Brentuximab and Hodgkin's Lymphoma; Is 30 the New 20?

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Hodgkin's Lymphoma (HL): Background

- Hematologic malignancy
  - CD30+ Reed-Sternberg cells diagnostic
  - Classic (95%) vs. nodular lymphocyte predominant
- Peak incidence: young adults and > 60 years
  - ~ 900 new cases per year in Canada
- Etiology unknown
  - Risk factors: Family history, Epstein Barr Virus, HIV infection

Bradley et al. ASHP. 2013.

Cotswold Staging

Stage	Criteria
I	Single lymph node or lymphatic structure
II	Involves ≥ 2 or more nodes on same side of diaphragm
III	Involves multiple nodes on both sides of the diaphragm
IV	Multiple extranodal sites or lymph nodes and extranodal disease
X	Bulky disease > 10 cm
E	Extranodal extension or single, isolated site of extranodal disease
A/B	Absence or presence of B symptoms

Jaffe et al Hematology Am Soc Hematol Educ Program. 2009.

HL: Treatment

- ~ 90% of patients respond to first line treatment
  - CT: ABVD, BEACOPP
  - Radiation if localized disease
- 10% primary refractory disease
  - Resistant to initial CT or relapse within 3 mo
- Relapse after primary CT
  - 10-15% with localized disease
  - 20-40% with advanced disease (Stage IIB, III, IV)
  - 50% occur within 12 months from initial induction therapy

Bradley et al. ASHP. 2013.

HL: Recurrent/Refractory

- High-dose CT + autologous stem cell transplant (ASCT)
  - CI: age or co-morbidities
  - Relapse rate ~ 50% post ASCT
    - Median survival 1.2 years if relapse within 1 year

- Salvage CT
  - No gold standard established
    - Vinblastine, lomustine, gemcitabine, bendamustine
  - Limited by hematologic/GI toxicities
  - Long-term complications: CV, pulmonary, fertility, secondary malignancies

- Refractory disease
  - 5 year OS: 36%

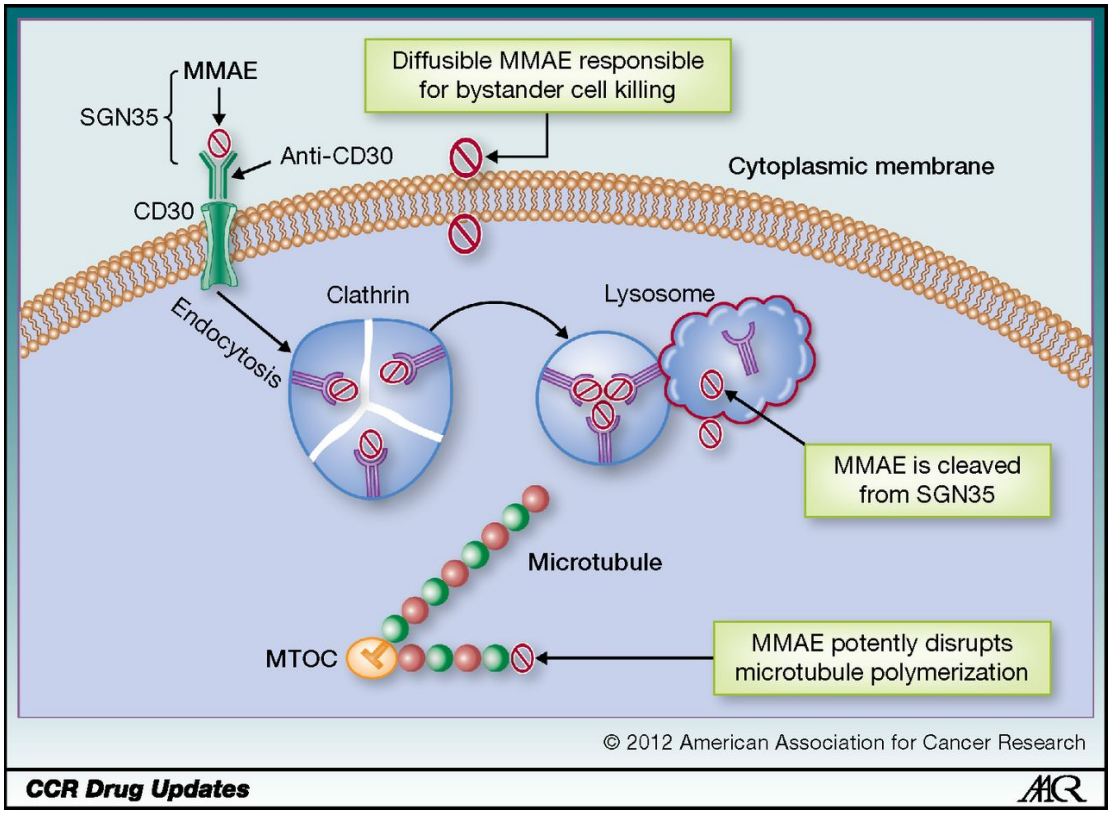
Bradley et al. ASHP. 2013.

