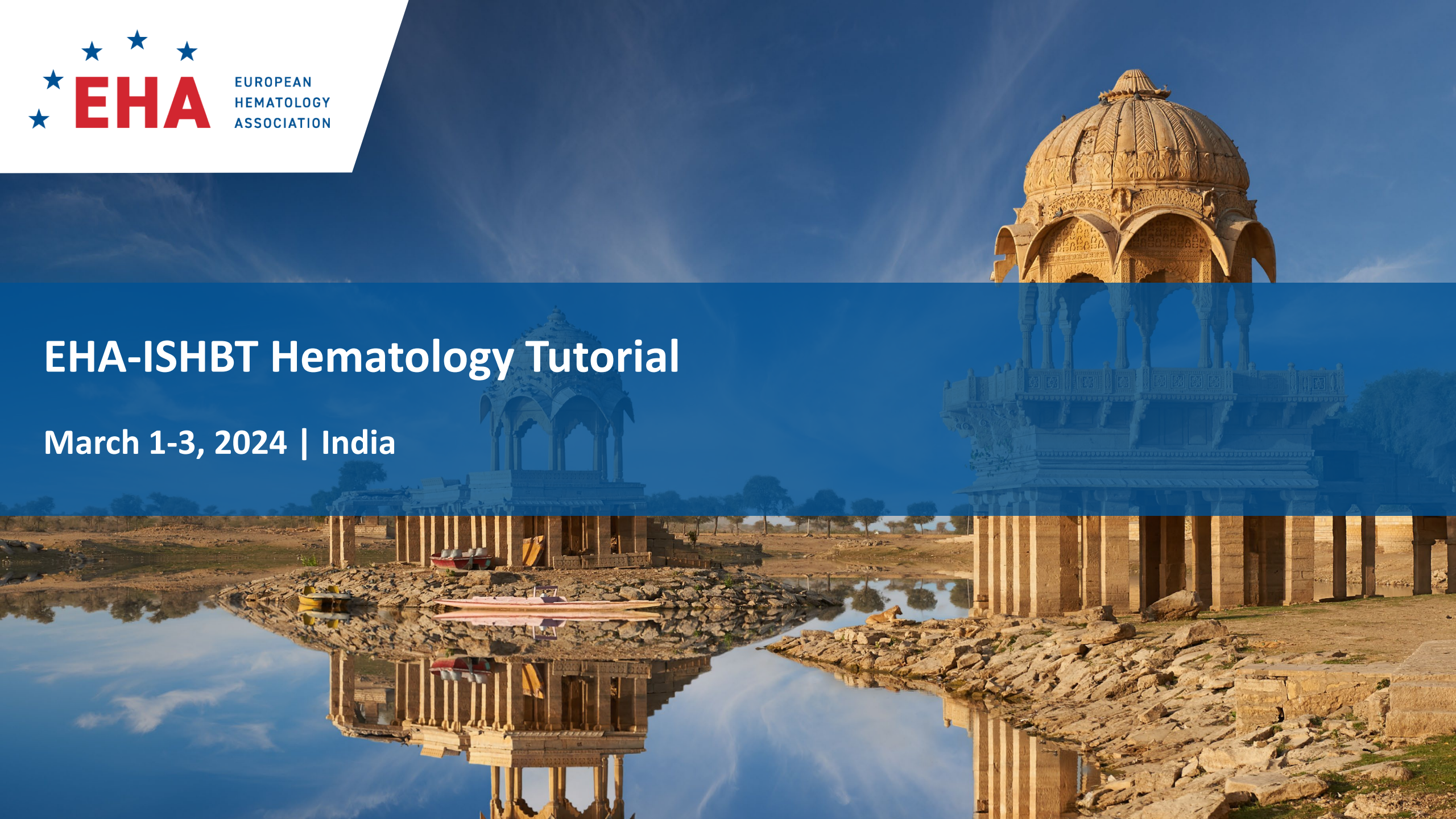
EUROPEAN HEMATOLOGY ASSOCIATION

EHA-ISHBT Hematology Tutorial

March 1-3, 2024 | India



What's new in the therapy of Hodgkin's lymphoma?

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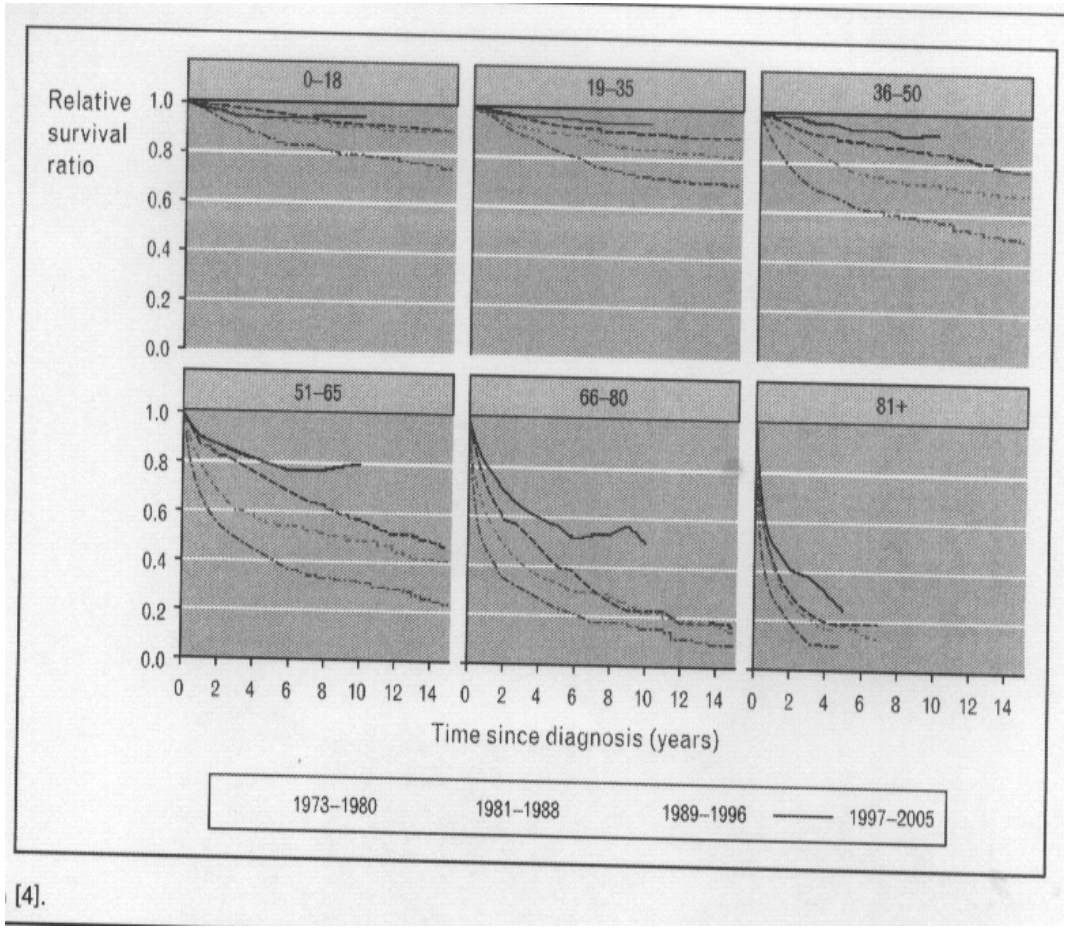
Medical School, University of Zagreb
Croatia

Disclosures

- Roche
- Takeda
- Janssen
- Astra-Zeneca
- Beigene
- Eli Lilly
- Sobi
- Novartis / Sandoz
- Genesis / Incyte
- Swixx

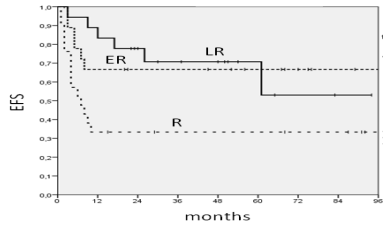
Outcomes in HL depend on age and treatment line

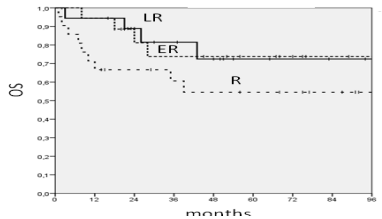


[4].

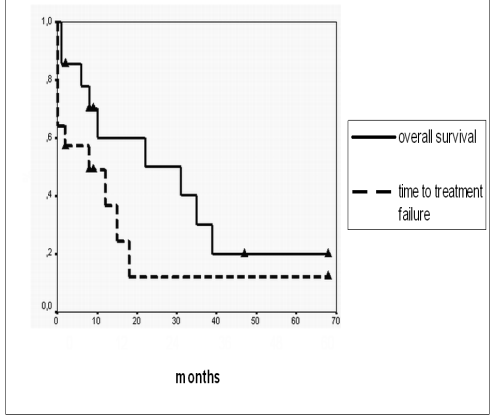
Bjorkholm et al, Curr Opin Onol 2011

2nd line





Beyond 2nd line



Aurer et al. Ann Hematol 2016

Aurer et al, Onkologie 2005.

Health problems in responding patients

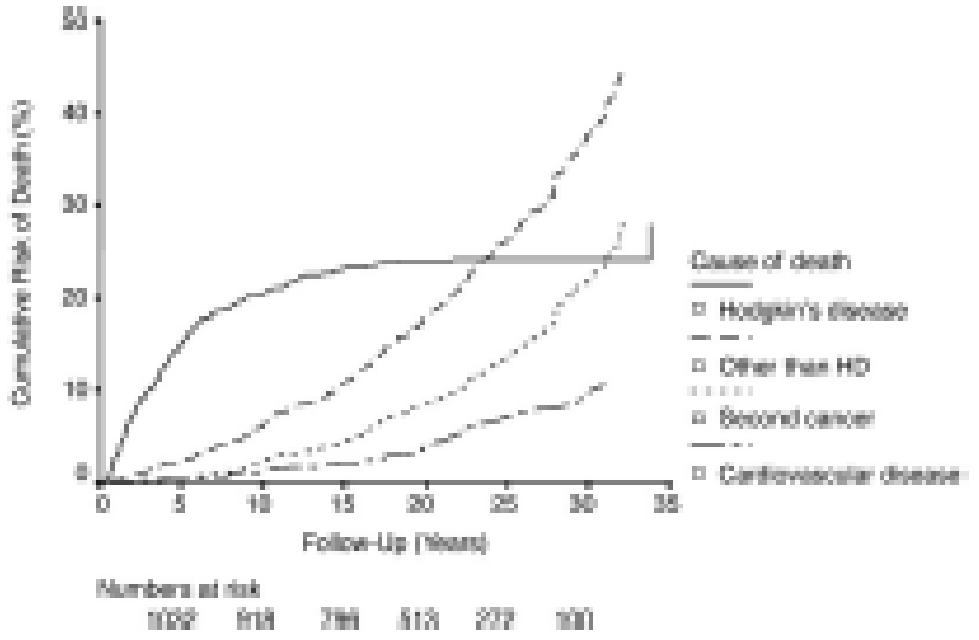


Fig 1. The actuarial risks of death from major disease categories. HD, Hodgkin's disease.

