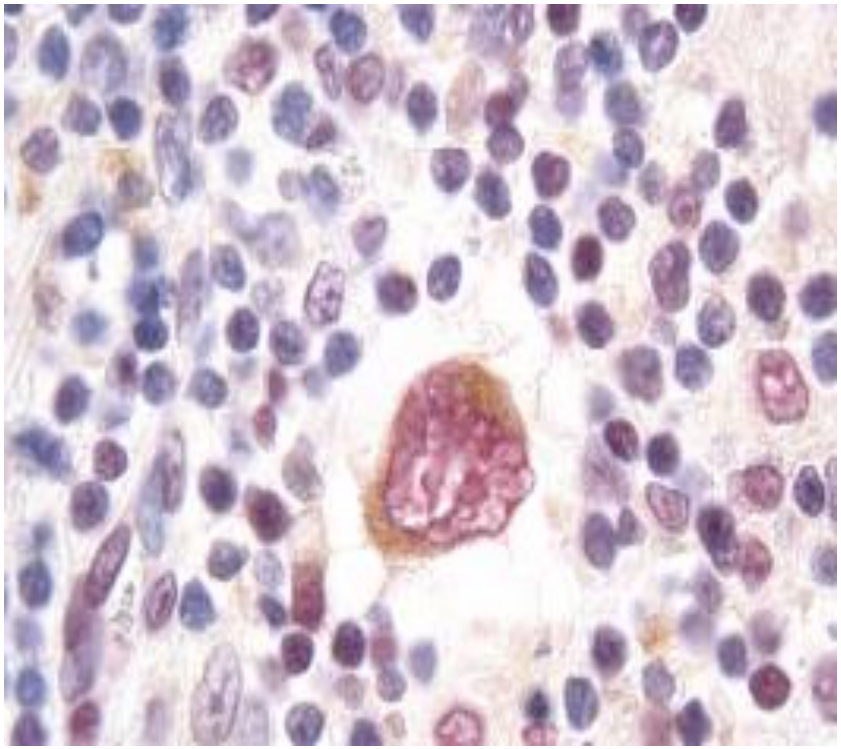
Hodgkin lymphoma

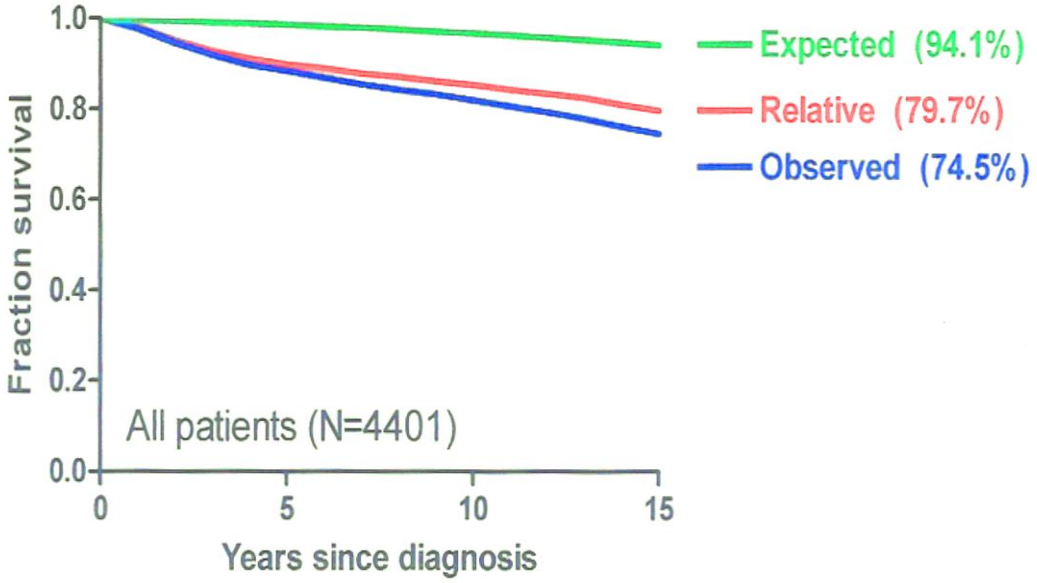
Marc ANDRE

Lysa
THE LYMPHOMA STUDY ASSOCIATION

CHU Dinant Godinne
UCL NAMUR



Survival of Hodgkin lymphoma



Causes of death

51% HL
10% treatment
18% second cancer
  5% cardiovascular
  2% infections
14% others.

Favier, Cancer 2009

Our need

- Maintain high cure rate
- Reduce toxicities

Main messages

- No bone marrow biopsy, 2 PET-CT
- Localised cHL
  - Combined modality
- Advanced cHL
  - CT (BEACOPPesc, ABVD)
- Relapse
  - Salvage chemo + HDCT
- New drug
  - Brentuximab vedotin and Anti-PD1 MoAb

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

JCO 2014

Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister

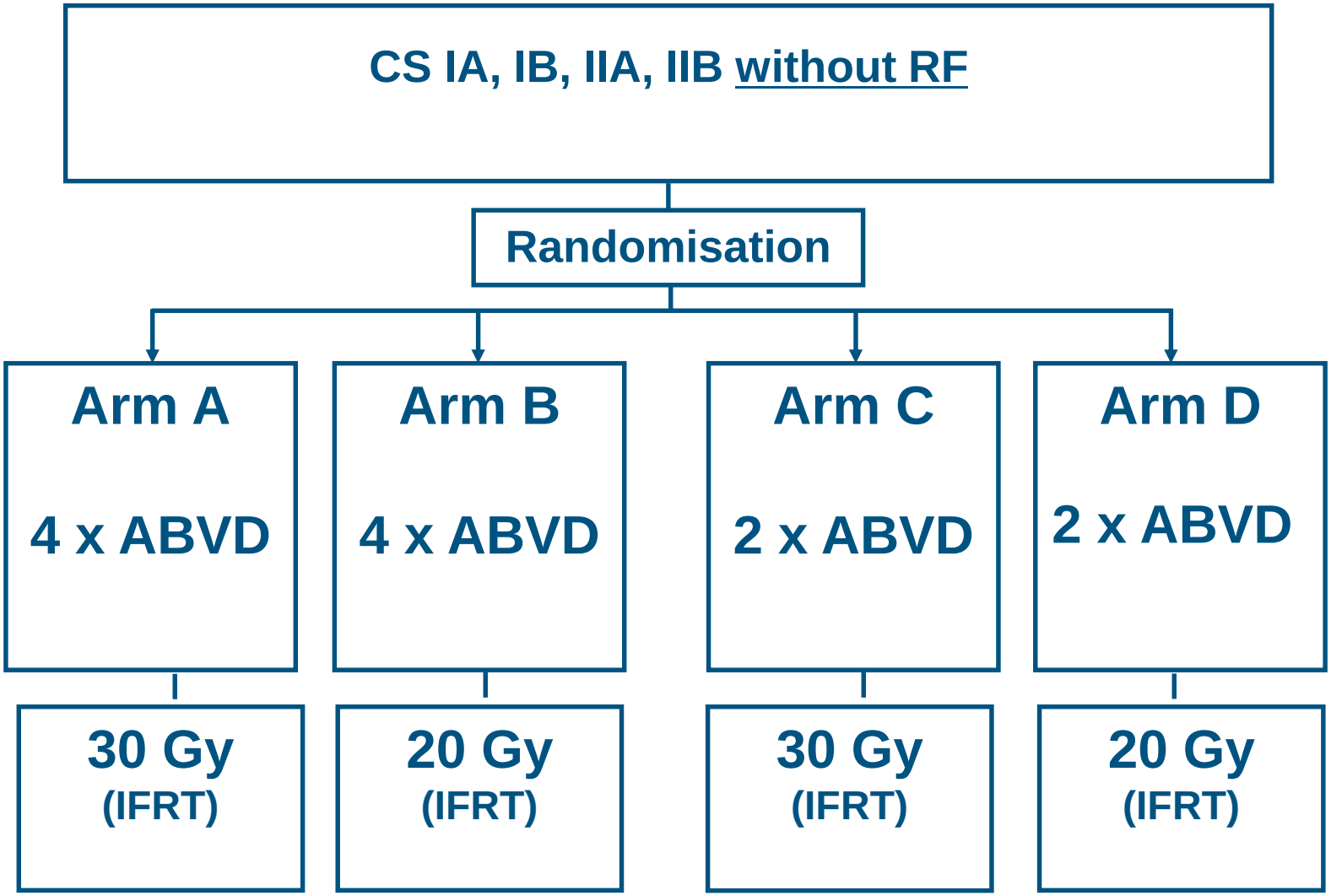
Changes :