Brentuximab (Adcetris®)

- Health Canada NOC/c issued Feb 1, 2013
  - Hodgkin's Lymphoma
    - After failure of ASCT **OR**
    - ≥2 multi-agent CT regimens in patients who are not ASCT candidates
  - Systemic anaplastic large cell lymphoma after failure of at least one multi-agent CT regimen

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php

Brentuximab: MOA



Deng C et al. Clin Cancer Res 2013;19:22-27

ADC binds CD30 on RS cells

ADC internalized , moves to lysosome

Linker cleaved, MMAE released

MMAE disrupts microtubules = apoptosis

Free MMAE = cytotoxicity in tumor microenvironment

Clinical Question

P	Adult patients with relapsed or refractory HL	
I	Brentuximab	
C	Salvage chemotherapy, no therapy	
O	<u>Efficacy</u> Overall survival Overall response Complete remission Partial response Progression free survival	<u>Safety</u> ADRs Dose intensity/ density

Search Strategy

Search terms	cAC10-vcMMAE, brentuximab vedotin, Hodgkin Disease, Hodgkins lymphoma
Databases	MEDLINE, EMBASE, Cochrane database of systematic reviews, CENTRAL, Google, Google Scholar, IPA, WHO ICTRP
Limits	None
Results	54 results → No completed RCTs, cohort or case controlled trials → 8 Results deemed relevant to PICO → **Excluded** -1 Phase I trial (dose-finding, pre-cursor to Phase II) -2 case-series (post-allogenic stem cell transplant) → **Included** -1 Phase II trial -3 case series -1 RCT abstract

Younes et al. 2012

D	MC, open-label, phase II trial US, Canada, Europe
P	Age >12 Relapsed or refractory HL Post ASCT
I	Brentuximab 1.8 mg/kg IV q3w until disease progression or 16 cycles completed
O	1°: Objective response rate (ORR) =CR+PR 2°: Duration of response Complete remission (CR) Progression free survival (PFS) Overall survival (OS) ADRs

Younes et al. Am J Clin Oncol. 2012.

Younes et al: Patients

- N=102
- Enrollment Feb 2009-Aug 2009
  - Followed until death or final follow-up (Mar 2011)
- Average patient
  - Caucasian, male, age 31 (15-77), ECOG 0,1
  - 71% primary refractory disease at study entry
  - Median no. of CT regimens: 3.5
  - 66% prior radiation therapy
  - Median time to relapse post ASCT: 6.7 months

Younes et al. Am J Clin Oncol. 2012.

Younes et al: Results

- Median number of brentuximab cycles: 9 (1-16)

Outcome	%	95% CI
ORR	75	64.9-82.6
CR	34	25.2-44.4
Overall disease control (CR +PR+ Stable disease)	96	90.3-98.9

- *Subgroup analysis by age, sex, disease type/burden did not reveal any differences in response*

Younes et al. Am J Clin Oncol. 2012.

Younes et al: Results

Outcome	Months	95% CI
Median duration ORR	6.7	(3.6-14.8)
Median duration if CR	20.5	(10.5 to NE)
Median PFS	5.6	(5.0-9.0)
Median OS	22.5	(21.7 to NE)

NE: Not able to estimate

Younes et al. Am J Clin Oncol. 2012.

