ASH update – aggressive lymphomas

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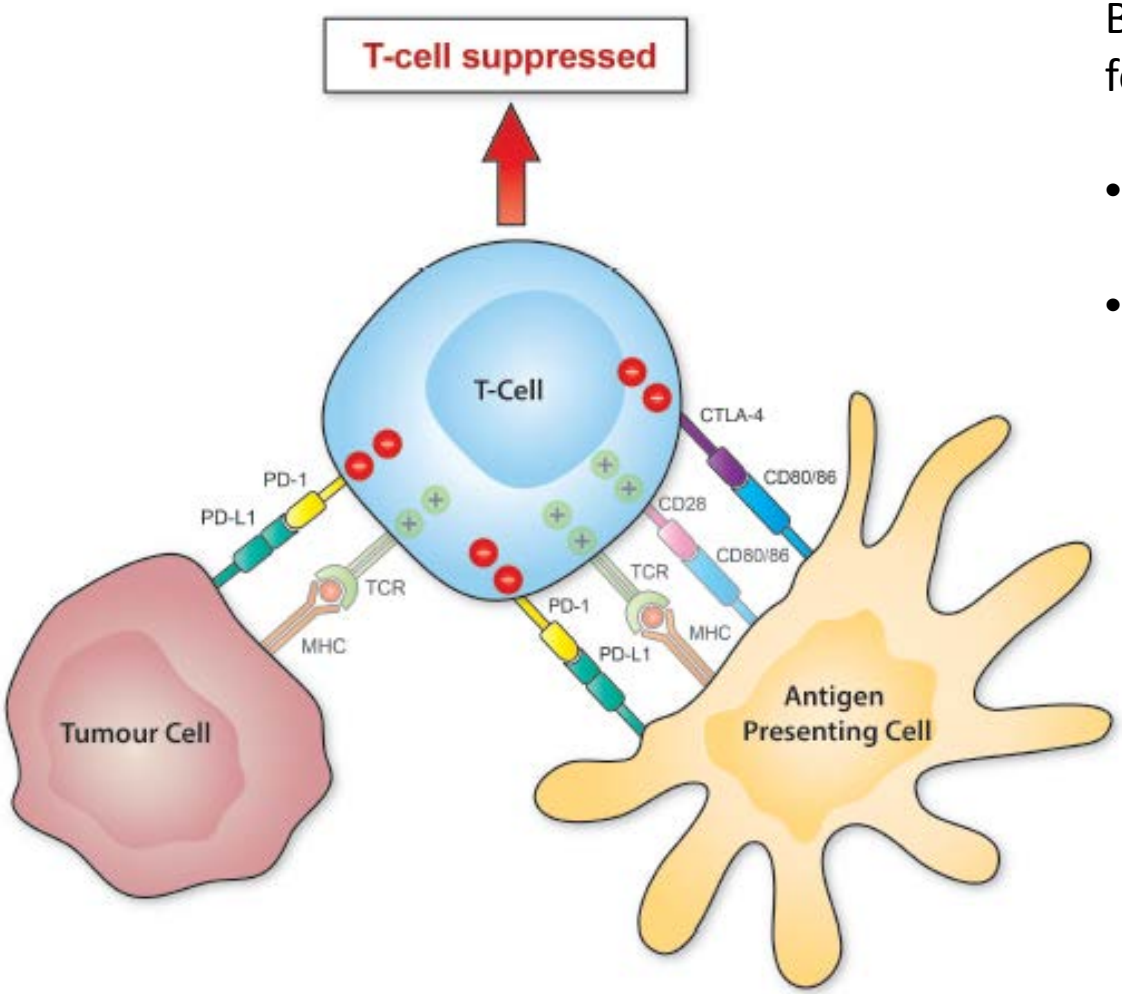
Topics to be covered

- Hodgkin – yet more new drugs
  - PD1 inhibition
  - Athera
- DLBCL – identifying the bad players
  - Interim PET
  - MRD
- DLBCL – tackling the bad players
  - CAR T-cells
  - Novel therapeutics
  - PD1 inhibition
- T- cell – BV still has the upper hand

Hodgkin – yet more new drugs

Immune checkpoints



Both CTLA-4 and PD1 are targets for drugs in clinical practice:

- Ipilumumab licensed for advanced melanoma
- Nivolumab FDA approved for advanced skin cancer in pts on ipilumumab

Courtesy of Dr Caroline Watson

The data in Hodgkin

Table 1. Characteristics of the 23 Patients at Baseline.

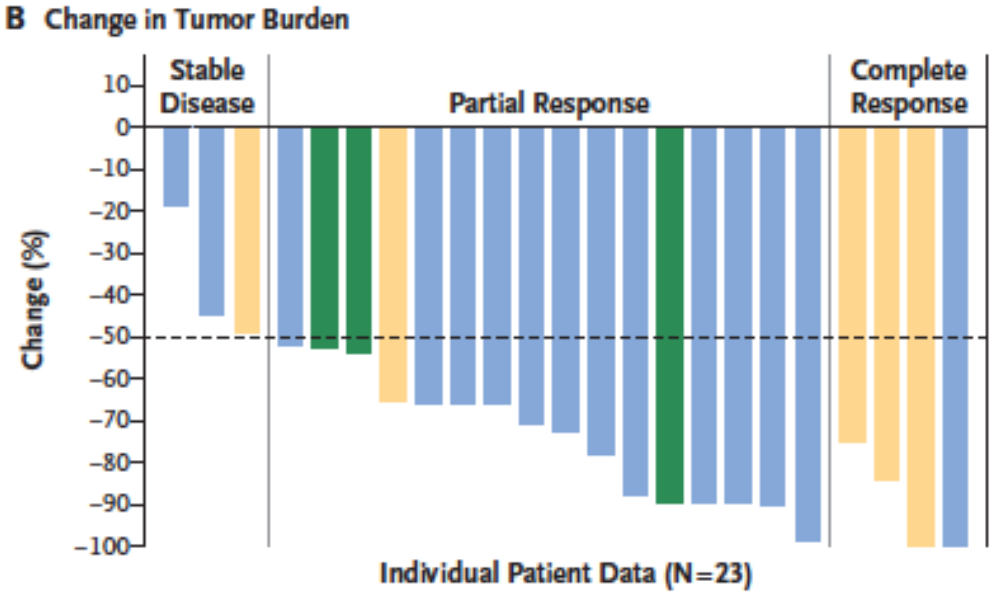
Characteristic	Value
Age — yr	
Median	35
Range	20–54
Male sex — no. (%)	12 (52)
Race — no. (%)*	
White	20 (87)
Black	2 (9)
Other	1 (4)
ECOG performance-status score — no. (%)†	
0	6 (26)
1	17 (74)
Histologic findings — no. (%)	
Nodular sclerosis	22 (96)
Mixed cellularity	1 (4)
No. of previous systemic therapies — no. (%)	
2 or 3	8 (35)
4 or 5	7 (30)
≥6	8 (35)
Previous treatment — no. (%)	
Brentuximab vedotin	18 (78)
Autologous stem-cell transplantation	18 (78)
Radiotherapy	19 (83)
Extranodal involvement — no. (%)‡	4 (17)