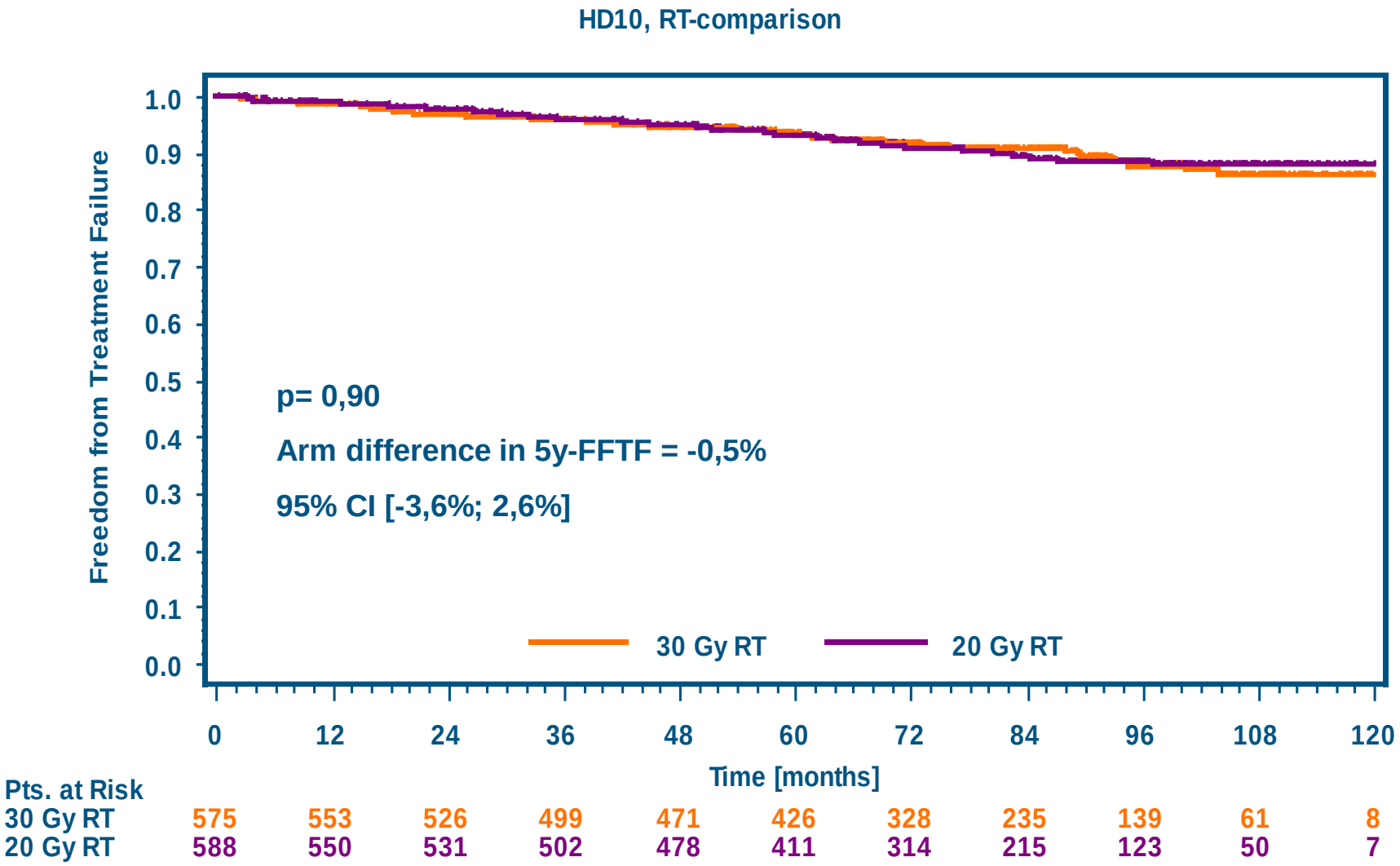
- Incorporation of FDG PET-CT into standard staging for FDG-avid lymphomas.
- No bone marrow biopsy in the routine staging of HL (and most DLBCL).
- Assessment of the response by PET-CT in FDG-avid histologies using the 5-point scale.
- No routine surveillance scans.

Preview

- Localised cHL
- Advanced cHL
- Relapse
- New drugs

HD10 Trial Design

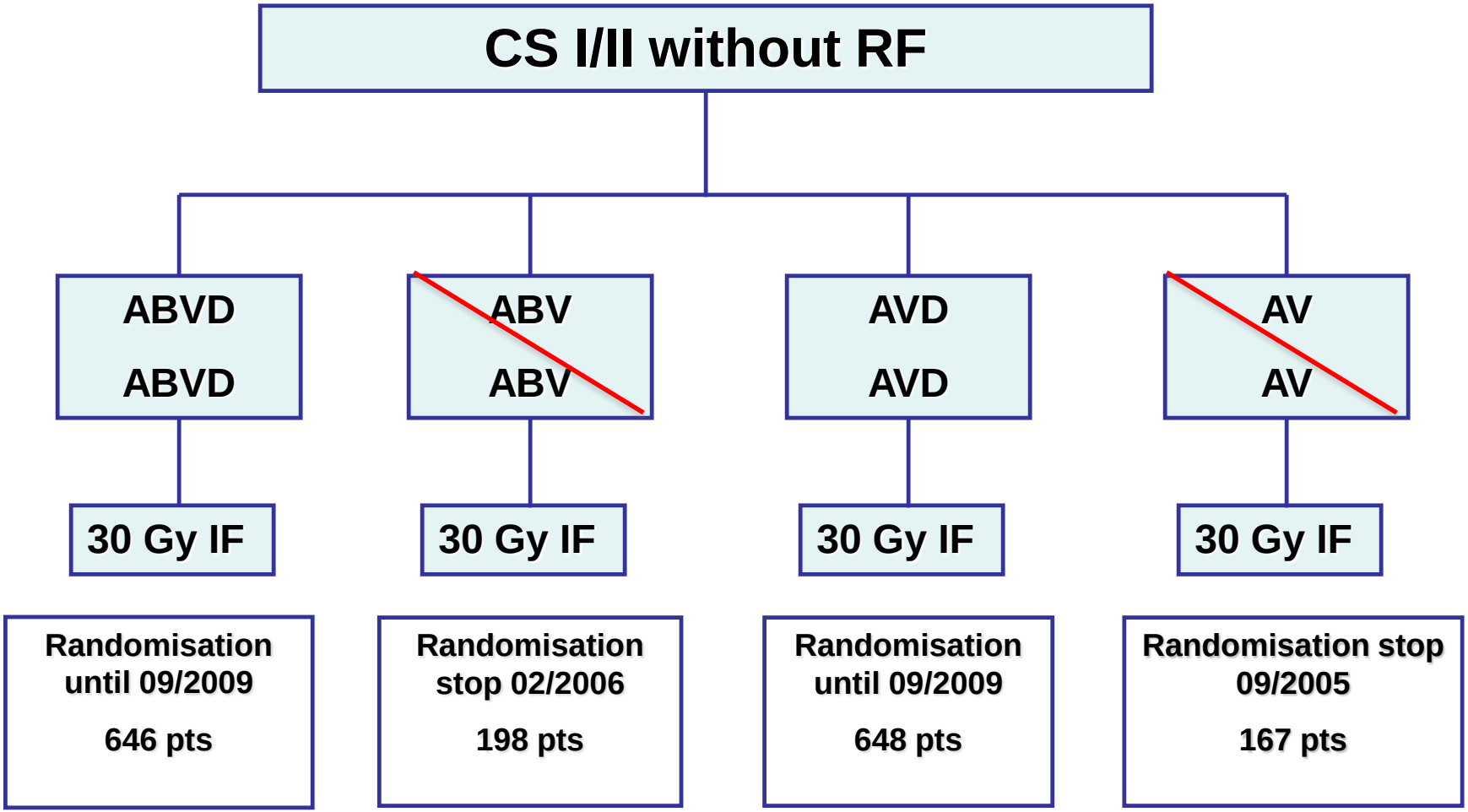




Median observation time = 79 months

Engert, NEJM, 2010

Early favorable stages
GHSG: HD13 (1730 pts randomised)