- secondary cancers
- heart disease

- infertility
- aseptic hip necroses
- thyroid disease
- chronic fatigue
- ...

Aleman et al, JCO 2003

What do we want from new treatment approaches?

- Reduce long-term toxicity of front-line treatment in younger
  - Without jeopardizing efficacy
- Improve efficacy of salvage treatments and front-line treatment of elderly
  - Aim for cure

Armamentarium

- Chemotherapy
  - eBEACOPP, ABVD, AVD, dacarbazine, bendamustine, high-dose chemotherapy
- Radiotherapy
  - 3D – 4D linear accelerators
- Conjugated monoclonal antibodies = targeted chemotherapy
  - Brentuximab vedotin
- PD1 (checkpoint) blockers
  - nivolumab, pembrolizumab, …

Risk assessment

- Front-line
  - Age: younger, fit
  - Stage: limited fav
- Later lines
  - Primary refractor
  - Transplantable vs

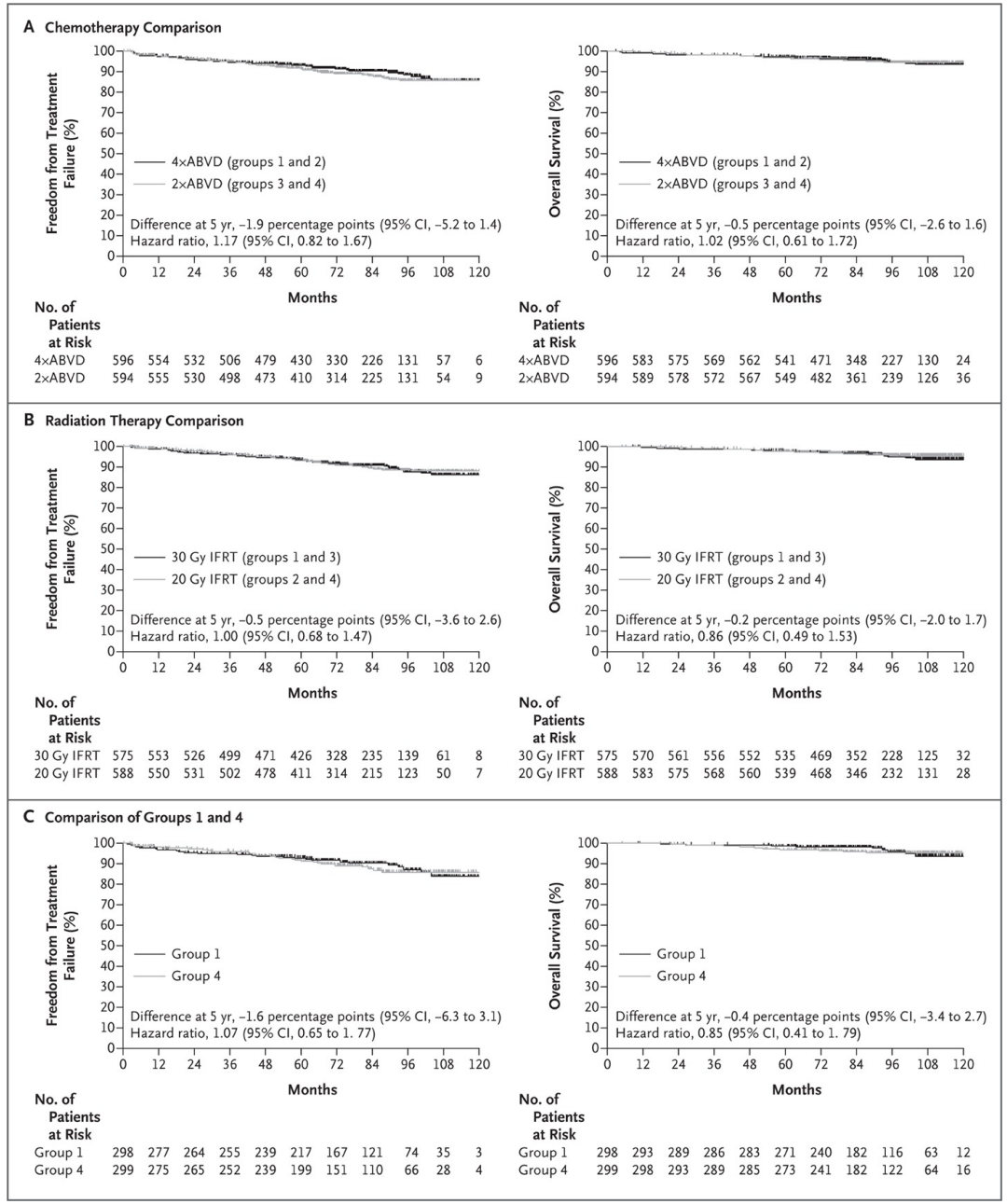
GHSG criteria

	Stage (Ann Arbor)			
Risk Factors	**IA, IB, IIA**	**IIB**	**IIIA, IIIB**	**IVA, IVB**
None	**Early favorable**		**Advanced**	
≥ 3 LK- Areas	**Early unfavor-able**			
Elevated ESR				
Large Mediastinal Mass				
Extranodal disease				

GHSG – German Hodgkin Study Group; HL – Hodgkin lymphoma; ESR - erythrocyte sedimentation rate

Limited stage favorable

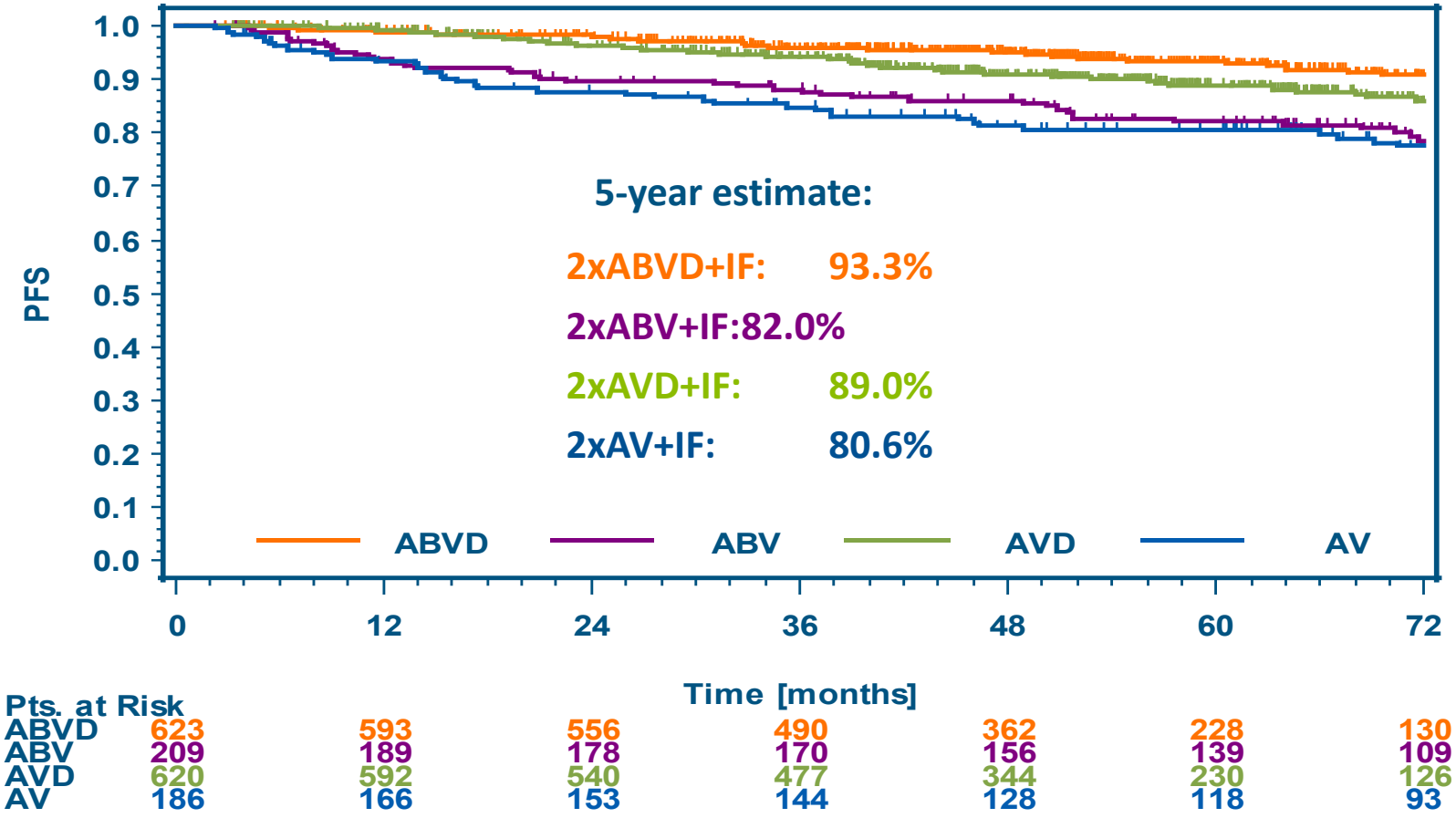
- 2xABVD = 4xABVD
- 20 Gy RT = 30 Gy RT
- 2xABVD + 20 Gy RT = 4xABVD + 30 Gy RT



Engert et al, NEJM 2010;

Reducing chemotherapy

GHLSG (H13): KT + 20 Gy RT - PFS

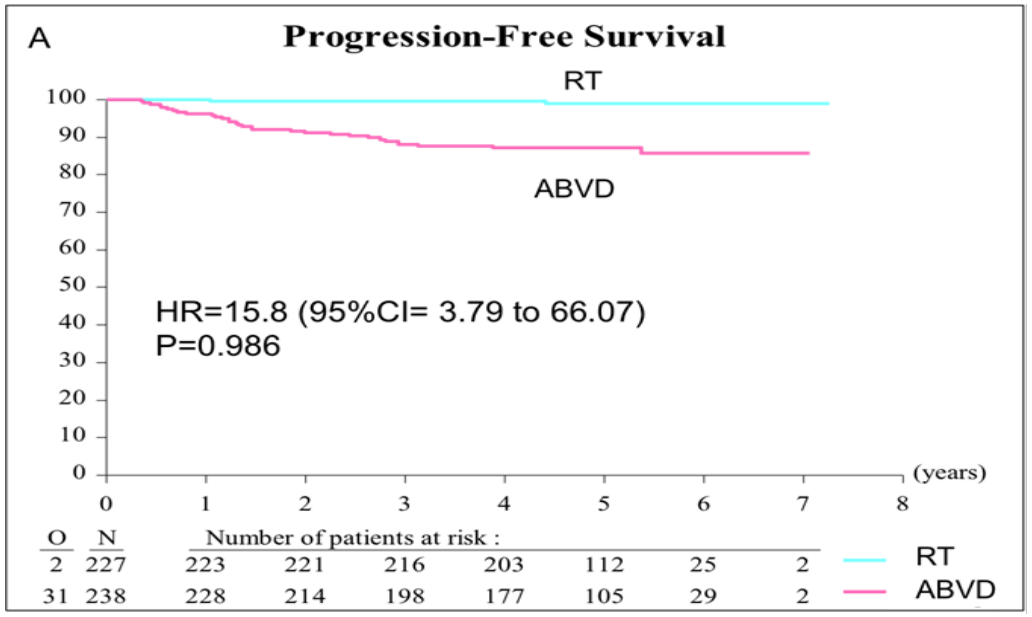


ABVD – doxorubicin, bleomycin, vinblastine, darcarbacine; ABV - doxorubicin, bleomycin, vinblastine; AVD - doxorubicin, vinblastine, darcarbacine; AV – doxorubicin, vinblastine; IF – involved field radiotherapy; pts – patients; PFS – progression free survival

