Please note, these are the actual video-recorded proceedings from the live CME event and may include the use of trade names and other raw, unedited content.

Hodgkin Lymphoma

Jonathan W. Friedberg M.D., M.M.Sc.

UR MEDICINE | WILMOT CANCER INSTITUTE

Disclosures

Data and Safety Monitoring Board	Astellas Pharma Global Development Inc, Bayer HealthCare Pharmaceuticals

Case presentation: Dr Bessnow

27-year-old man with Stage IVB classical HL

- Disease in nodes, spleen and bones
  - Albumin = 3.1
  - Hgb = 8.6
  - WBC = 17,500
  - International Prognostic Score (IPS) = 5

Case presentation: Dr Johl

63-year-old man with HL

- Presented with supraclavicular adenopathy, eczema and pruritus of the skin
- Core biopsy of neck lymph node: HL, nodular sclerosing, classical type
- PET/CT: Hypermetabolic lymphadenopathy above and below hemidiaphragms; splenomegaly with hypermetabolic splenic mass; hypermetabolic osseous lesions and hepatic mass
- Bone marrow biopsy: Normal

Recent HL Trials: advanced stages

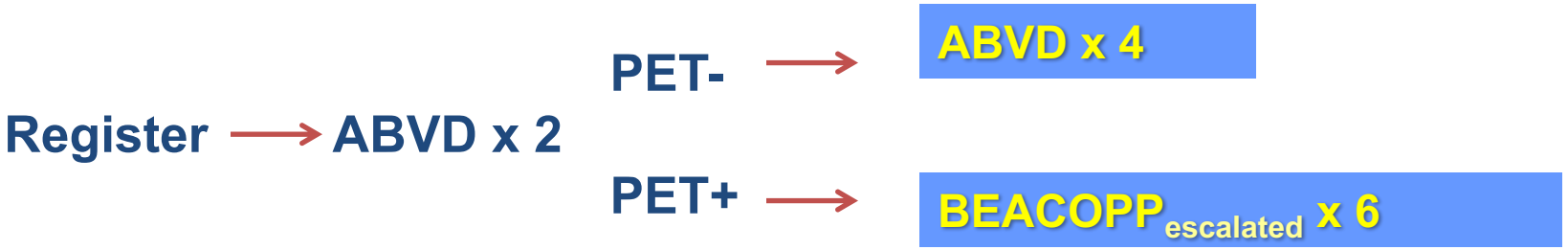
	N	PFS*
• S0816	336	79% (2 yr; 75% at 5 yrs)
• RATHL	1203	79% (3 yr, advanced, <60)
• Echelon-1	670	82% (2 yr “modified”)
• HD18	1945	92% (3 yr)

Press et al. *JCO* 34:2020 2016
Johnson et al. *NEJM* 374:2419 2016
Connors et al. *NEJM* online 2017
Borchmann et al. *Lancet* 390:2790 2017

PFS definitions

- S0816: Disease progression or death due to any cause, from date of registration to date of PD or death.
- RATHL: Disease progression, relapse or death.
- Echelon: Disease progression, death, or “modified progression”: less than complete remission to frontline therapy (PET Deauville 3, 4, or 5) ***AND*** the delivery of subsequent treatment. This was determined by central review, as “planned” XRT was not included.

S0816 Schema for HIV-negative patients



Primary end-points (2 year PFS)

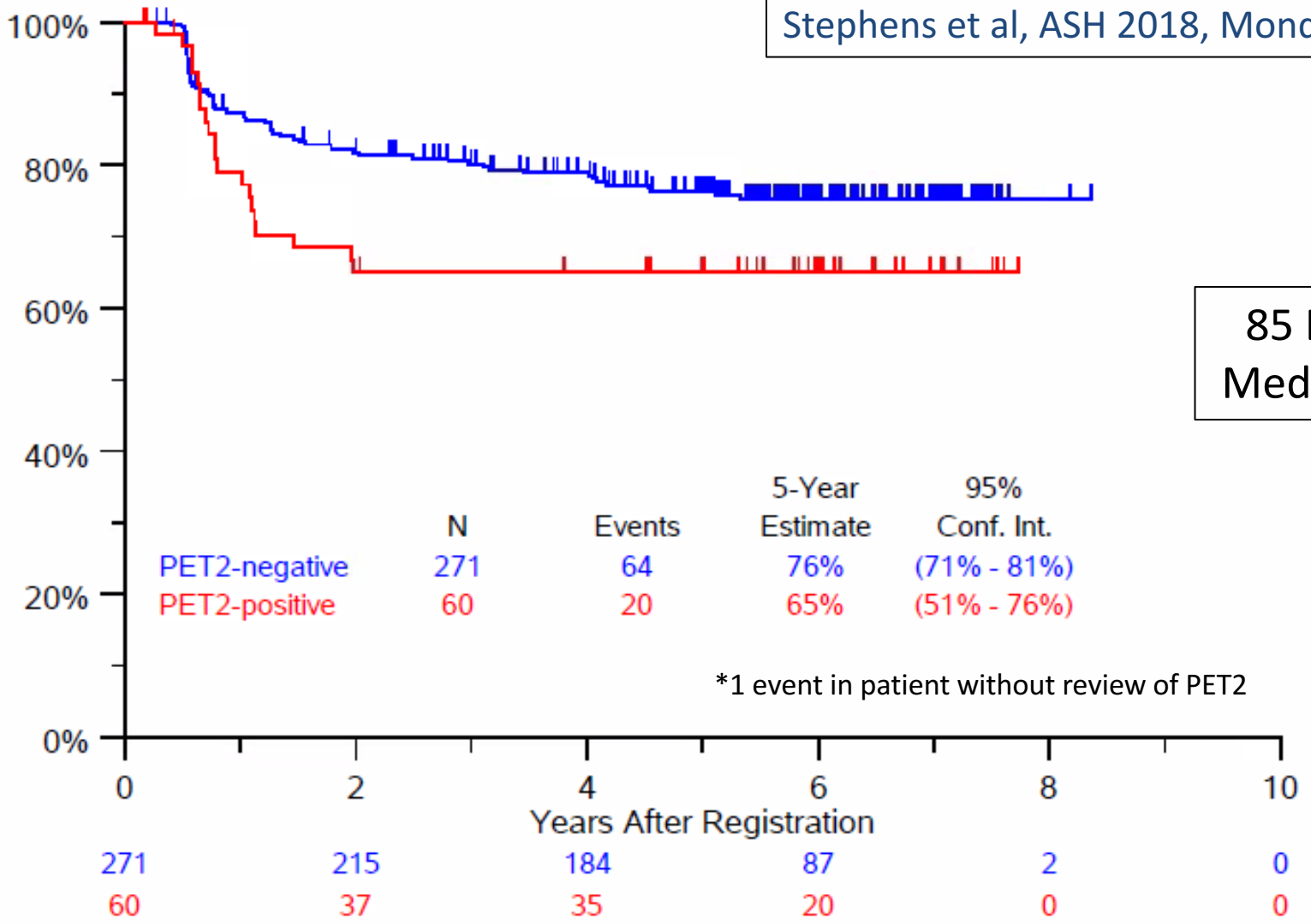
1. 2-year PFS will be improved from the historical 70% with ABVD to 78% with risk adapted therapy.

