MADRID 2017 ESMO congress

ESMO Clinical Practice Guidelines

Treatment of Hodgkin lymphoma

Clinical Case Discussion

Pr Stefano Luminari, MD

Università di Modena e Reggio Emilia

Reggio Emilia, Italy

DISCLOSURE

- Advisory boards/consultant: Roche, Celgene, Sandoz, Pfizer, Gilead
- Lectures: Gilead
- Travel grant: Takeda, Celgene, Jannsen

Key points and unmet medical needs in HL

Rare haematological cancer of the young patient (M>F)

95% are cHL; 5% are nodular lymphocyte-predominant HL (NLPHL)

Staging refers to the Lugano update of the Ann Arbor system and includes:

- Ph and lab exams (including viruses)
- B symptoms evaluation
- CT scan and FDG-PET
- BMB no longer indicated with FDG-PET
- Lung and cardiac function tests, reproductive counseling

High cure rates (90-95%) but 10-30% early failures and excess of late events

BMB, bone marrow biopsy; cHL, classic Hodgkin lymphoma; CT, computed tomography; FDG- PET, fludeoxyglucose-positron emission tomography; Ph, Philadelphia

Cheson BD et al. JCO 2014,
Barrington SF et al. JCO 2014
El-Galaly TC et al. JCO 2012

2014 ESMO GUIDELINES
Eichenauer et al. Ann Oncol 2014

Early Favourable (stage I-II without risk factors*)

- 2-3 x ABVD + 20 Gy IFRT or ISRT

Early Unfavourable/intermediate (stage I-II with risk factors*)

- 4x ABVD + 30 Gy IFRT
- 2x ABVD + 2x escBEACOPP + 30 Gy IFRT or ISRT (< 60 years)

Advanced (stage IIB#, stage III-IV or stage IIB with LMM)

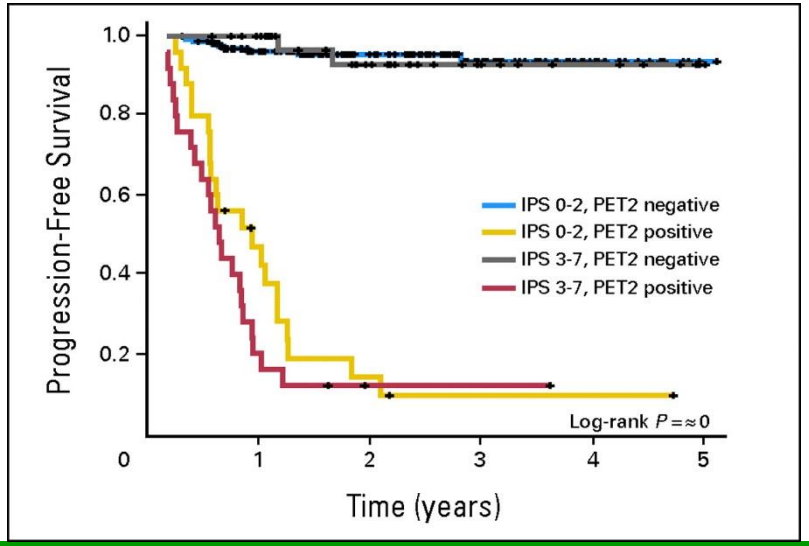
- 6-8x escBEACOPP (< 60 years) + IFRT to PET+ve residual lymphoma > 2.5 cm
- 6-8x ABVD and IFRT to residual lymphoma > 1.5cm

Risk Factors:
* B-symptoms; High ESR; Bulky tumour; > 3 lymph node areas; extranodal disease
# B-symptoms and extranodal disease or bulky tumour

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ASCT, autologous stem cell transplant; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ESR, erythrocyte sedimentation rate; HL, Hodgkin lymphoma; IFRT, involved field radiotherapy; ISRT, involved site radiotherapy; PET, positron emission tomography

Recommendations for initial evaluation, staging, and response assessment of HL and non-HL: the Lugano classification

Early Interim FDG-PET Is Prognostically Superior to IPS in Adv-Stage HL: Italian-Danish Study



PFS according to IPS group and PET results after two cycles of ABVD

Gallamini A et al. JCO 2007

5 point scale Deauville criteria

CMR

Score 1: no uptake

Score 2: uptake ≤ mediastinum

Score 3: uptake > mediastinum but ≤ liver

Score 4: moderately increased uptake > liver

Score 5: markedly increased uptake > liver and/or new lesions related to lymphoma