Younes et al: Results

Estimated 12 mo survival:
89% (95% CI: 83-95%)

Median PFS:
5.6 months (95%CI: 5-9 months)

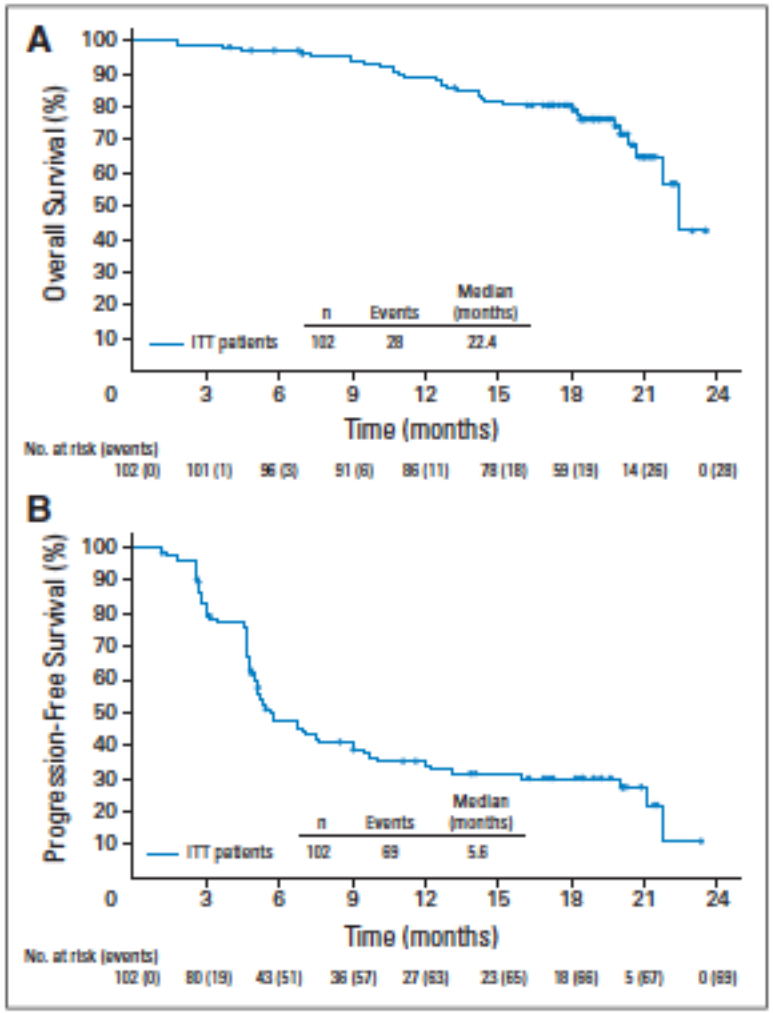


Fig 2. Secondary end points of overall survival (A) and progression-free survival (B). ITT, intent to treat.

Younes et al. Am J Clin Oncol. 2012.

