Memorial Sloan Kettering Cancer Center

When to use brentuximab vedotin in Hodgkin lymphoma?

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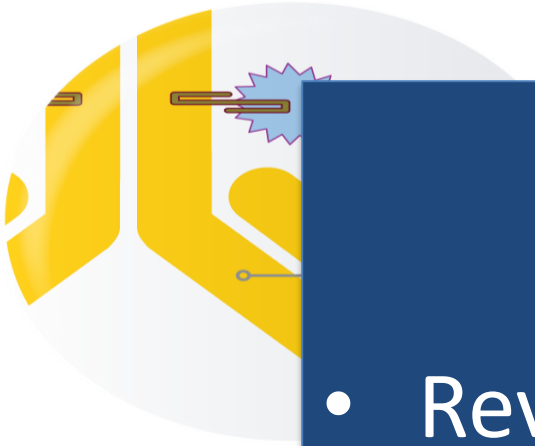
Brentuximab Vedotin Mechanism of Action



Brentuximab vedotin (SGN-35) ADC

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Objectives

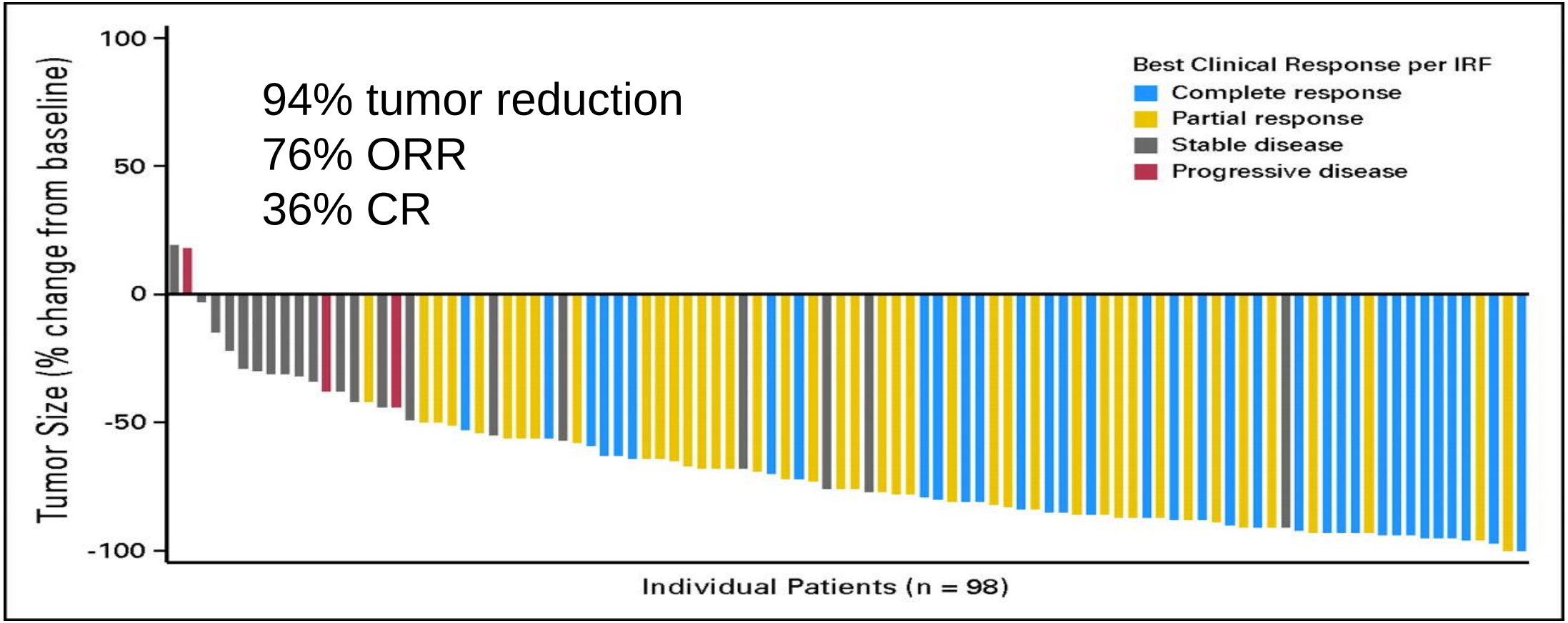
- Review data leading to initial approval in relapsed/refractory Hodgkin lymphoma
- Discuss use in front-line, second-line, and post-transplant settings

Brentuximab vedotin – pivotal study

	N=102
Age, median (range)	31 yr (15–77)
Gender	48 M / 54 F
ECOG status	
0	42 (41%)
1	60 (59%)
Refractory to frontline therapy	72 (71%)
Refractory to most recent treatment	43 (42%)
Prior chemotherapy regimens*	3.5 (1–13)
Prior radiation	67 (66%)
Prior ASCT	102 (100%)
Time from ASCT to first post transplant relapse*	6.7 mo (0–131)