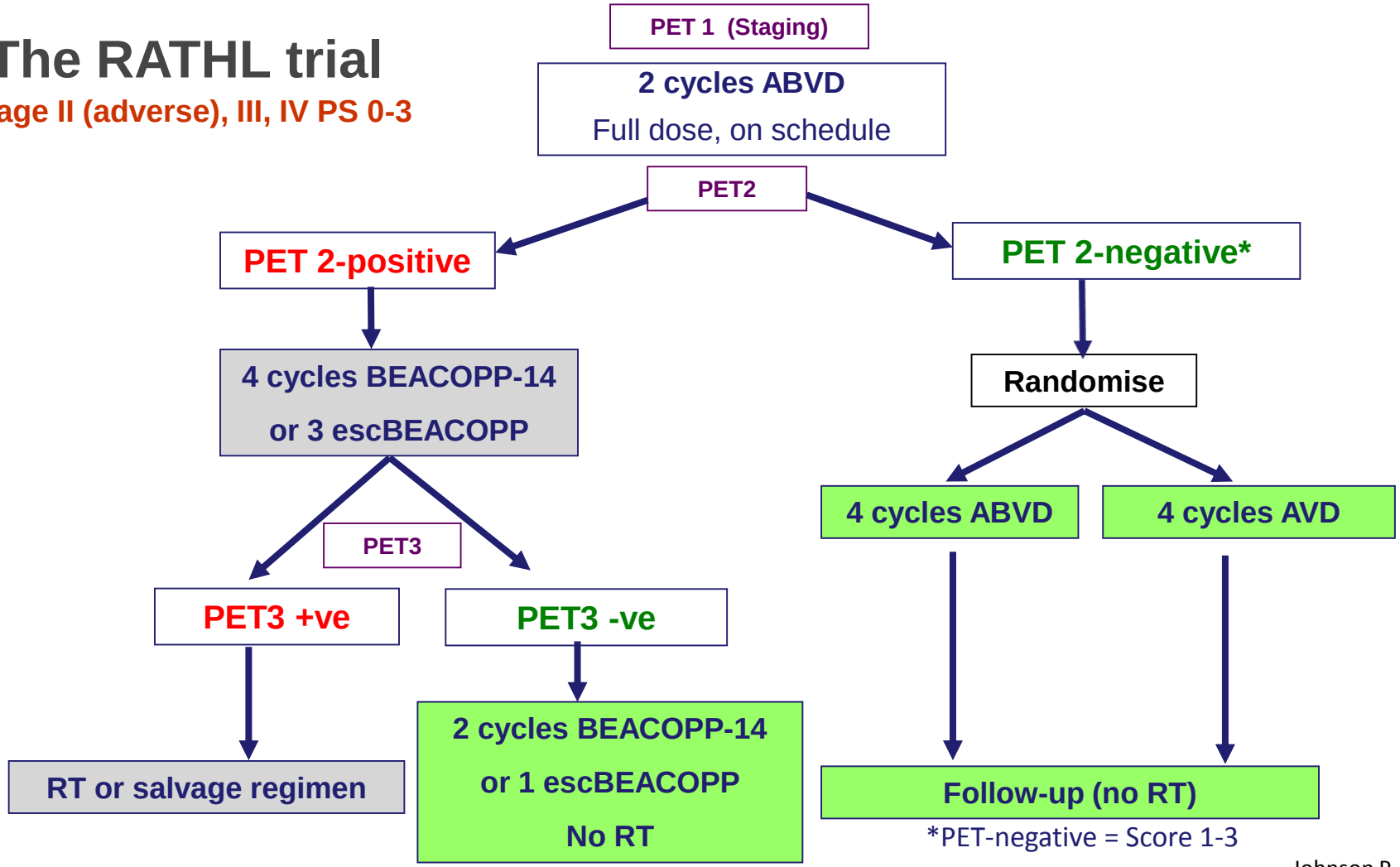
Score X:
New areas of uptake unlikely to be related to lymphoma

Cheson BD et al. JCO 2014

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; FDG- PET, fludeoxyglucose-positron emission tomography; HL, Hodgkin lymphoma; IPS, International Prognostic Score; PFS, progression-free survival CMR Complete Metabolic response

The RATHL trial

Stage II (adverse), III, IV PS 0-3



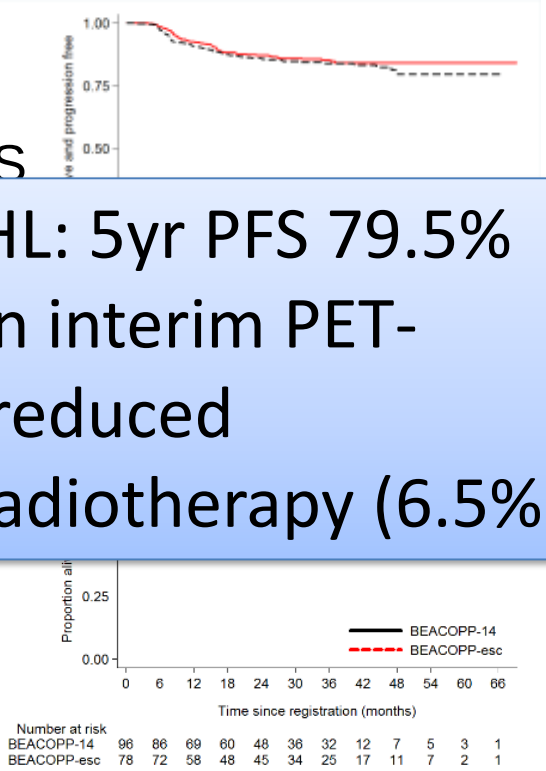
Johnson P. NEJM 2016

The RATHL trial

In advanced HL, with a negative interim PET scan after two cycles of ABVD, it is safe to omit further bleomycin (↓ pulm toxicity) and reduce use of consoli

Escalating the BEACOPP14 positive patients delivers a promising PFS (5yrs PFS 65.7% (58 – 73))