Younes et al: Results

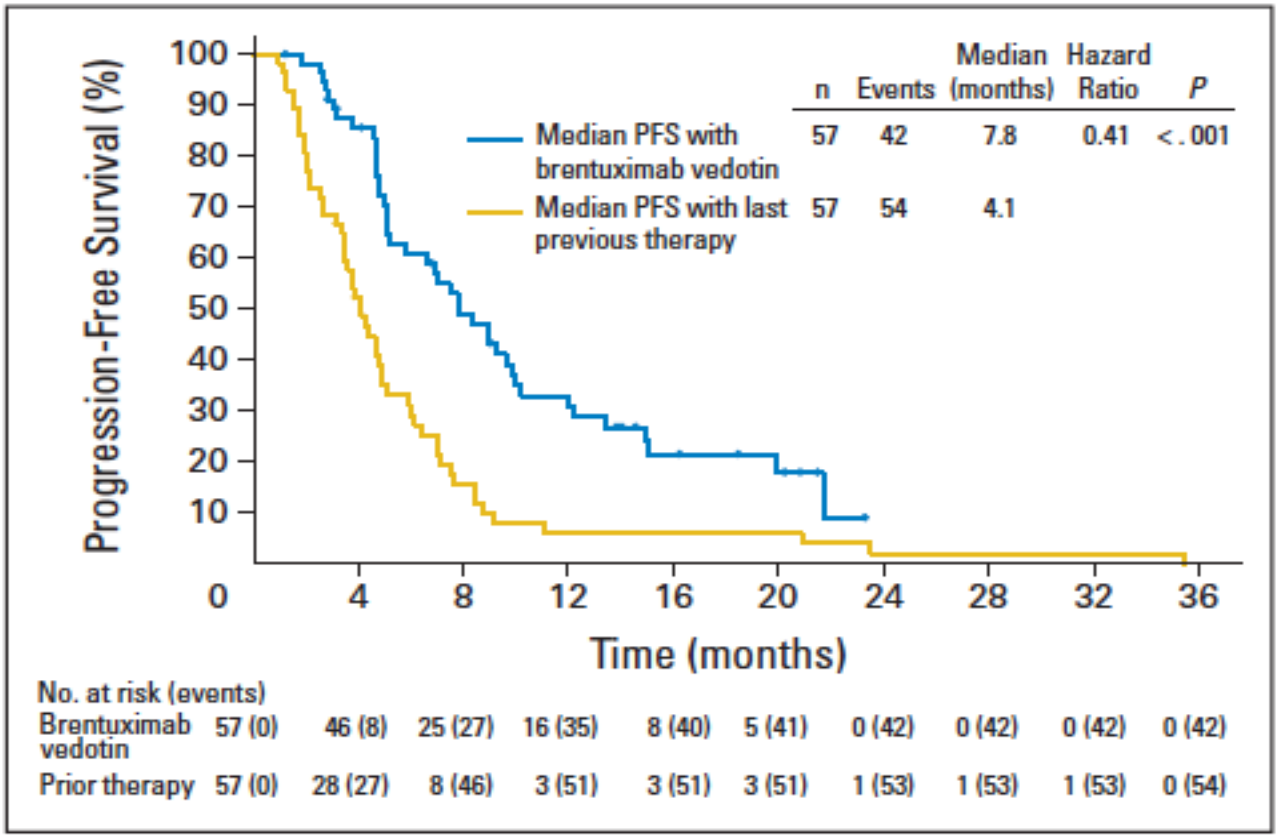


Fig 3. Progression-free survival (PFS) achieved with brentuximab vedotin compared with PFS achieved with the last prior therapy. Data shown are median PFS as assessed by investigator in the subset of patients (n = 57) who received systemic therapy after autologous stem-cell transplantation and before receiving brentuximab vedotin.

Younes et al. Am J Clin Oncol. 2012.

Younes et al: Safety

- 20 subjects discontinued treatment due to ADRs
- 47% experienced a dose delay
- Median relative dose-intensity: 96%

ADR	
PSN* Grade 1/2 Grade 3:	 34% 8%
Nausea	35%
Fatigue	34%
Neutropenia	19%
Diarrhea	18%

*23% of patients had pre-existing peripheral neuropathy

Younes et al. Am J Clin Oncol. 2012.

Younes et al: Summary

- Substantial number of patients achieving durable CR
  - Heavily pre-treated patients with poor prognosis
- Potentially more effective in terms of sustained response compared to current mono-salvage CT
  - Less toxicities
- Significantly longer inter-patient PFS compared to most recent prior therapy
  - Traditionally successive treatments lead to diminished PFS

Younes et al. Am J Clin Oncol. 2012.