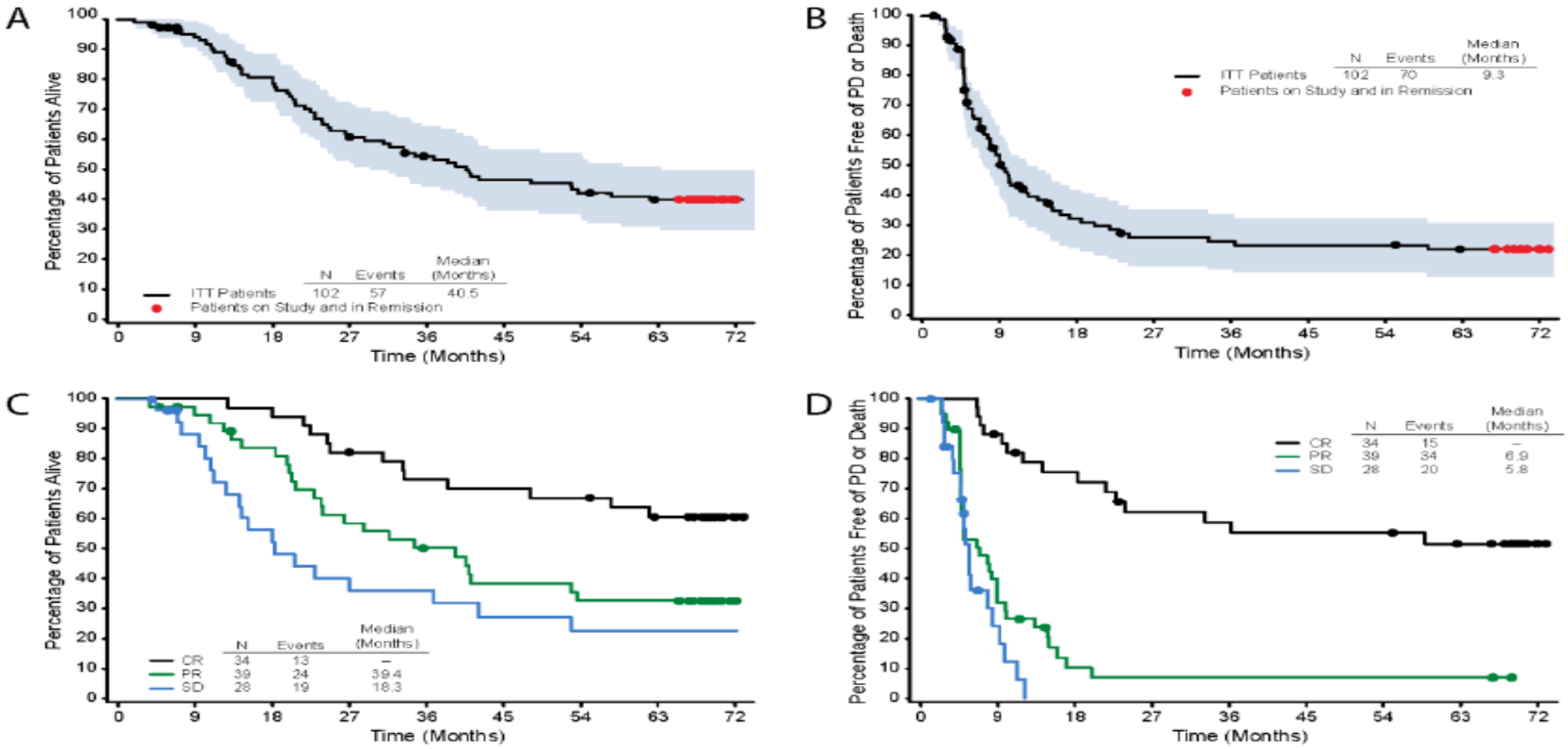
Younes et al. JCO 2012;30:2183-2189

Brentuximab vedotin - efficacy



Younes et al. JCO 2012;30:2183-2189

BV – 5 year follow-up



Chen R., et al. Blood 2016.

Tolerability of brentuximab vedotin

- **Peripheral neuropathy** – 55%
  - 9% grade 3
  - At 5 years – 14% ongoing neuropathy
    - 10% grade 1; 4% grade 2
- **Nausea** – 35% (all grade 1 or 2)
- **Fatigue** – 34% (only 2% grade 3)
- **Rash** – 31%
- **Neutropenia** – 19% (14% grade 3; 6% grade 4)

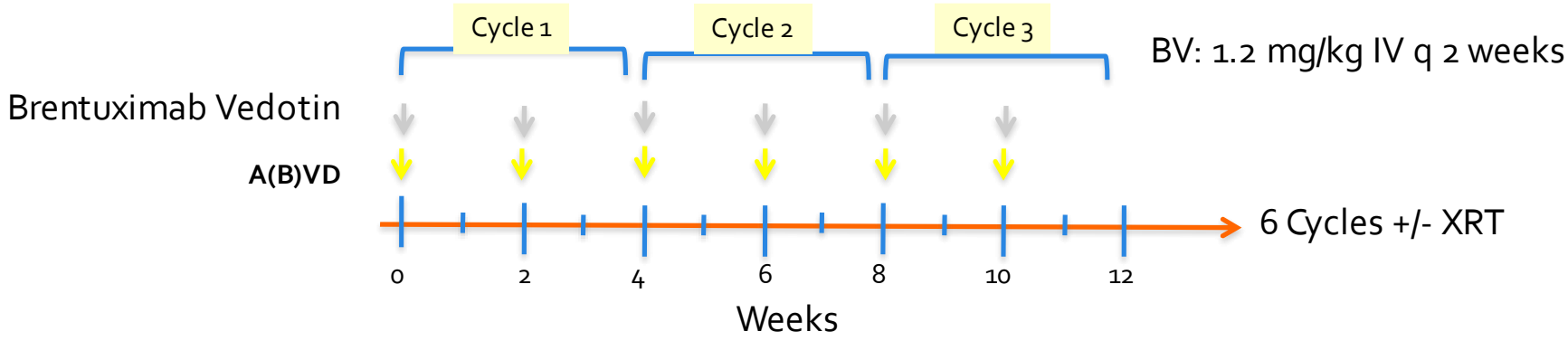
- **Rare but serious (<1%)**
  - Pancreatitis
  - Progressive multifocal leukoencephalopathy (PML)

