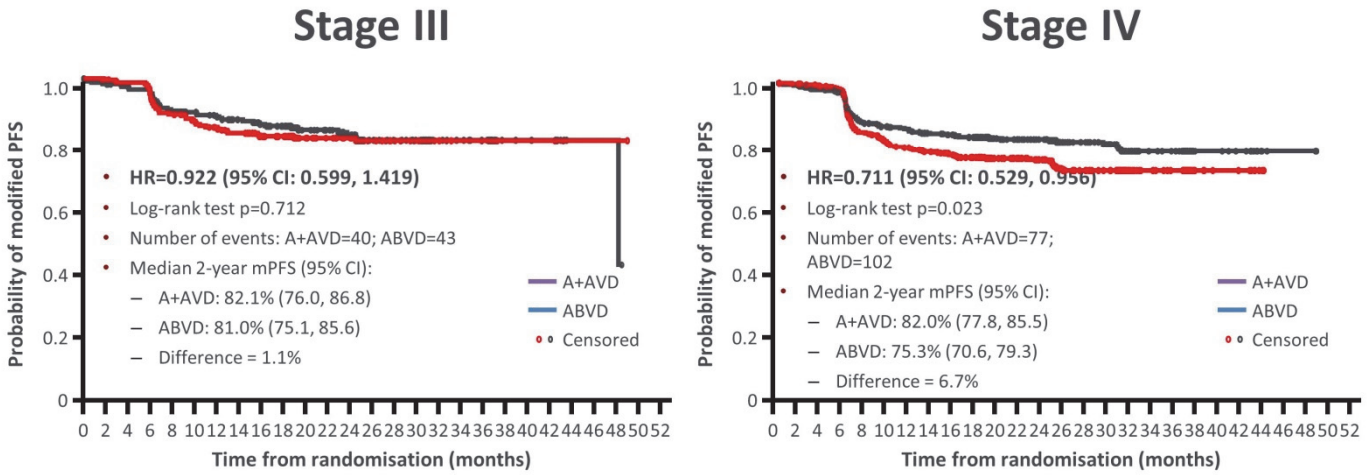
M. Hutchings et al., Abstract S112



*Ad hoc analysis.
HR, hazard ratio; IRF, independent review facility

Stage III vs IV prespecified subgroups: mPFS per IRF

M. Hutchings et al., Abstract S112



(S114) Nivolumab for Newly Diagnosed Advanced-Stage Classical Hodgkin Lymphoma: Results From the Phase 2 CheckMate 205 Study

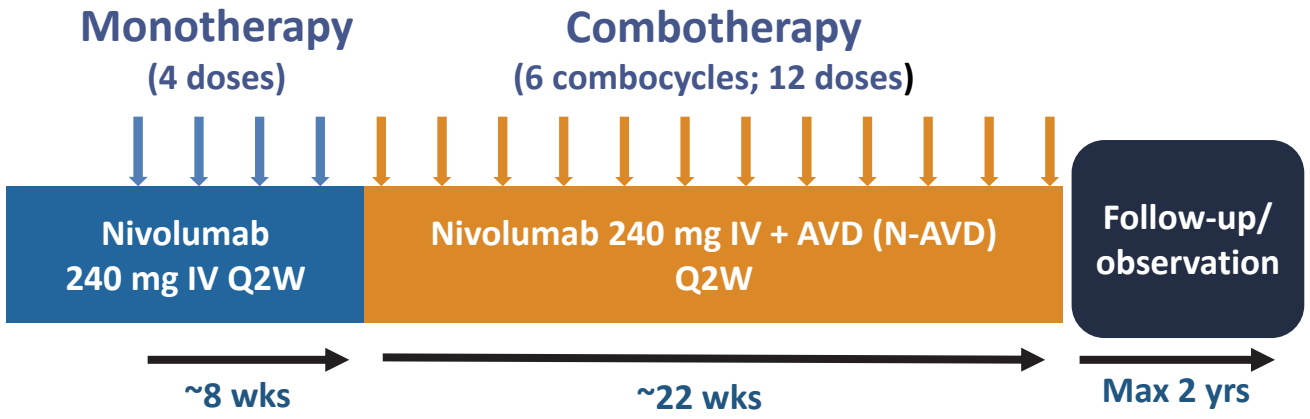
Presenter: Radhakrishnan Ramchandren, *Detroit, USA*