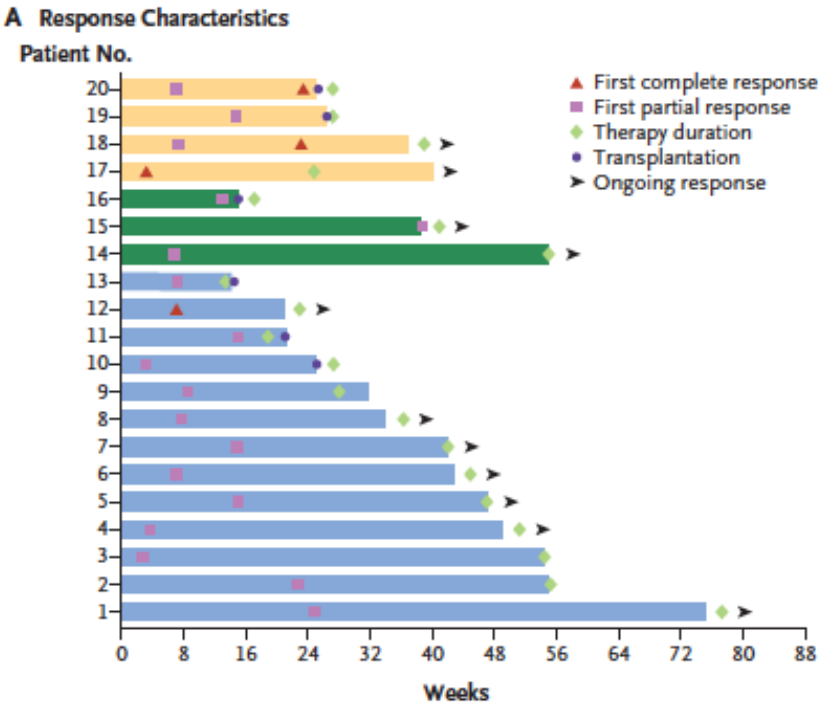
- 23 patients
- Relapsed / refractory cHL
- Most had had ASCT and BV
- 87% had 3 or more lines of Rx
- 87% initially had ABVD

Schedule:

- 3mg/kg iv every 2 weeks
- 1h infusion, no pre-med
- For max 2y or progression or toxicity

Activity

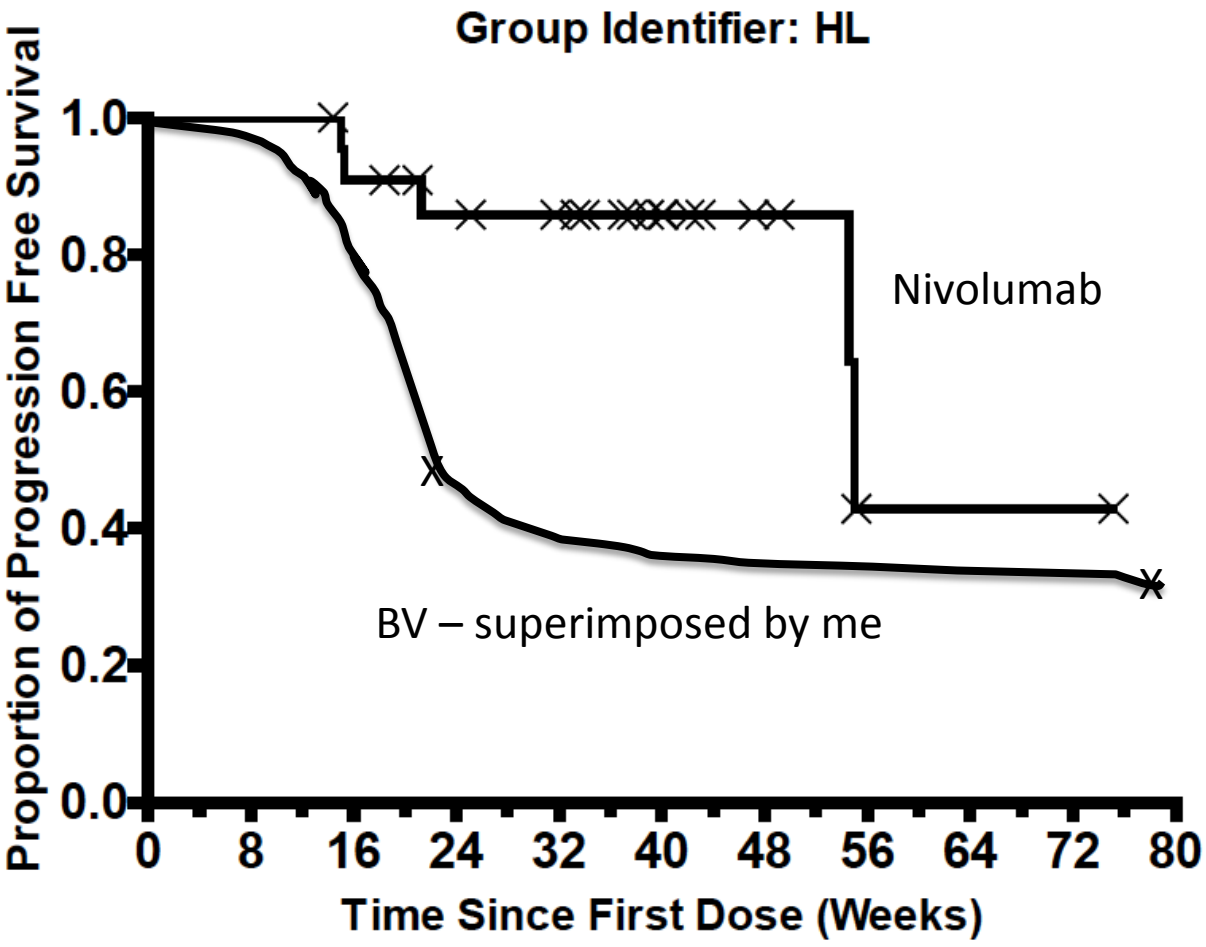




- 87% ORR
- Every patient had some tumour reduction
- Only 17% (4 pts) had CR – why?
- 5 pts had had no BV: 80% ORR with 60% CRR (3 pts) - ?due to CD30 cell presence