Chen R., et al. Blood 2016.
Younes et al. JCO 2012;30:2183-2189

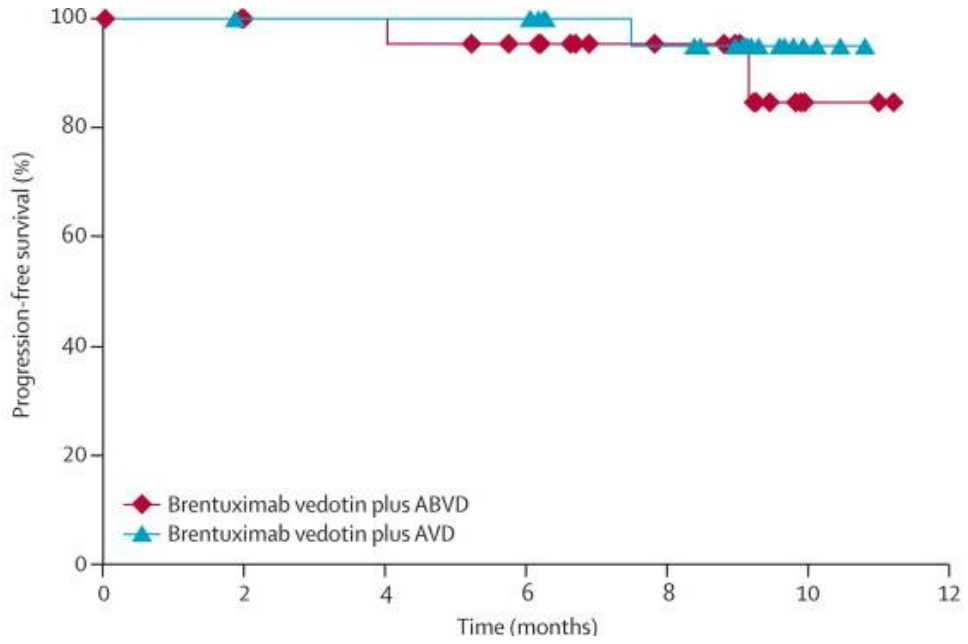
Brentuximab vedotin in front-line setting?

- Advanced stage patients
  - –ECHELON-1
- Older patients
  - –Single agent, doublets, and sequential therapy
- Early stage patients
  - –Strategy to avoid radiation?

BV+A(B)VD for advanced stage cHL (phase I)



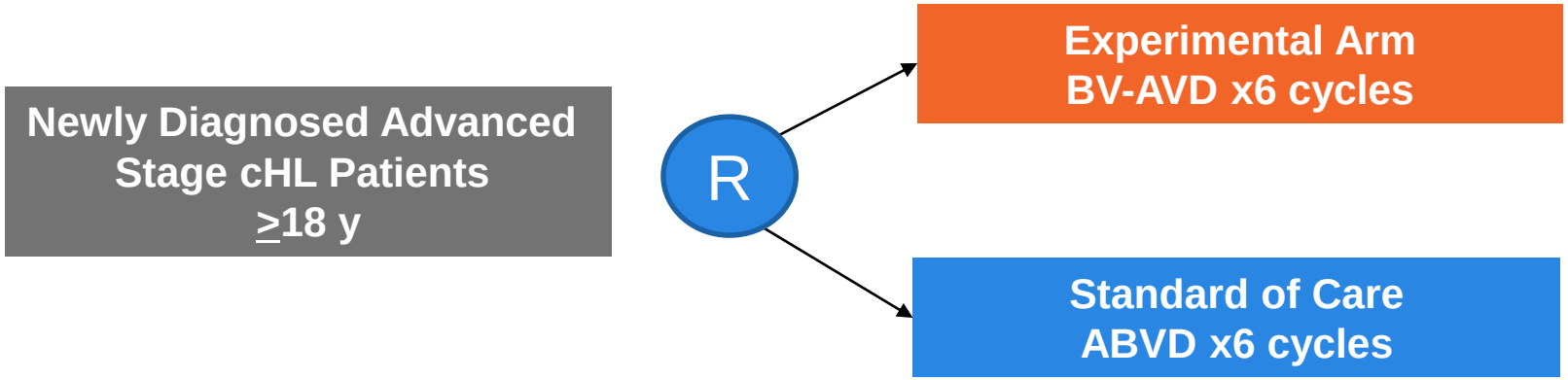
Pulmonary tox	BV-ABVD (n=25)	BV-AVD (n=26)
Any event	11 (44%)	0
Pulmonary toxic effects	9 (36%)	0
Interstitial lung disease	1 (4%)	0
Pneumonitis	1 (4%)	0



