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Memorial Sloan Kettering Cancer Center

HL in the near future

Craig Moskowitz, MD
Stephen A. Greenberg Chair in Lymphoma Research
Member, Memorial Sloan-Kettering Cancer Center
Professor of Medicine, Weill Medical College of Cornell University

Disclosures

Consulting Agreements	Celgene Corporation, Genentech BioOncology, Merck, Seattle Genetics
Contracted Research	Merck, Pharmacyclics LLC, an AbbVie Company, Seattle Genetics

Case presentation 1: Dr Matt-Amaral

80-year-old previously active, healthy woman

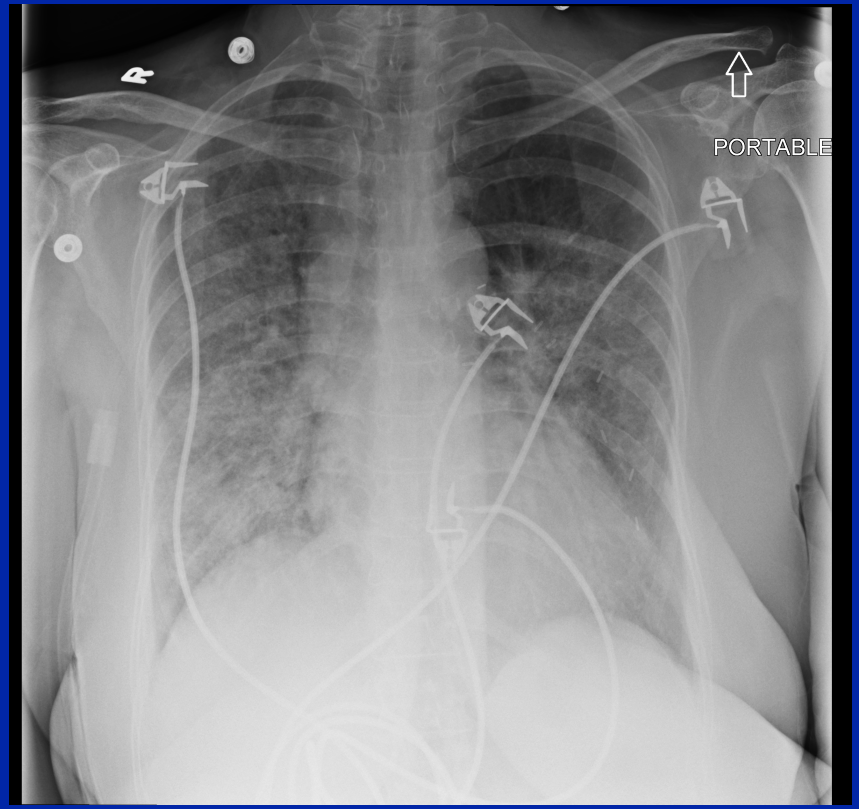
- Presents with fatigue, weakness and inability to perform ADLs and care for herself; wheelchair-bound and lack of desire to get out of bed
- CT: Generalized lymphadenopathy in the abdomen, chest, mediastinum and axilla but not bulky disease
- CT-guided biopsy: Classical Hodgkin lymphoma
- Patient concerned that she's too frail to tolerate chemotherapy