Ansell *et al* NEJM December 6, (2014) DOI: 10.1056/NEJMoa1411087

Progression free survival (compared with BV)



- Nivo produces excellent PFS – 87% 24 week PFS
- BV has more rapid tail off due to poor DOR for PR
- Note: Much longer FU for BV patients
- Treatment duration longer for nivo
- So direct comparison is unfair!

Safety

Table 2. Drug-Related Adverse Events in the 23 Patients.*

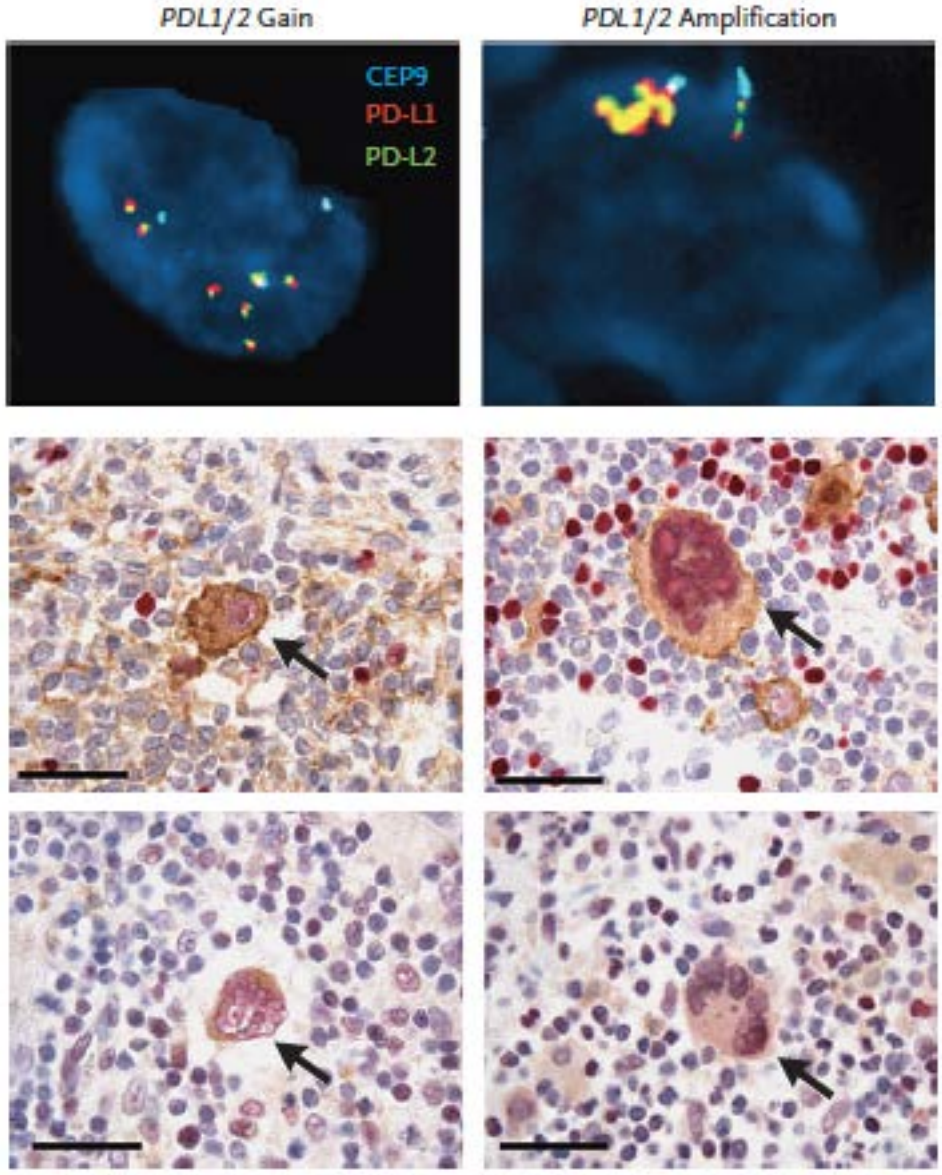
Event	Any Grade	Grade 3
	no. of patients (%)	
Any adverse event	18 (78)	5 (22)
Drug-related adverse events reported in ≥5% of patients		
Rash	5 (22)	0
Decreased platelet count	4 (17)	0
Fatigue	3 (13)	0
Pyrexia	3 (13)	0
Diarrhea	3 (13)	0
Nausea	3 (13)	0
Pruritus	3 (13)	0
Cough	2 (9)	0
Hypothyroidism	2 (9)	0
Decreased lymphocyte count	2 (9)	1 (4)
Hypophosphatemia	2 (9)	0
Hypercalcemia	2 (9)	0
Increased lipase level	2 (9)	1 (4)
Stomatitis	2 (9)	1 (4)
Drug-related serious adverse events		
Myelodysplastic syndrome	1 (4)	1 (4)
Lymph-node pain	1 (4)	0
Pancreatitis	1 (4)	1 (4)

Very well tolerated
No grade 4 or 5 events
Rash and low platelets most common

Note: in other trials, autoimmune side effects have been seen e.g.