PFS

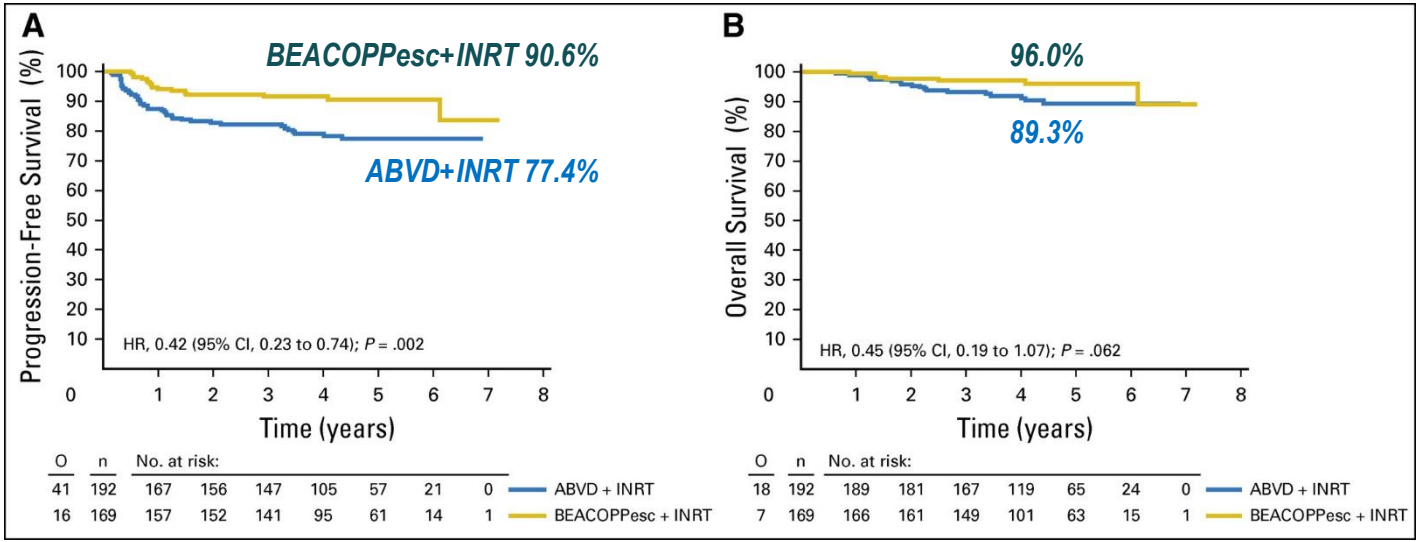


Overall results from RATHL: 5yr PFS 79.5% and OS 93.5%, support an interim PET-adapted approach, with reduced chemotherapy and less radiotherapy (6.5%)

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; HL, Hodgkin lymphoma; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival

Johnson P. NEJM 2016

Response adapted therapy in early HL
The H10 TRIAL by EORTC/LYSA/FIL
PET+ group: escBEACOPP versus ABVD



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Marc Andre et al. J Clin Oncol 2017

Exploring the BEACOPP side of response adapted therapy

- Interim PET is not prognostic in advanced HL treated with BEACOPP due to the very low PPV
- The high NPV makes it reasonable to conduct response adapted trials investigating de-escalation strategies
- AHL2011-LYSA Casasnovas ASH 2015
  - Randomised comparison of escBEACOPP versus response adapted strategy (i.e. shift to ABVD after 2 escBEACOPP and negative iPET (DS 1-3)
- HD18-GHSG Borchmann EHA 2017
  - Randomised study comparing 4 versus 2 escBEACOPP in patients with negative iPET after 2 escBEACOPP

BOTH trials concluded in favor of Tx de-escalation in patients PET-ve after 2 escBEACOPP

Treatment of relapsed/refractory HL

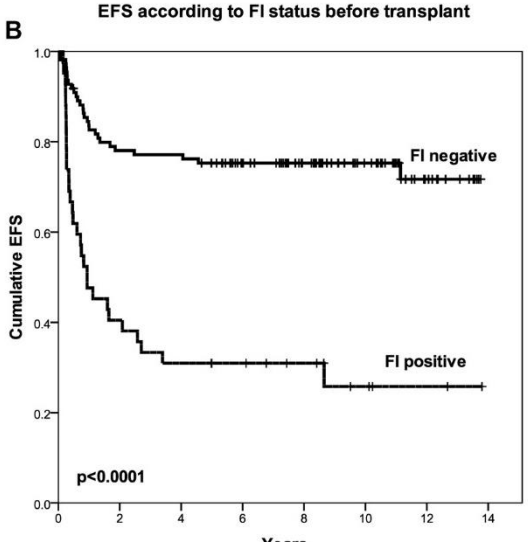
2014 ESMO GUIDELINES

- For most patients with RR HL the treatment of choice consists of high dose chemotherapy followed by ASCT
- Several salvage regimens are available (DHAP, IGEV, ICE) to mobilise PBSC prior to ASCT
- Brentuximab vedotin represents an option in patients failing ASCT
- Allogeneic stem cell transplantation is an active option (RIC)

ASCT, autologous stem cell transplantation; DHAP, high-dose cytarabine, cisplatin, and dexamethasone; ICE, ifosfamide, carboplatin and etoposide; IGEV, ifosfamide, gemcitabine, vinorelbine; PBSC, peripheral blood stem cells; RIC, reduced-intensity conditioning; RR HL relapsed/refractory Hodgkin lymphoma

ESMO consensus conference on malignant lymphoma: general perspectives and recommendations for prognostic tools in mature B-cell lymphomas and chronic lymphocytic leukaemia

M. Ladetto[1]*, C. Buske[2], M. Hutchings[3], M. Dreyling[4], G. Gaidano[5], S. Le Gouill[6], S. Luminari[7,8], C. Pott[9], A. Zamò[10], E. Zucca[11]& the ESMO Lymphoma Consensus Conference Panel Members[†]



Alison J. Moskowitz et al. Blood 2010

…the panel recognised that interim FDG-PET is prognostic when used after reinduction chemotherapy and before a preplanned high-dose therapy programme in relapsed or refractory HL… [III, A]

Ann Oncol 2016

RR HL after ASCT or not eligible to ASCT

brentuximab vedotin (anti-CD30 MoAb conjugated with monomethil auristatin - MMAE)

Pivotal phase II study, single agent, RR HL after ASCT. ORR 75%; CRR 34%; mPFS 5.6m (CR 20m) Good safety profile. Younes A. et al. JCO 2012

Randomised data support the use of Brentuximab vedotin consolidation to improve the tumor control in High risk patients: AETHERA Trial Moskowitz CH et al Lancet 2015