2. Projected 48% 2 yr PFS for PET+ pt switched to e-BEACOPP (15-30% estimated PFS if continued on ABVD).

Press et al. *JCO* 34:2020 2016

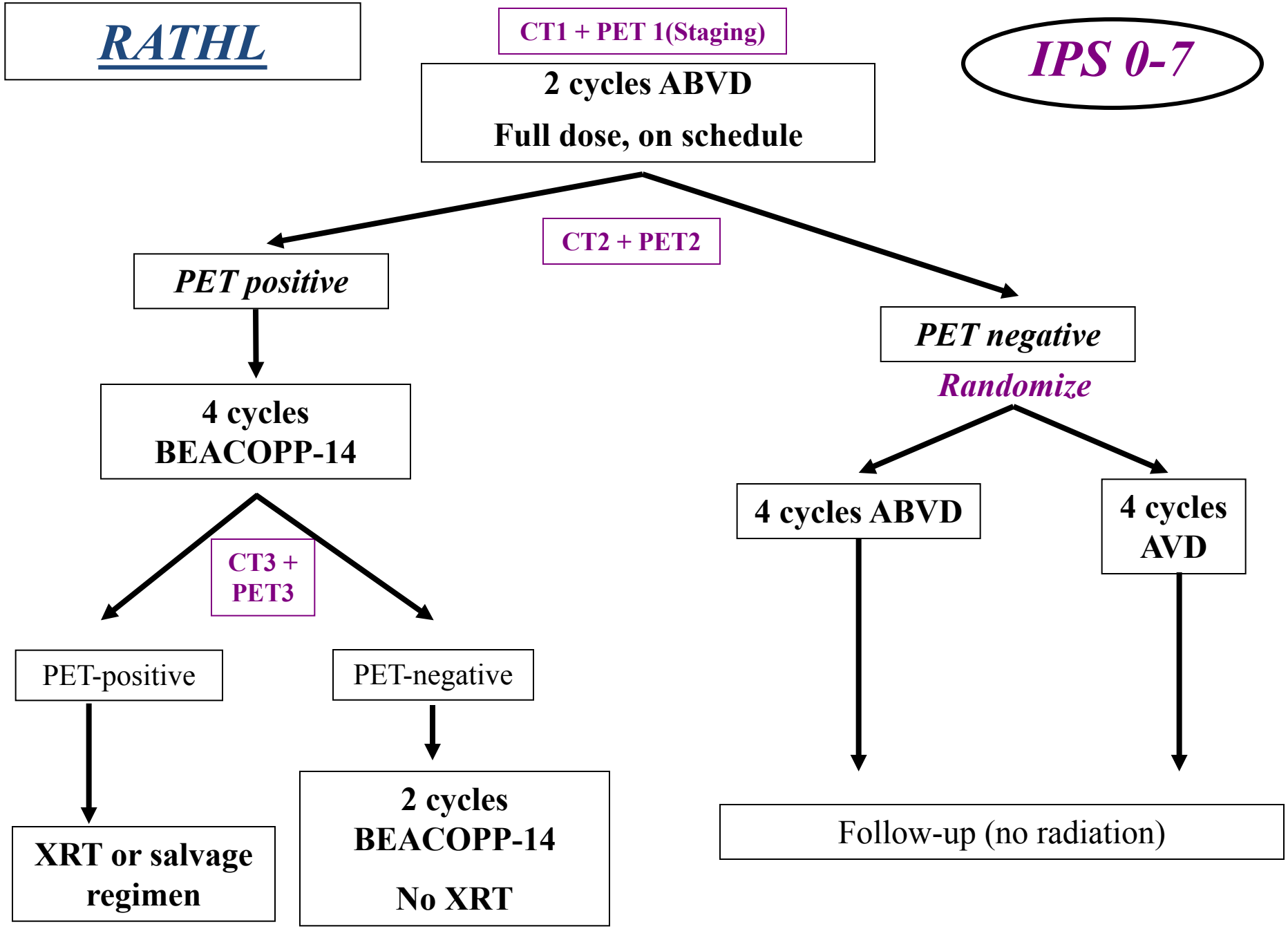
S0816: 5-Year Progression-Free Survival

Stephens et al, ASH 2018, Monday



85 Events (25%)
Median f/u 5.9 yrs

*1 event in patient without review of PET2



Johnson et al. *NEJM* 374:2419 2016

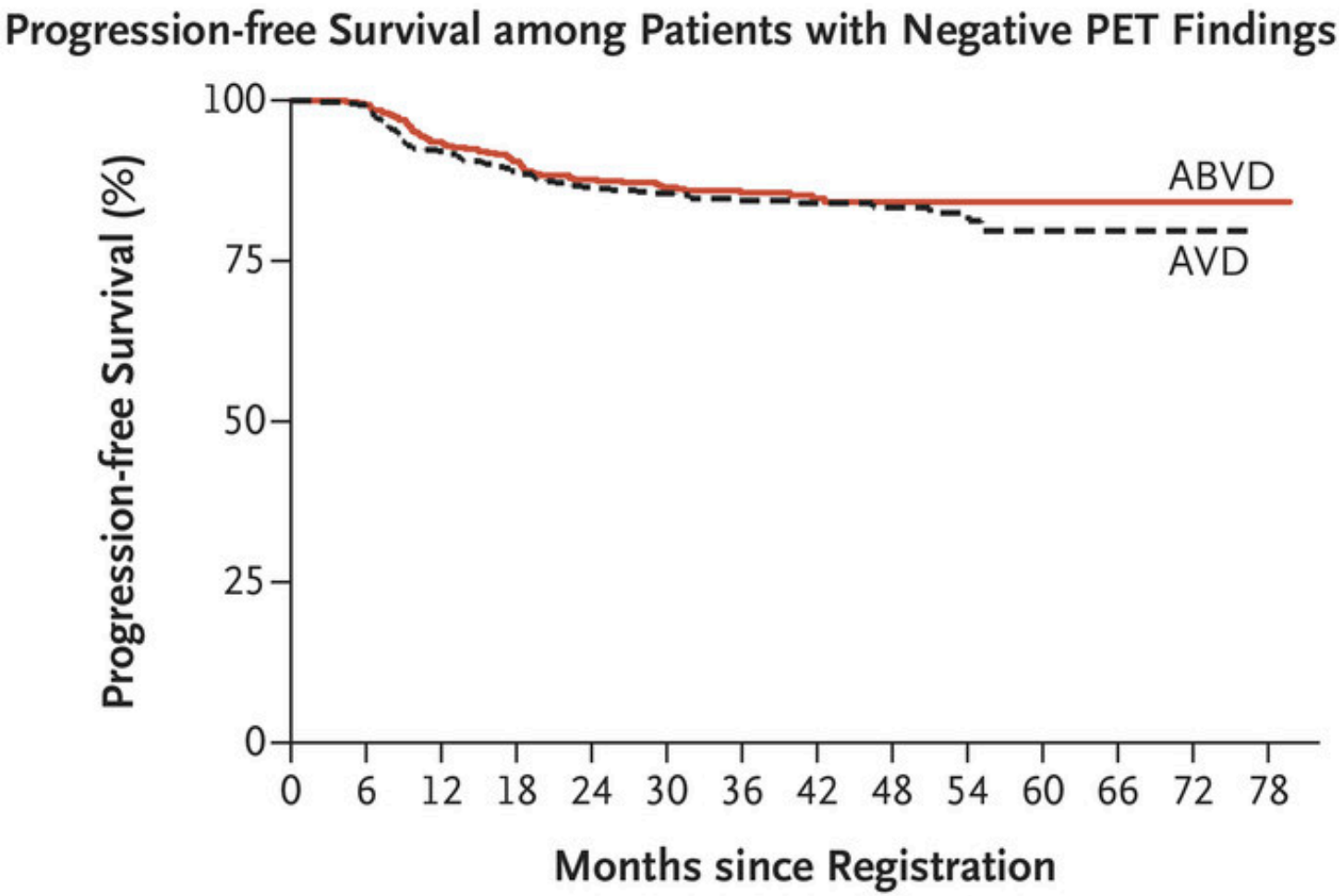
RATHL outcomes of therapy

Table 2. Outcomes of Therapy.