- Pneumonitis (5%)
- Colitis
- Nephritis
- uveitis

Correlative science



Gains or amplifications in PDL1 / L2 loci seen in every patient (more frequently than newly diagnosed patient - ?poor prognostic factor)

PDL1 and PDL2 overexpression of protein seen on HRS cells in every case

PD1 expression on infiltrating T-cell only weakly to moderately expressed

Shameless advertisement no.1

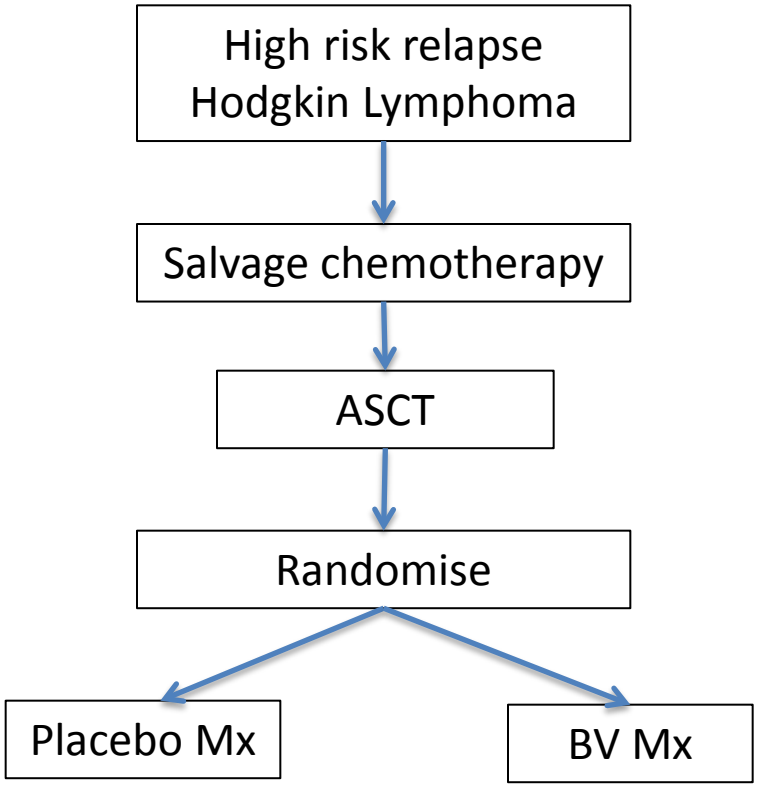
Checkmate 205 study for patient with relapsed / refractory cHL post-ASCT

Brentuximab naïve patients especially needed

3 English sites:

1. Oxford
2. Christie
3. Marsden

BV in Hodgkin – the Athera trial



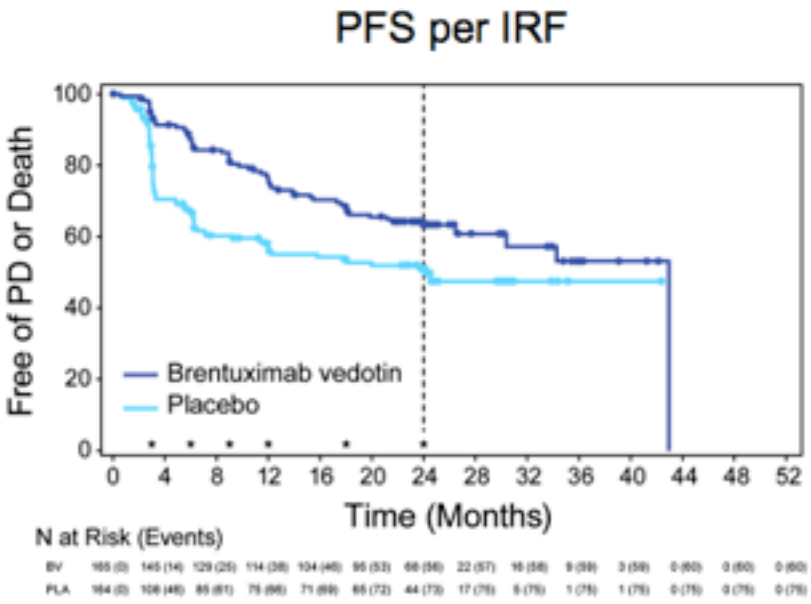
High risk defined as:

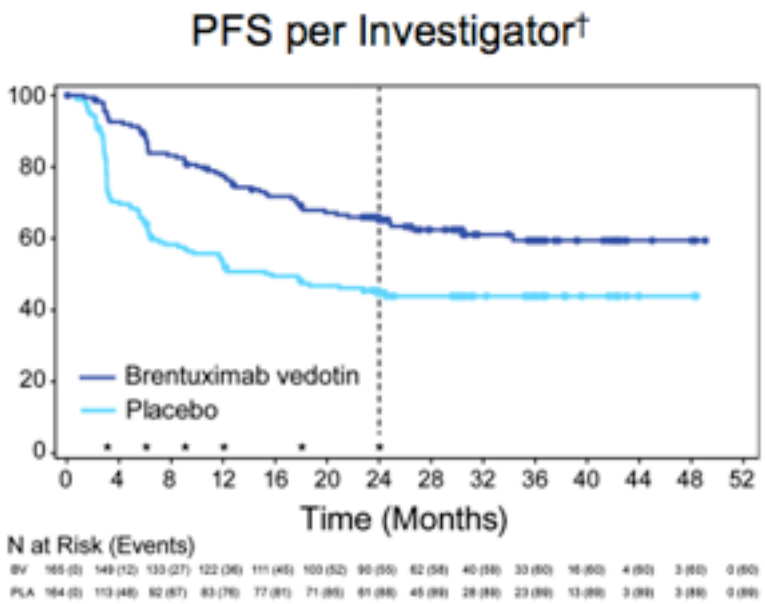
- Relapse within 1y of 1st line
- Primary refractory
- Extranodal site of relapse

Treatment was with BV 1.8 mg/kg iv every 3 weeks for a maximum of 16 cycles (1y) or placebo

Primary EP: Progression free survival

Survival curves





	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%

	BV (N=165)	Placebo (N=164)
Hazard Ratio (95% CI)	0.50 (0.36–0.70)	
Events	60	89
Median PFS (months)	--	16
2-year PFS rate	65%	45%

* Regularly scheduled CT scans
† Includes information from both radiographic assessments and c

Will this change practice?