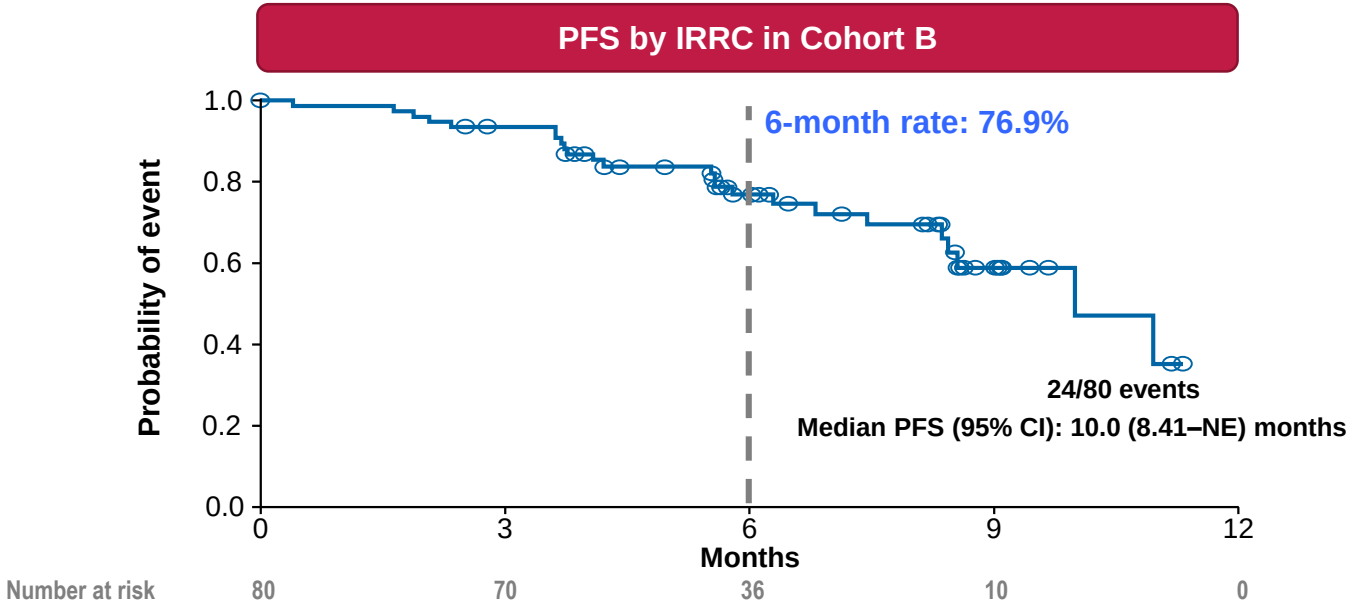
Ph-II study of PET-adapted sequential salvage therapy with BV followed by augICE and/or ASCT at 1° relapse. (N=45; 28% PET–ve after 4 BV). Moskowitz AJ et al. Lancet Oncol 2015

Ph-II study of BV combination with bendamustine at 1° relapse (CRR 83%) La Casce Blood 2014

ASCT, autologous stem cell transplantation; BV, brentuximab vedotin; CRR, complete response rate; ORR, objective response rate; MoAb, monoclonal antibody; RR HL relapsed/refractory Hodgkin lymphoma;

CHECKMATE 205: nivolumab in RR HL after ASCT and BV

- Nivolumab demonstrated:
  - **High response rate** per IRRC (66%)
    - A complete response in 9% of patients (n = 7)
  - **Durable response** (median duration of response 7.8 months)



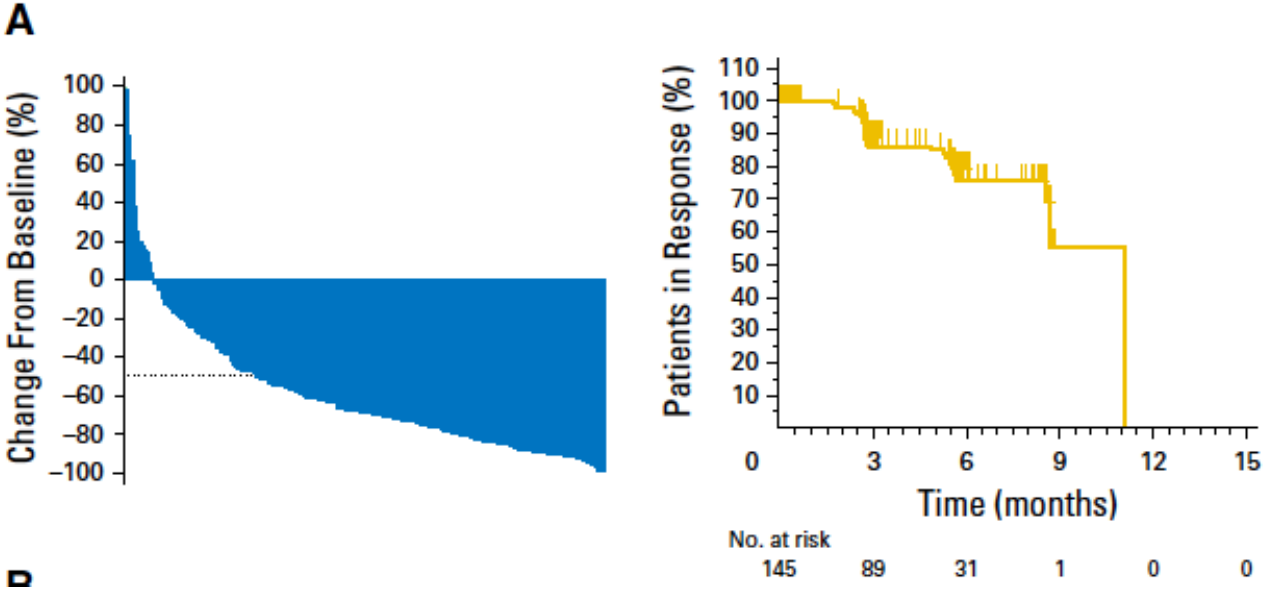
ASCT, autologous stem cell transplantation; BV, brentuximab vedotin; NE, not estimable

Younes A et al. Lancet Oncol 2016

Response rate and duration of response, pembrolizumab and RR HL (keynote 0-87)

Multicohort study N=210

ORR 69.0% (95% CI, 62.3% to 75.2%), CRR 22.4% (95% CI, 16.9% to 28.6%).