Younes et al: Critique

- Study design/lack of comparator
  - ? magnitude of benefit
- Long-term efficacy for relapse prevention unknown
- Only ECOG 0 or 1 patients included
- Improved PFS but ? QOL
- Effect of treatment regimens pre-brentuximab
- Manufacturer funded
  - Outcomes adjudicated by independent review facility

Brentuximab: Case Series

	Rothe et al 2012 N=45	Gib et al 2013 N=24	Zinzani et al 2013 N=65
Setting	-Refractory/relapsed HL -Multi-center German Study	-HL (n=18) ALCL (n=5) refractory to ≥2 chemo or ASCT -Single UK Center	-HL refractory to ≥2 chemo or ASCT -Multi-center Italian study
Average patient	• 35 yo, 50% male • Stage 3-4 HL • 4 previous CT regimens • 87% previous ASCT • ECOG 0-1	• 42 yo, 54% female • Stage 2A-4B HL • 3 previous CT regimes • 33% previous ASCT	• 27.5 yo, 52% male • 4 previous CT regimens • 87.6% previous ASCT • ECOG 0-1
CT regimen	1.8 mg/kg IV q3w Median 7 cycles (1-12)	1.8 mg/kg IV q3w Median 5.5 cycles (1-13)	1.8 mg/kg IV q3w Median 8 cycles (3-16)

Brentuximab: Case Series

	Rothe et al 2012 N=45	Gib et al 2013 N=24	Zinzani et al 2013 N=65
Efficacy Results	ORR: 60% at 12 mo CR: 22% Median PFS: 8 months OS 12 mo: 83% PFS 12 mo: 43% (28-58) PFS at 12 mo high vs low risk: 14 vs 59% (p<0.001)	ORR: 72% at 12.9 mo CR: 17% Median PFS: 5.1 mo OS at 12.9 mo: 67% *Note:* *No difference in outcomes for prior ASCT vs no ASCT, 27% proceeded to allotransplantation*	ORR: 70.7% CR:21.5% Median PFS: 6.8 mo OS 20 mo: 73.8% PFS 20 mo: 24.2%

Brentuximab: Case Series

	Rothe et al 2012 N=45	Gib et al 2013 N=24	Zinzani et al 2013 N=65
PSN	**Grade 1/2**: 31% **Grade 3/4**: None -Dose reduction required in 4 pts	**Grade 3/4**: 12.5%	**Grade1/2**: 13.5% **Grade3/4**: 7% Dose reduction required in 4 pts
Other toxicities	**Grade 3/4:** Neutropenia: 13.3% Thrombocytopenia: 6.7% Fatigue: 6.7% Infection: 6.7%	**Grade 3/4 :** Sepsis: n=3 Bowel obstruction: n=1	-Neutropenia: 4.6% -Thrombocytopenia: 4.6%

Brentuximab: Case Series

	Rothe et al 2012 N=45	Gib et al 2013 N=24	Zinzani et al 2013 N=65
Limitations	-No comparator, small sample sizes, heterogenous populations, short term f/u		
Authors conclusions	-Effective and well tolerated in heavily pretreated and refractory HL patients	-Role for bridge to transplant -"Real world" setting shows results similar to phase 2 trial	-Best ORR after 3-4 cycles, an effective bridge to further therapeutic intervention
Comments	-Higher risk patient population than Phase II trial	-More refractory patients, most had not already received ASCT -? benefit in non-ASCT patients	-Results similar to other published data -Less neutropenia

Abstract: AETHERA trial

D	MC, DB, RCT, Phase III trial
P	Age ≥18 relapsed or refractory HL ASCT in past 30-45 d High risk for HL progression ECOG 0 or 1
I	Brentuximab 1.8 mg/kg IV q3w x 16 cycles
C	Placebo
O	1°: PFS 2°: OS ADRs Incidence of anti-therapeutic antibodies to brentuximab

Moskowitz et al. Feb 26, 2014: BMT Tandem Meetings, Texas.

AETHERA: Interim results

- N=329
  - 40% US, 15% Western Europe, 45% Central/Eastern Europe/Russia
- Median age: 32 (18-76), 52.6% male

- Disease burden
  - 60% refractory
  - 33% relapse within 12 months of initial CT

- 49% of patients received full 16 cycles
- 19% of patients discontinued treatment early due to ADR
- 11% have died
  - n=31 occurring after disease progression (off brentuximab)

Moskowitz et al. Feb 26, 2014: BMT Tandem Meetings, Texas.

So…is 30 the new 20?