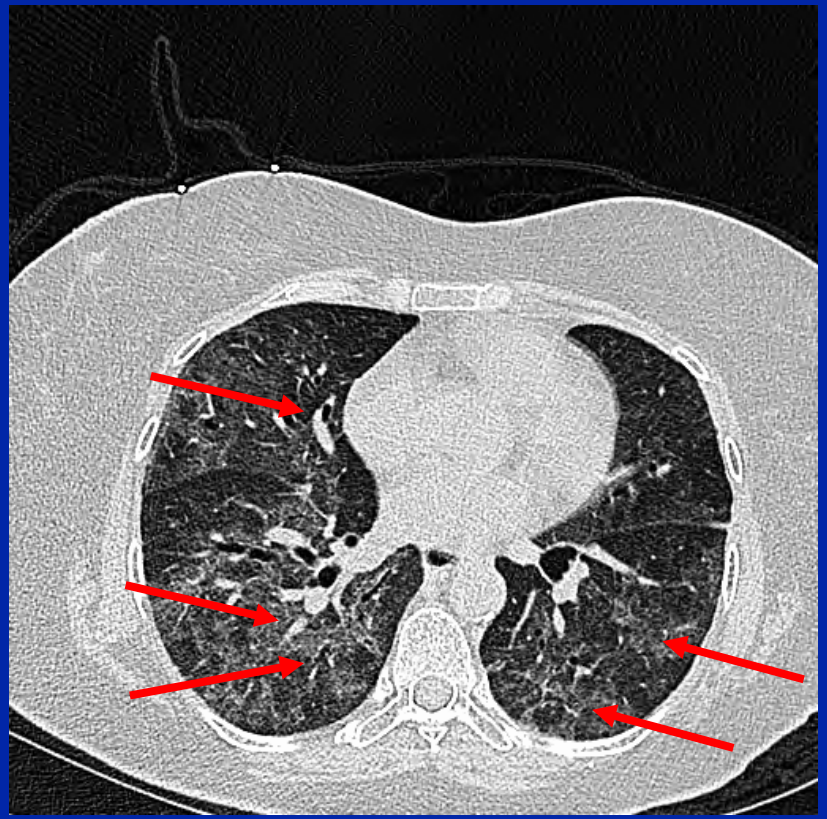
Case presentation 2: Dr Favaro

61-year-old woman

- 1994: Stage IV Hodgkin lymphoma → MOPP
- 2007: Relapse → ABVD x 6
- 2011: Relapse → ICE → ASCT
- 2014: Relapse → brentuximab vedotin
  - Progressed after 3 cycles
- Nivolumab x 3 with PR, discontinued due to pulmonary toxicity
- Admitted to ICU with hypoxia; bilateral pulmonary infiltrates; recovered with steroids; renal insufficiency (Cr: 3.5)
- Currently under observation

Bilateral inflammatory pulmonary infiltrate





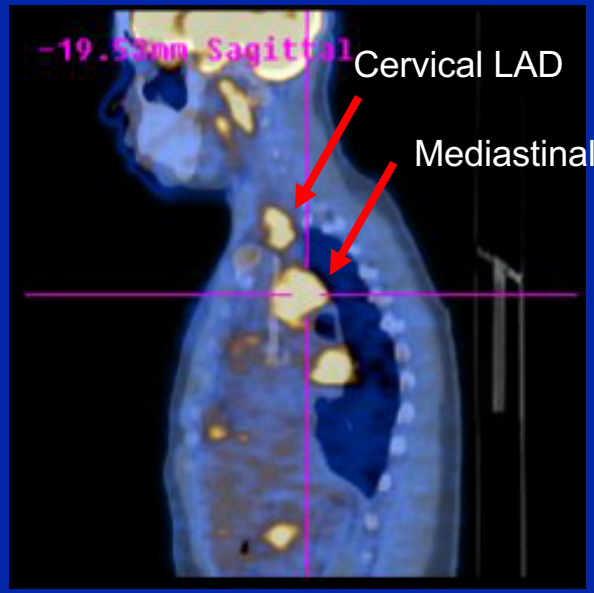
Case presentation 3: Dr Morganstein

32-year-old man with well-controlled HIV

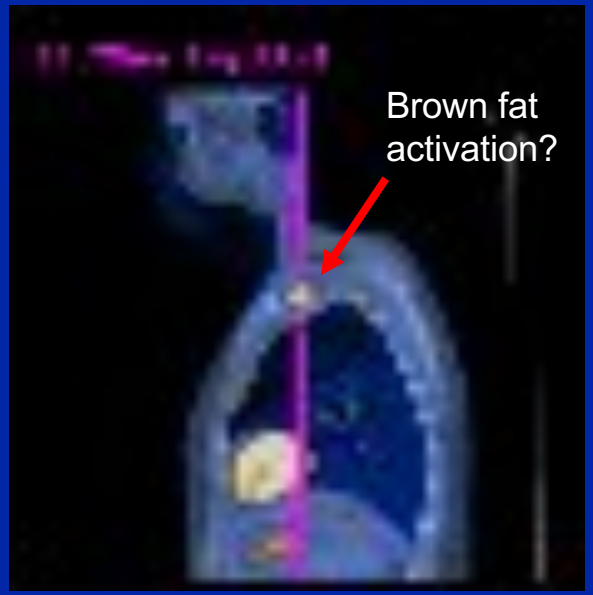
- 2014: Presents with cervical lymphadenopathy
  - Biopsy: Nodular sclerosing Hodgkin lymphoma
  - Staging: IIA
- ABVD → PET-negative after 2 cycles