Outcome	ABVD (N=470)	AVD (N=465)	BEACOPP (N=172)	All Eligible Patients (N=1203)*
Alive without disease progression — no. of patients	402	391	117	999
Alive after disease progression — no. of patients	49	57	33	142
Died — no. of patients	19	17	22	62
From Hodgkin's lymphoma	4	8	10	24†
Owing to initial therapy	4	0	4	8
Owing to salvage therapy	4	1	5	10
From second cancer	4‡	6§	0	11†
From cardiac event	1	1	1	4†
From cause unrelated to Hodgkin's lymphoma or treatment	2	1	2	5
3-Yr progression-free survival (95% CI) — %¶‖	85.7 (82.1–88.6)	84.4 (80.7–87.5)	67.5 (59.7–74.2)	82.6 (80.2–84.7)
3-Yr overall survival (95% CI) — %**	97.2 (95.1–98.4)	97.6 (95.6–98.7)	87.8 (81.5–92.1)	95.8 (94.4–96.8)
Second cancer — no. of patients	13	11	3	29
Ann Arbor stage III or IV and age ≤60 yr				
3-Yr progression-free survival (95% CI) — %	82.1 (76.5–86.5)	82.1 (76.3–86.4)	63.9 (52.9–72.9)	79.8 (76.3–82.9)
3-Yr overall survival (95% CI) — %	95.9 (92.2–97.9)	97.8 (94.8–99.1)	87.8 (78.9–93.0)	94.6 (92.5–96.2)

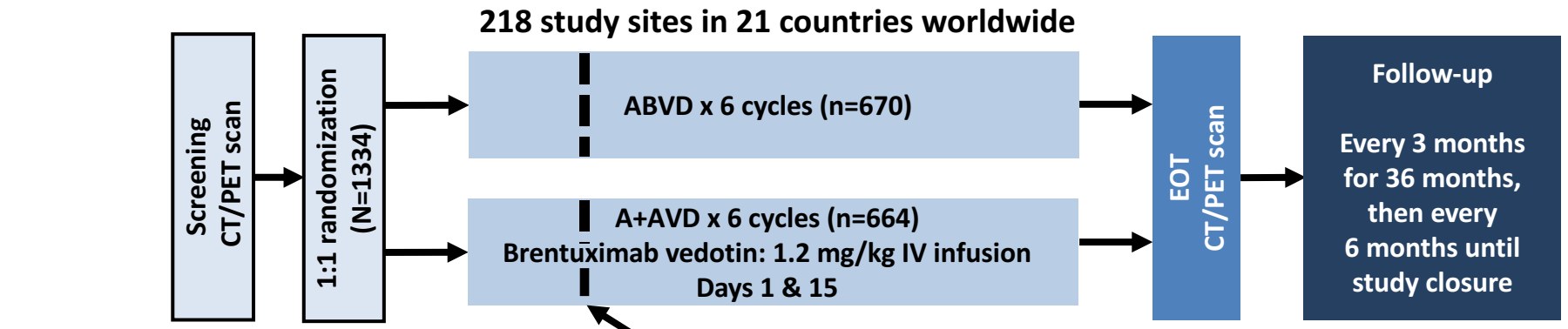
Johnson et al. *NEJM* 374:2419 2016

RATHL: PFS outcomes



Johnson et al. *NEJM* 374:2419 2016

ECHELON-1: A+AVD versus ABVD in advanced cHL



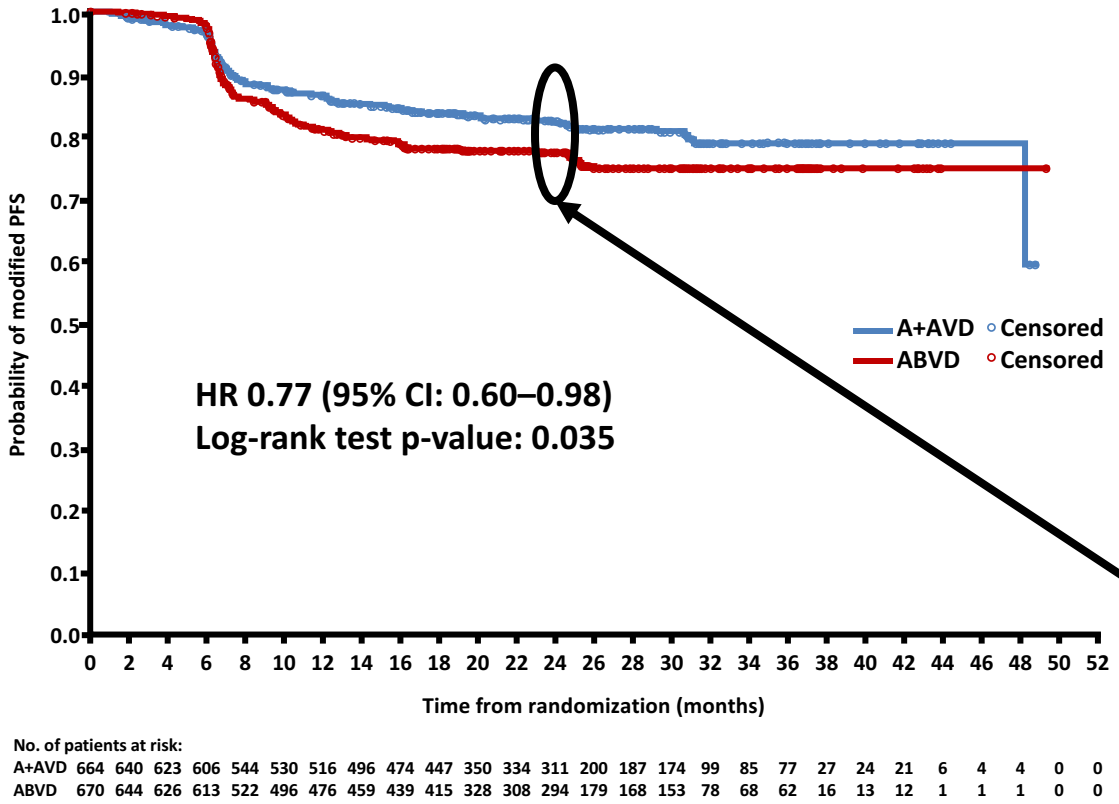
- Inclusion criteria
  - cHL stage III or IV
  - ECOG PS 0, 1 or 2
  - Age ≥18 years
  - Measurable disease
  - Adequate liver and renal function

End-of-Cycle-2 PET scan

- Deauville 5; could receive alternate therapy per physician's choice (not a modified PFS event)