Younes et al. Lancet Oncology (2013) 14:1348-1356

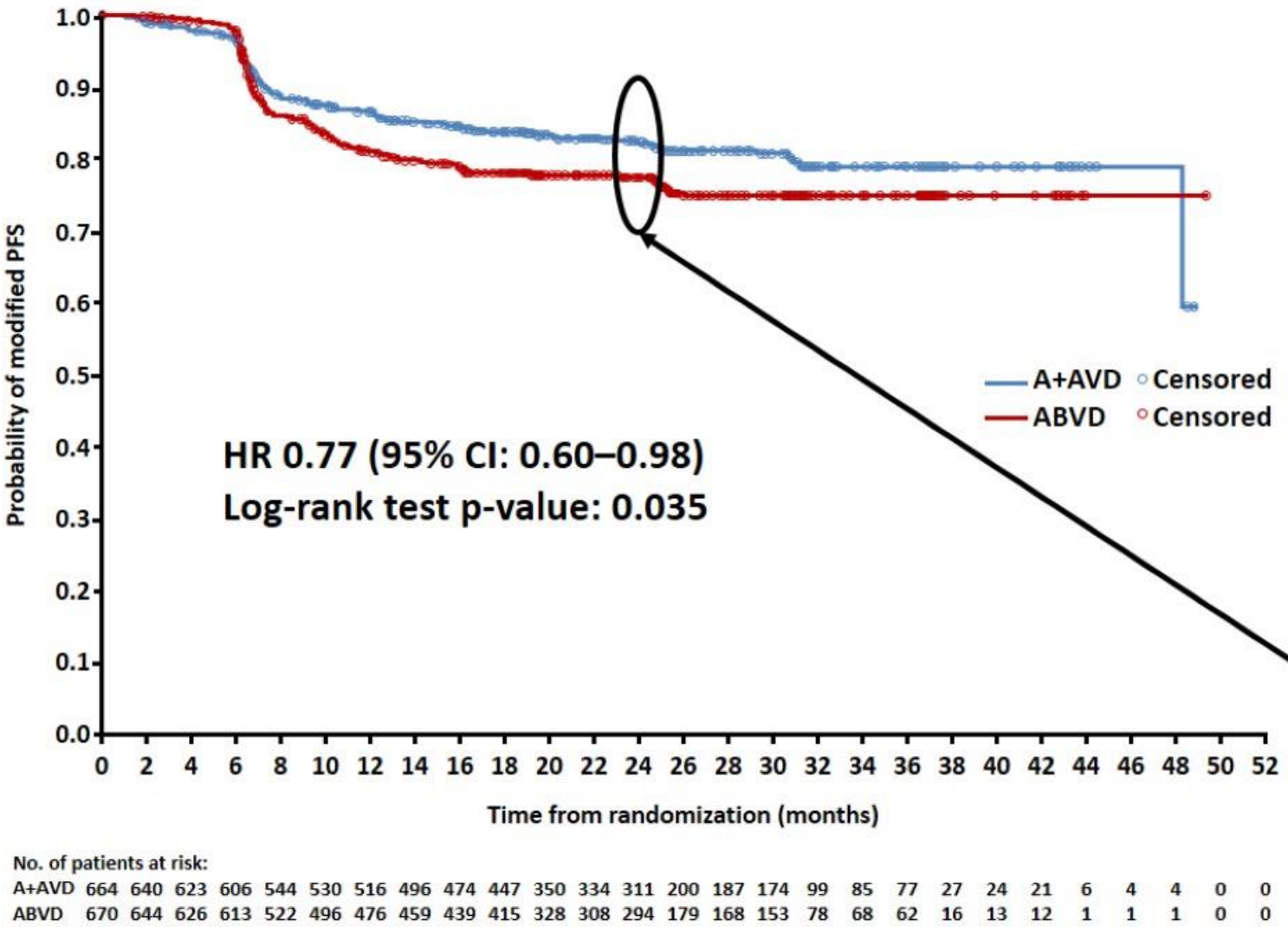
Phase III Frontline HL (ECHELON-1)

- **Design**



- **N=1334**
- **Primary endpoint: improvement in 2 year modified PFS (mPFS)**
- **Secondary Outcome Measures: Overall survival rate**

Modified PFS per independent review



Number of events

Category	A+AVD N=117	ABVD N=146
Progression	90	102
Death	18	22
Modified progression	9	22
Chemotherapy	7	15
Radiotherapy	2	7

Modified PFS estimates

Time	A+AVD (95% CI)	ABVD (95% CI)
2-year	82.1 (78.7–85.0)	77.2 (73.7–80.4)

Median follow-up (range): 24.9 months (0.0–49.3)

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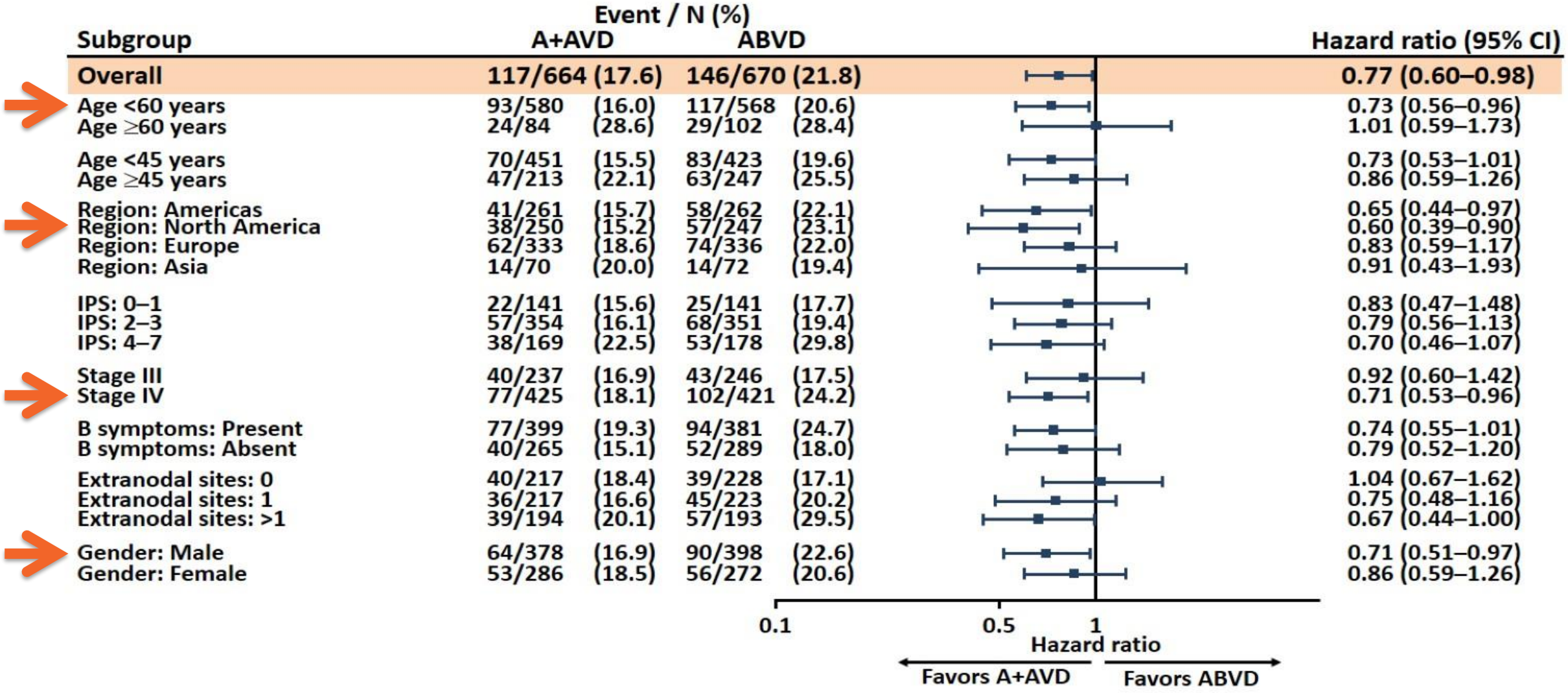
Connors, et al. N Engl J Med (2018) 378: 331-344