PET/CT scans before and after ABVD x 2

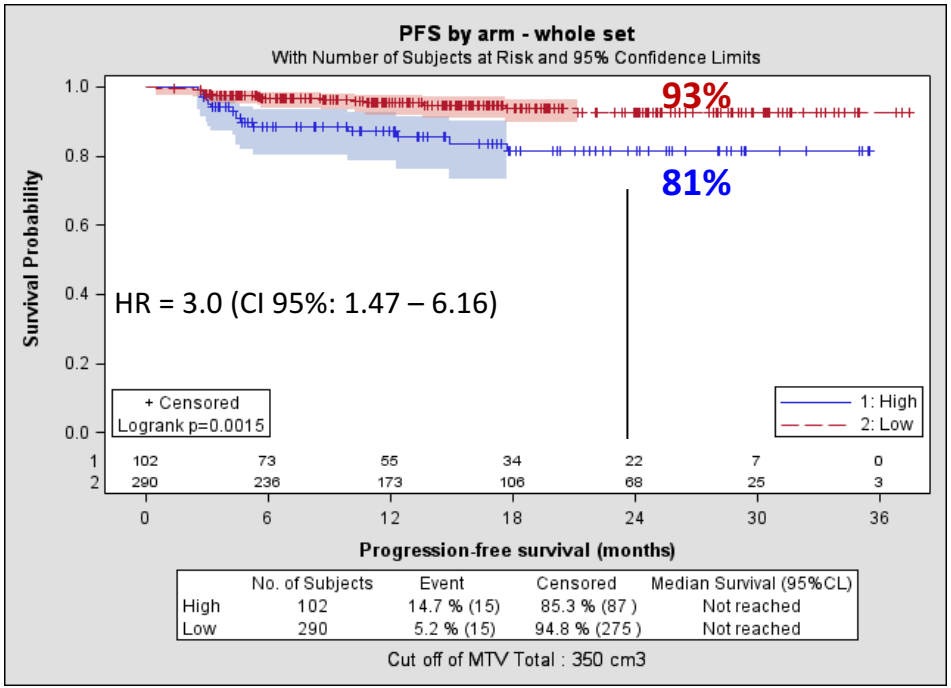
Baseline: Before ABVD



After ABVD x 2: PET-negative



AHL2011: PFS according to total metabolic volume (TMTV) assessed by FDG-PET

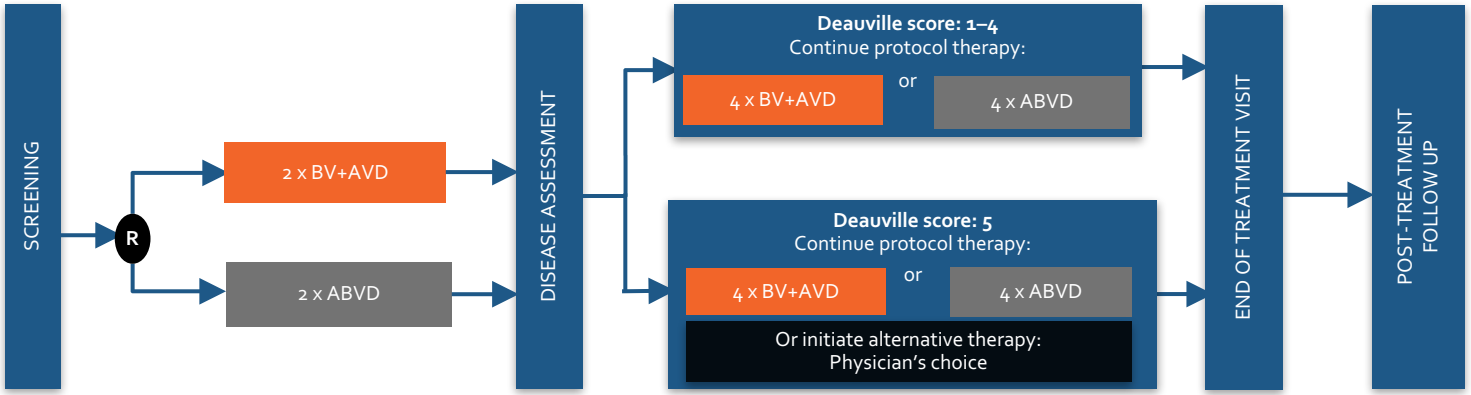


26% High TMTV

CI, confidence interval; CL, confidence limit; HR, hazard ratio; PFS, progression-free survival; TMTV, total metabolic tumour volume

Casasnovas R-O, et al. *J Clin Oncol* 2016;34(Suppl):abstract 7509.

ECHELON-1: Phase 3 trial of brentuximab vedotin and AVD vs ABVD in advanced-stage HL



Primary endpoint: modified PFS per IRF
Secondary endpoint: OS
Others: CR rate, safety, EFS, DFS, ORR, DOR, duration of CR, rate of irradiation for those not in CR, CR at the end of front-line therapy, rate of cycle 2 PET negativity, HRQoL, PK, immunogenicity

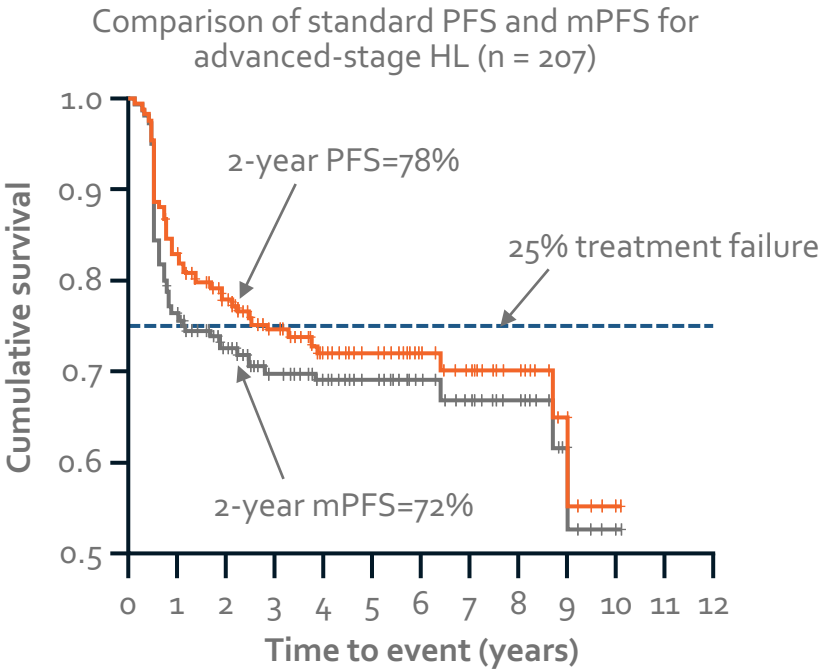
BV+AVD (up to 6 cycles):
Brentuximab vedotin 1.2 mg/kg IV infusion Days 1&15
Doxorubicin 25 mg/m² IV infusion Days 1&15
Vinblastine 6 mg/m² IV infusion on Days 1&15
Dacarbazine 375 mg/m² on Days 1&15

ABVD (up to 6 cycles):
Doxorubicin 25 mg/m² IV infusion on Days 1&15
Bleomycin 10 units/m² IV infusion on Days 1&15
Vinblastine 6 mg/m² IV infusion on Days 1&15
Dacarbazine 375 mg/m² on Days 1&15

ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01712490. Accessed March 2017.

Modified PFS is a superior endpoint for the evaluation of chemotherapy effectiveness compared with PFS

- PFS for ineffective chemotherapy may be effectively 'rescued' by subsequent radiotherapy, artificially enhancing the PFS results achieved by chemotherapy alone
- Using data from 207 patients in the British Colombia Cancer Agency Lymphoid Cancer Database:
  - Under standard PFS criteria 56 events were detected, with a 2-year PFS of 78%
  - Under modified PFS criteria, 64 events were detected, with a 2-year modified PFS rate of 72%



mPFS, modified PFS (death, disease progression, receipt of chemotherapy or radiotherapy by pts not in CR after completing front-line therapy)

Connors JM, et al. *Haematologica* 2016;101 (Suppl s5): 22–3.