Connors et al. *NEJM* online 2017

Echelon-1: 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

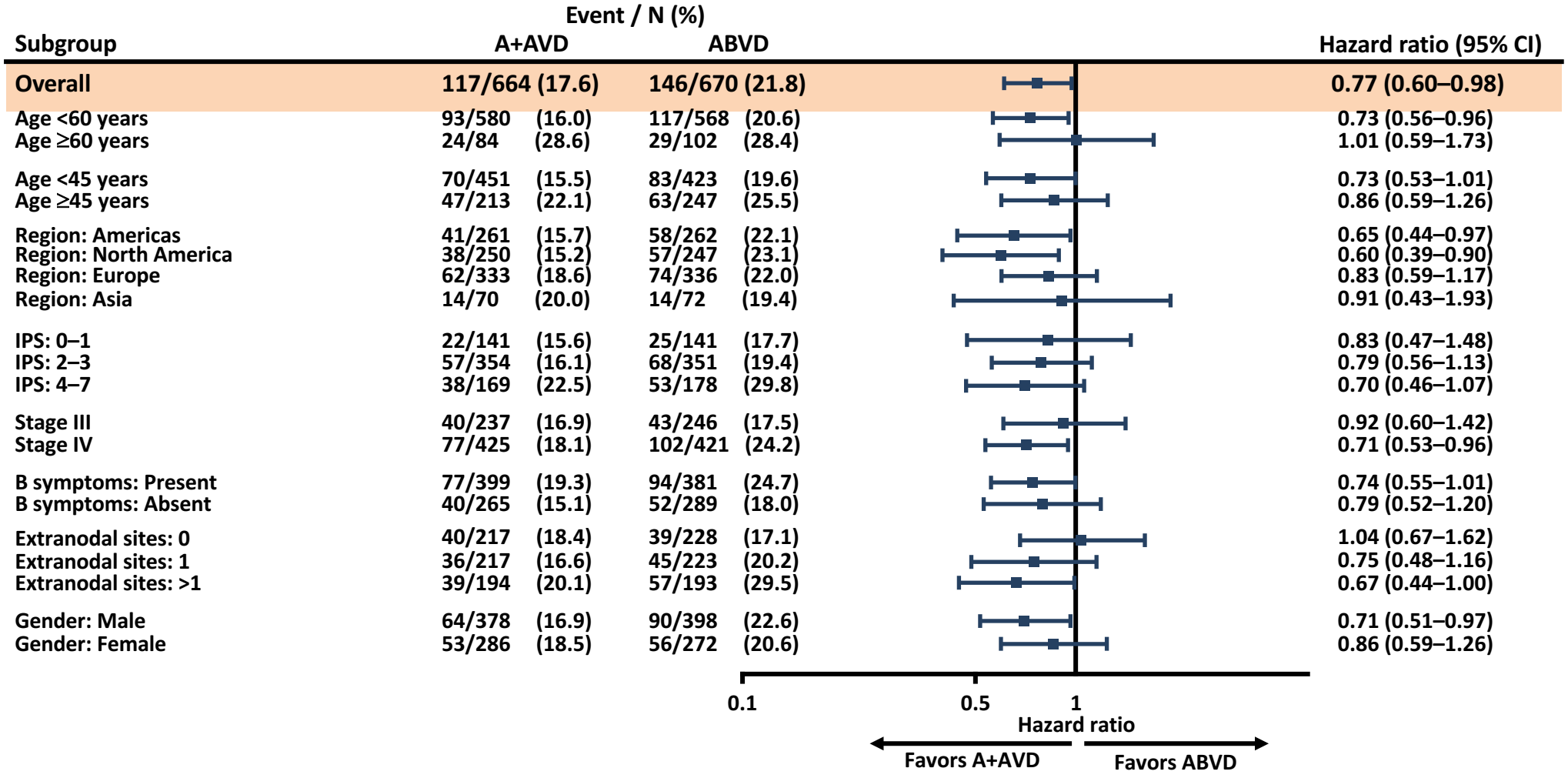
Modified PFS estimates

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)

Connors et al. *NEJM* 378:331-44, 2017

Echelon-1 Forest plot of modified PFS per IRF



Connors et al. *NEJM* 378:331-44 2017

Echelon-1: mPFS/PFS per IRF/INV by region

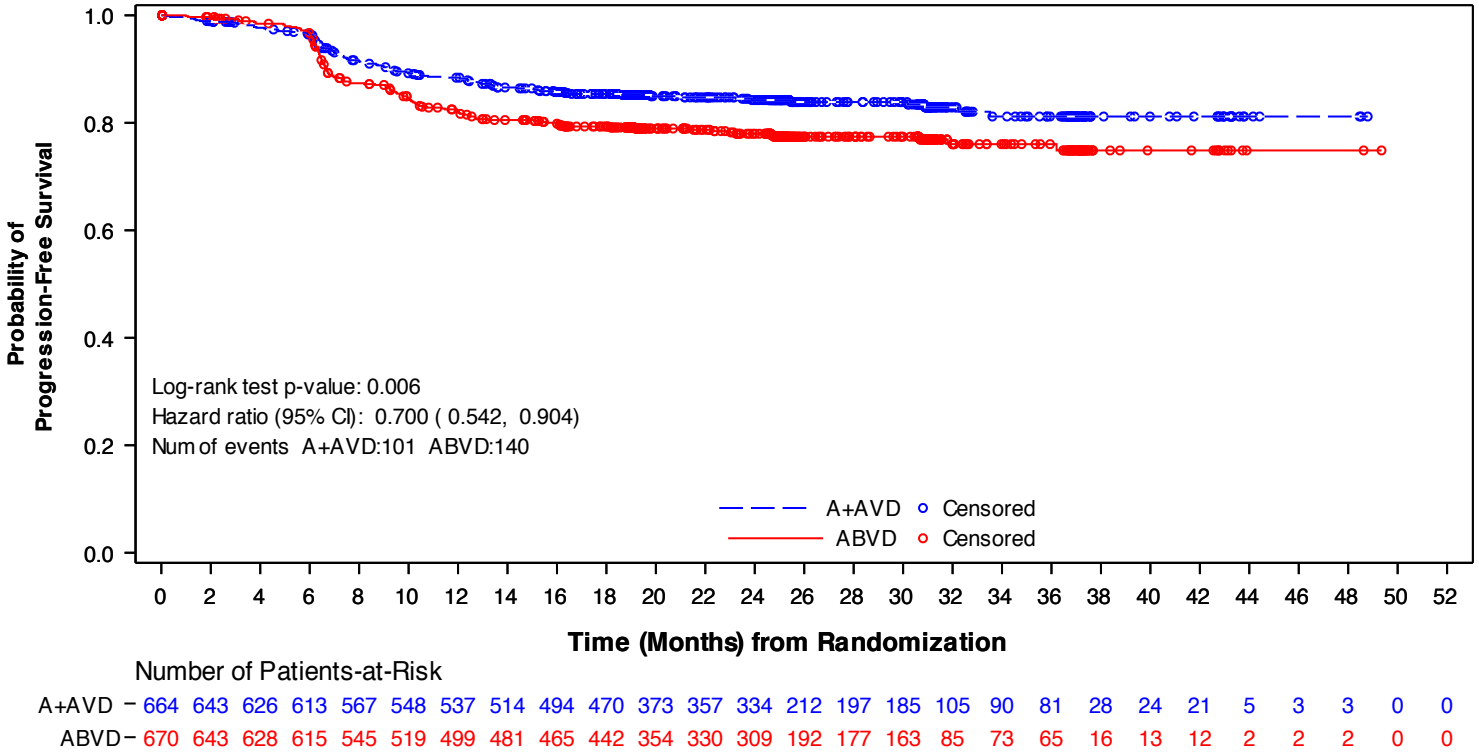
mPFS at 2 years						
	IRF			INV		
	A+AVD	ABVD	Delta	A+AVD	ABVD	Delta
North America	84.3	73.7	10.6	86.3	73.6	12.7
Europe	81.3	78.6	2.7	78.3	74.0	4.3

Ramchandren. *Proc ASCO* 2018;Abstract 7541

Echelon-1
"True" PFS per INV

- HR=0.70, p=0.006
- 2 year event rates: 84.2 % vs 78.0%; delta = 6.2%

- NOTE: subsequent therapy is not considered an event nor censored in this analysis



Kaplan-Meier Estimates	A+AVD (95%CI)[at risk]	ABVD(95%CI)[at risk]	Difference
1 year	88.4 (85.6, 90.7) [n=537]	82.2 (78.9, 84.9) [n=499]	6.2
2 year	84.2 (81.1, 86.9) [n=334]	78.0 (74.4, 81.1) [n=309]	6.2

Ramchandren. *Proc ASCO* 2018;Abstract 7541; Radford J et al. *Proc ISHL* 2018;Abstract P072