- Given lack of other options, would consider use in HL patients who have relapsed post ASCT +/- salvage CT
  - No direct comparisons with salvage CT
  - Relatively favourable toxicity profile
- Limited data in older adult population or those with poorer performance status, renal/liver impairment
- Await further prospective study to expand indication
  - ? Potential role as bridge to SCT

Questions/Comments

Supplementary Slides

Brentuximab: Practical Considerations

- Pan-Canadian Oncology Drug Review
  - Notification to implement issued Sept 2013
  - Small patient population with no other options

- Not yet on BCCA formulary
  - Current requests being handled through CAP

- Manufacturer list price $4,840 per 50 mg vial

  ~Cost per cycle for 70 kg patient: $12,200

  -Likely drug wastage

  -24 hour stability following reconstitution

Brentuximab: Prescribing information

- Black Box Warning
  - PML and/or death
    - 2 cases reported to date
- Contraindication
  - Concomitant use with bleomycin
    - pulmonary toxicity
- Drug interactions
  - MMAE metabolized by CYP3A4/5
    - Potent inhibitors/inducers may alter plasma levels
    - Avoid use with rifampin if possible

BCCA Adcetris® Interim Monograph. June 2013.

Brentuximab: Monitoring

- Efficacy
  - Clinical and radiologic evidence of tumor response
- Toxicity
  - S+S of CNS abnormalities indicative of PML
  - Peripheral neuropathies (motor or sensory)
    - Hypoesthesia, hyperesthesia, paresthesia, discomfort, burning, neuropathic pain, weakness
  - Infusion related reactions
  - CBC prior to each dose
    - More frequently if neutropenic
  - S+S of tumor lysis syndrome

BCCA Adcetris® Interim Monograph. June 2013.

Brentuximab: Toxicity management

- Neutropenia
  - Grade 3/4
    - Withhold dose until resolved
    - Consider GCSF for subsequent cycles
    - If grade 4 despite GCSF, reduce dose to 1.2 mg/kg or discontinue
- Neuropathies
  - Grade 2/3
    - Withhold dose until improved then restart at 1.2 mg/kg
  - Grade 4
    - Stop therapy

BCCA Adcetris® Interim Monograph. June 2013.

Brentuximab: PK

A	MMAE Tmax 1-2 days
D	Vd: 6-10 L MMAE 68-82% protein bound
M	MMAE: Hepatic via CYP3A4/5
E	MMAE: Renal up to 24%, 72% unchanged in the feces t1/2: 4-6 days

Micromedex Drug Product Database: Brentuximab Vedotin Drug Monograph. 2014.

Ongoing research…

- Brentuximab with bendamustine after first relapse
- Brentuximab as salvage therapy prior to ASCT
- Brentuximab as adjuvant therapy post allographic stem cell transplant
- Brentuximab as first line therapy + ABVD