ECHELON-1: Phase 3 trial of brentuximab vedotin and AVD vs ABVD in advanced-stage HL

- The study is powered on the following assumption:
  - A 2-year modified PFS of 81% for patients in the BV+AVD treatment group vs 73% for patients in the ABVD treatment group (HR = 0.67, assuming an emergent plateau in the PFS event rate after 2 years).
  - A total of 260 modified PFS events will provide 90% power to detect a HR of 0.67 at a 1-sided significance level of 0.025 using a log-rank test
  - To be presented at ASH at plenary session
    - 5% improvement on mPFS; p value 0.035; HR 0.77
    - So what? Escalated BEACOPP or PET-adapted therapy is better
    - Should we give 100 pts BV to help 5? Subset analyses?
    - The tremendous financial burden
    - Remember in ESHL there is a 5% improvement in PFS with RT and we generally do not give it!

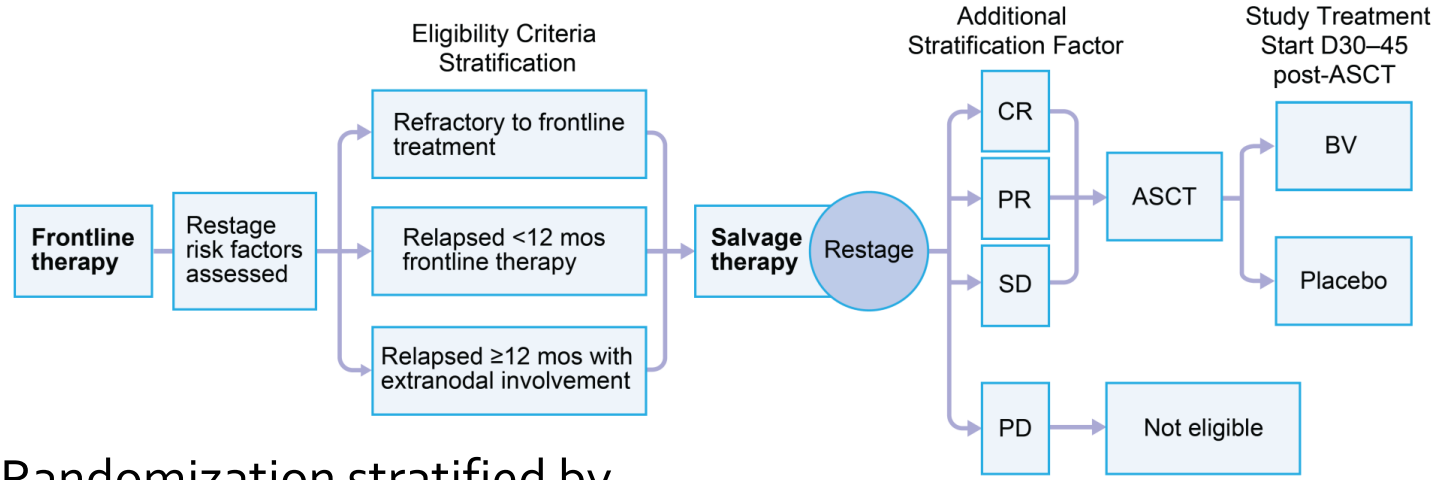
Will BV-AVD become standard of care in advanced-stage HL?