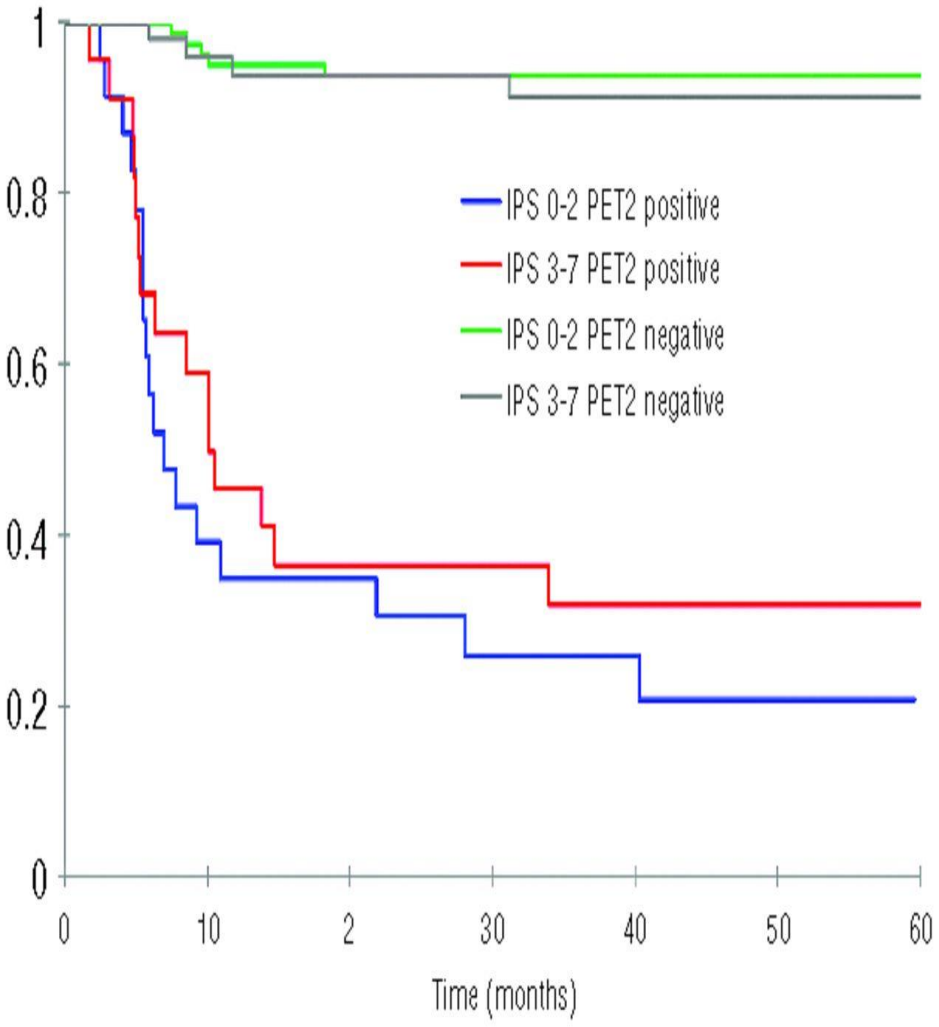


Early favorable stages
GHSG: HD13

	ABVD (n= 586)		AVD (n=571)	
Median obs. time	52 months		55 months	
Progression	3	0,5%	2	0,4%
Early relapses	4	0,7%	6	1,0%
Late relapses	20	3,5%	37	6,4%
Number events				
1	22	3,9%	42	7,4%
2	5	0,9%	3	0,5%
Total	27	4,8%	45	7,9%

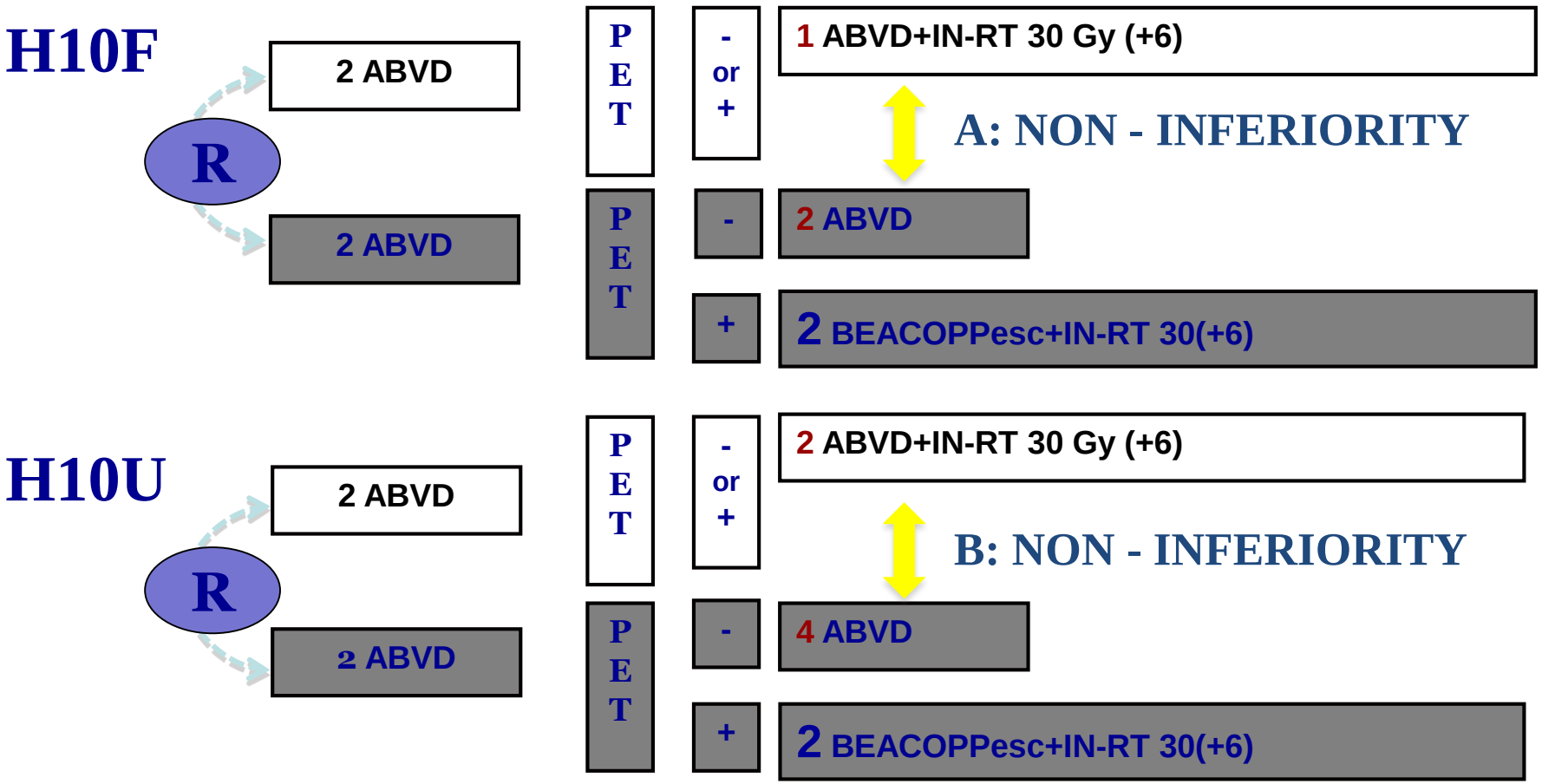
P= 0,04

The next trials



Andrea Gallamini et al. Haematologica 2014;99:1107-1113

Study design and primary objectives



Primary endpoint : Progression-free survival

Group A (favourable)

	Standard	Experimental
Events	1	9
Relapse	1	9
Death w/o relapse	0	0

Group B (unfavourable)

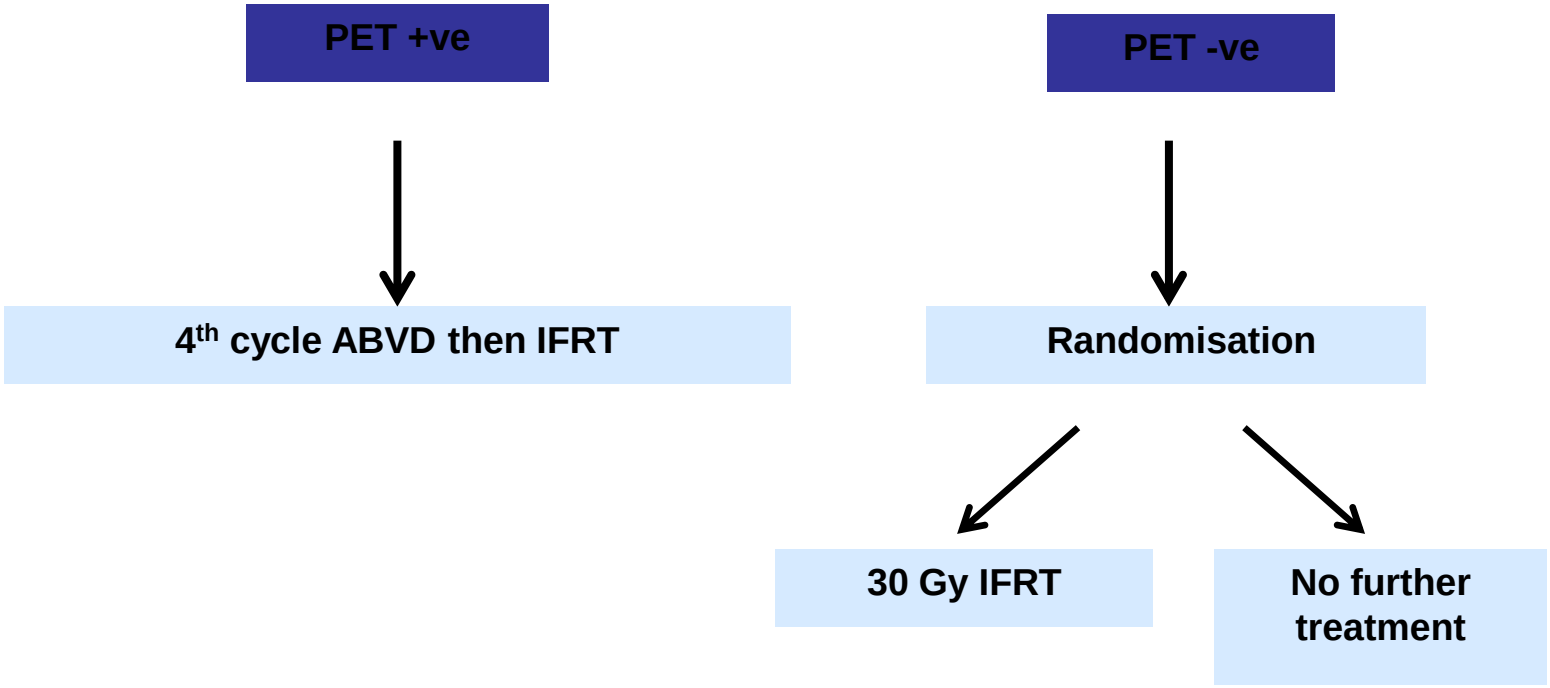
	Standard	Experimental
Events	7	16
Relapses	7	15
Death w/o relapse	0	1