Forest plot of modified PFS per IRF: subgroup analysis



Connors, et al. N Engl J Med (2018) 378: 331-344

Initial treatment of advanced stage HL, age <60

- Favor PET-adapted approach (as per RATHL study)
- Consider BV-AVD for:
  - High risk (IPS 4-7)
  - Patients who cannot receive bleomycin

Connors, et al. N Engl J Med (2018) 378: 331-344

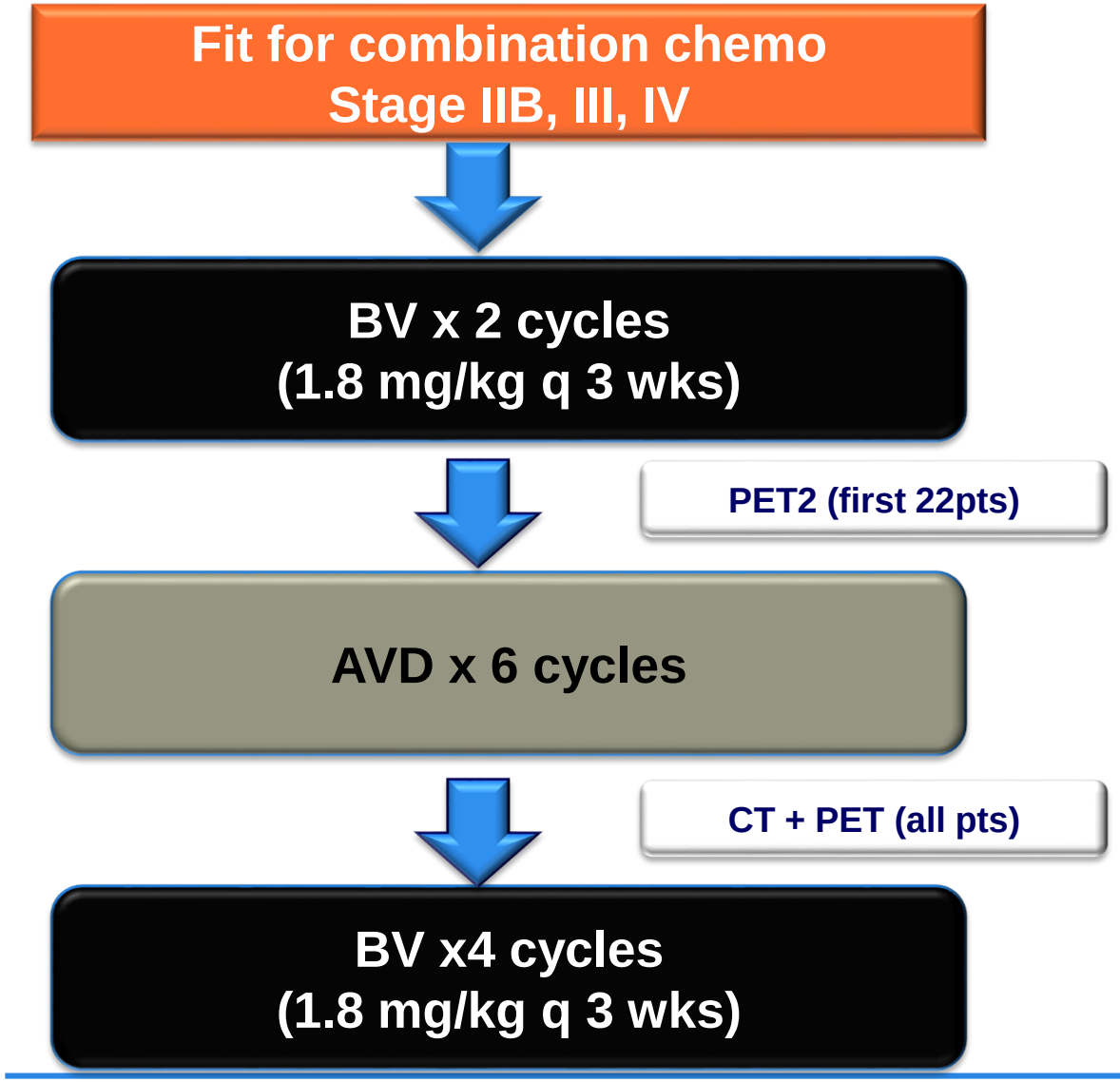
Front-line BV for elderly?