Author(s): Radhakrishnan Ramchandren, Eva Domingo Domenech, Antonio Rueda, Philippe Armand, Marek Trněný, Tatyana Feldman, Stephen Ansell, Mariano Provencio, Ulrich Jäger, Jonathon B. Cohen, Kerry J. Savage, Wolfgang Willenbacher, Mariana Sacchi, Anne Sumbul, Michelle Fanale

Presented at the 59th American Society of Hematology (ASH) Annual Meeting; December 9–12, 2017; Atlanta, GA, USA

CheckMate 205 Cohorte D (Nivo-AVD in advanced stage HL)

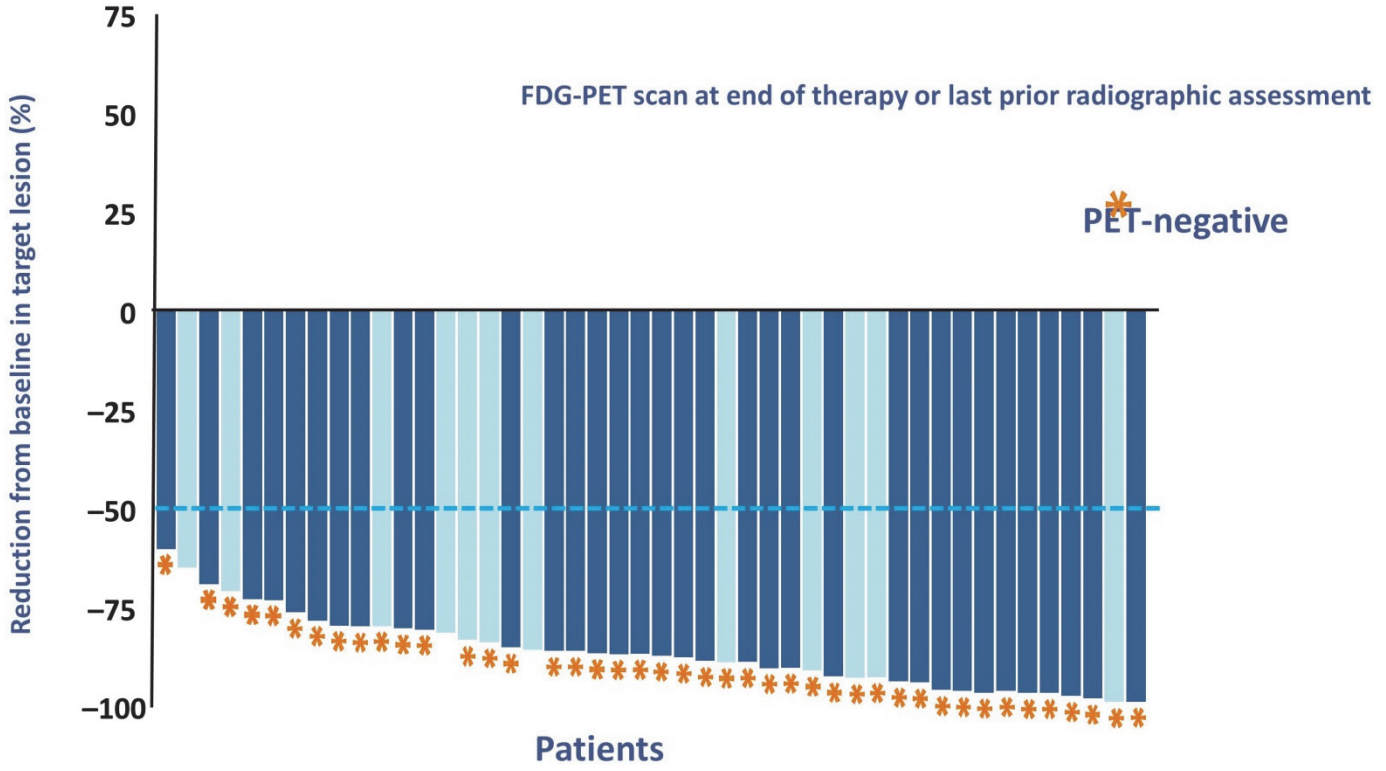
R. Ramchandren et al., Abstract S114



- 51 untreated advanced stage cHL pts (IIB, III, IV)
- Median follow-up 11.1 months (cut-off 31.8.17)
- Bleomycin excluded due to potential overlapping pulmonary toxicity
- Primary EP: G3-5 safety and tolerability