Behringer et al, Lancet 2014

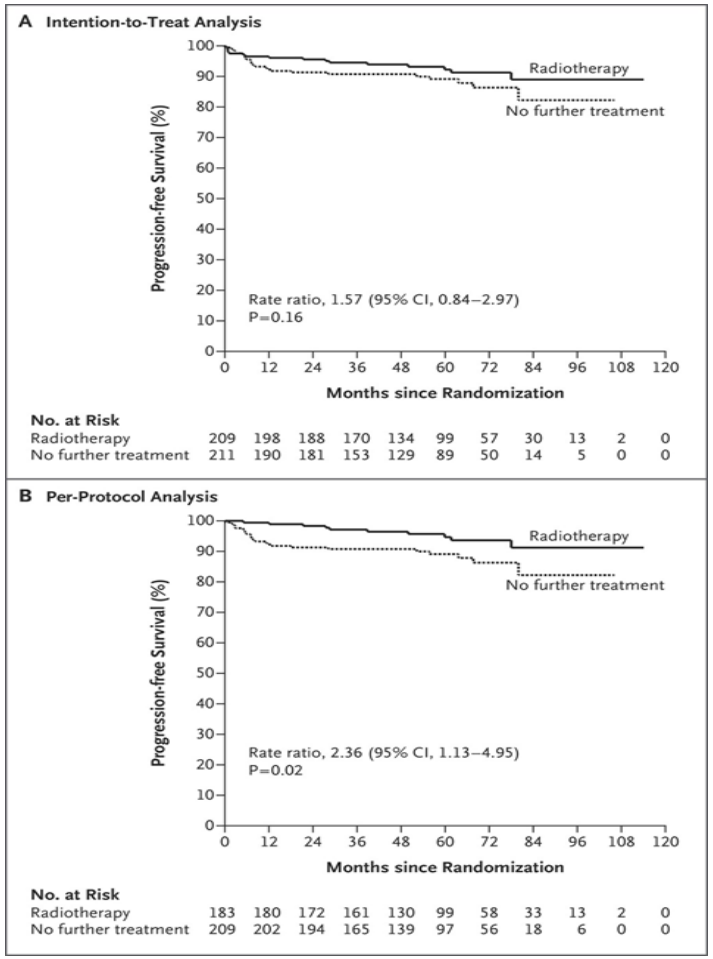
Reducing radiotherapy

H10 favorable



Raemaekers et al, ICML 2015

RAPID

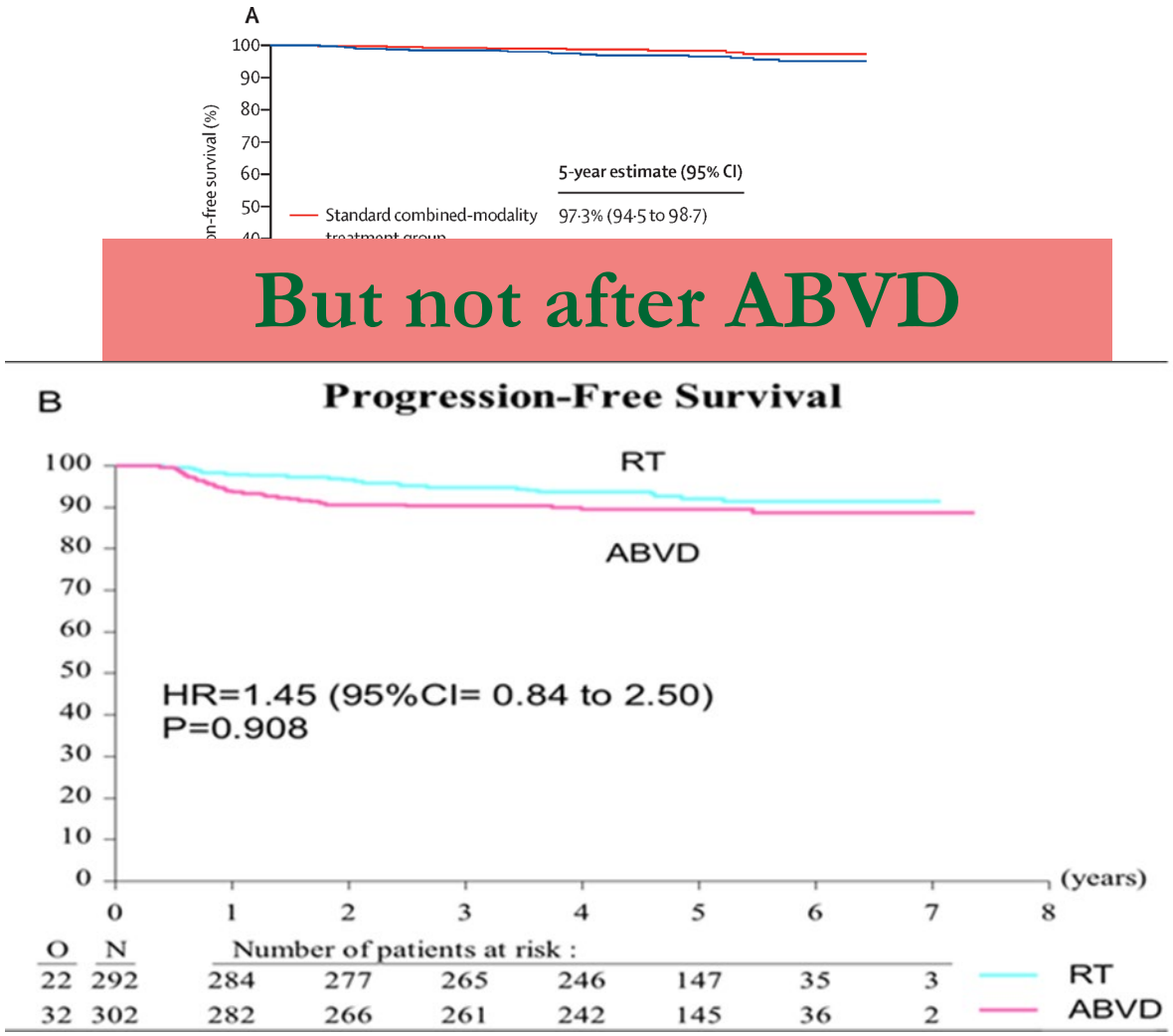


Radford et al, NEJM 2015

Limited stage, unfavorable

Borchmann et al, Lancet Oncol 2021

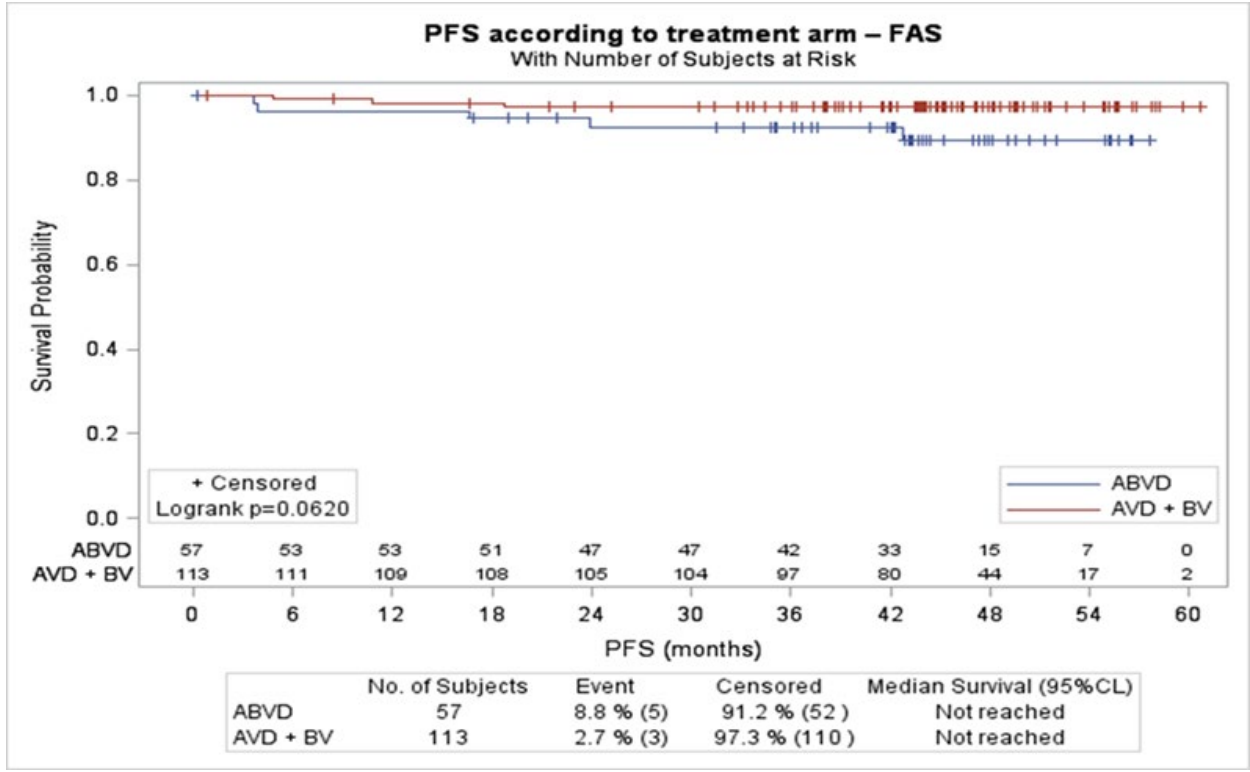
In pts. with localised unfavorable disease RT can safely be avoided if they are PET- after 2x eBEACOPP + 2x ABVD



New agents in this setting

- **BREACH**

- 4x AVD-Bv + RT 30 Gy
  vs. 4x ABVD + RT 30 Gy

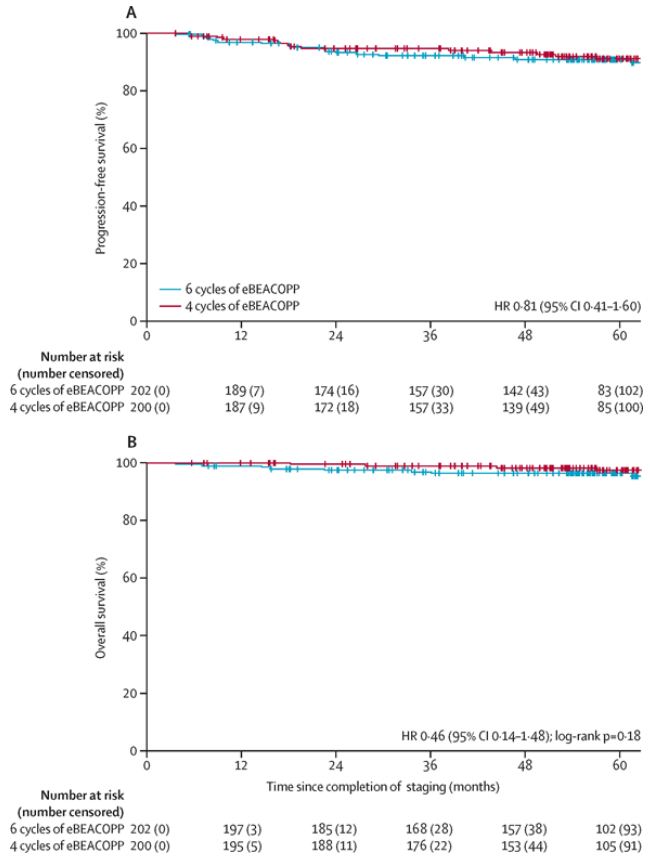


2y PFS 97% vs. 93%

Fornecker LM et al, JCO 2022

Advanced stage

- eBEACOPP
  - 4 cycles if PET- after 2nd
    - 5y PFS 91%
    - 5y OS 98%
  - 6 cycles ± RT if PET+ after 2nd
    - 5y PFS 91%
    - 5y OS 96%