- I suspect yes and general oncologists will use it for sure and therefore lymphoma docs may have to as well
- If true, BV use will change dramatically and pre-ASCT, post-ASCT maintenance and palliation use will be minimal

Some updates on AETHERA

AETHERA Trial Design

Moskowitz CH, et al. Lancet,385; 1852-1862, 9 May 2015



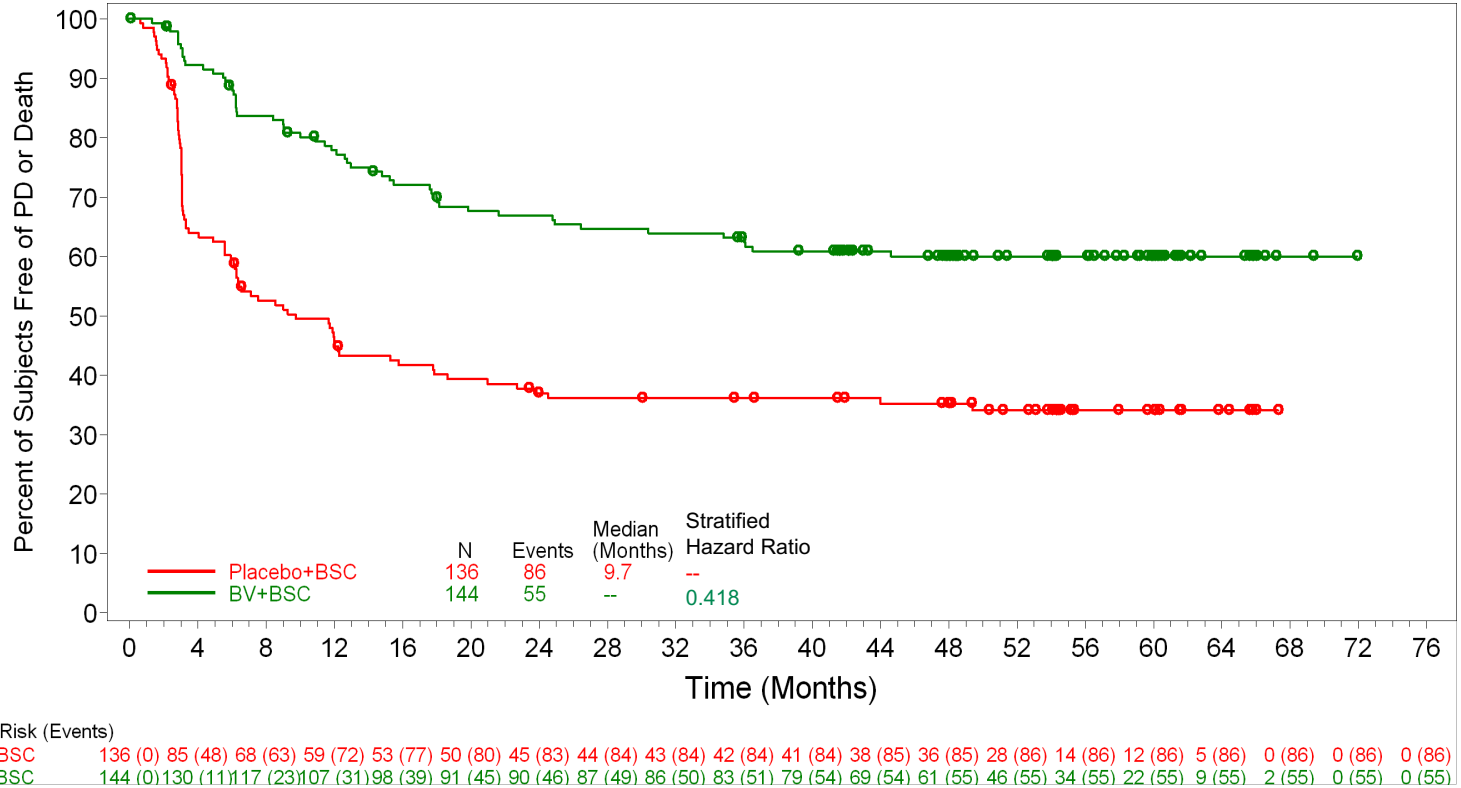
- Randomization stratified by
  - Risk factors after frontline therapy;
  - Best clinical response to salvage therapy before ASCT.
- Patients with progressive disease after salvage therapy were not eligible.