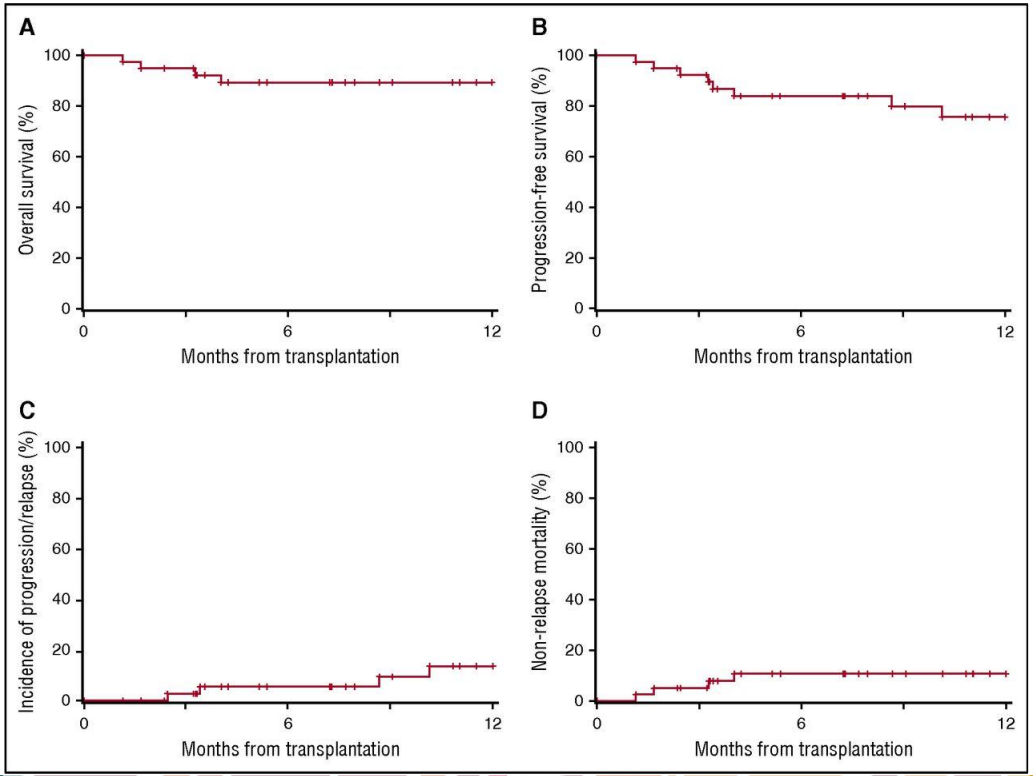


CRR, complete response rate; ORR, objective response rate

Chen R et al, JCO 2017

allo-HSCT can be safely performed in patients after checkpoint inhibitors

OS, PFS, CIR, and NRM following HSCT in patients previously treated with a PD-1 inhibitor



blood

Reid W. Merryman et al. Blood 2017

CONCLUSIONS

Outcome of HL patients has greatly improved with currently available therapi… …and treatment tolerability should now be considered as primary goals

Interim FDG_PET has shown to be the strongest prognostic fa… …e development of reponse adapted therapies

- ABVD lovers:

  Randomised data support the ch… …in adv HL from cycle 3-6 in i-PET–ve (DS 1-3)

  Randomised data supp… …scBEACOPP in early stage who are i-PET+ve (DS 3-5)

  Non randomis… …iation to BEACOPP iPET+ve pts (DS 4-5) is a good option

- BEACOPP …

  Ra… …n published data suggest that it is safe to de-escalate therapy (ABVDx4 of BEA… …patients who are iPET negative

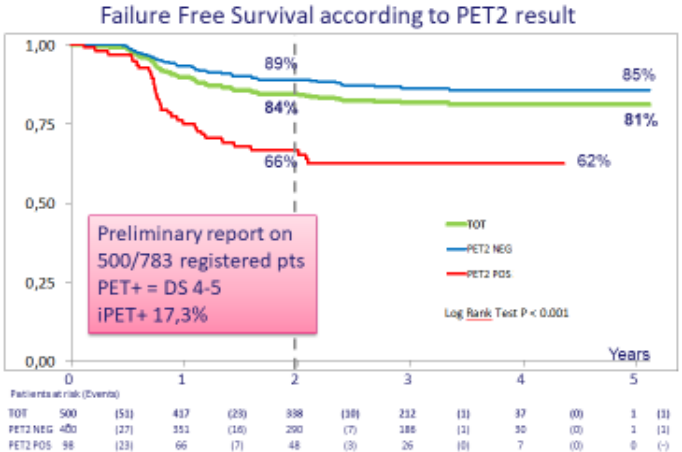
Response adapted therapy will be included in the 2017 update of ESMO guidelines for HL!!

CONCLUSIONS

- In the R/R setting ASCT is still the treatment of choice for patients who are chemosensitive to salvage therapy (response adapted trials needed)
- BV and checkpoint inhibitors are currently available for the management of patients who relapse after ASCT but guidelines remain undefined.
- Relevant open questions for new agents in HL
  - Position in 1st line: ECHELON1 (BV) PhIII results at ASH 2017
  - Phase III studies at 1st relapse
  - Biomarker driven studies
  - Elderly patients
  - Long term data (efficacy and safety)

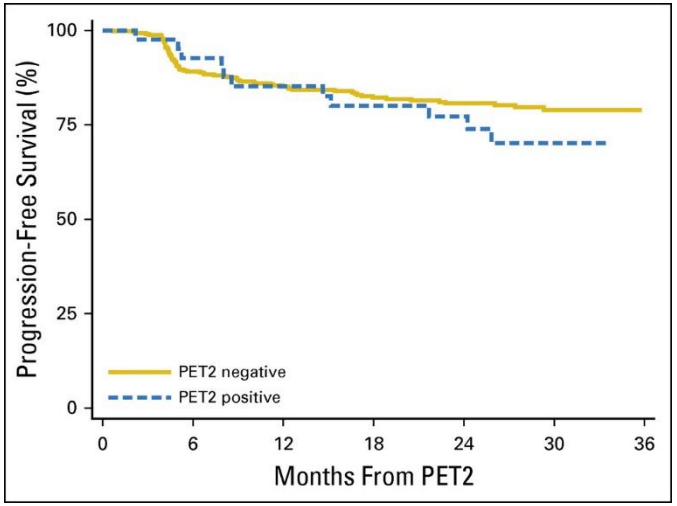
Other phase III response adapted trials in advanced HL (PET+ve patients)