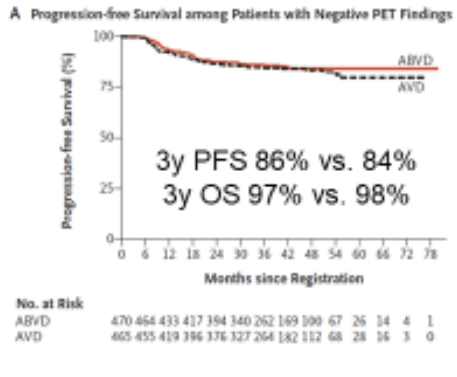


Kreissl S et al, Lancet Haematol 2021

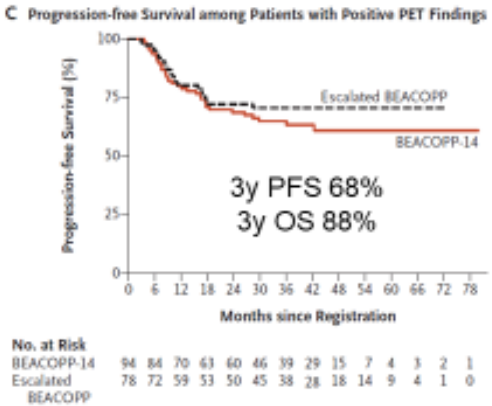
- RATHL

ABVDx2 followed by iPET

PET- AVDx4

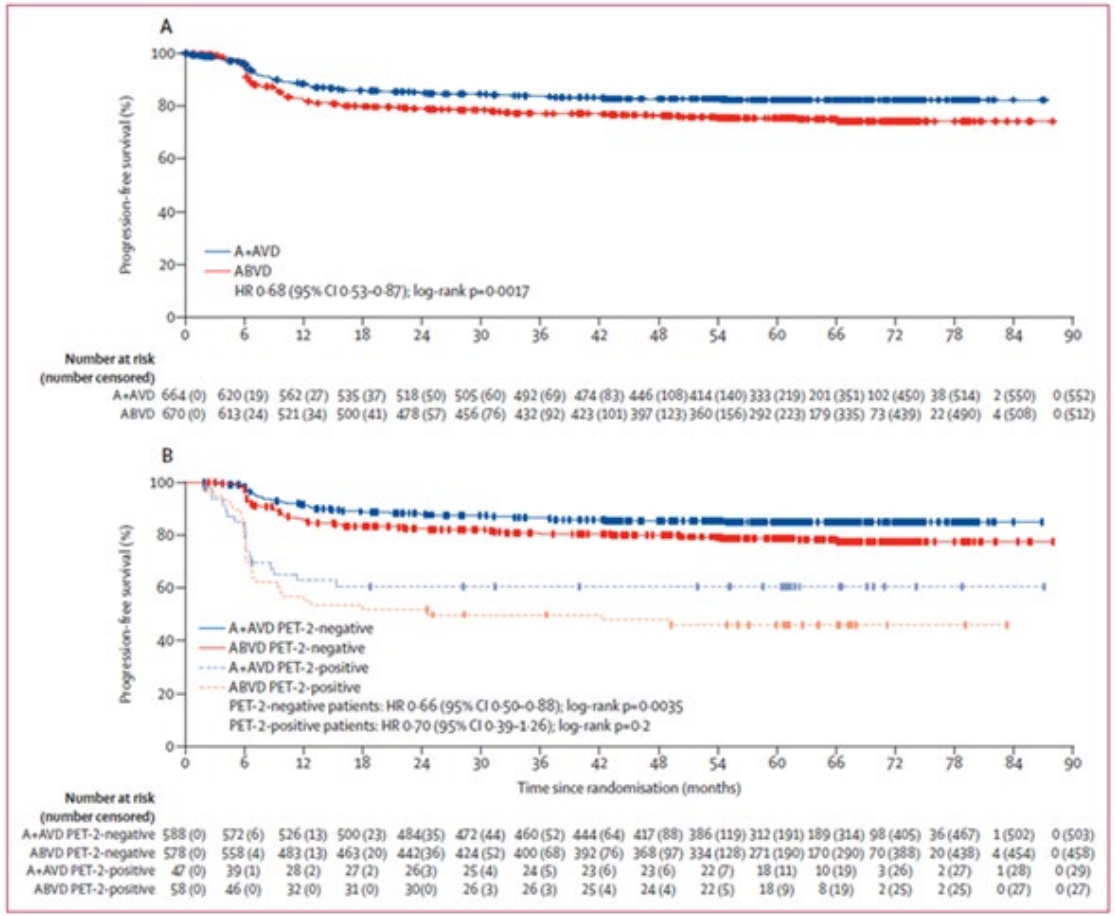


PET+ eBEACOPPx4



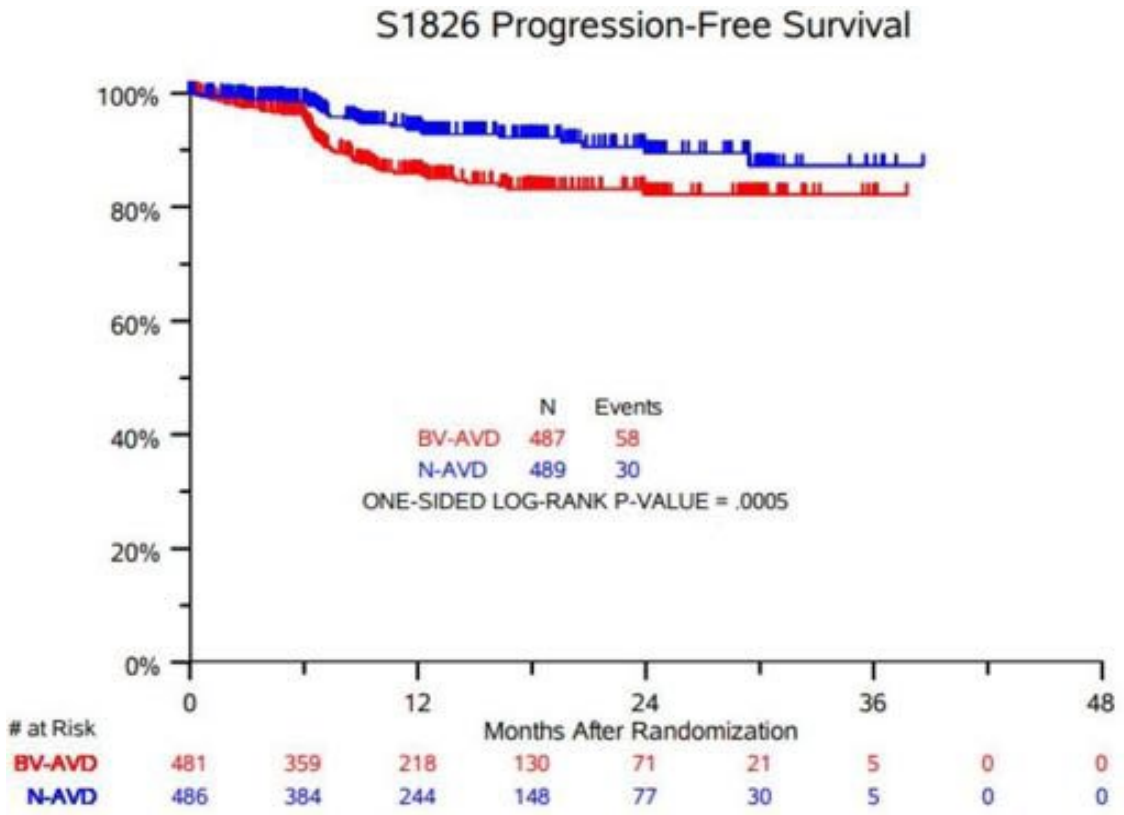
Johnson P et al, NEJM 2016

- ECHELON 1
- 6x AVD-Bv vs. 6x ABVD
- 5y PFS 82% vs. 75%



Straus DJ et al, Lancet Haematol 2021

PD-1 blockers



Herrera AF et al, ICML 2023

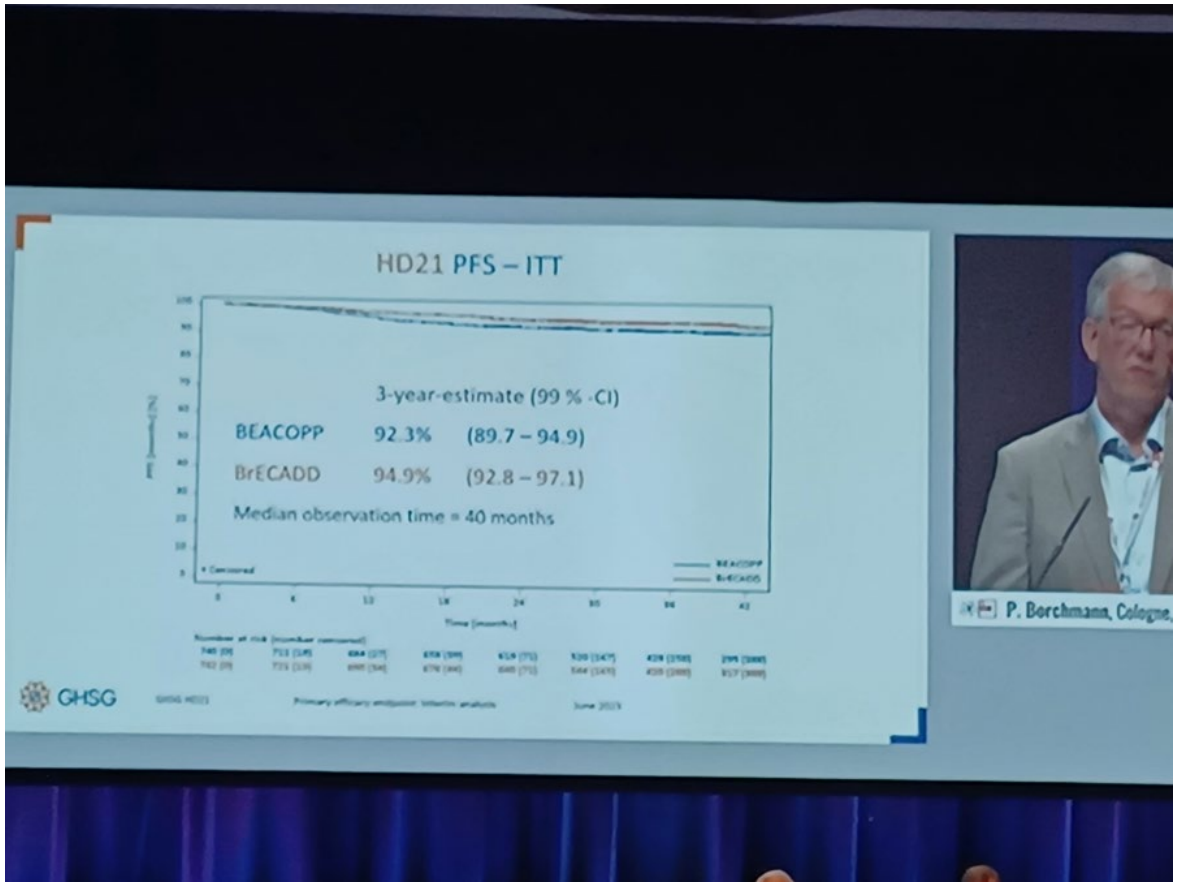
cHL stage III-IV, > 12y

6x AVD + nivo vs. 6x AVD + Bv

1y PFS 94% vs. 86%

BrECADD x 4-6 for advanced-stage cHL 18-60 y

- q 3 wks — day
  - Bv — 1,8 mg/kg — 1
  - Etoposide — 150 mg/m^2 — 2-4
  - Cyclophosph. — 1250 mg/m^2 — 2
  - Doxorubicin — 40 mg/m^2 — 2
  - Dacarbazine — 250 mg/m^2 — 3-4
  - Dexamethasone — 40 mg — 2-5
  - Peg-G-CSF — 6 mg sc — 5



Borchmann P et al, ICML 2023

HL in elderly – an unresolved problem

- Pts > 60 do not tolerate >2 cycles of eBEACOPP
- Pts > 70-75 do not tolerate >2 cycles of bleomycine
  - 6 cycles of ABVD 5% (7%) lethal lung toxicity*
  - 2 cycles ABVD 2% lung toxicity+
  - 4 cycles ABVD 9% lung toxicity+

- BV monotherapy is not the solution*