http://www.clinicaltrials.gov/

Rothe et al: Results

PFS

OS

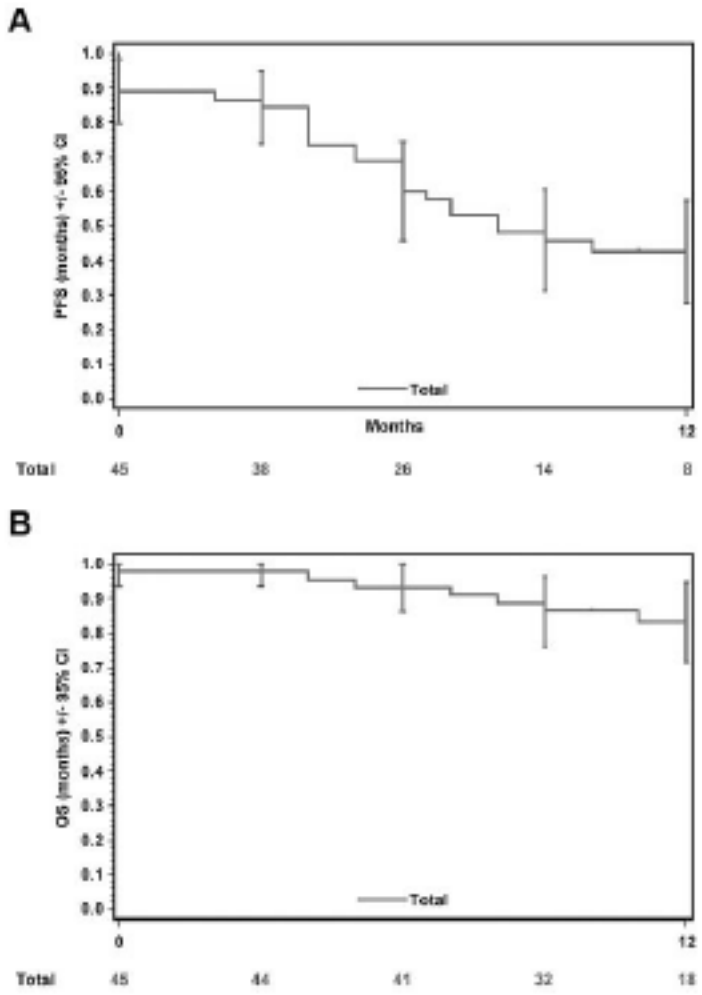
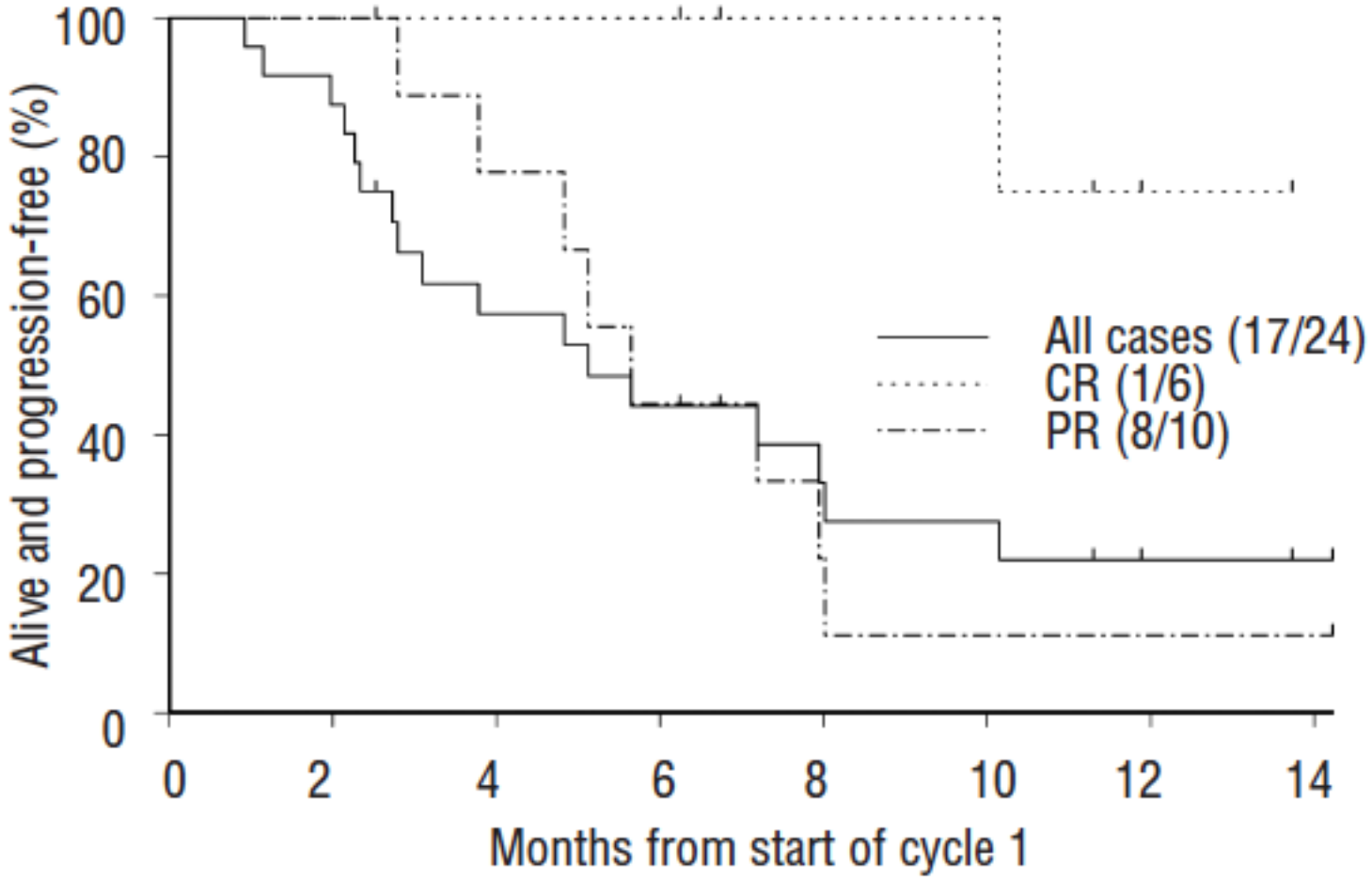