CheckMate 205 Cohorte D (Nivo-AVD in advanced stage HL)

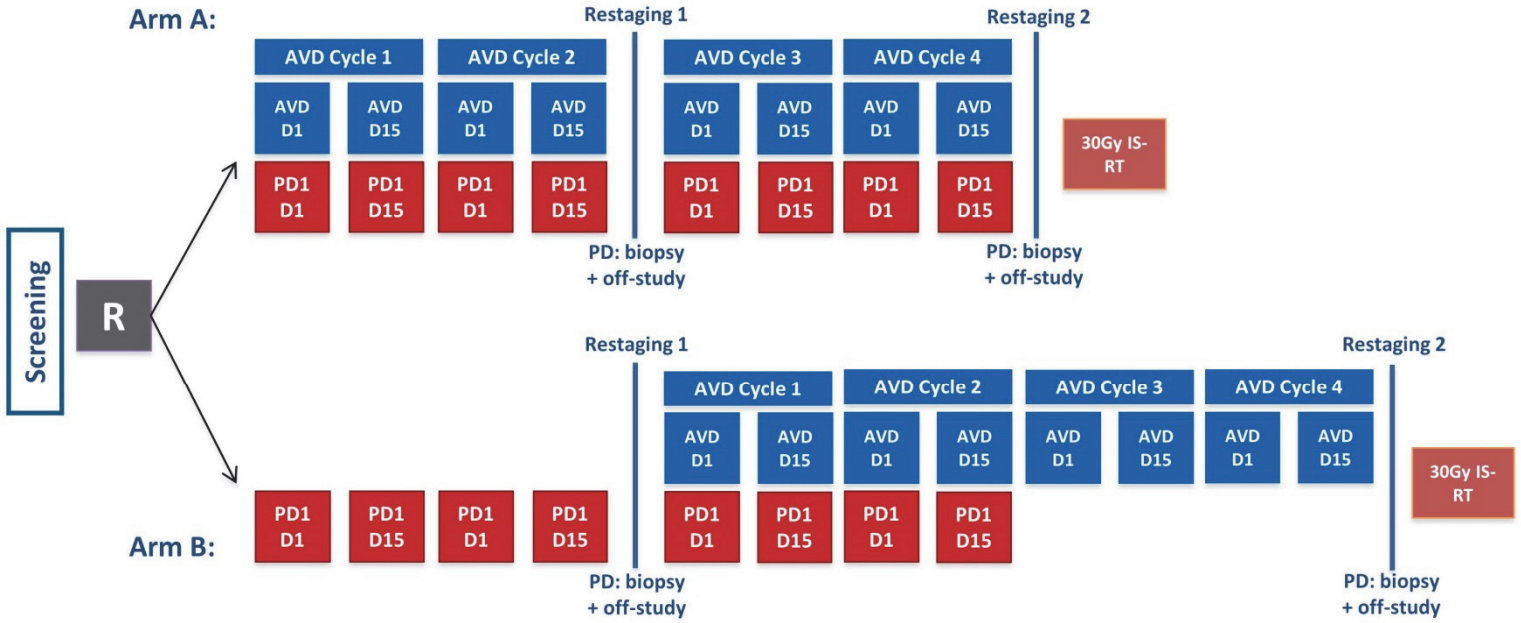
R. Ramchandren et al., Abstract S114



46/51 patients had available response data. Response assessed by IWG 2007 criteria

Ramchandren et al, EHA 2018

Randomized GHSG Phase II Pilot
PD1 Inhibition in 1st-line early unfavorable HL (ongoing)



AVD: Adriamycin, Vinblastin, Dacarbazine
PD1: Nivolumab (anti-PD1 moab)

GHSG 2017

(ASH 2015) Evaluation of the Regimen Brentuximab Vedotin Plus ESHAP (BRESHAP) in Refractory or Relapsed Hodgkin Lymphoma Patients: Preliminary Results of a Phase I-II Trial from the Spanish Group of Lymphoma and Bone Marrow Transplantation (GELTAMO)