  - neuropathy
  - short DOR

- BV + dacarbazine > BV + bendamustine+

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*Stamatoullas et al, BJH 2015
+Behringer et al, Lancet 2015
*Forero-Torres et al, Blood 2015
+Friedberg et al, Blood 2017

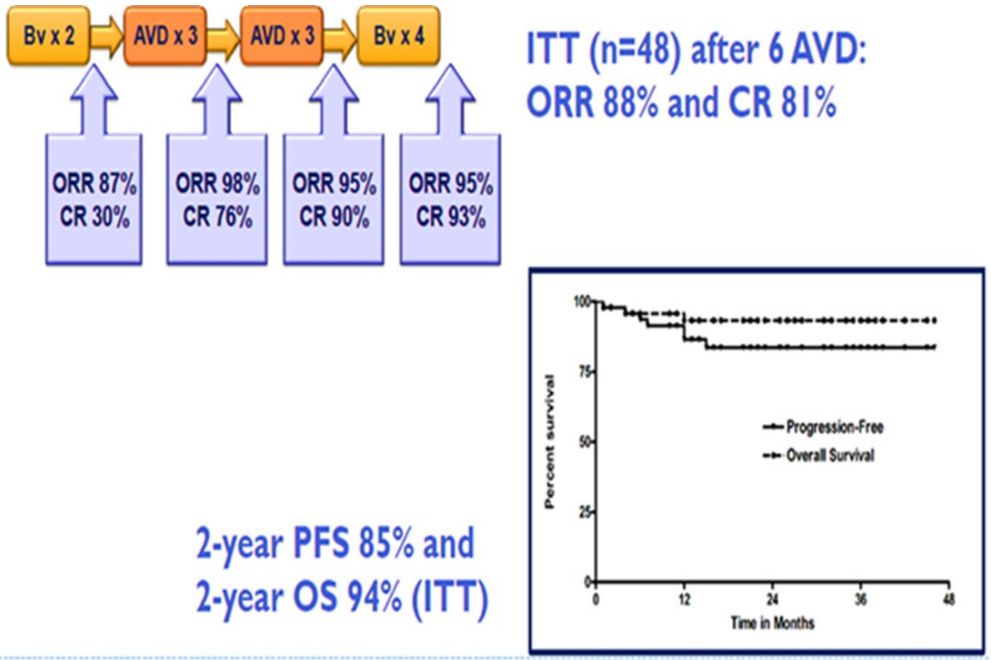
Classical front-line treatment options for elderly

- 60-70 (75) y: ABVD
- > 70 (75) y: ?
  - CHOP, bendamustine, AVD, LVPP...

Zallio et al, Br J Haematol 2016; Walewski et al, Med Oncol 2010

Elderly

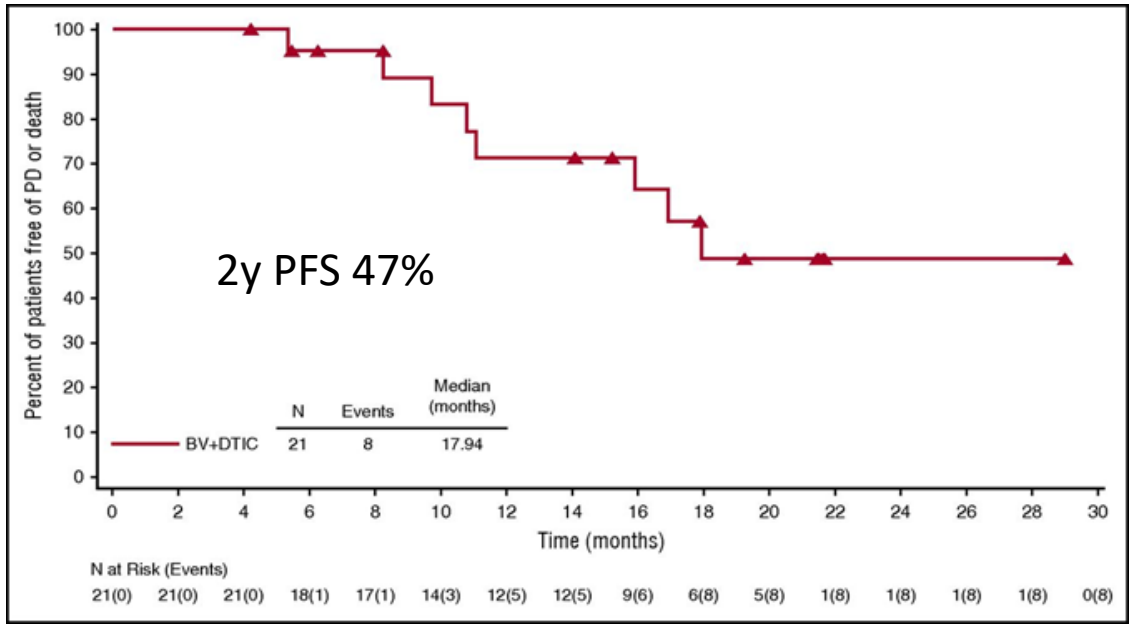
- Fit



AVD: doxorubicin, vinblastine, dacarbazine; BV: brentuximab vedotin; CR: complete remission; PFS: progression-free survival; ORR: overall response rate; OS: overall survival

Evens AM, et al. Presented at the 59th Annual Meeting of the American Society of Hematology 2017; Atlanta, GA, USA (Abstract 733).

- Unfit

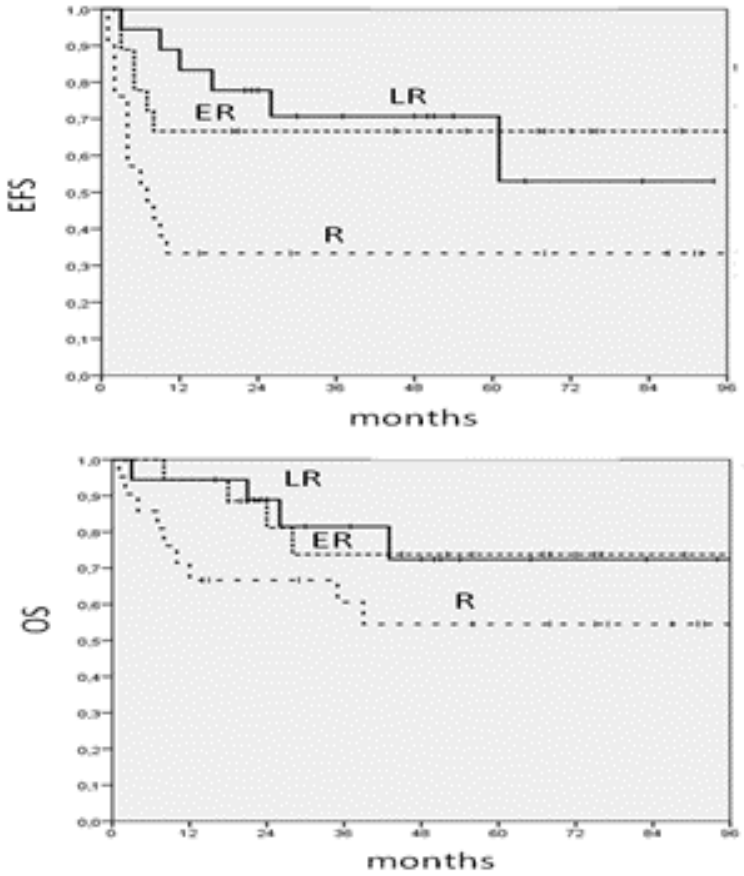


Evens at al. 2018. J Clin Oncol 36:3015-3022

Friedberg JW et al, Blood 2017

2nd line, transplantable

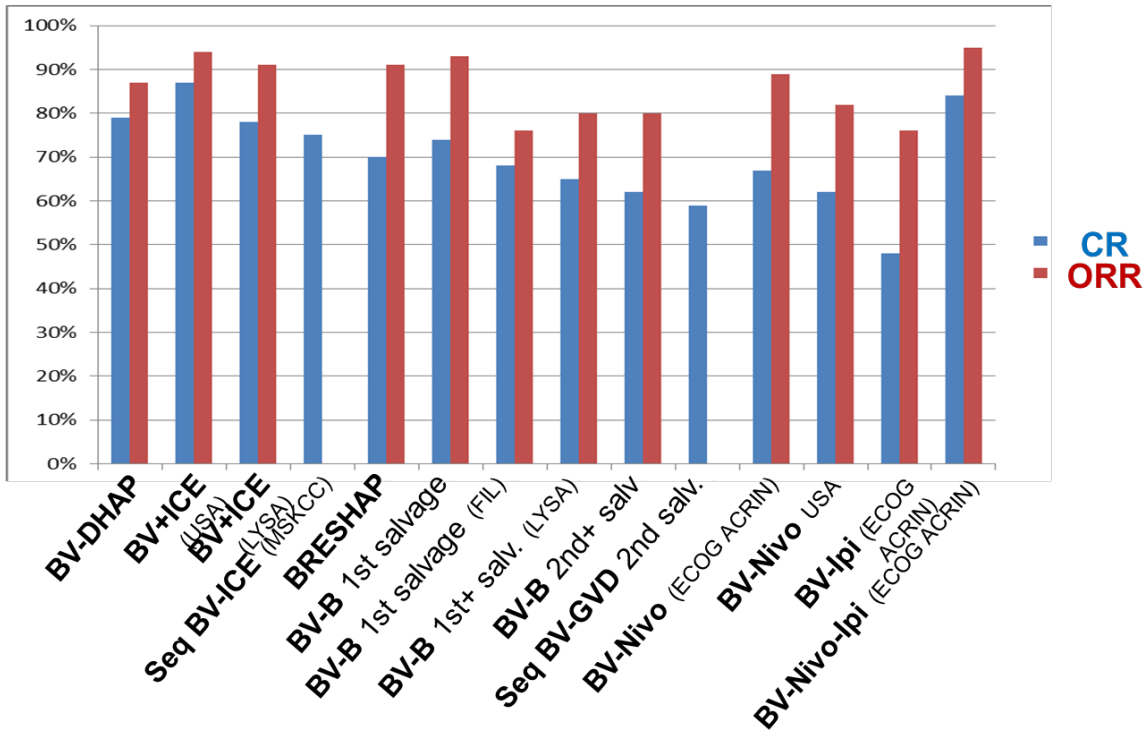
- Old standard
  - HD-CT (DHAP, ICE, IGEV, HDIM, ESHAP)…
    - All produce similar outcomes
  - ASCT in responding patients
  - RT consolidation