Echelon-1: Select Adverse Events

Adverse Event	BV + AVD		ABVD	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Neutropenia	58%	54%	45%	39%
Febrile neutropenia	19%	NR	8%	NR
Peripheral sensory neuropathy	29%	5%	17%	<1%
Infections	55%	18%	50%	10%

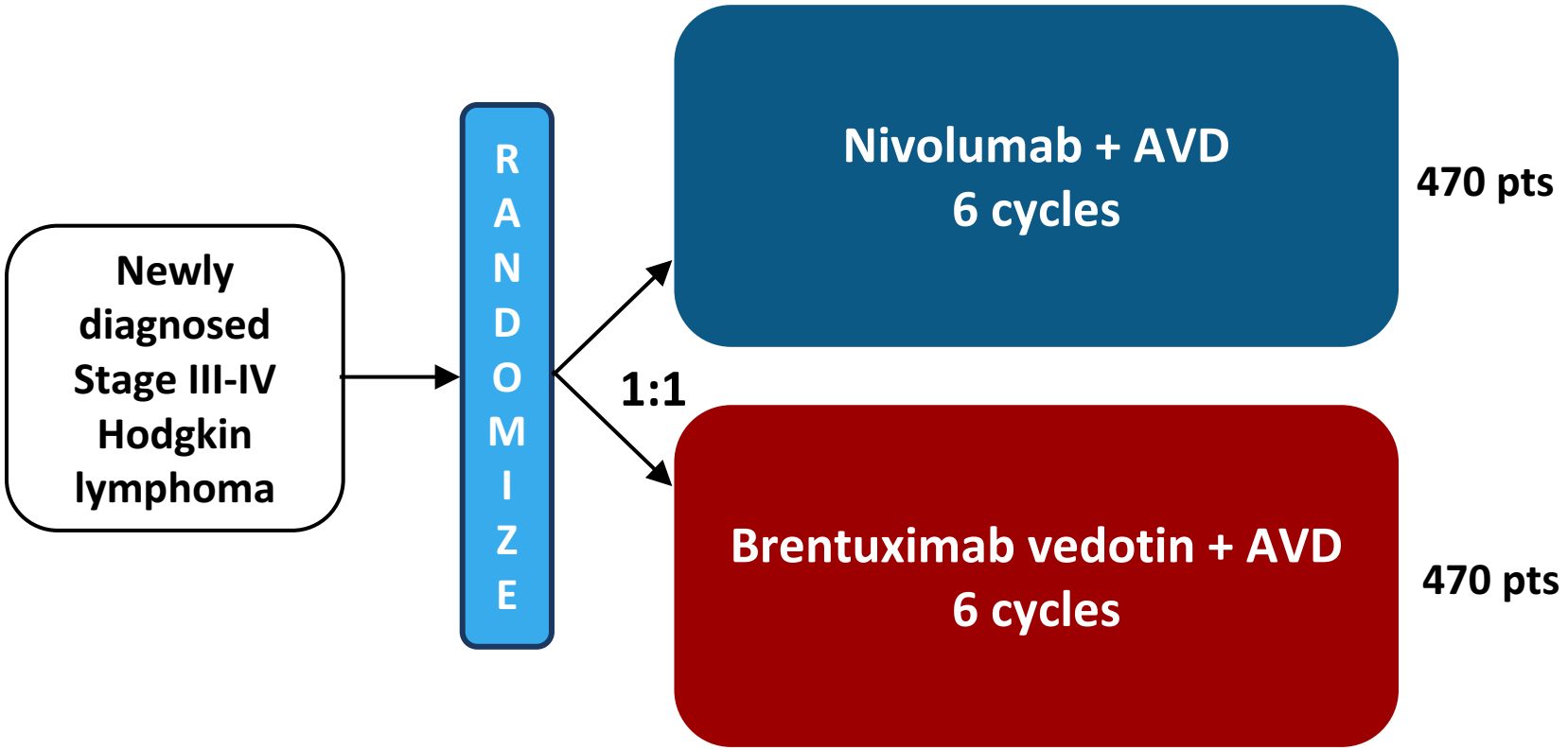
NR = Not reported

Connors et al. *NEJM* 378:331-44 2017

AVD-brentuximab: A new standard?

- Arguments in favor
  - Echelon-1 trial results.
  - “Novel” agent may be appealing to patients.
  - Would not require response-adaptation.
  - Eliminates bleomycin.
  - Avoids BEACOPPesc.
  - FDA approval.
- Arguments against
  - Toxicity and Cost.
  - mPFS endpoint.
  - Response adaptation now eliminates bleo for most after 2 cycles.
  - Echelon-1 control was not response-adapted.
  - Less long-term experience with upfront brentuximab.
  - Will failures be salvageable?