Andre M, ASH 2012

UK NCRI RAPID trial in early favorable HL

Initial treatment: **ABVD x 3**

Re-assessment: **if response, PET scan performed**



Intention to treat analysis, n=420

3 year PFS 94.5% (91.3%, 97.7%) vs 90.8% (86.8%, 94.7%)

HR 1.51 in favour of IFRT, p=0.23

Per protocol analysis, n=392

3 year PFS 97% (94.5%, 99.6%) vs 90.7% (86.7%, 94.7%)

HR 2.39 in favour of IFRT, p=0.03

Radford J, ASH 2012

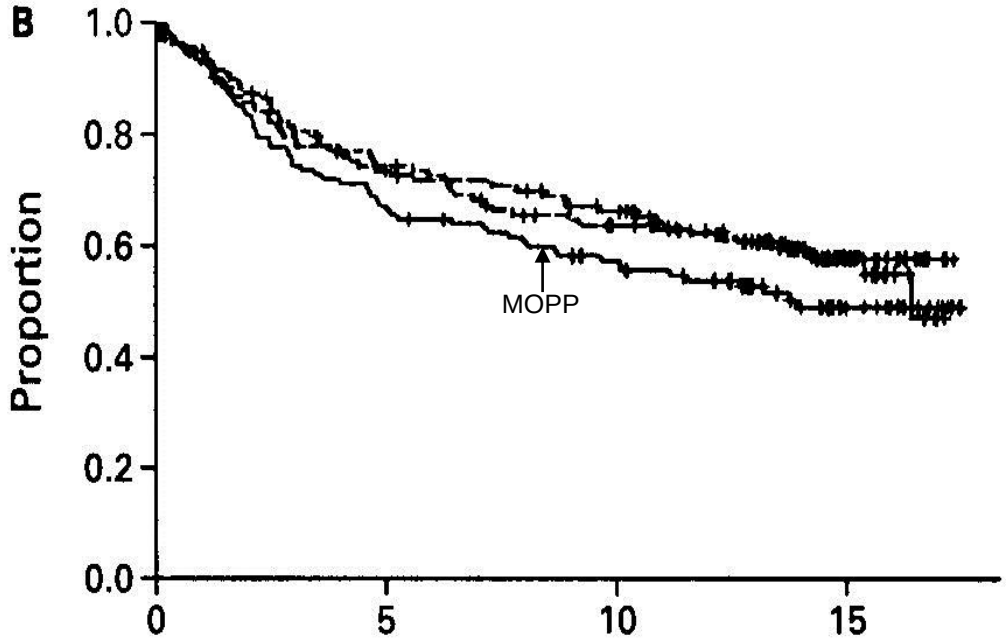
Our recommandation

- 2- 4 ABVD + RT (20 -30G)

Preview

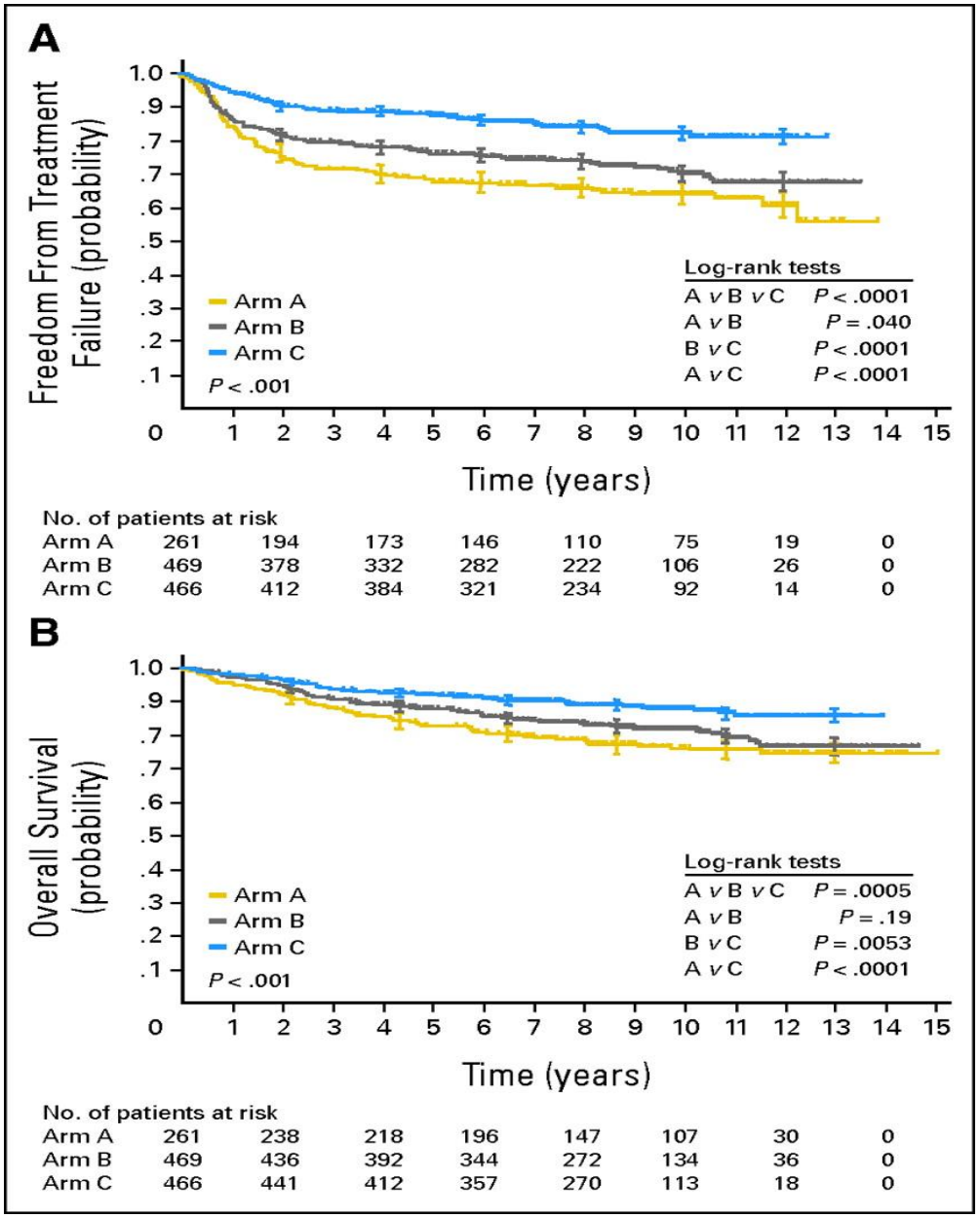
- Localised cHL
- Advanced cHL
- Relapse
- A new drug