FIL-GITIL
HD0607 Trial



Gallamini et al. XIII ICML Lugano 2015 Abstract #118

HD0801 Trial



Zinzani PL et al JCO 2016

HL, Hodgkin lymphoma; PET, positron emission tomography

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clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii70–iii75, 2014
doi:10.1093/annonc/mdu181
Published online 25 July 2014

Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

D. A. Eichenauer[1], A. Engert[1], M. André[2], M. Federico[3], T. Illidge[4], M. Hutchings[5], & M. Ladetto[6]
on behalf of the ESMO Guidelines Working Group*

Other phase III response adapted trials in advanced HL (PET+ve patients)

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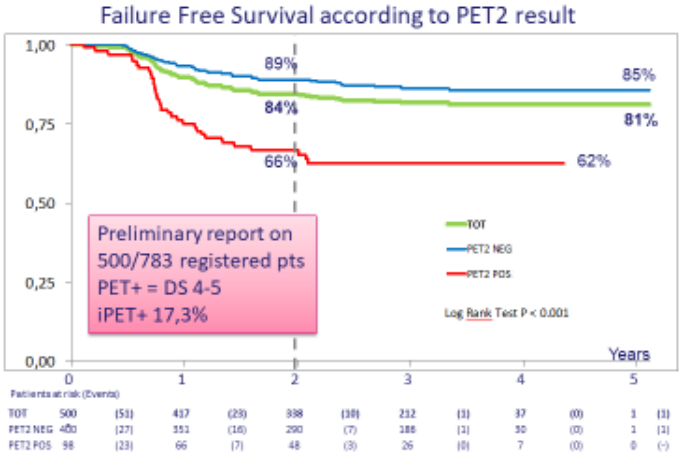

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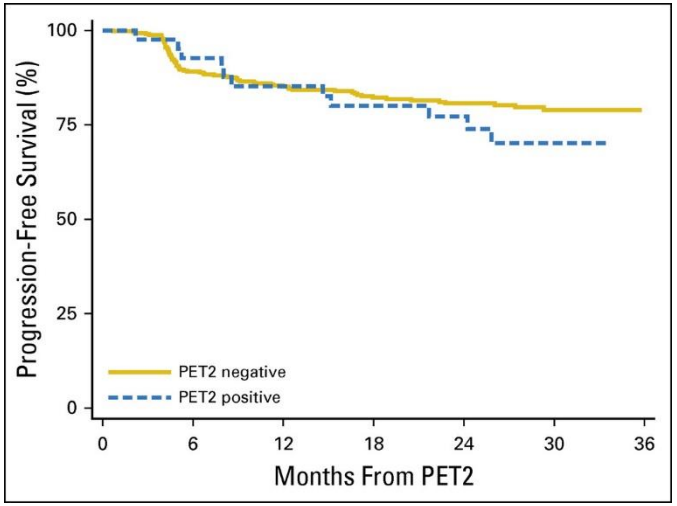

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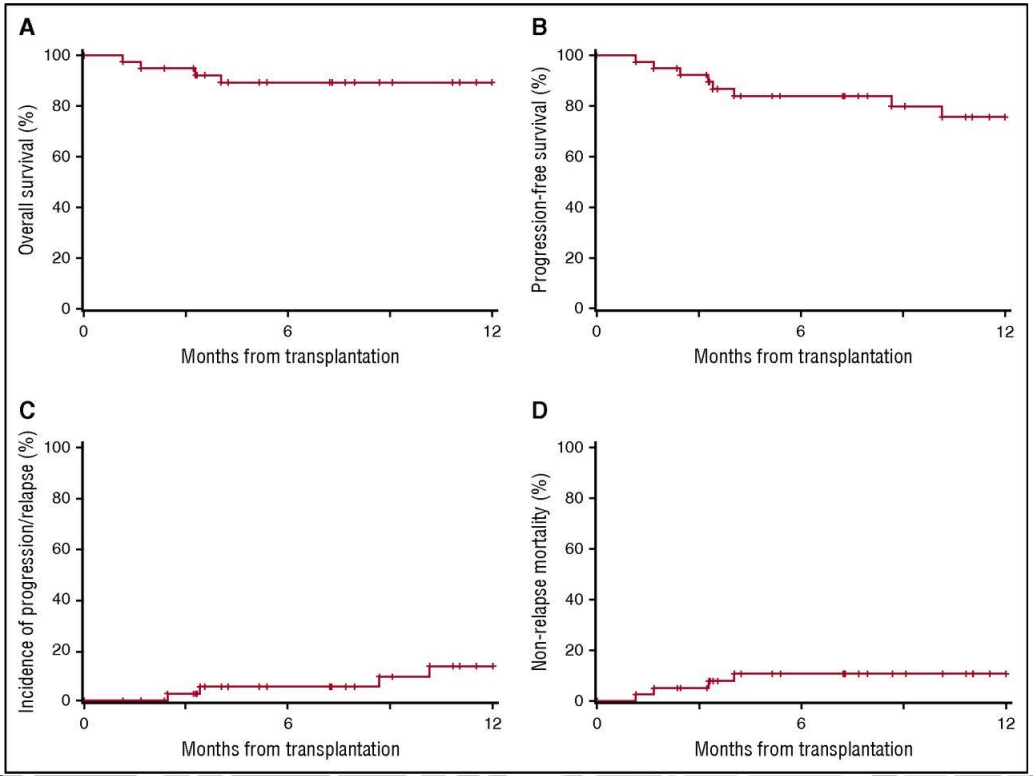