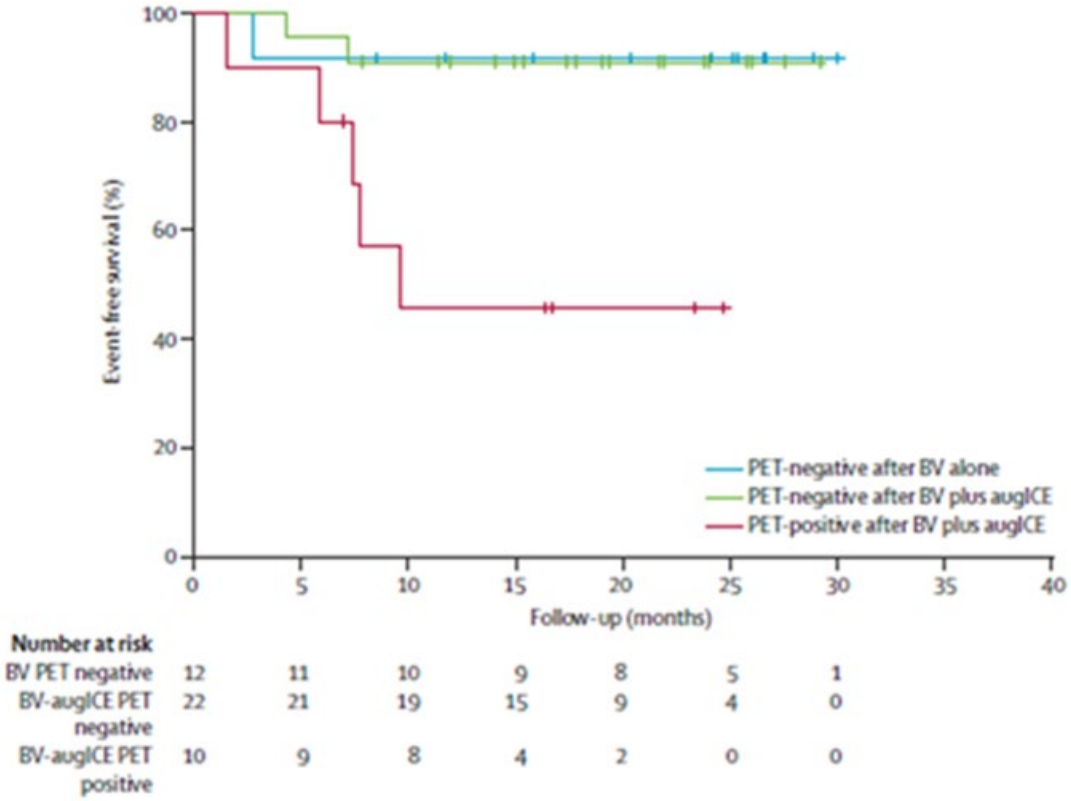


Aurer et al. Ann Hematol 2016

Improvements in induction

- The importance of being PET-!