ABVD vs. MOPP vs. MOPP/ABVD



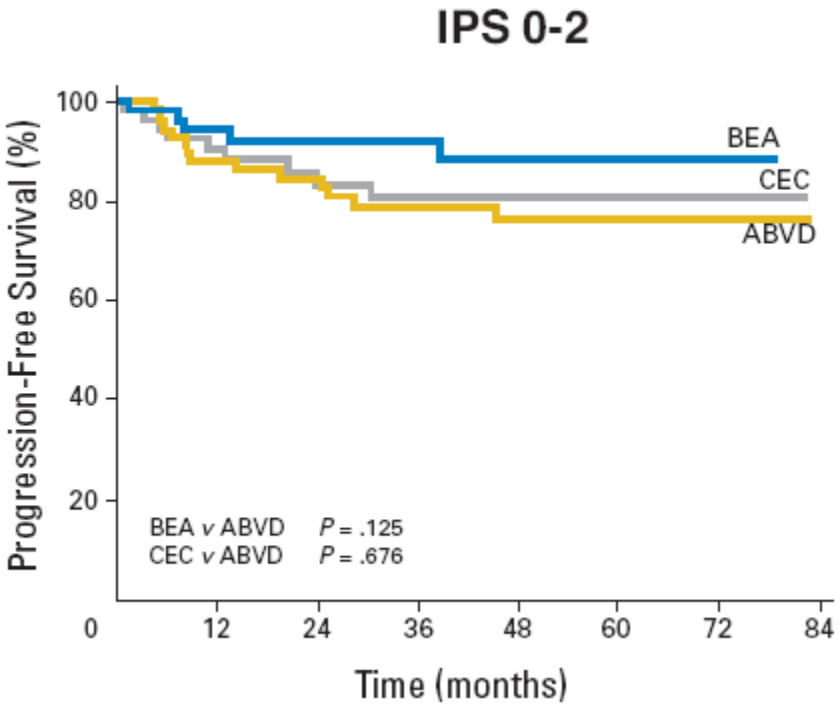
Overall survival

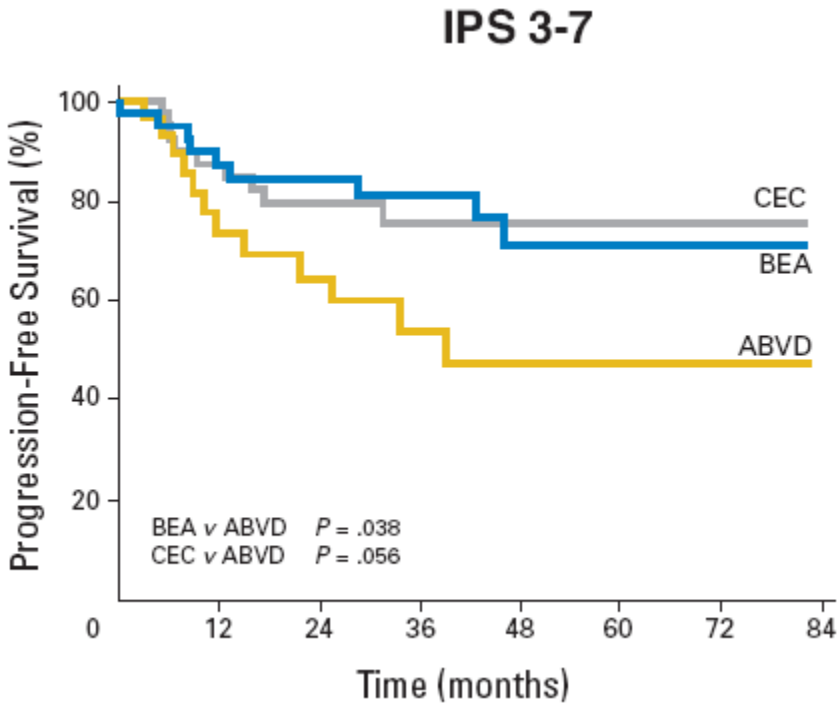
Canellos, NEJM, 2002



BEACOPPesc
BEACOPP baseline
COPP/ABV

Engert , JCO 2009





Federico, JCO, 2009

BEACOPP

ABVD

Our recommandation

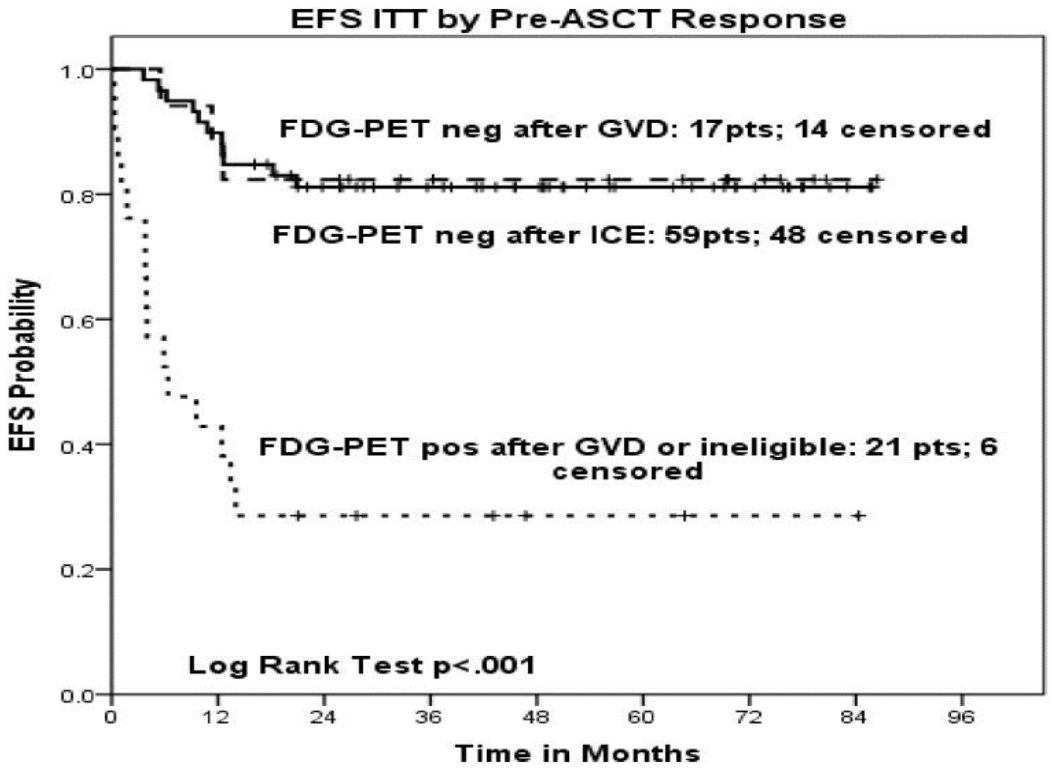
- BEACOPPesc x6
- 6-8 ABVD

Preview

- Localised cHL
- Advanced cHL
- Relapse
- A new drug

Our recommandation

- Salvage chemo (DHAP, ICE) + 1-2 HDCT

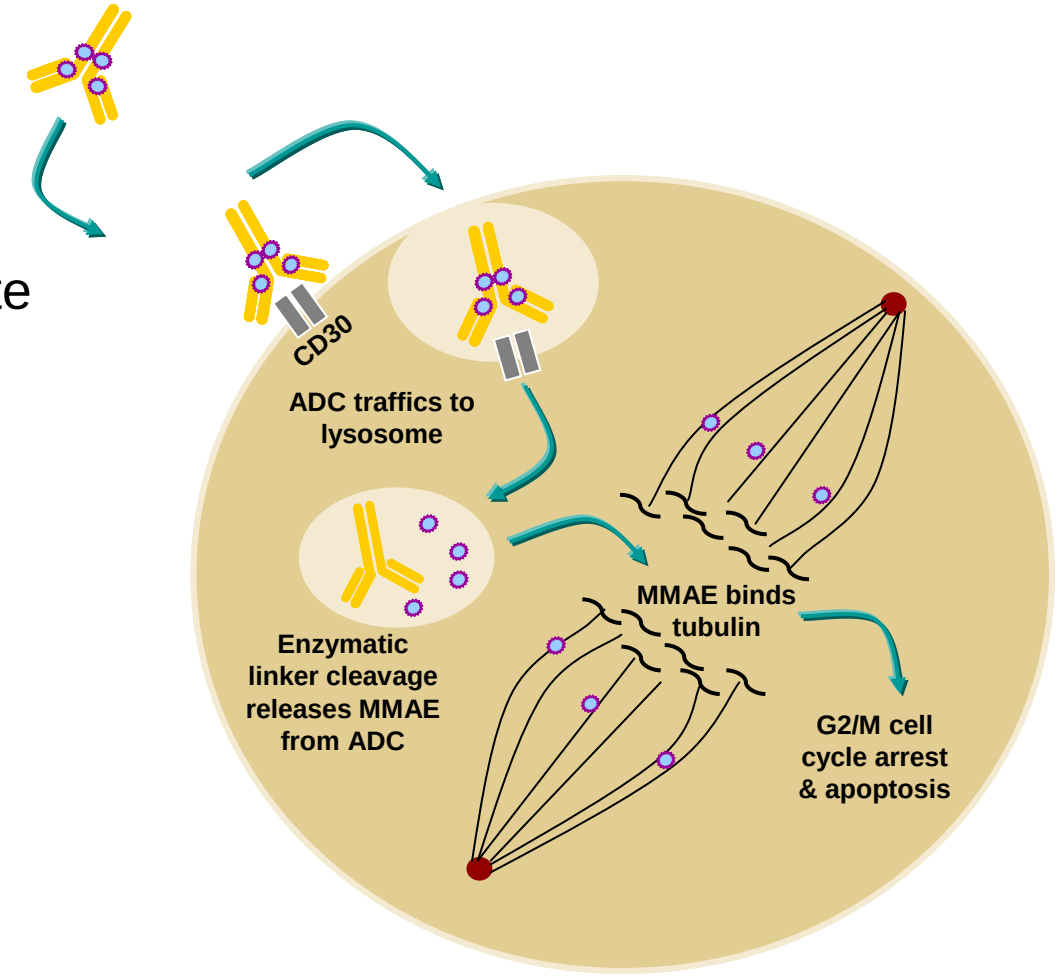


Preview

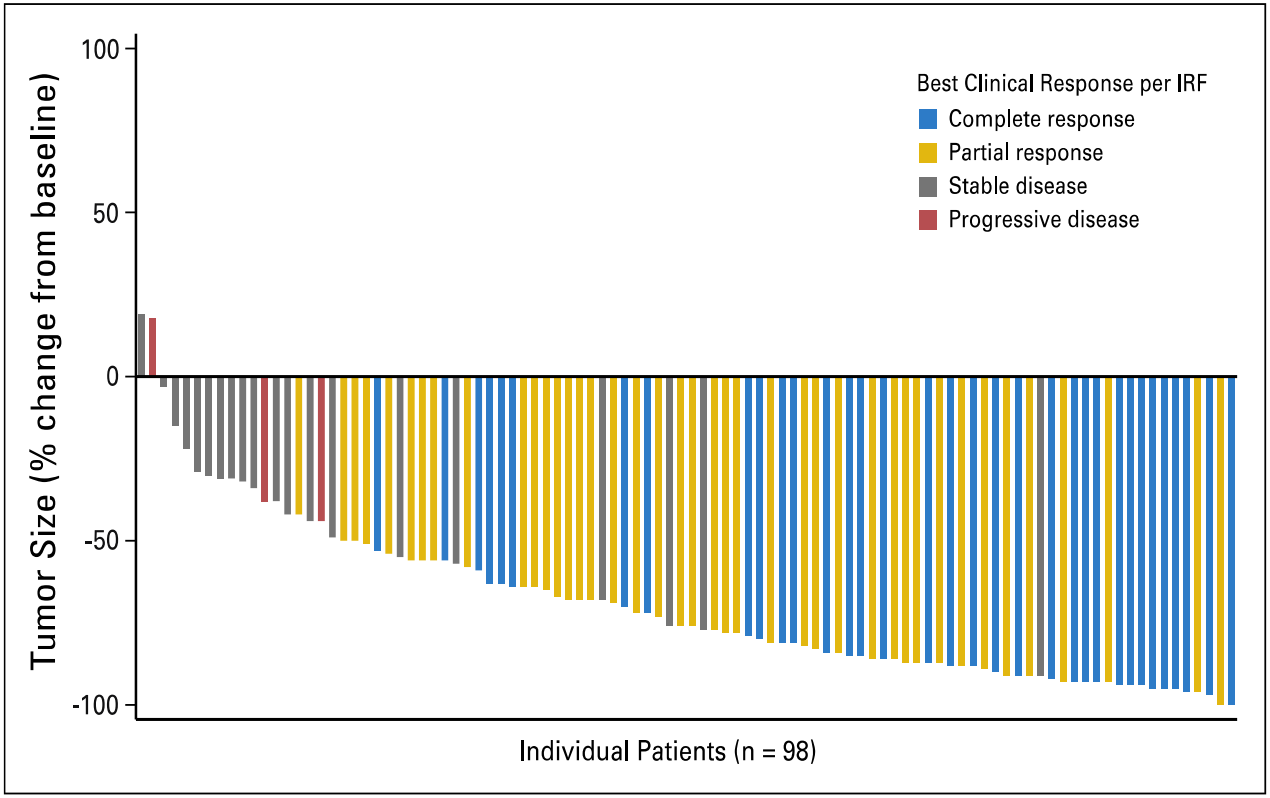
- Localised cHL
- Advanced cHL
- Relapse
- A new drug

SGN-35 Mechanism of Action

- SGN-35 antibody-drug conjugate
  - CD30-targeted antibody (cAC10) conjugated to an auristatin (MMAE), an anti-tubulin agent