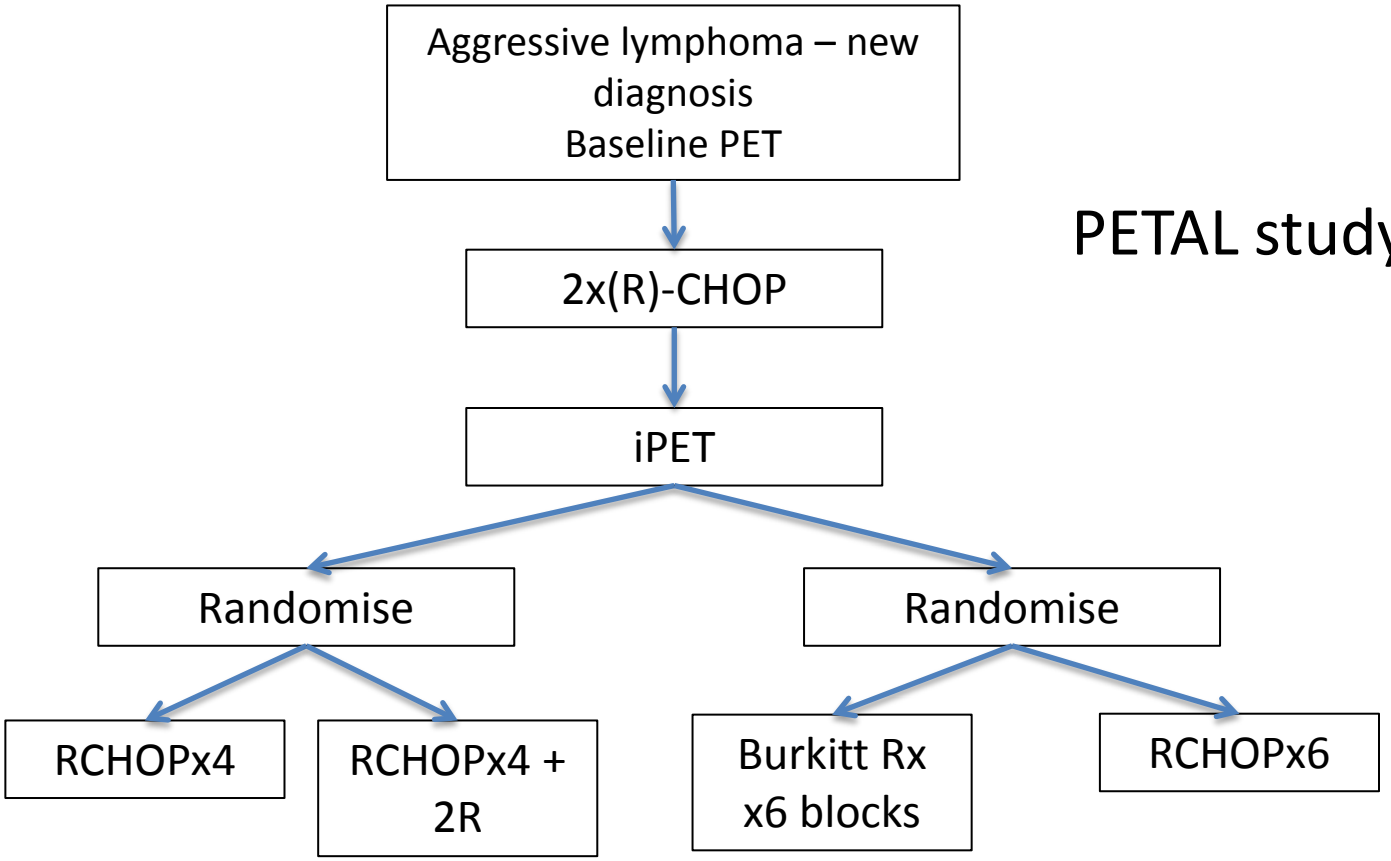
'Brentuximab maintenance represents a new standard of care in treating high risk Hodgkin Lymphoma' Craig Moskowitz – ASH 2014

BUT if BV maintenance is used:

- 51% patients will be treated unnecessarily to avoid relapses in 12%
- Therefore, of patients at risk of relapse (49%), 24% of them will not relapse due to Mx BV
- However, of those who do relapse, 34% would have achieved a CR if given brentuximab AT RELAPSE (and these CR patients MAY not need a subsequent allograft)
- Cost of Mx for 100 patients: £11.25 million
- Cost of treating only those who relapse – all to 6 cycles and then only the CRs to 16 cycles: £3.41 million

DLBCL – identifying the bad players

DLBCL – are iPETs of value?



PETAL study

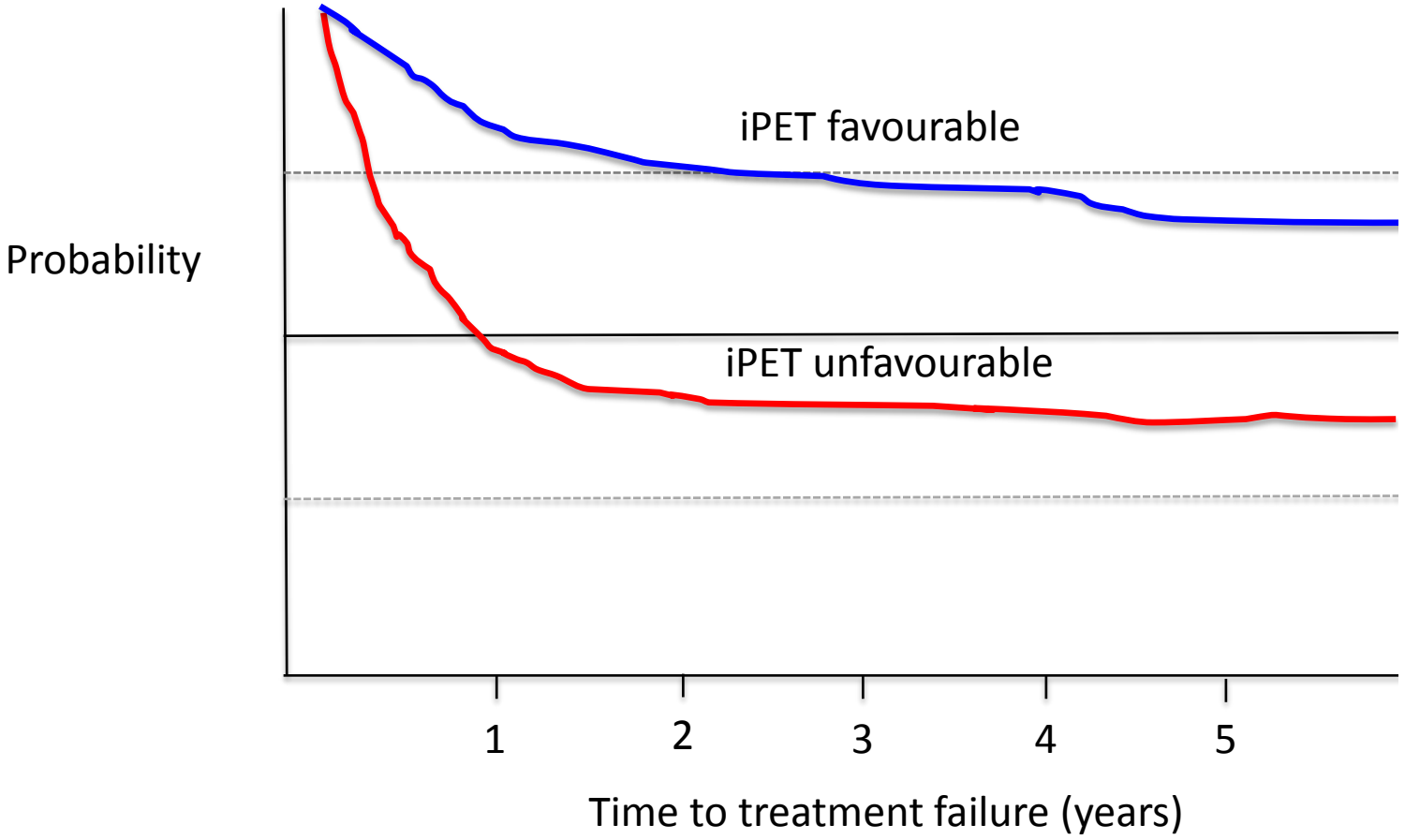
Duerhsen et al December 6, 2014; Blood:124 (21)