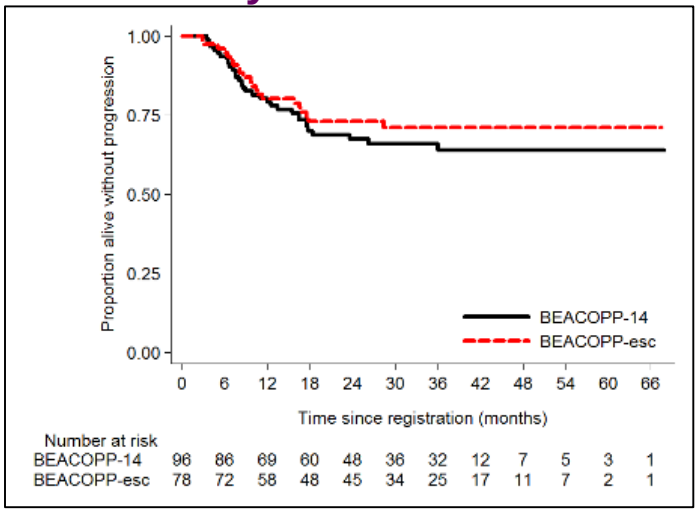
blood

Reid W. Merryman et al. Blood 2017

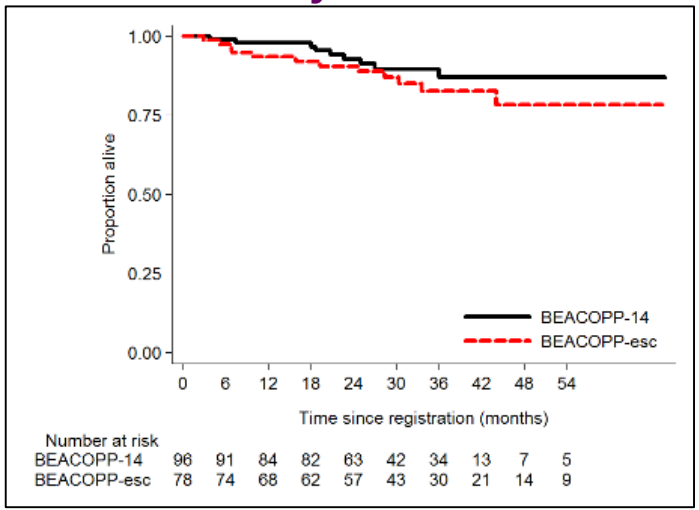
PFS and OS in patients with positive PET2

- 16% patients PET2-positive
- 5 year PFS 65.7% (58-73), 5year OS 85.1% (78-90)
- No significant difference between escBEACOPP and BEACOPP-14

5 year PFS %



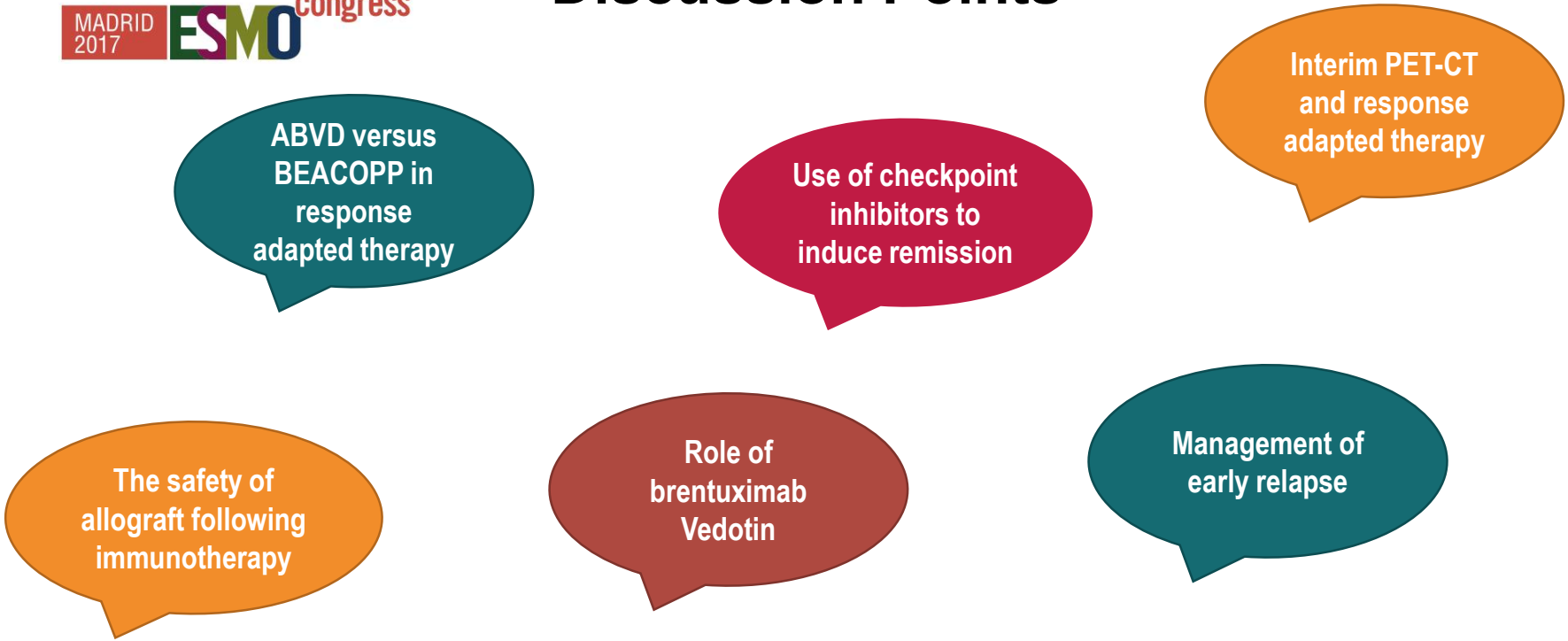
5 year OS %



BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone;
OS, overall survival; PET, positron emission tomography; PFS, progression-free survival