- Selectively induces apoptosis in HL and ALCL cells:
  - Binds to CD30
  - Becomes internalized
  - Releases MMAE



Phase II pivotal trial

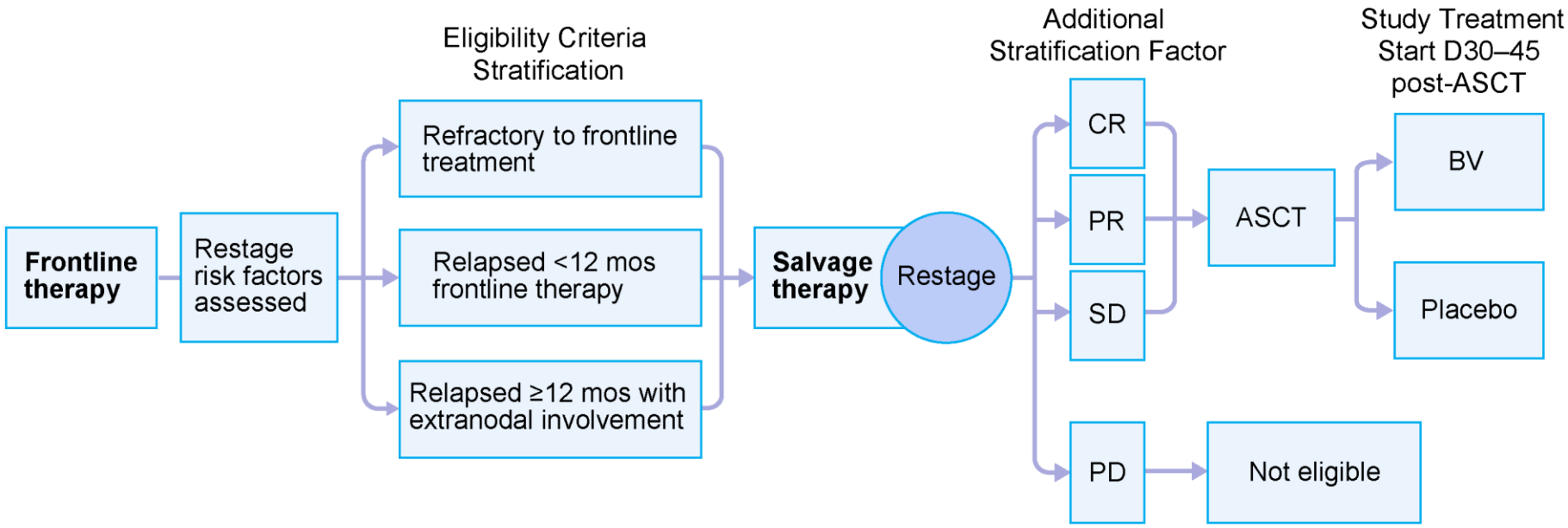


Indications: in relapse after HDCT and ASCT, failure after the first two lines of treatment

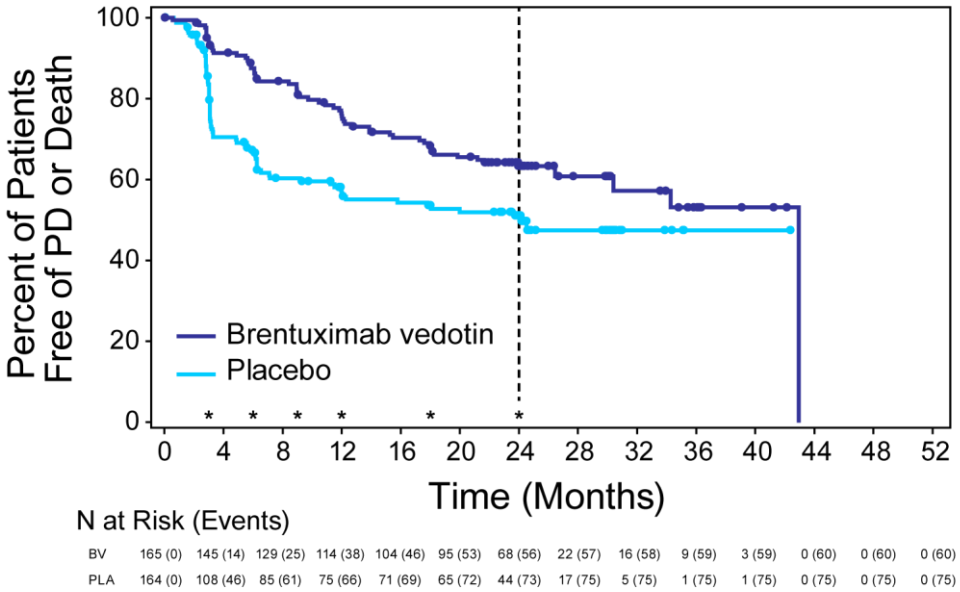
Younes A, J Clin Oncol 2012

Aethera Study Design and Key Eligibility Criteria

- **329 patients were randomized at 78 sites in North America and Europe**

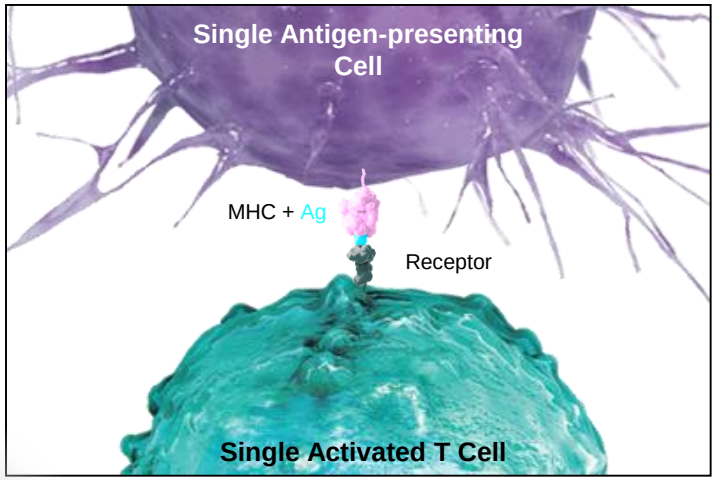


Progression-Free Survival

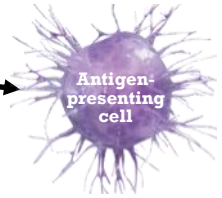


	BV (N=165)	Placebo (N=164)
Hazard Ratio (95% CI)	**0.57 (0.40–0.81, P=0.001)**	
Events	60	75
Median PFS (months)	43	24
2-year PFS rate	63%	51%