- Patients unfit for standard combination chemotherapy

Treatment	n	ORR	CR	Median PFS
BV alone[1]	27	92%	73%	10.5 months
BV plus bendamustine[2]	20	**Closed early due to toxicity**		
BV plus dacarbazine[2]	22	100%	62%	17.9 months

[1]Forero-Torres A, et al. Blood (2015) 26:2798-2804; [2]Friedberg JW, et al. Blood (2017) 130: 2829-2837

Sequential BV and AVD for patients ≥ 60 years old

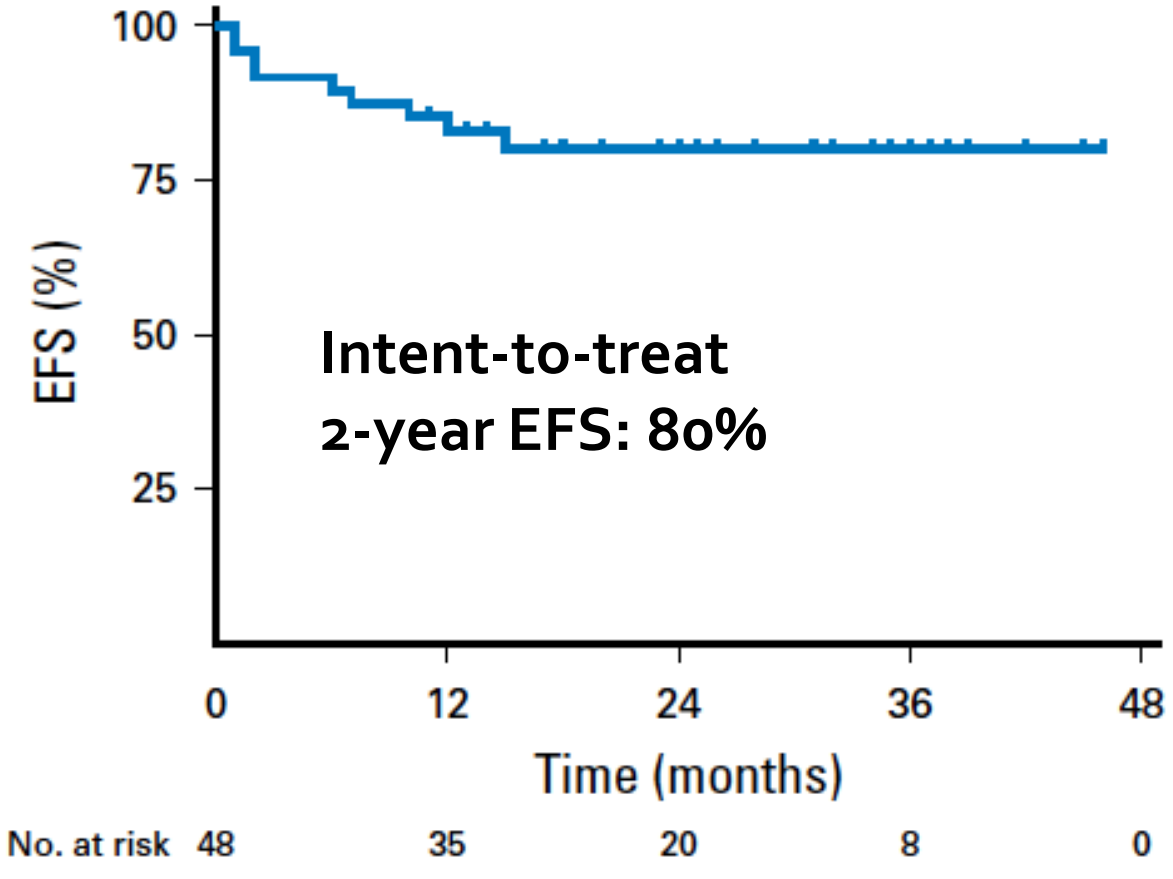


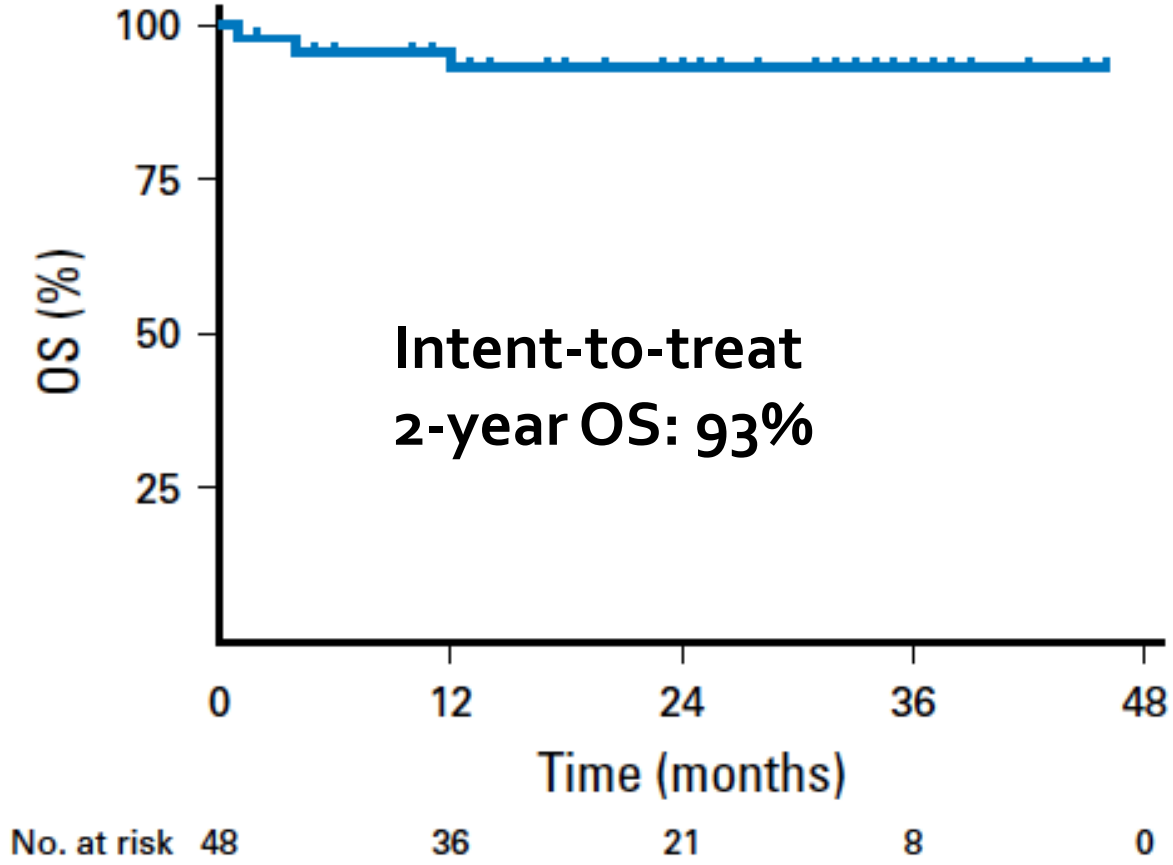
48 patients enrolled

- 52% age 60-70; 17% >80
- 81% stage III or IV
- 58% IPS 3-7
- 10% disease bulk (10cm)

Evens AM, et al. JCO 2018

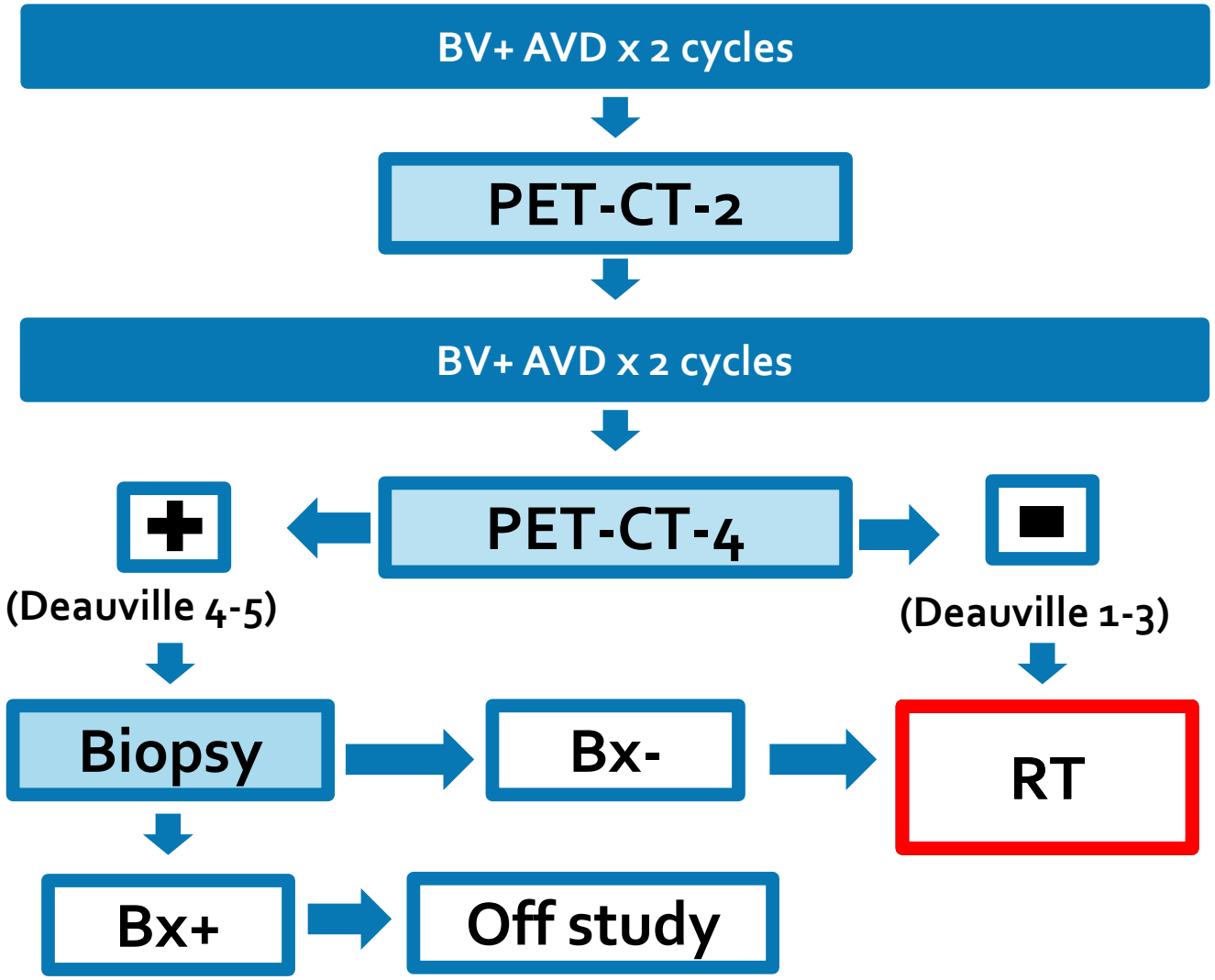
Sequential BV and AVD for patients ≥ 60 years old





Evens AM, et al. JCO 2018

Front-line BV for early stage patients?