Author(s): García-Sanz R, Sureda A, González AP, Salar A, Rodríguez A, de la Cruz F, Domingo-Domenech E, Canales M, López J, Moreno M, Rodríguez G, Piñana JL, Rodríguez MJ, López-Guillermo A, Caballero MD, Jiménez S, Martínez C

ESHAP	DHAP
• Cisplatin 25 mg/m², continuous infusion, days 1-4	• Cisplatin 100 mg/m², 24 hr continuous infusion, only day 1
• Etoposide 40 mg/m²/day, 2 hr infusion, días days 1-4	• No etoposide
• Metilprednisolone 200 mg/day, days 1-4	• Dexamethasone 40 mg/day, days 1-4
• Citarabine 2000 mg/m² 2 hr infusion, day 5 (1 dose)	• Citarabine 2000 mg/m²/12h 2 hr infusion, day 2 (2 doses)
• G-CSF support	• G-CSF support

Aparicio et al, Ann Oncol. 1999, 10:593;
Labrador et al, Ann Hematol. 2014; 93: 1745
(ORR, 67%; CR 50%)

Velasquez et al. Blood. 1988; 71: 117;
Josting et al, Ann Oncol. 2002; 13: 1628.

ESHAP Treatment Protocol

BV: 0,9-1.8 mg/Kg, day 1 of each course, & at 21 days post 3th ESHAP.

BRESHAP: every 21 - 28 days

BV post-APBSCT: from day +28 to +56, 3 doses, every 21 days

CD34+ quantification: ≥ 2 x 10^6/kg CD34+ cells

G-CSF ± Plerixafor

Prophylaxis for neutropenia: G-CSF mandatory from day+7, Peg-Filgastrim recommended

ESHAP: Phase I + Phase II

- N=36: Male/Female 20/16; age 33 (18-60)
  - Primary refractory: 21 (58%); Relapse: 15 (42%)
- 145 courses; SAEs: N=20. Febrile Neutropenia: n=9
  All resolved, no deaths, only one discontinuation due to PD
- Stem cell collection: 24 valid patients, no mobilization failures:
  - 17 patients, 1 apheresis
  - 6 patients, 2 apheresis
  - 1 patient, 4 apheresis
- Evaluable for pre-transplant response: n=24. Pre-APBSCT response:
  - ORR 96%
  - CR 83%

(S111) PRETREATMENT VITAMIN-D DEFICIENCY IS ASSOCIATED WITH LOWER PROGRESSION-FREE AND OVERALL SURVIVAL IN PROSPECTIVELY TREATED HODGKIN LYMPHOMA

Presenter: S. Borchmann, *Köln, Deutschland*

Author(s): Sven Borchmann, Helen Görgen, Stephanie Sasse, Stefanie Kreissl, Paul J. Bröckelmann, Bastian von Tresckow, Michael Fuchs, Volker Diehl, Andreas Engert