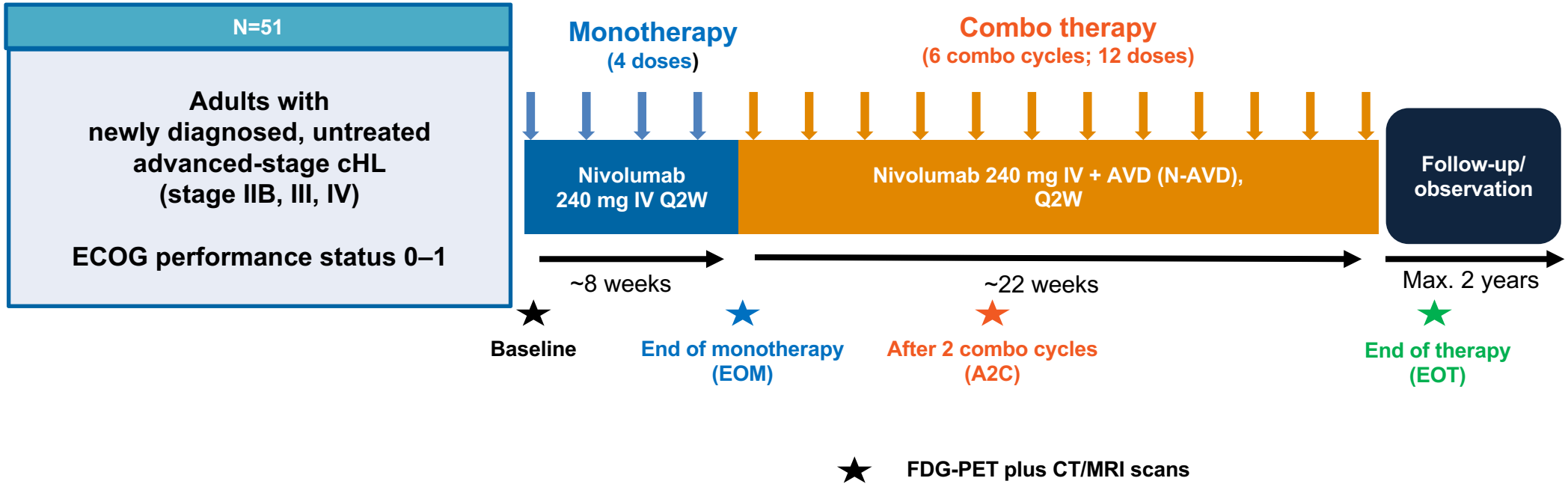
Upcoming Study: S1826



Moving checkpoint blockade earlier in treatment course of Hodgkin lymphoma

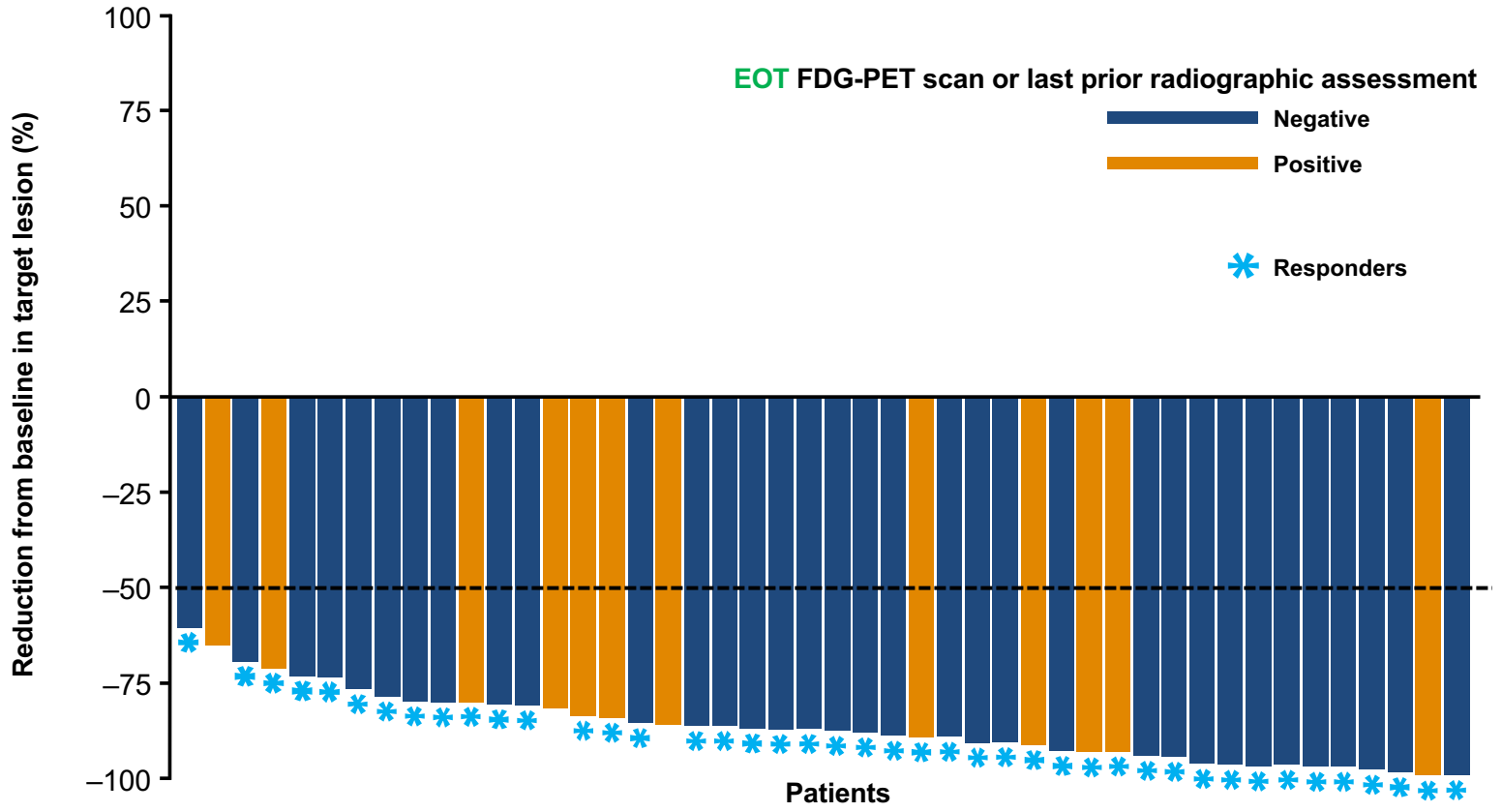
Upfront and first salvage studies

Phase 2 CheckMate 205 Newly Diagnosed cHL Study Design



Ansell et al. ISHL 2018

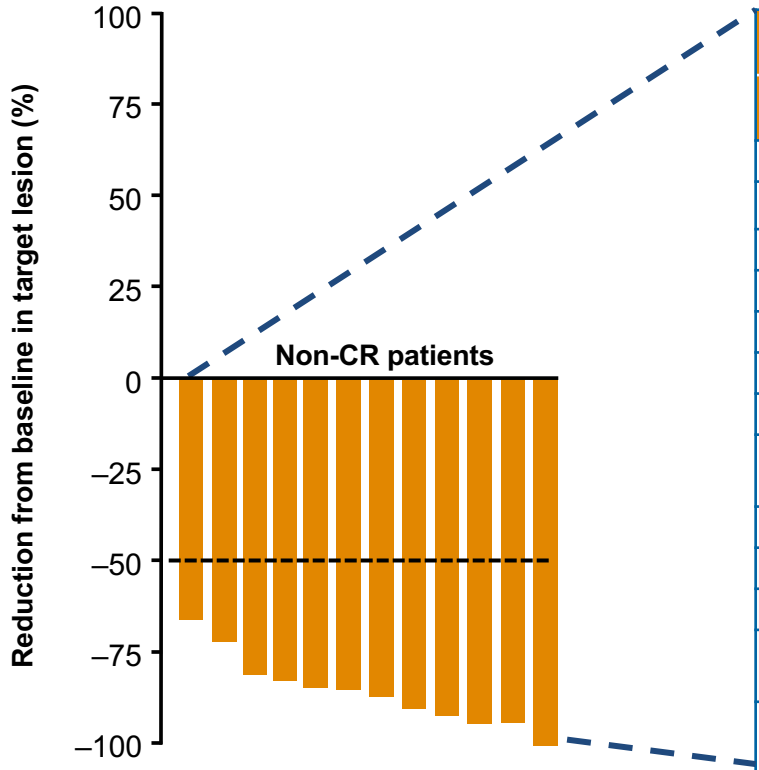
CheckMate 205:
Change in Target Lesion at End of Therapy



- All response-evaluable patients had a tumor burden reduction of >50% at EOT

Ansell et al. ISHL 2018

Status of IRC Non-CR Patients at End of Therapy



Status of IRC Non-CR Patients (n=12)		
IRC	INV	Subsequent Therapy
PR*	CR	None
PR*	CR	None
PR*	CR	None
PR*	CR	None
PR*	CR	None
PR*	CR	None
PD*	CR	None
PR*	PR	Bendamustine, nitrogen mustard analog
PD*	SD	None
PR*	PD	None[a]
PR*	PD	None[a]
PD	PD	Cisplatin, cytarabine, etoposide, methylprednisolone

Asterisk (*) represents adjudication required
[a]Subsequent therapy reported after database lock

- 7 of 12 deemed in CR by investigator

Ansell et al. ISHL 2018

Phase 1/2 Trial Design: Open Label, Multicenter Study of Brentuximab Vedotin (BV) in Combination with Nivolumab (Nivo)