Risk Factors on AETHERA

Only 10% of patients had one unfavorable prognostic factor

- Initial remission duration < 1 year
- PET positive response to most recent salvage therapy
  - 1 of 5 risk factors
- ≥2 salvage therapies
- Extranodal disease at pre-ASCT relapse
- B symptoms at pre-ASCT relapse
- I administer maintenance to patients with >1 risk factor

PFS Per Investigator: ≥ 2 Risk Factors



The issues concerning AETHERA

- Neuropathy
  - 90% resolution to grade 1 or less ; remember to dose reduce if grade II
- Overall Survival
  - With the cross over design and the new era with CPI; only time will tell if there will be a difference but unlikely,
  - indefinite palliative therapy is not fun
- Previous BV therapy
  - Common sense approach
- Pre-ASCT PET and outcome
  - Only 1 of 5 risk factors in this study
  - Not prospectively done , read centrally or defined by Deauville criteria

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Clinical trials including older patients with novel agents, and comprehensive care will hopefully improve the outlook for older HL patients.

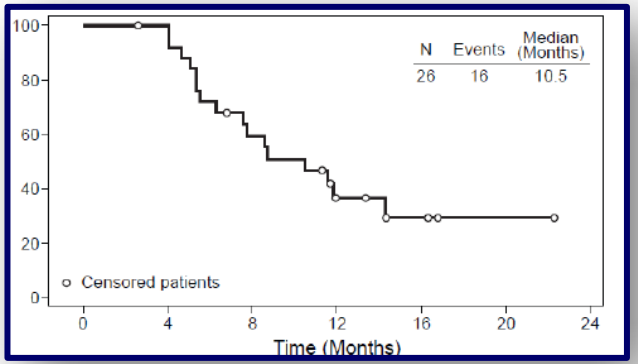
I believe nearly all patients can be treated with curative intent at least give it a try

C-MOPP can be given to a 90 yr old with DLBCL!

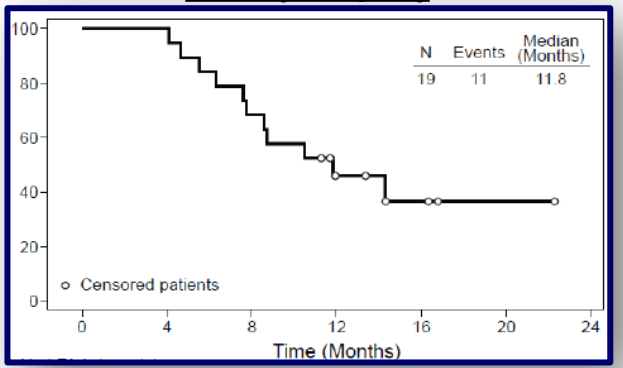
Brentuximab Vedotin in Elderly Patients with HL

- Single agent brentuximab vedotin:
  - 1.8 mg/kg q 3 wks in 27 elderly HL pts
  - Median age 78 yrs, 63% stage III/IV
- ORR 92% (73% CR)
- *30% pts grade 3 neuropathy*

PFS (all pts)



PFS (CR pts)



Forero-Torres et al. *Blood*, 2015

Phase II study of brentuximab vedotin in the first line treatment of Hodgkin lymphoma patients considered unsuitable for standard chemotherapy (brevity)

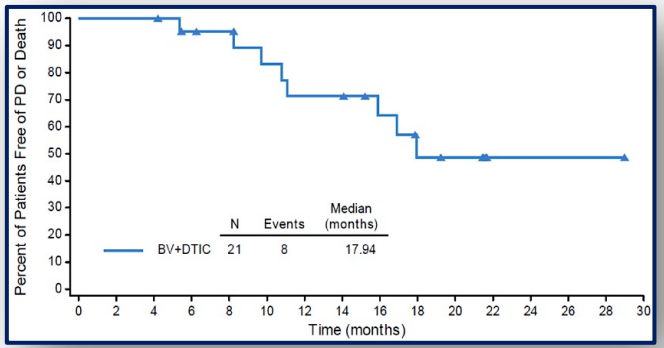
- Response adaptive phase II, Simon 2-stage, single arm study required 30 evaluable pts. Primary outcome was complete metabolic response (CMR, Deauville Score 1-3) by centrally reviewed PET-CT after 4 cycles of BV. Secondary outcomes included PFS, OS, toxicity and comorbidity assessment (CIRS-G).
- Advanced stage considered "unfit" for chemo
- 35 pts evaluable for toxicity, dose reduced in 14 and 11 stopped treatment for adverse events (infection, myelosuppression or neuropathy)
- High overall response rate although the CMR (26%) rate after 4 cycles did not meet the pre-specified 40% level, and PFS was short
- Maybe CPI alone or in combination with BV is next step

Gibb A et al. *Proc ICML* 2017;Abstract 069.