Study details

- Recruited B and T-cell patients; only B-cells were randomised in the favourable arm
- iPET performed 3 weeks after course 2 (R)-CHOP
- NO GCSF was given during course 2
- SUV-based approach used:
  - Favourable: SUVmax reduction > 66%
  - Unfavourable: SUVmax reduction Not > 66%

926 patients randomised; median follow up 33 months
83 patient had PTCLs
iPET favourable in 87% patients; unfavourable in 23%

PET predicted prognosis



TF: 2y probability was 79% in favourable group; 47% in unfavourable group
OS: HR 3.9, CI 2.7 – 5.7, p<0.0001

Randomisation results

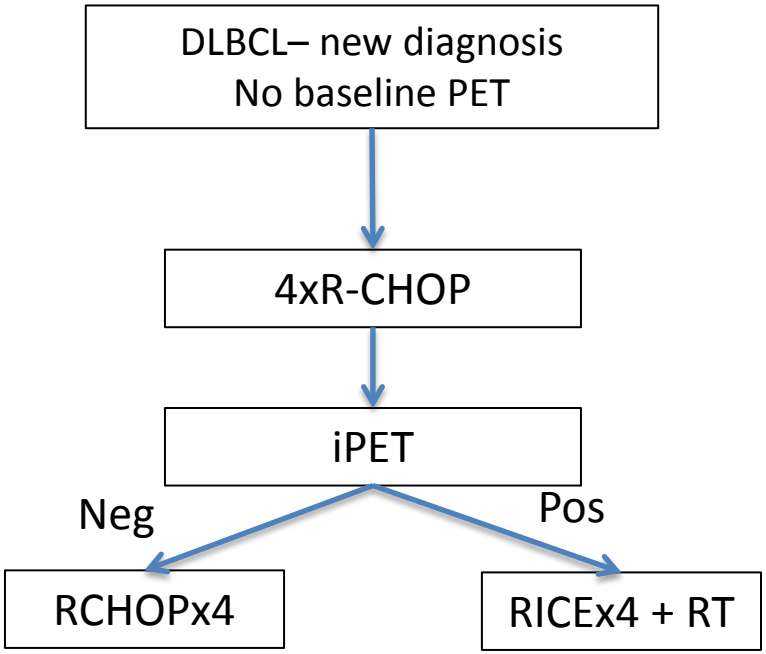
Low risk patients: HR for 2 extra doses 1.2, CI 0.8 – 2.1

High risk patients TF: HR for Burkitt Rx 1.6, CI 0.9 – 2.7
High risk patients OS: HR for Burkitt Rx 1.0, CI 0.5 – 2.1
Burkitt protocol associated with more toxicity

Multivariate analysis, 3 predictive factors for good prog:

- B versus T-cell
- Low IPI
- Favourable iPET

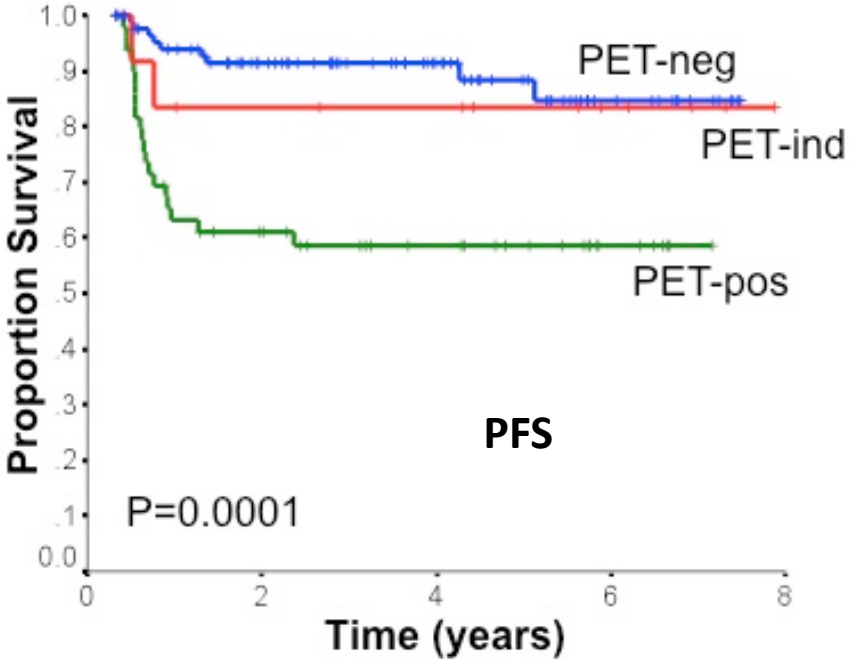
Canadian experience

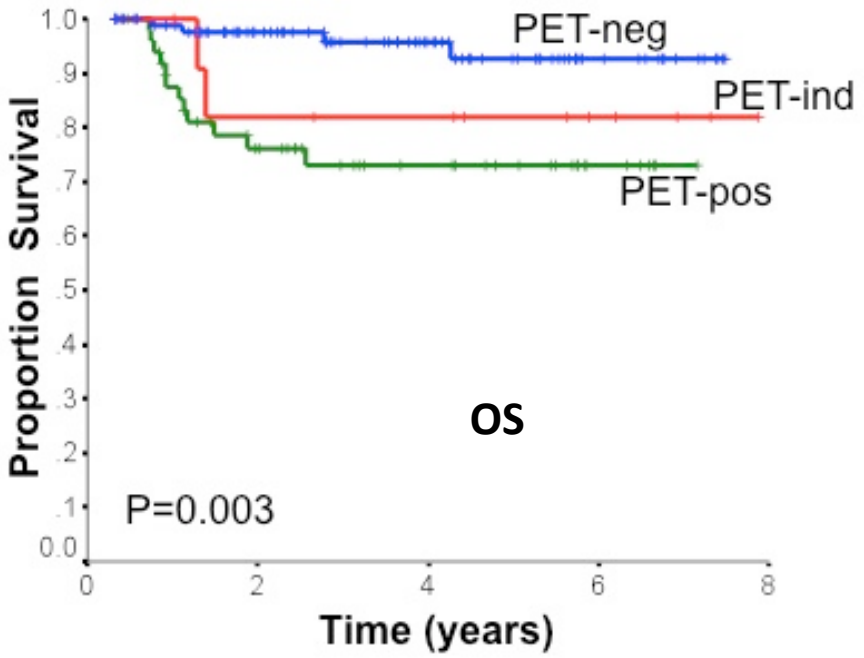


Sehn *et al* 2014; Blood: 124 (21)

- Phase 2 study
- 155 patients
- IPI 3-5 in 42%
- PET: between 21-28d after no.4
- International harmonisation project
- All PETs performed in 1 centre
- 59% PET neg; 33% PET pos
- 8% PET indetermindate
- Of PET pos:
  - 9 didn't complete 4x
  - 2 refused to switch
  - 3 progressed on RICE

Survival





	4y PFS	4y OS
Whole cohort	79%	87%
PET neg	91%	96%
PET pos	59%	73%

PET pos still do fairly badly
Relatively few converted to PET neg

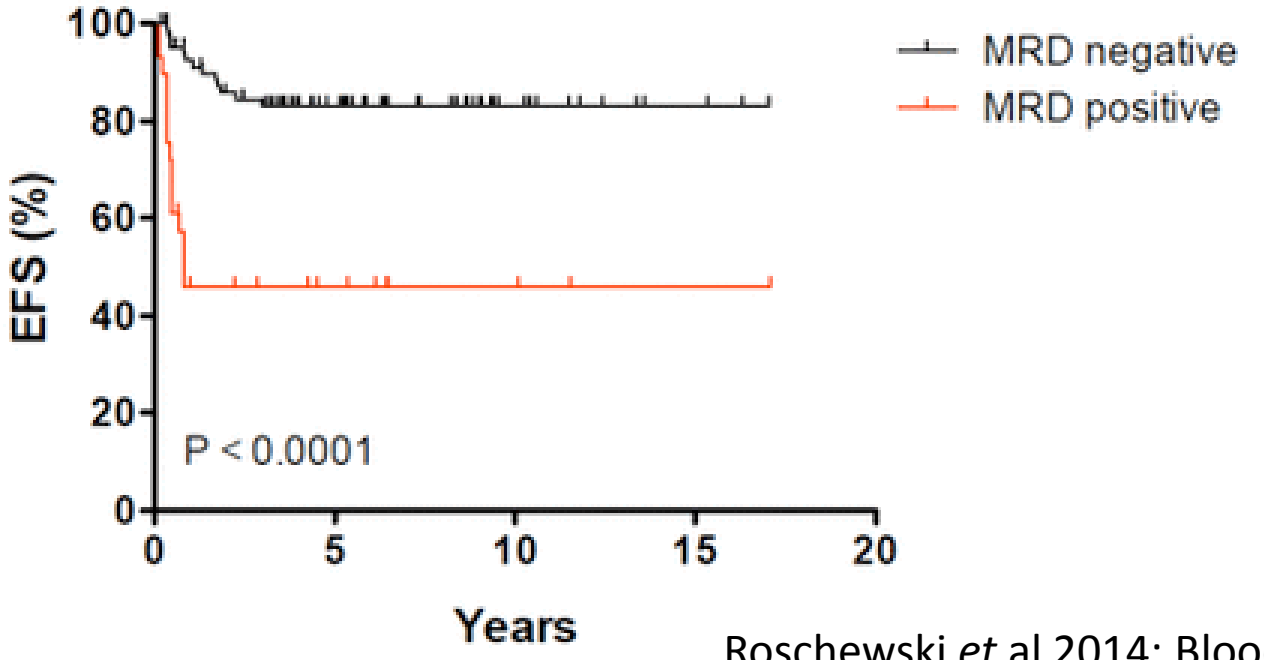
Circulating DNA in DLBCL

- 198 DLBCL patients treated at NCI with EPOCH-based treatment
- Serum samples collected per-Tx, each cycle and each surveillance visit
- Pre-Tx serum and FFPE Bx analysed for clonotype specific DNA
- Tumour specific clonotypes then quantified in serum as MRD

- When FFPE Bx available, 86% had tumour clonotype Ided
- When FFPE Bx not available, only 37% obtained from serum

- All patients MRD pos at end of induction relapsed
- 101 patients had remission > 6 months; 11 relapsed and 10/11 had MRD positivity at a median of 7 months prior to relapse
- Monitoring of MRD at each cycle identified early Rx failure with a PPV of 60% and NPV of 95.4%

Interim MRD predicting EFS



Roschewski *et* al 2014; Blood: 124 (21)