A NORMAL IMMUNE RESPONSE

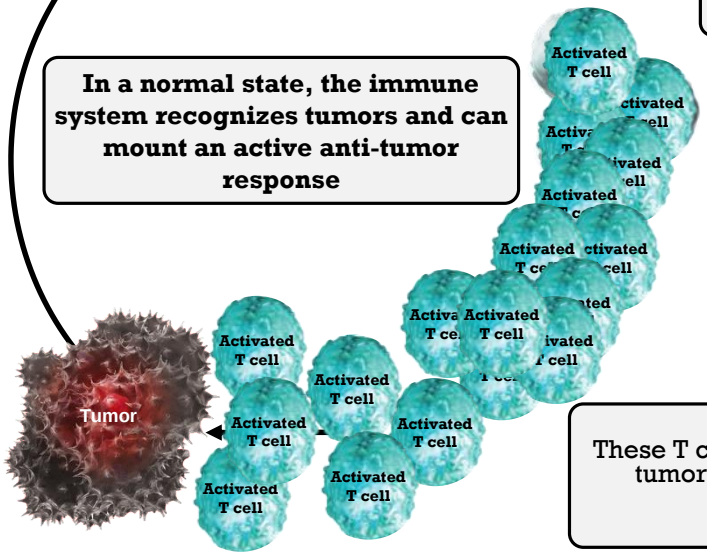


Antigen-presenting cells (APCs) present these tumor antigens which activates T cells



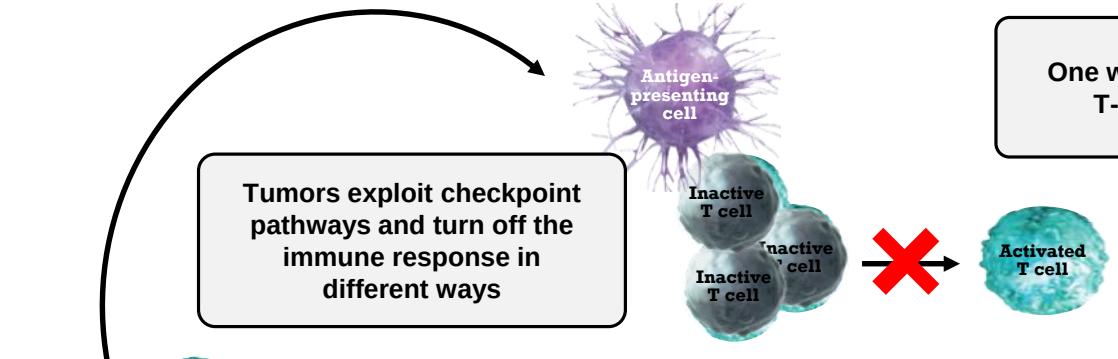
In a normal state, the immune system recognizes tumors and can mount an active anti-tumor response

Tumor releases antigens



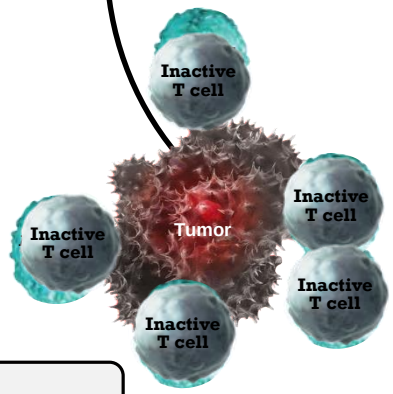
These T cells proliferate, migrate to, and attack the tumor, recognizing the tumor by the surface antigens presented

TUMOR-INDUCED IMMUNE SUPPRESSION

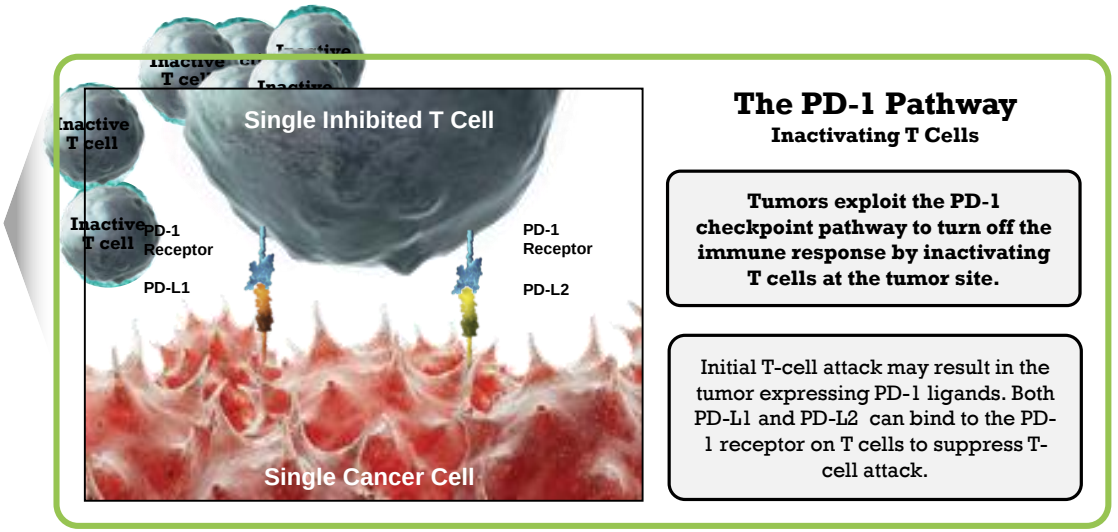


One way is by decreasing T-cell proliferation

Tumors exploit checkpoint pathways and turn off the immune response in different ways



Another way is by inactivating T cells



The PD-1 Pathway

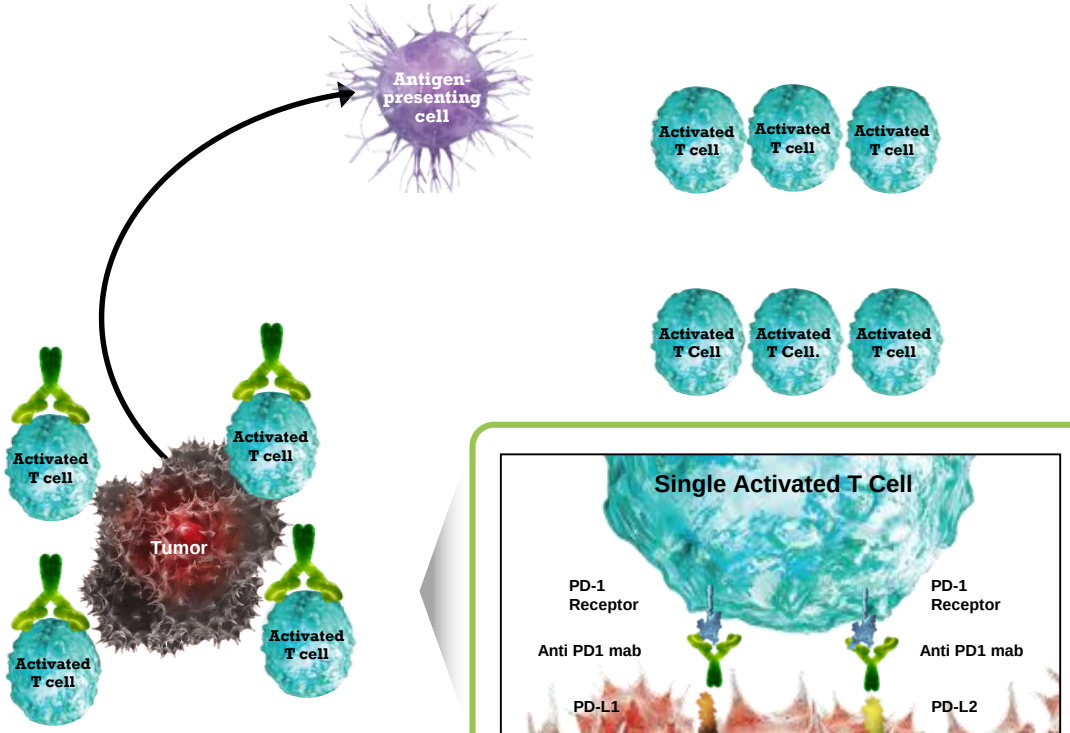
Inactivating T Cells

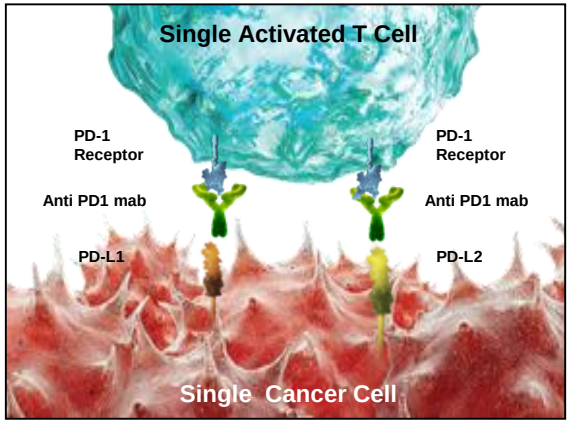
Tumors exploit the PD-1 checkpoint pathway to turn off the immune response by inactivating T cells at the tumor site.