Cohort 1: 30Gy
- 30 patients stage I, II
- 77% bulky (>7cm)
- CR rate 93%
- 1-year PFS 93%

Cohort 2: 20Gy
- 29 patients stage I, II
- 69% bulky (>7cm)
- CR rate 93%
- 1-year PFS 93%

Cohort 3: Consolidation volume radiation (CVRT)
- All bulky

Cohort 4: No RT
- All bulky

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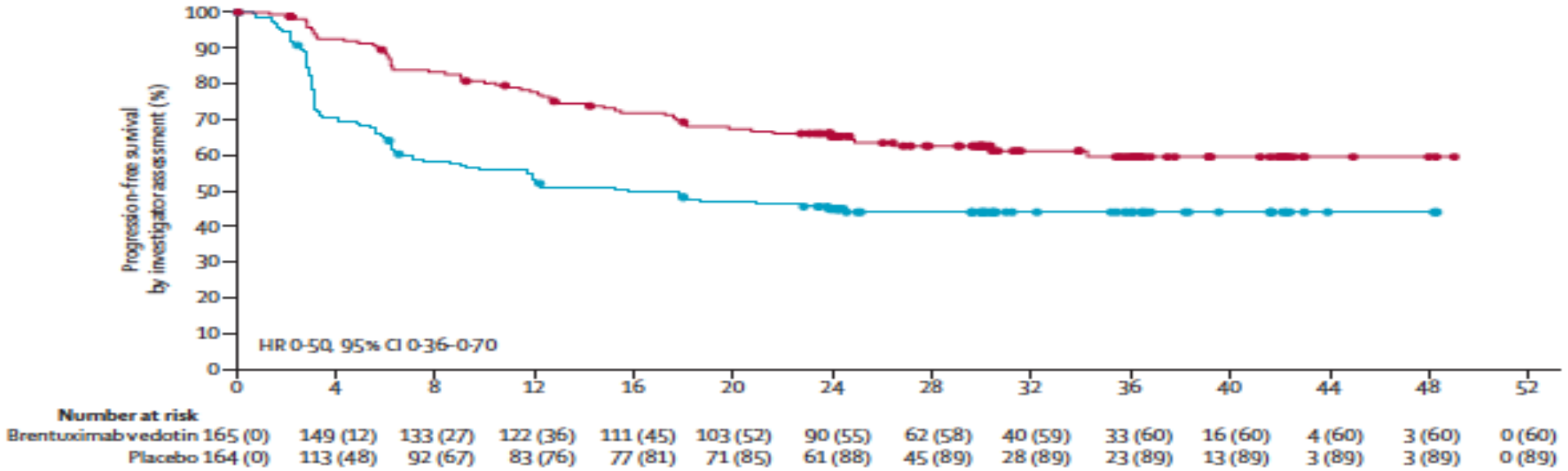
Kumar A, et al. Blood (2016) 128:1458-1454
Kumar A, et al. ASH 2017, Abstract 734

Brentuximab vedotin in the second-line setting

	Regimen	% PET-neg	PFS	Reference
Sequential BV and chemo	BV->augICE	83% 27% (BV alone)	82% @ 3 yrs	Moskowitz AJ, et al. Blood 2017; Lancet Oncol 2015
	BV->ICE and others	73% 35% (BV alone)	72% @ 1.5 yrs	Chen R, et al. BBMT 2015
Combined BV and chemo	BV-bendamustine	74%	62.6% @ 2 yrs 69.8% (ASCT pts)	LaCasce, et al. Blood 2018
	BV plus: ICE DHAP ESHAP	 69% 90% 70%	Too soon	Cassady, et al. ASH 2016 Hagenbeek, et al. Haematologica 2016 Garcia-Sanz, et al. ASH 2016
BV plus CPI	BV-nivolumab	61%	89% @ 6 mo	Herrera, et al. Blood 2018

Brentuximab vedotin in the post-transplant setting

- AETHERA: Phase III study evaluating post-transplant **maintenance BV** for higher risk patients
- Risk factors: **Relapse within 1 year of initial treatment, primary refractory disease, extranodal disease**
- 329 patients received brentuximab vedotin (BV) (n=165) or placebo (n=164)
- Increased # risk factors predicted for more benefit from BV maintenance (additional risk factors assessed: less than CR to salvage therapy, B symptoms at relapse, requiring ≥ 2 salvage regimens)



Median PFS:
42.9 vs 24.1 mo

2-year PFS:
63% vs 51%

Moskowitz CH et al Lancet 2015;385:1853-62

Incorporating brentuximab vedotin into Hodgkin lymphoma treatment

Front-line

- Advanced stage, age <60
  - Consider BV-AVD for IPS 4-7
  - Consider if bleomycin ineligible
- Age ≥ 60
  - Consider sequential BV and AVD

Second-line

- Consider BV alone or BV-combination (if BV naïve)

Post-ASCT (in remission)

- BV maintenance if higher risk and BV-naïve or previous response to BV

Post-ASCT (relapse or refractory)

- Consider single-agent BV or BV-combination if BV naïve or ineligible for checkpoint inhibitors