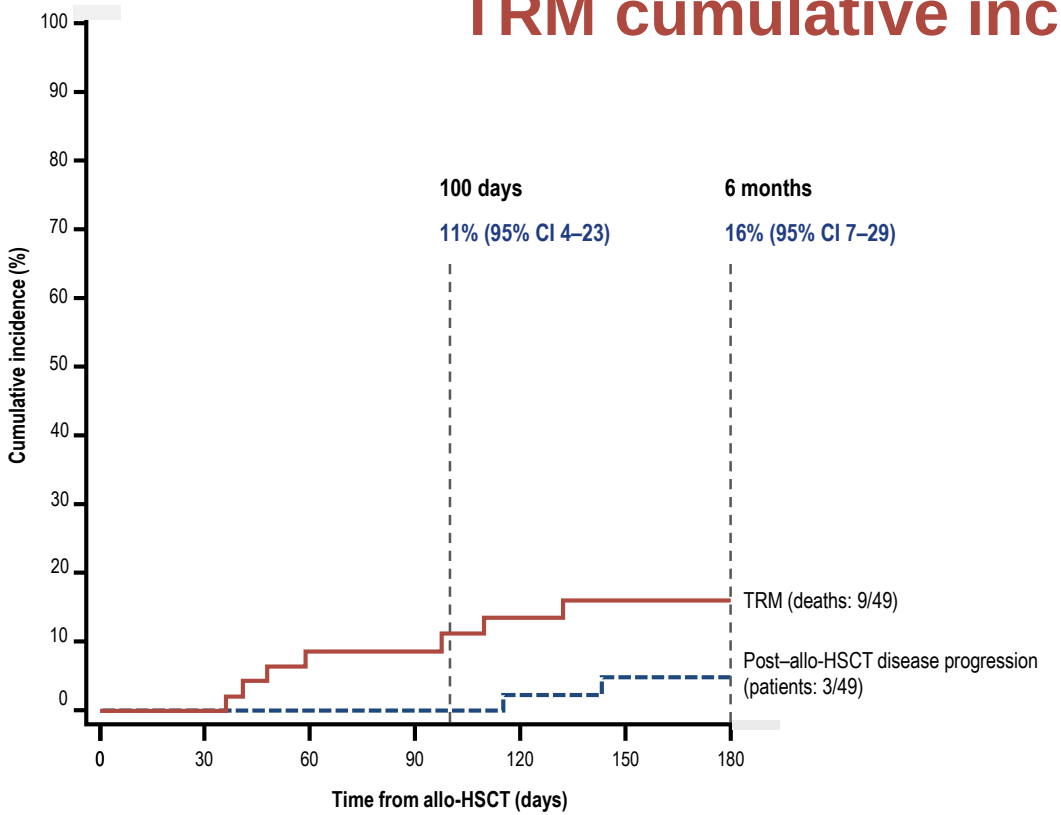
Trotman J et al. XIV ICML Lugano 2017

Discussion Points



ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; PET-CT, positron emission tomography-computed tomography

alloHSCT after nivolumab
TRM cumulative incidence

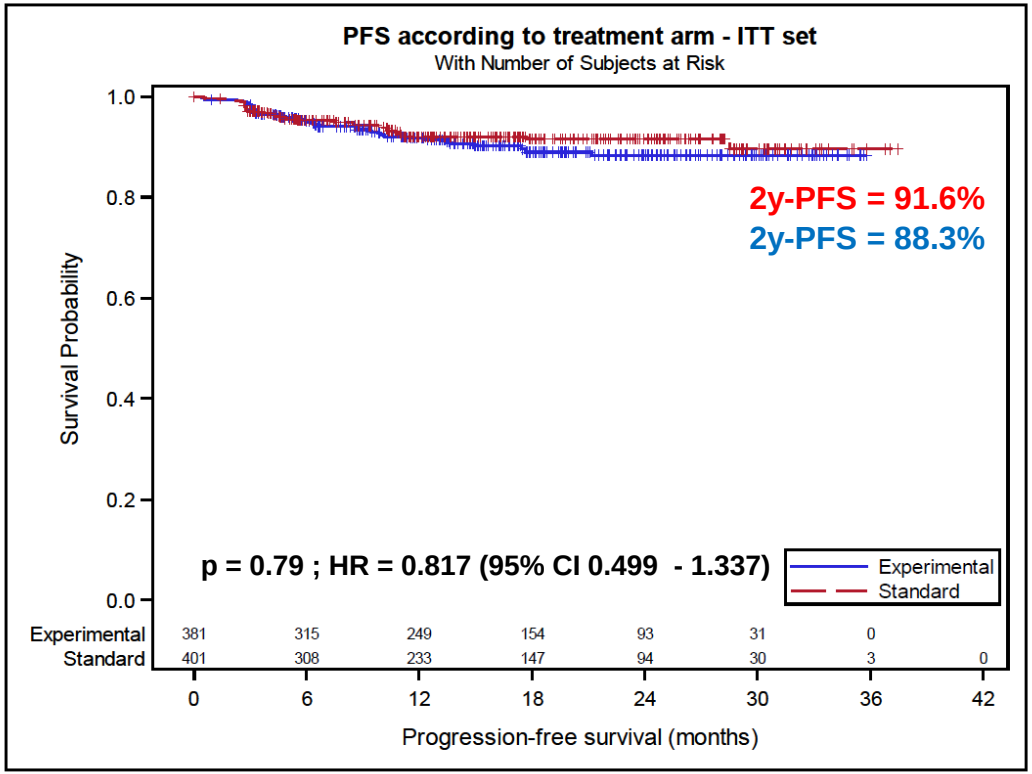


Disease progression was considered a competing risk to TRM

TRM, treatment-related mortality

Carlo-Stella C et al, EBMT 2017
(unpublished information, with permission)

AHL 2011



Median follow-up = 16.3 months (0.1-37.4)

- 87% of patients were PET2 neg (DS1-3)
- 84% patients in the exp arm treated with 2 escBEACOPP + 4 ABVD

Casasnovas et al. ASH 2015