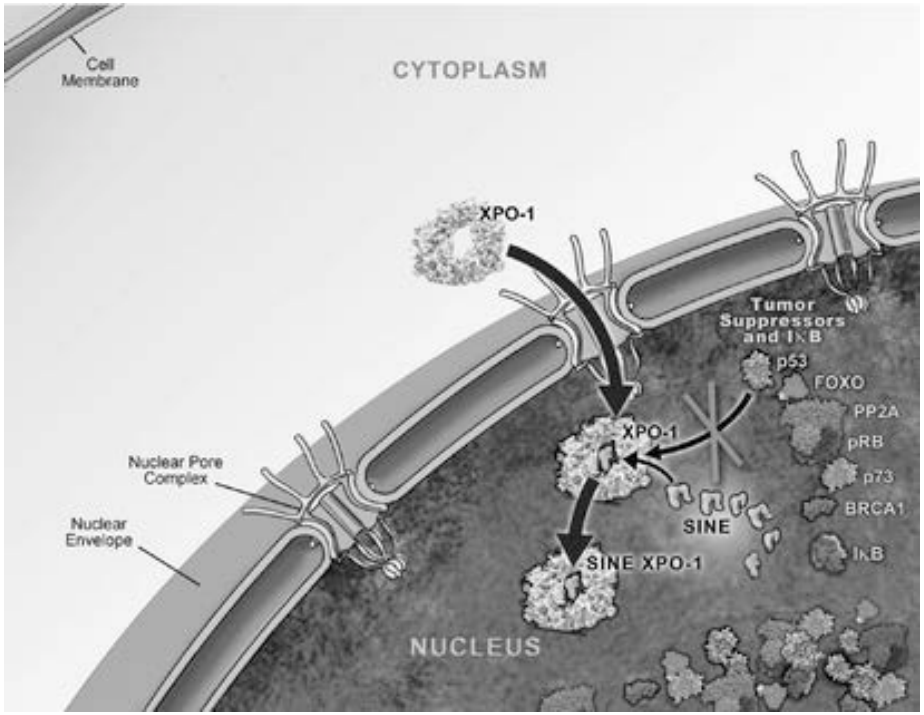
5y EFS was:

- 45.9% in those who were interim MRD positive
- 83% in those who were interim MRD negative

Q: can this be used to enhance prognostic ability of interim PET / IPI

DLBCL – tackling the bad players

New therapeutics - selinexor



Kuruvilla *et al* 2014; Blood: 124 (21)

Example of a SINE: Selective Inhibitor of Nuclear Export

Slowly reversible XPO1 inhibitor

Inhibitors pathophysiology of TSPs and oncogenic RNAs

Phase 1 study, 13 dose schedules
MTD: 60mg/m^2

Grade 3/4: thrombocytopenia, neutropenia, anaemia, fatigue

- 58 patients treated; all with R/R HG-NHL with documented progressive disease
- ORR: 31%; in B-cell lymphomas ORR 40%; 5 CRs seen
- 9 patients remain on treatment for 6-23 months

Shameless advertisement no.2

SADAL study:

Selinexor in R/R diffuse large B-cell lymphoma
Single agent phase II

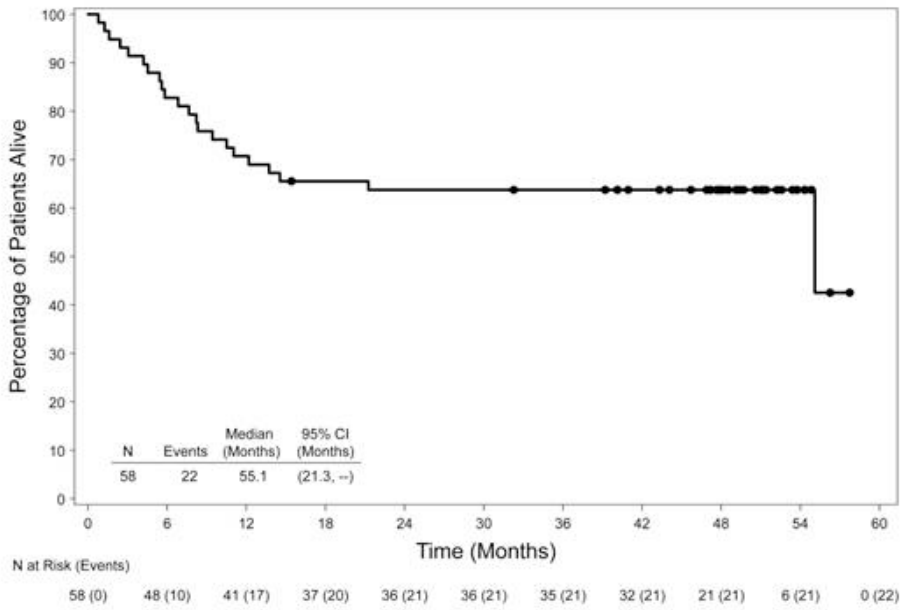
SIRRT study:

Selinexor in relapsed / refractory Richter's transformation
Single agent phase II (Anna Schuh is UK CI)

Several UK centres – Oxford is one of them!

T-cell lymphoma – BV has the upper hand

BV and ALCL – 4y follow up



Pro *et al* (2014): ASH abstract 3095

- 46 month median observation time after 1st dose
- 4y estimated OS of 64% for cohort
- CR – median OS NR
- PR – median OS 11.6 mo
- SD – median OS 6.9 mo
- All – median 55.1 mo

18/57 had had an SCT: 9 ASCT and 9 allo SCT

Median PFS for allcomers: 20 months
PFS for those who had CR + SCT: NR
PFS for those who had CR no SCT: 39 months

So BOTH patients who had a SCT and those who did not did very well

Question: Is stem cell transplantation now routinely indicated?

Take home messages

Hodgkin:

1. PD1 inhibitors have impressive activity in Hodgkin and we will see much more of them – their use in NHL is less certain
2. The Athera trial was positive but it's far from clear if this will become standard of care (at least in the UK)

DLBCL:

1. We are getting better at identifying front line DLBCL patients who will do badly but at the moment we don't know what to do about it
2. A number of possible approaches: CAR T-cells, novel therapeutics and immune checkpoint inhibition

T-cell lymphoma:

1. BV in relapsed ALCL may be curative – long term results are excellent