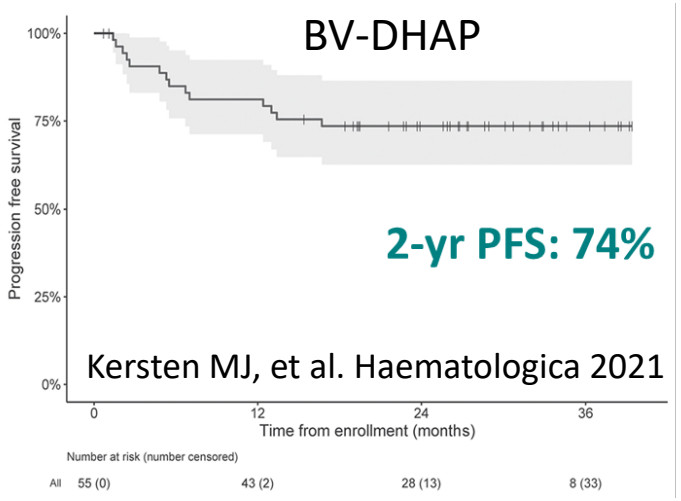


Moskowitz et al, Lancet Oncol 2015

Improvements in induction

PFS

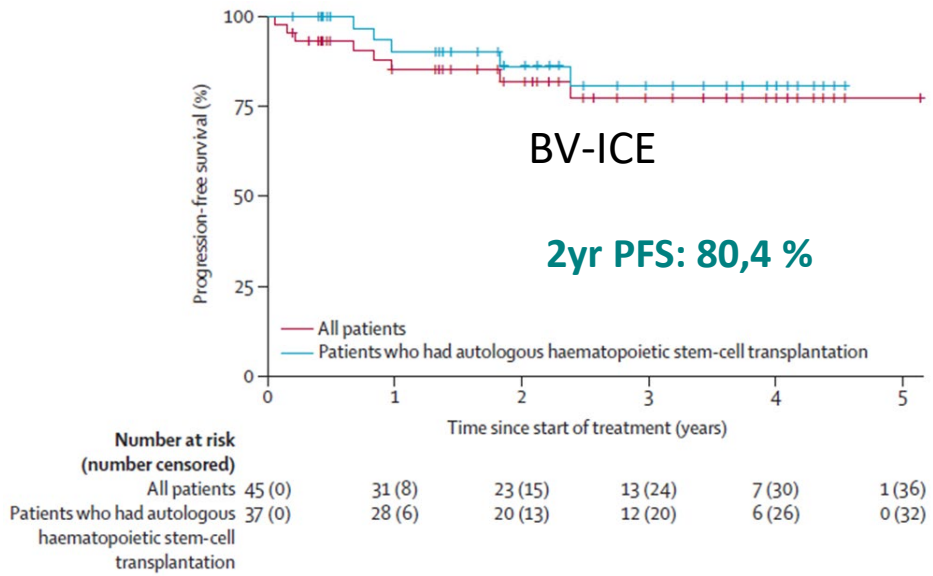
BV-DHAP



2-yr PFS: 74%

Kersten MJ, et al. Haematologica 2021

BV-ICE

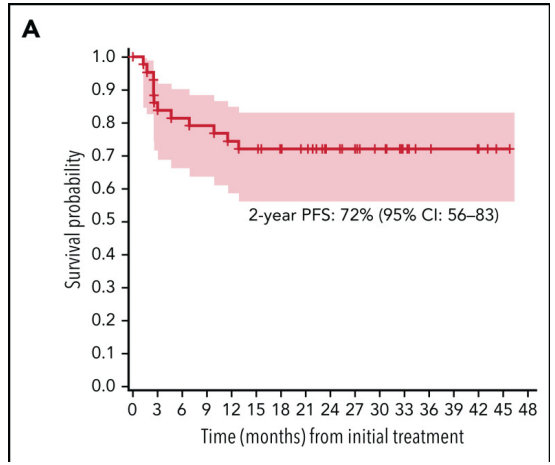


2yr PFS: 80,4 %

Lynch RC, et al. Lancet Haematol 2021

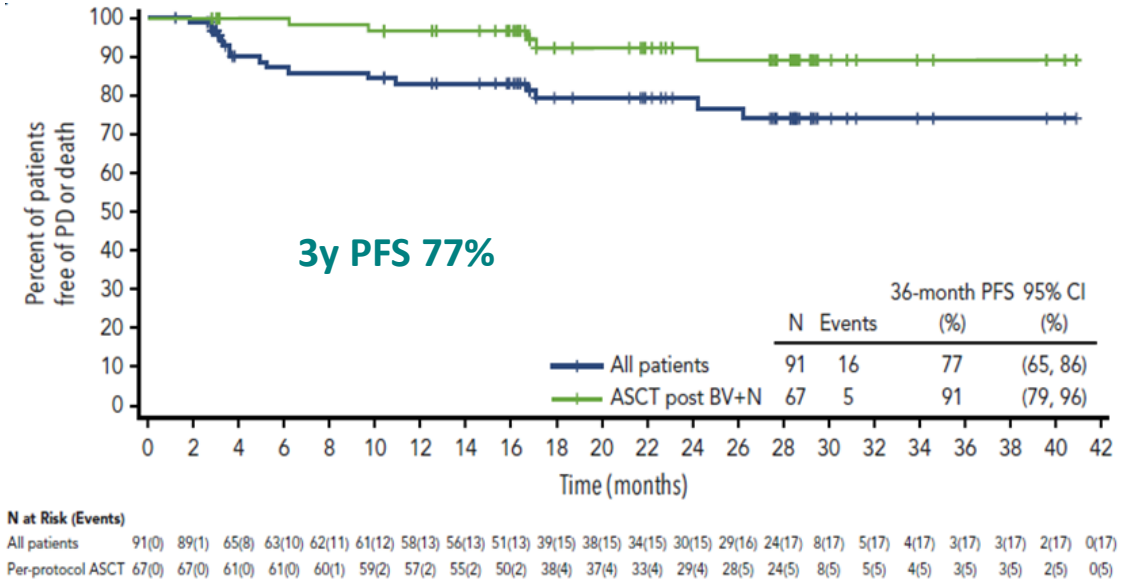
Nivo ± ICE

2y PFS 72%



Mei GM et al, Blood 2022

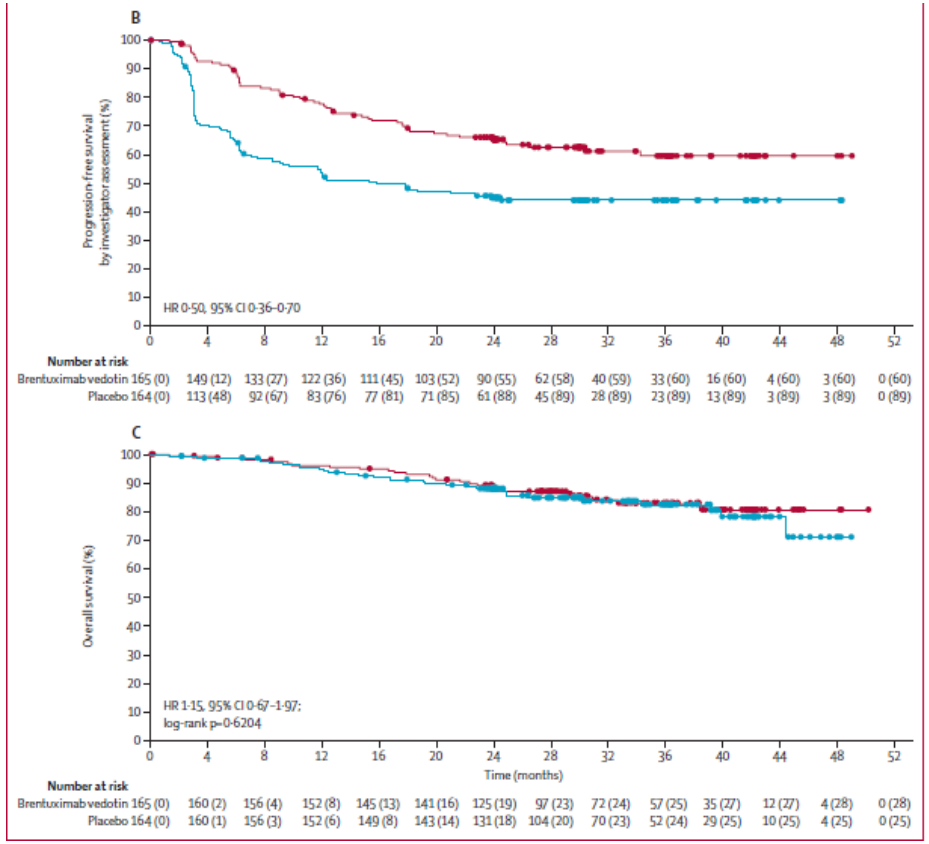
BV-Nivo



Advani R, et al. Blood 2021

BV after ASCT - AETHERA study

BV after ASCT improves PFS of high-risk patients:
primary refractory, early relapse, stage IV at relapse



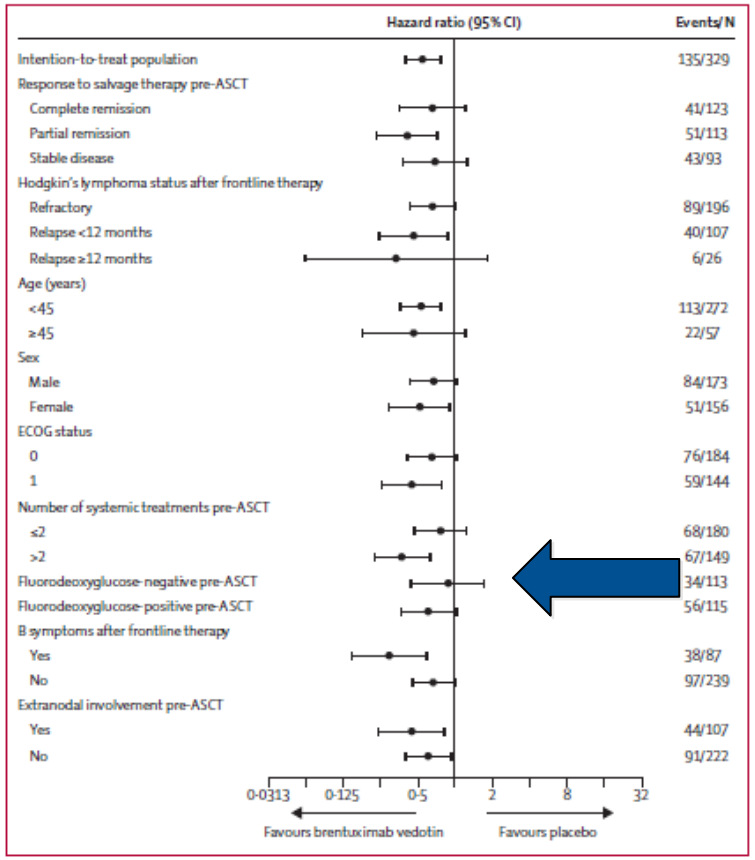


Figure 3: **Subgroup analysis of progression-free survival by independent review**
ASCT=autologous stem-cell transplantation. ECOG=Eastern Cooperative Oncology Group.

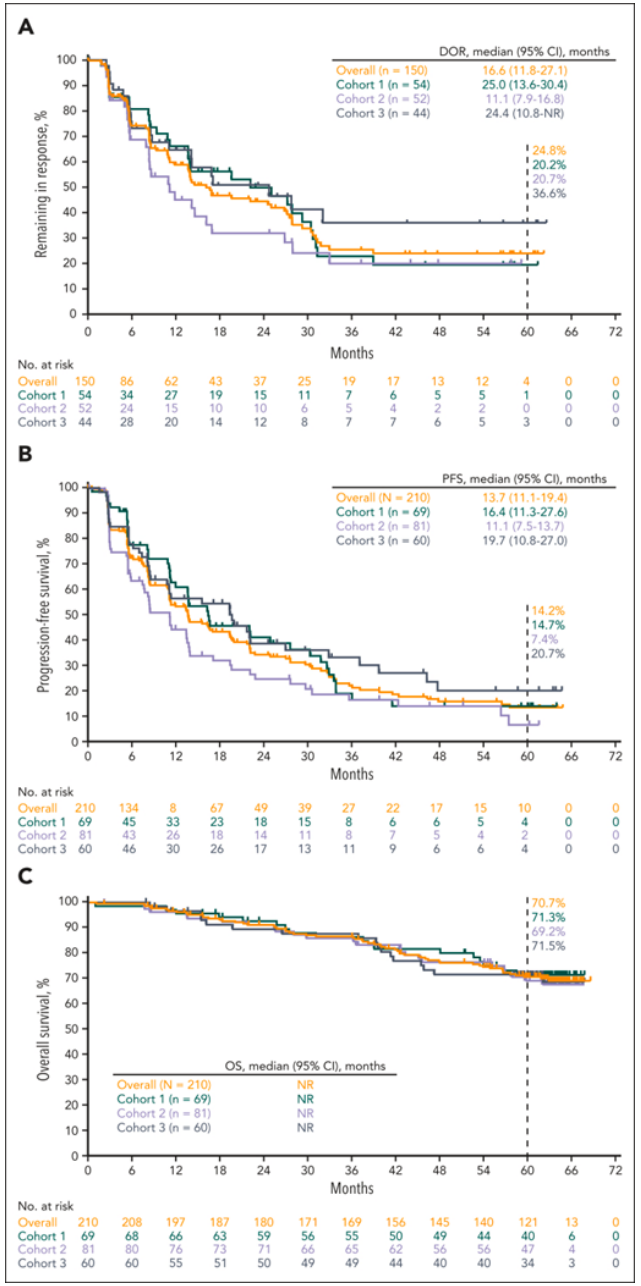
PET -

Moskowitz et al, Lancet 2015.

Beyond 2nd line

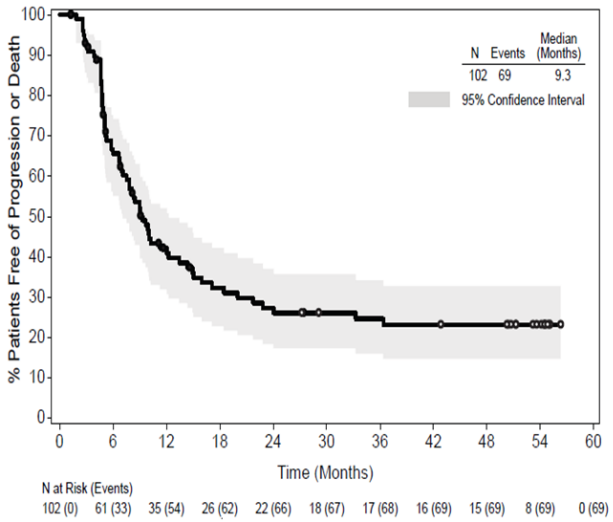
PD1 blockade

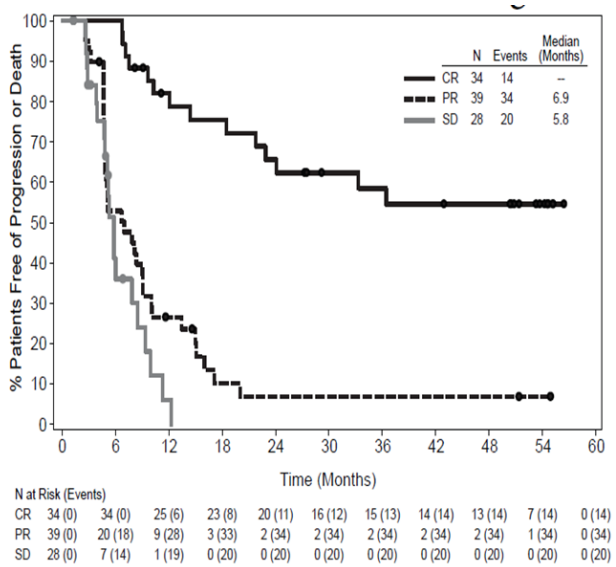
Armand et al, Blood 2023



Bv monotherapy

Gopal et al. Blood 2015





Bendamustine + Bv

full doses of both agents q 3 wks well tolerated

Sawas et al, ASH 2015: > 2nd line: RR 69%

How to cure the incurable?