Figure 1. Kaplan-Meier plots and 95% CIs for PFS and OS. (A) The median PFS was 8 months. (B) The OS at 12 months was 83%. The median OS has not yet been reached.

Rothe et al. Blood. 2012.

Gibb et al: Results



Gibb et al. Haematol Hematol J. 2013

Zinzani et al: Results

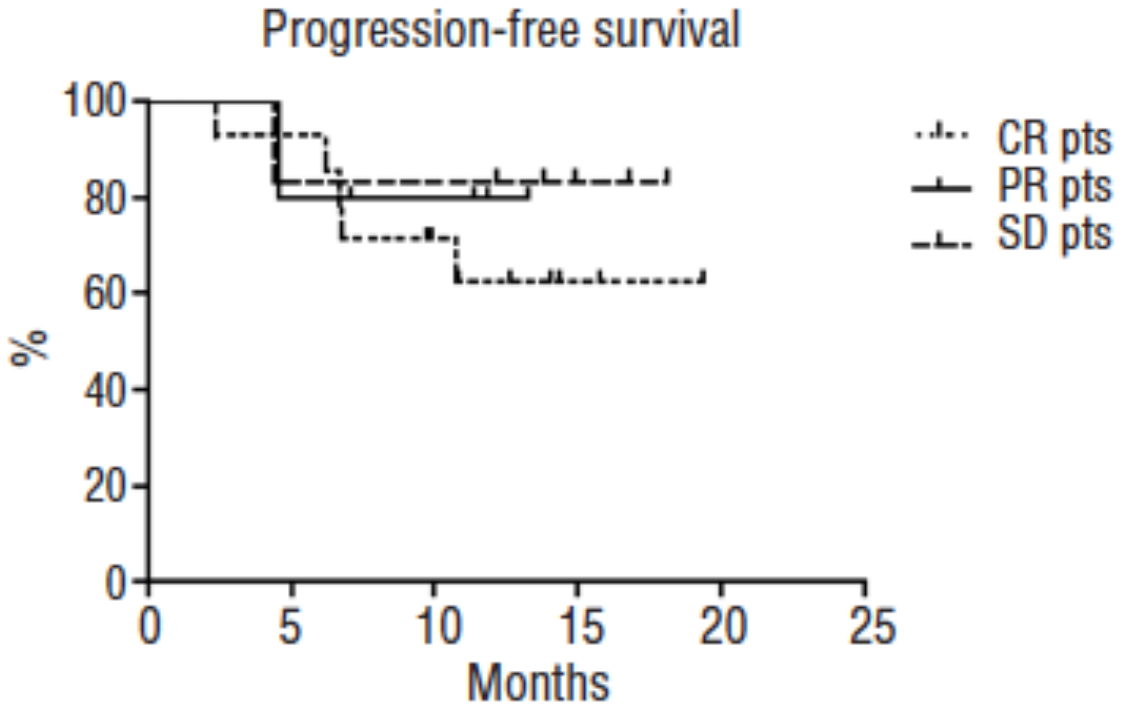


Figure 4. Progression-free survival of patients divided according to response. CR: complete response; PR: partial response; SD: stable disease; pts, patients.

Zinzani et al. Haematol Hematol J. 2013.

Oncology Clinical Trial Response Rates

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Cheson et al 2007