Initial T-cell attack may result in the tumor expressing PD-1 ligands. Both PD-L1 and PD-L2 can bind to the PD-1 receptor on T cells to suppress T-cell attack.

RESTORING AN IMMUNE RESPONSE

Anti-PD1 antibodies affect the immune checkpoint pathways that regulate T-cell activity and restore the anti-tumor response





The PD-1 Pathway

Reactivating T cells at the tumor

PD-1 immune checkpoint inhibitor breaks down tumor defenses directly at the tumor site, either by preventing inactivation or by reactivating T cells, turning the immune response back on to attack the tumor.

- Anti PD1 prevents the interaction of the PD-1 receptor on T cells with PD-L1 and PD-L2 ligands on the tumor, reactivating T-cell activity to induce tumor cell death

9p24.1/*PD-L1*/*PD-L2* Locus Integrity and Protein Expression

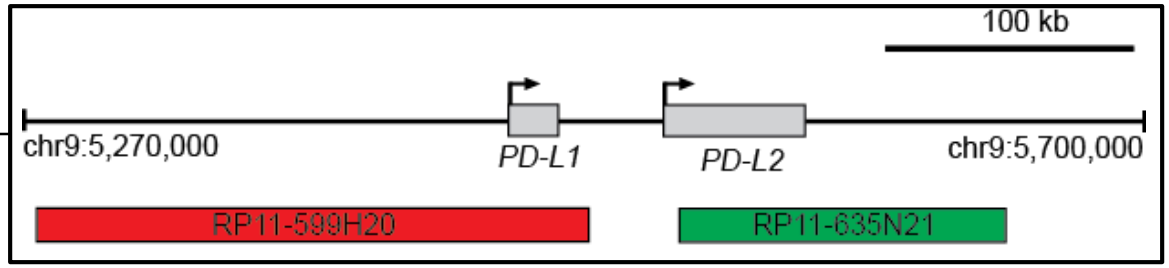
PD-L1/2 locus integrity

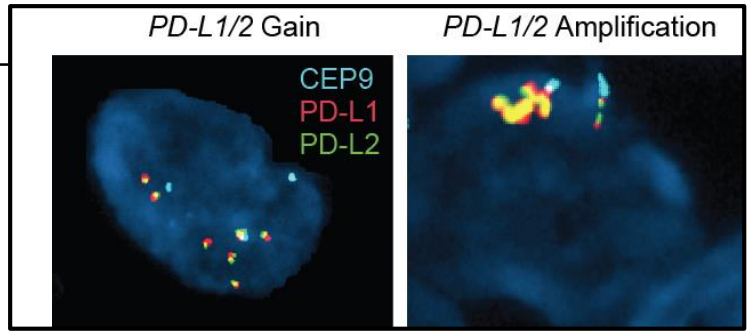
Red=PD-L1

Green=PD-L2

Yellow= Red + Green

Cyan=Centromere

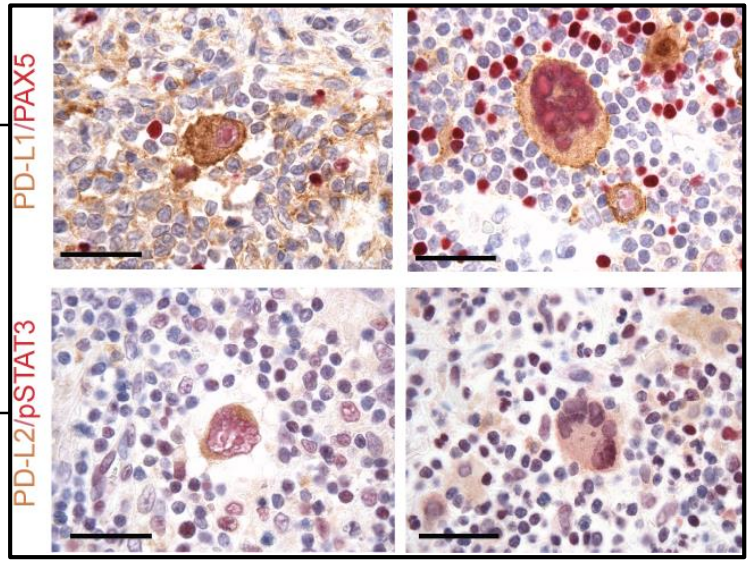




Immunohistochemistry

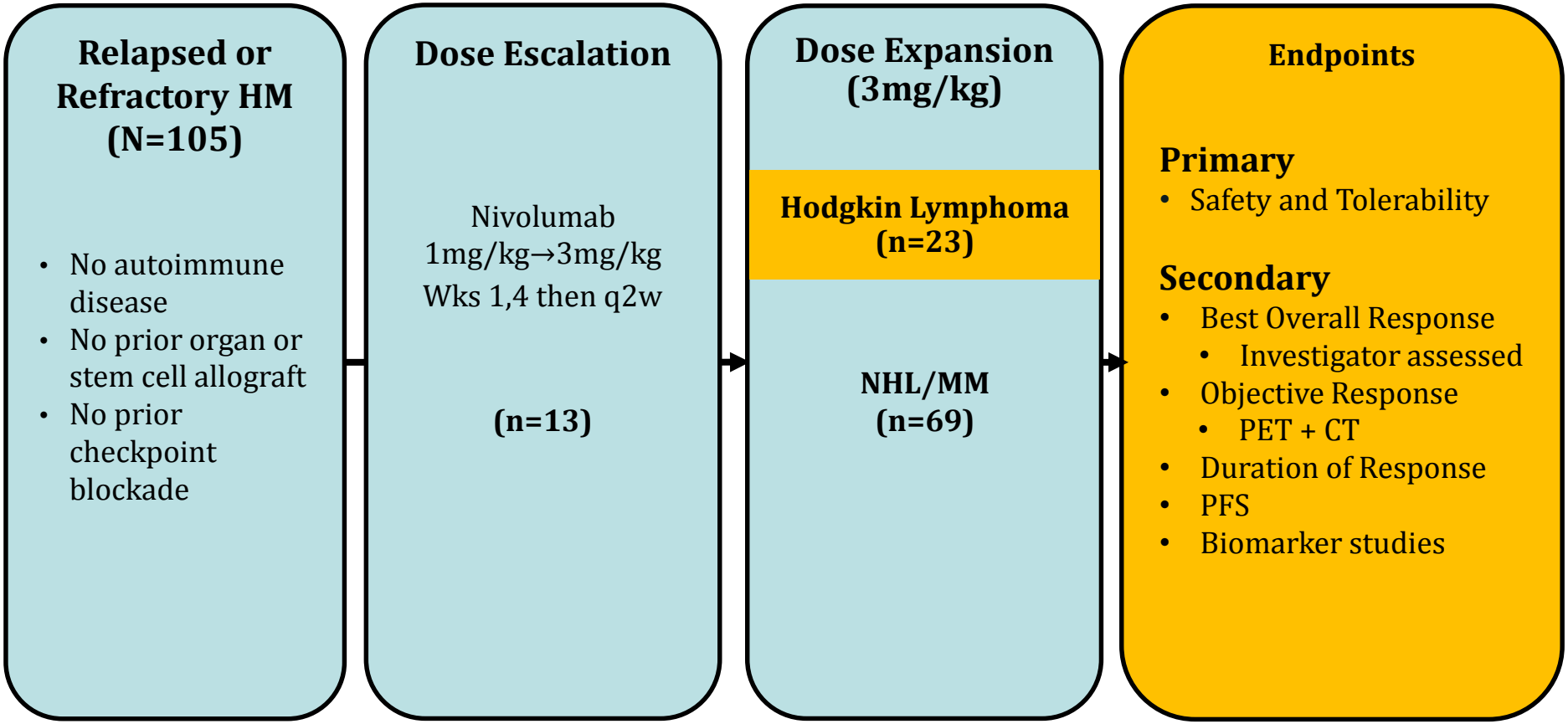
PD-L1 (brown)
PAX-5 (red)

PD-L2 (brown)
pSTAT3 (red)



Rationale and Design

- Based on potential vulnerability to PD-1 blockade, cHL included as independent expansion cohort in Phase 1b study of nivolumab in hematologic malignancies.



Efficacy

	Total (N = 23) n (%)	ASCT Failure Brentux Failure (N = 15) n (%)	ASCT-Naïve Brentux Failure (N = 3) n (%)	Brentux Naïve (N=5) n (%)
Overall Response	**20 (87)**	**13 (87)**	**3 (100)**	**4 (80)**
Best Response **CR**	**4 (17)**	1 (7)	0	3 (60)
PR	**16 (70)**	12 (80)	3 (100)	1 (20)
SD	**3 (13)**	2 (13)	0	1 (20)
PD	**0**	0	0	0
24-week PFS	**86%**	**85%**	n/c	**80%**

Review

- No BM, 2 PET-CT
- Localised cHL
  - Combined modality
- Advanced cHL
  - CT (BEACOPPesc, ABVD)
- Relapse
  - Salvage chemo + HDCT
- New drug
  - Adcetris® reimbursed since 11/2014
  - Anti-PD1 MoAb

Conclusion

The balance between efficacy and toxicity