On behalf of the GHSG

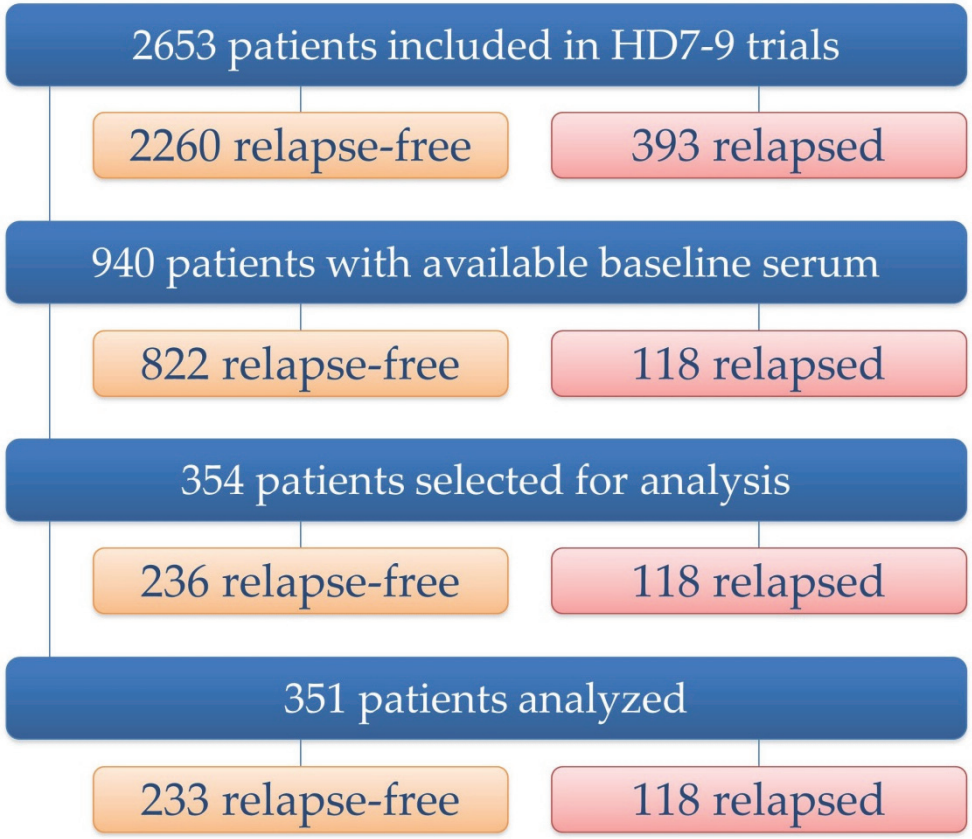
Background

S. Borchmann et al., Abstract S111

- Vitamin D has been implicated as a prognostic factor in various cancers
- Breast cancer, Colorectal cancer, NHL (e.g. DLBCL/CLL)
- No data for Hodgkin lymphoma
- Seasonality of HL incidence and mortality (Sven Borchmann et al., Sci Rep 2017)
- Vitamin D receptor strongly expressed on HRS cells (Renne et al., 2009, BMC Cancer)
- HL might be exacerbated by Vitamin D deficiency (Fleet et al., 2012 Biochem J)

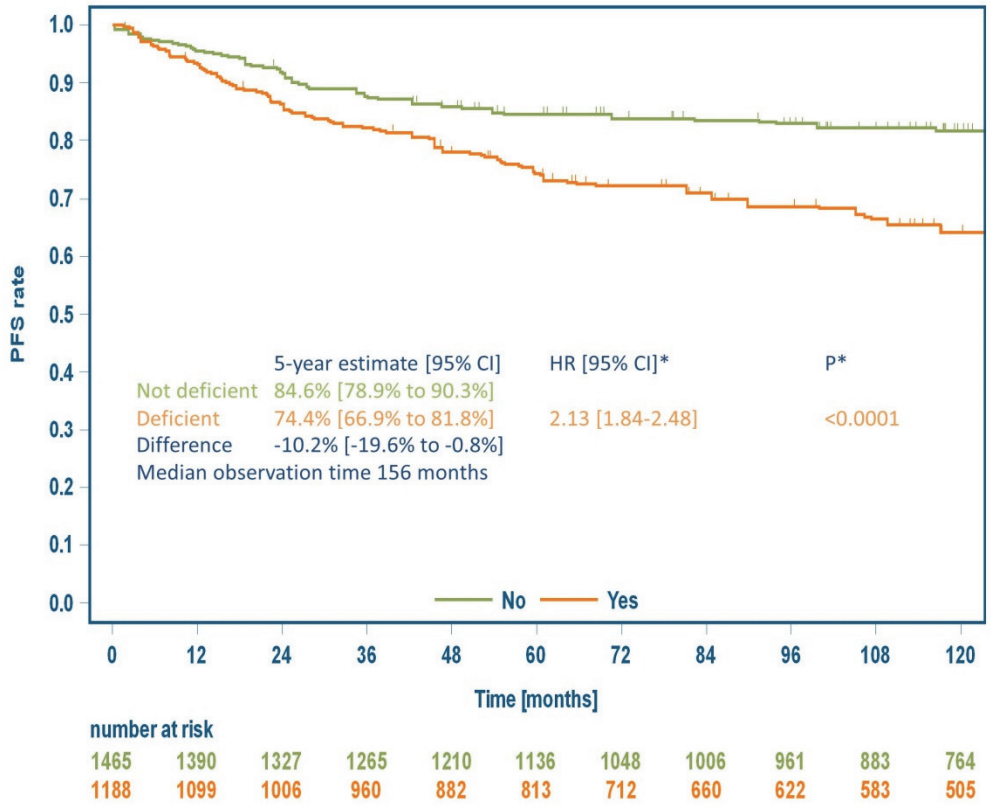
Vitamin D in patients with HL: Patients – Study flow chart