Diseases desperate grown

By desperate appliance are relieved

Or not at all*

*Shakespeare W, Hamlet

RIC followed by HLA-(haplo)identical SCT

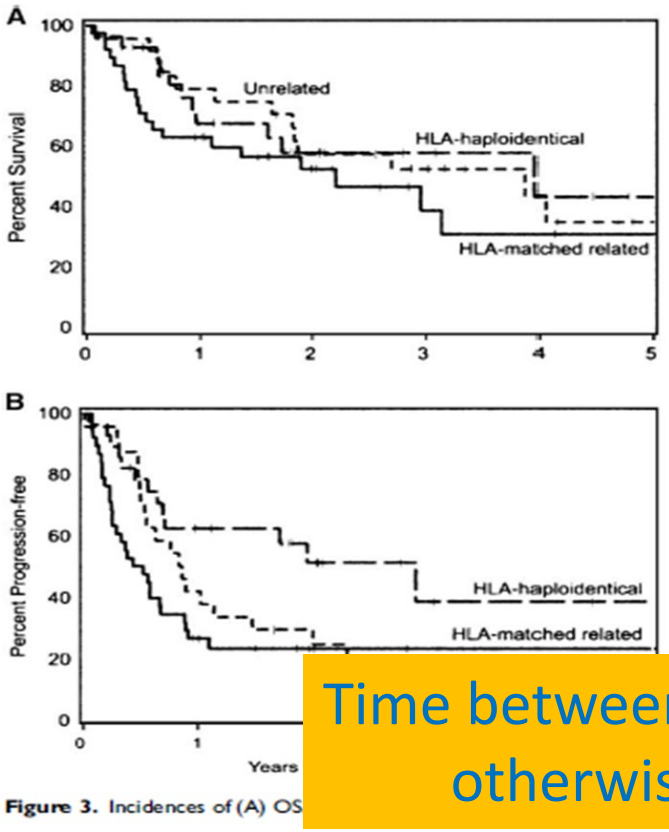
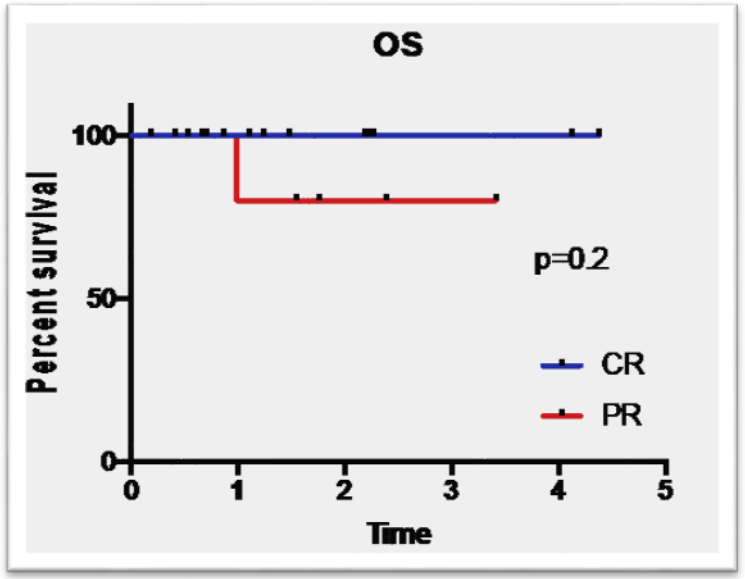
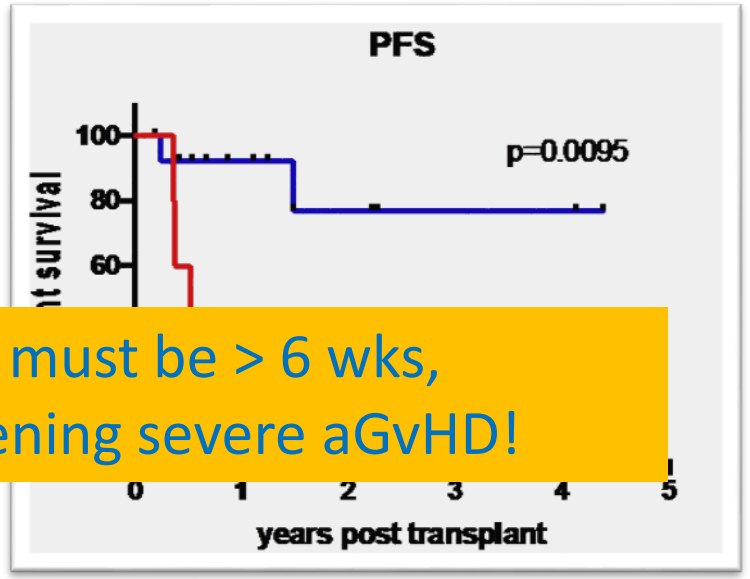


Figure 3. Incidences of (A) OS





Time between last dose of PD1i and alloSCT must be > 6 wks, otherwise high incidence of life-threatening severe aGvHD!

Burroughs et al, Biol Blood Marrow Transplant 2008

Duraković N et al, Clin Hematol Int 2021

Conclusions 1 – front-line therapy

- With risk-adapted front-line therapy ≈ 90% newly diagnosed pts. < 60-70 y can be cured
  - eBEACOPP > AVD+BV > ABVD
- Regimens including BV or PD1i will become standard of care
  - BrECADD, AVD + PD1i
- To ameliorate toxicity
  - Use peg-G-CSF for primary prophylaxis in all regimens > ABVD
  - Use sperm cryopreservation in men and GnRH analogues, oocyte or ovary tisuue cryopreservation in women
  - Start routine breast imaging <7 y from th. start, consider LD lung-CT in smokers
  - Keep in mind, it’s not only RT that causes secondary cancer!
- Irradiate only involved nodes or, at most, regions

Conclusions 2 – relapsed / refractory

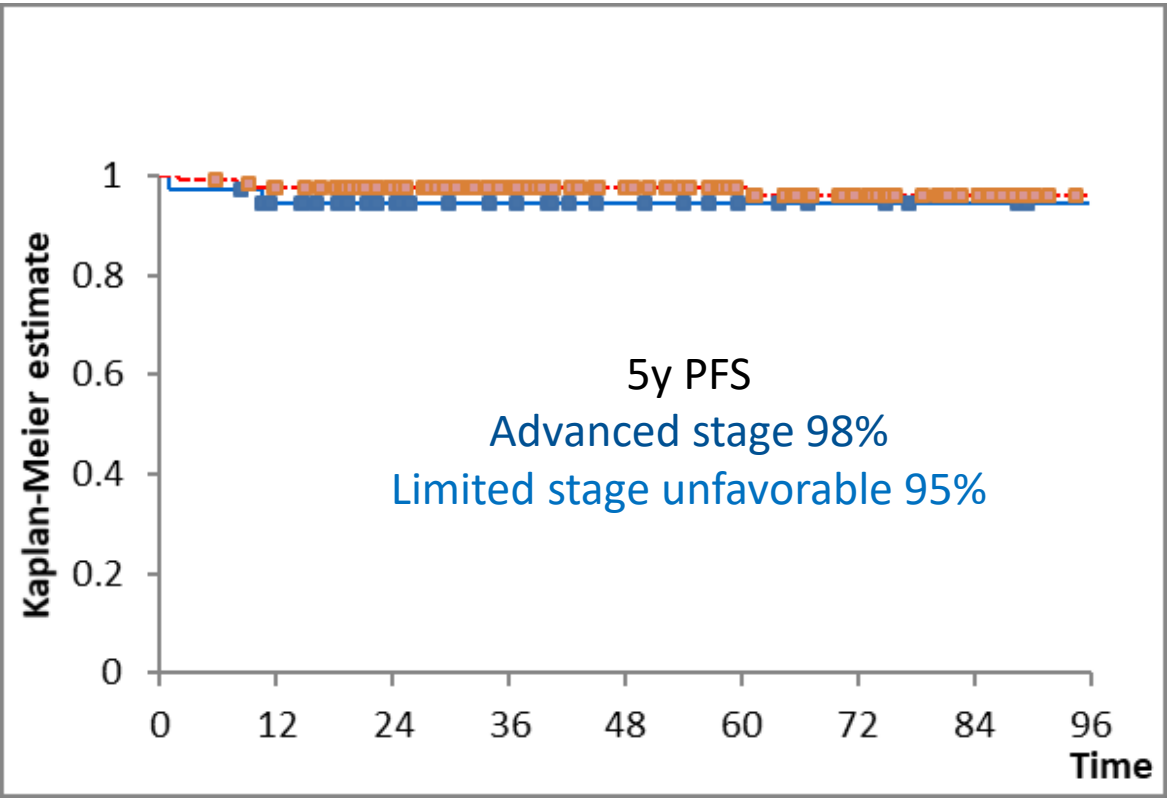
- HD-CT + Bv or PD1i seems more effective than HD-CT alone
  - Which group of pts benefits and role of ASCT currently unclear
- Consolidation with Bv or PD1i after ASCT useful in high-risk patients
  - Do not forget RT!

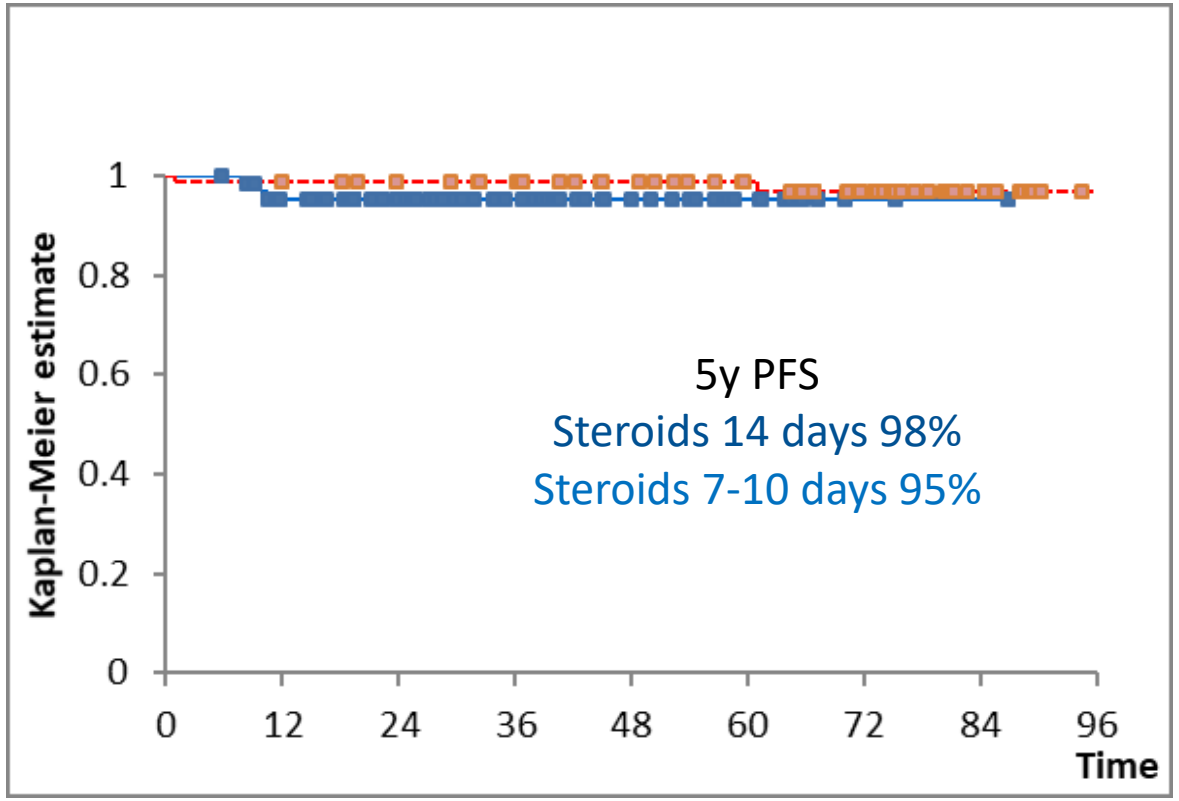
- Allo SCT using haploidentical related donors and RIC can cure some, otherwise incurable, young pts. with treatment-sensitive disease

- Optimal approach:
- Cure the patient with front-line therapy!

If you do your best, you might have real-life results like this:

cHL, front-line, 18-60 y, 4-8x eBEACOPP, N=162





Hude Dragičević I et al, ISHL 2022

KBC ZAGREB

HRVATSKO DRUŠTVO ZA HEMATOLOGIJU
HRVATSKOG LIJEČNIČKOG ZBORA

SVEUČILIŠTE U ZAGREBU
MEDICINSKI FAKULTET

KroHem
Hrvatska kooperativna grupa za hematološke bolesti

EHA LyG
EHA Lymphoma Group