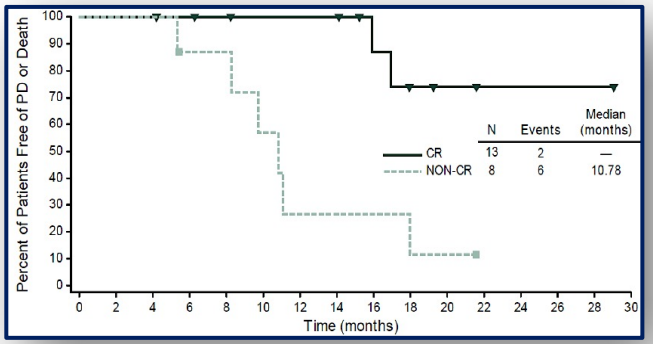
BV + DTIC or Bendamustine in Elderly Patients with HL

- 1.8 mg/kg BV + 90/70 mg/m^2 bendamustine
  - 65% SAE (including 2 toxic deaths)
- 1.8 mg/kg BV + 375 mg/m^2 DTIC (12 cycles)
  - BV + DTIC: ORR 100% (62% CR)
  - *27% pts grade 3 neuropathy*

PFS (all pts)

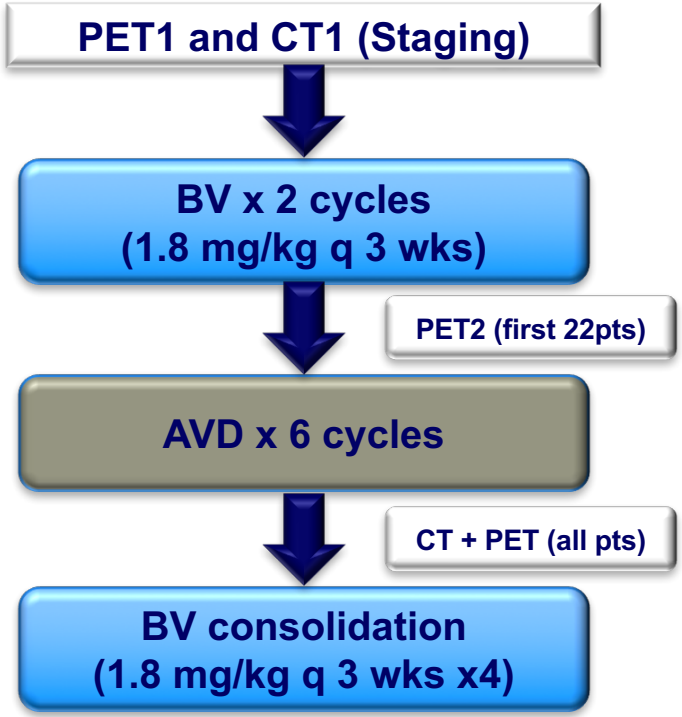


PFS (CR pts)



Friedberg J et al. *Blood*, 2017

Incorporation of Brentuximab Vedotin into Frontline Therapy



- Phase II investigator-initiated study
- Untreated advanced-stage elderly HL (≥ 60 yo)
- Participating institutions: Tufts, Northwestern, Univ. of Chicago, UMass, Ohio State, MDACC, Stanford Nebraska, and MSKCC
- Window (lead in) study with brentuximab vedotin
- CGA (CIRS-G) and HRQL assessments
- Study of "early" FDG-PET

Evens AM et al. ASH 2017;Abstract 733

Data from Abstract

- BV incorporated sequentially before and after AVD feasible for older HL pts
- High CR rate (>90%)
- Overall well tolerated
- Excellent survival rates
  - Longer follow-up warranted
  - Maintain outcomes with less therapy
  - Significant need to identify less toxic therapy for less fit (co-morbid) patients

Evens AM et al. ASH 2017;Abstract 733