S. Borchmann et al., Abstract S111



Progression-free survival

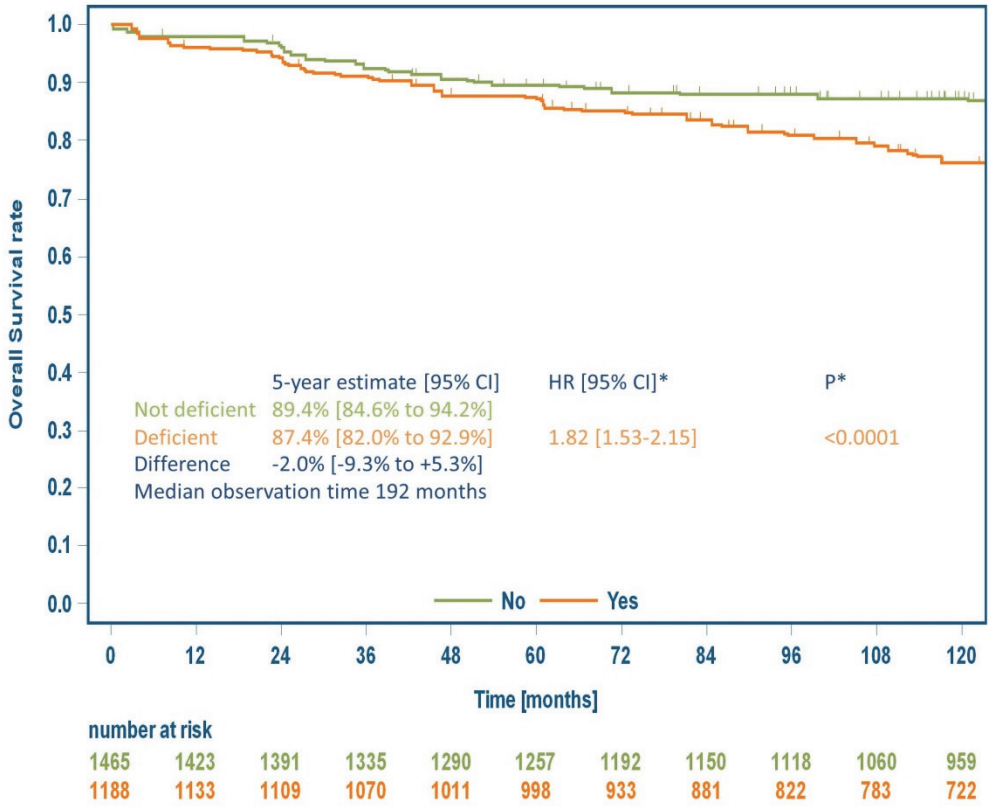
S. Borchmann et al., Abstract S111



* P value obtained from weighted Cox regression stratified by study/ treatment arm and adjusted for diagnosis season, age and sex

Overall survival

S. Borchmann et al., Abstract S111



* P value obtained from weighted Cox regression stratified by study/ treatment arm and adjusted for diagnosis season, age and sex

Summary

S. Borchmann et al., Abstract S111

- Vitamin D status is significantly associated with season of diagnosis -> sufficient levels were observed mostly in the summer months
- Apart from the seasonality effect, Vitamin D status did not correlate with any of the analyzed baseline factors
- Vitamin D at baseline is largely independent from other known risk factors
- Exhibits the expected seasonality pattern of patients treated in the northern hemisphere
- Is a clinically modifiable risk factor for PFS and OS across multiple studies with long term follow-up
- OS difference mainly due to fewer HL-associated deaths

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT EHA Stockholm 14.–17. Juni 2018

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Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT EHA Stockholm 14.–17. Juni 2018

Die Kurzpräsentationen sind online unter

www.lymphome.de/eha2018

Für den Inhalt verantwortlich:

Prof. Dr. med. Dr. h.c. Andreas Engert

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