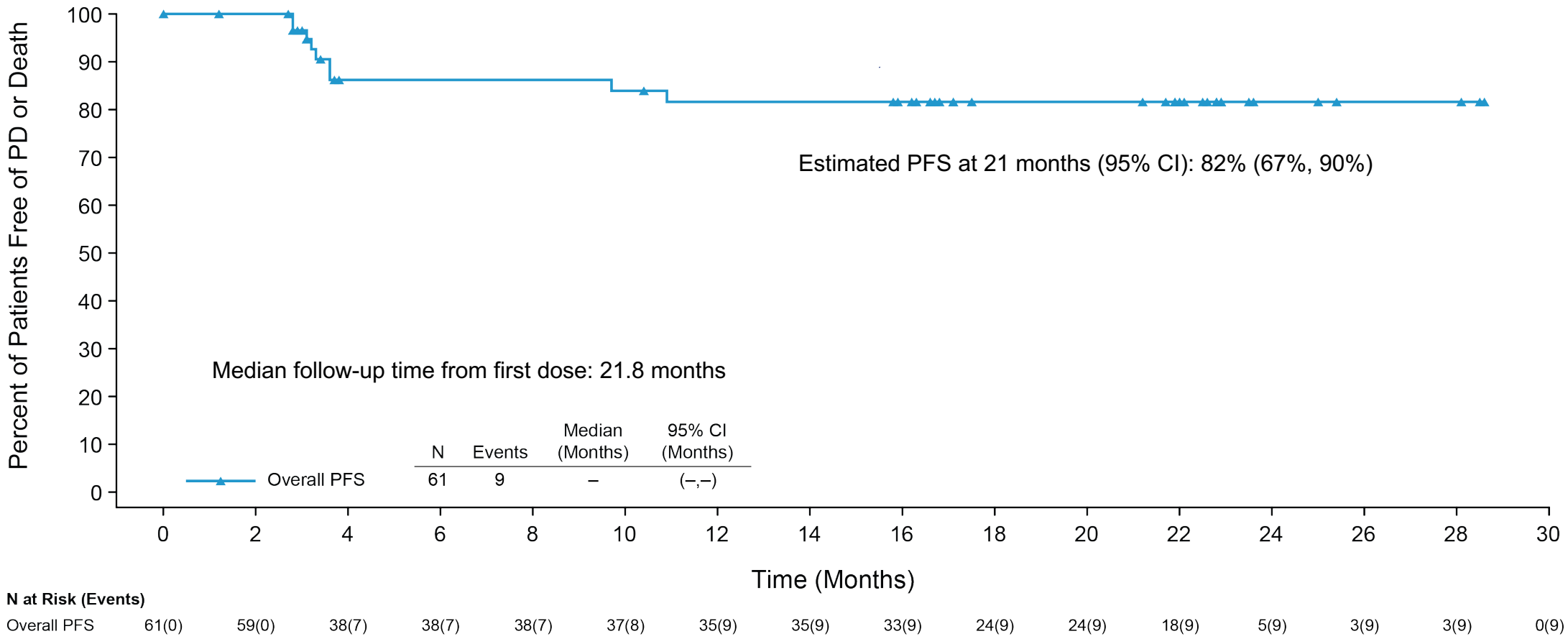
- 62 adult patients with classic R/R HL

- Treatment = 3-week cycles for up to 4 cycles (12 weeks)
  - Cycle 1: BV on Day 1 and Nivo on Day 8
  - Cycles 2 - 4: Both BV and Nivo on Day 1

- Exclusion criteria:
  - Prior salvage therapy for RR HL
  - Prior BV treatment
  - Prior immuno-oncology therapy affecting the PD-1, CTLA4, or CD137 pathways
  - Prior allogeneic or autologous stem cell transplant (ASCT)

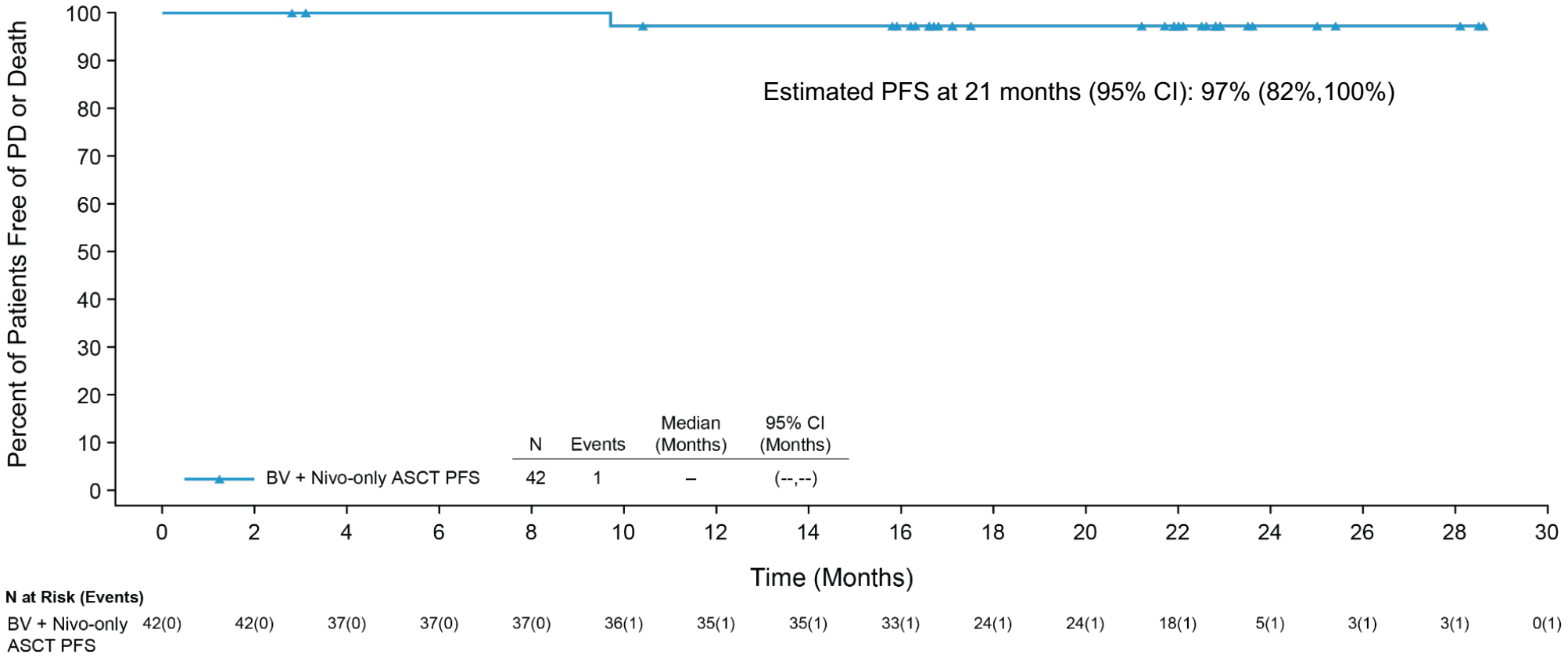
Herrera et al. ISHL 2018

BV + Nivo: Progression-free Survival (PFS)



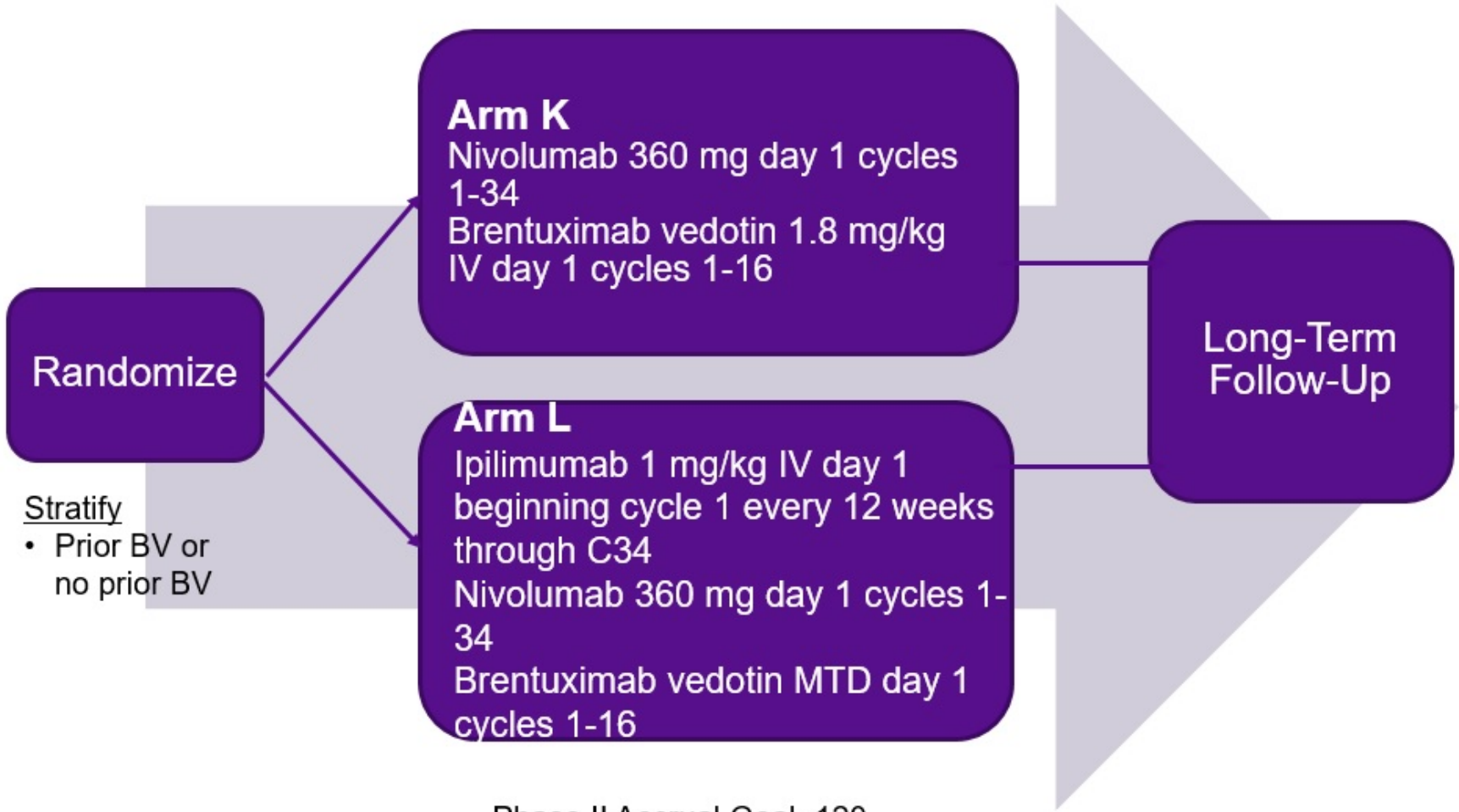
Herrera et al. ISHL 2018

BV + Nivo:
ASCT directly after BV + Nivo



Herrera et al. ISHL 2018

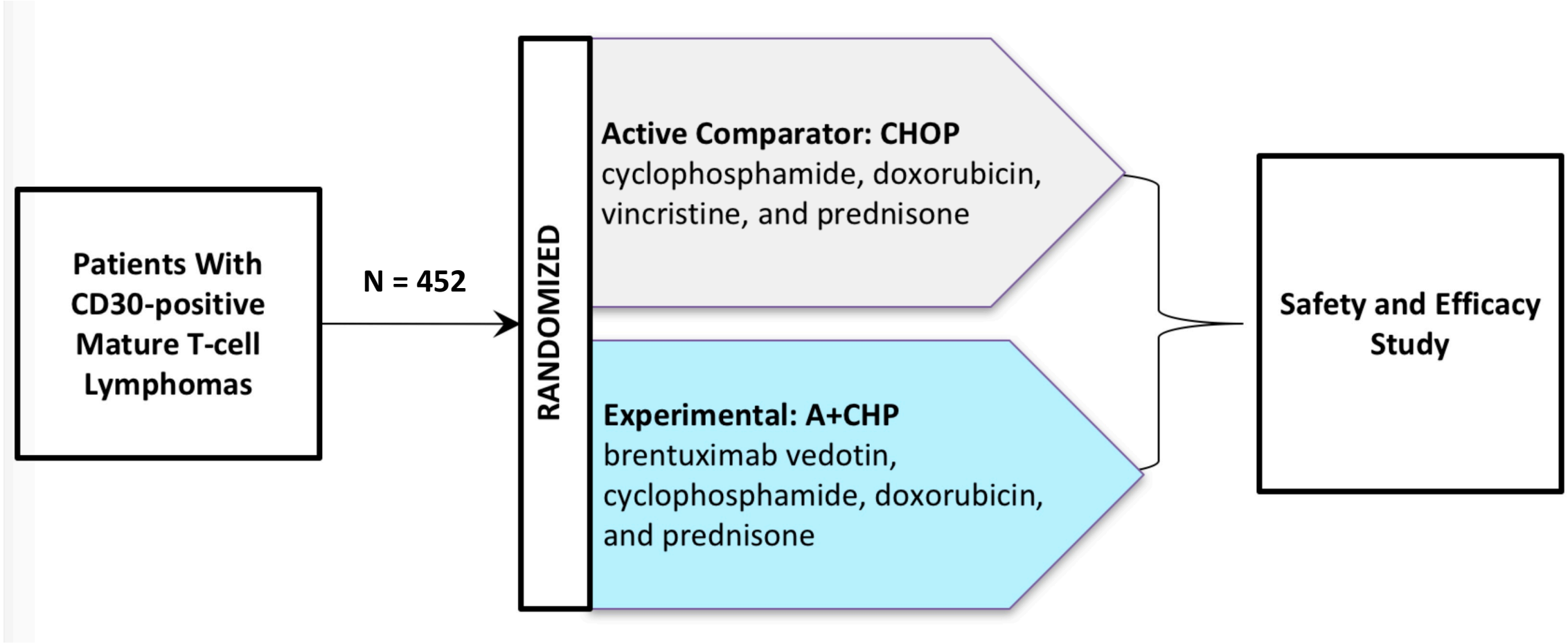
E4412 Phase 2 is Activated



Phase II Accrual Goal=120 patients
Cycle=21 days

ECOG-ACRIN cancer research group
Reshaping the future of patient care

Phase 3 ECHELON-2 Trial Schema in Newly Diagnosed, CD30-Positive Mature T-Cell Lymphomas



Clinicaltrials.gov, November 30, 2018

Phase III ECHELON-2 Trial of Front-Line BV with Chemotherapy for CD30-Positive Peripheral T-Cell Lymphoma Meets Its Primary Endpoint – Significant Improvement in PFS

Press Release – October 1, 2018

"Results from the trial demonstrated that combination treatment with BV plus CHP was superior to the control arm (CHOP) for PFS as assessed by an Independent Review Facility (IRF; hazard ratio = 0.71; *p*-value = 0.0110).

The BV plus CHP arm also demonstrated superior overall survival (OS), a key secondary endpoint, compared to CHOP (hazard ratio = 0.66; *p*-value = 0.0244).

The safety profile of BV plus CHP in the ECHELON-2 trial was comparable to CHOP and consistent with the established safety profile of BV in combination with chemotherapy."

The primary analysis by treatment regimen will be presented at the American Society of Hematology (ASH) 2018 Annual Meeting, December 3, 2018 at 6:15 PM in San Diego, California.

https://www.takeda.com/newsroom/newsreleases/2018/seattle-genetics-and-takeda-announce-positive-results-from-phase-3-echelon-2-clinical-trial/

FDA Approval of BV in Combination with Chemotherapy for Adults with Previously Untreated Systemic Anaplastic Large Cell Lymphoma (sALCL) or Other CD30-Expressing Peripheral T-Cell Lymphomas (PTCL)

Press Release – November 16, 2018

The FDA has approved BV in combination with CHP chemotherapy (cyclophosphamide/doxorubicin/prednisone) for adults with previously untreated sALCL or other CD30-expressing PTCL, including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified. The approval is based on the successful outcome of the Phase III ECHELON-2 clinical trial that compared BV with CHP to CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone). The FDA granted breakthrough therapy designation and priority review to this supplemental biologics license application and reviewed it under the Real-Time Oncology Review pilot program leading to approval less than 2 weeks after submission of the completed application.

https://finance.yahoo.com/news/seattle-genetics-announces-fda-approval-155200190.html