INITIAL THERAPY FOR ADVANCED-STAGE HODGKIN LYMPHOMA:

THE CASE FOR BRENTUXIMAB-BASED THERAPY

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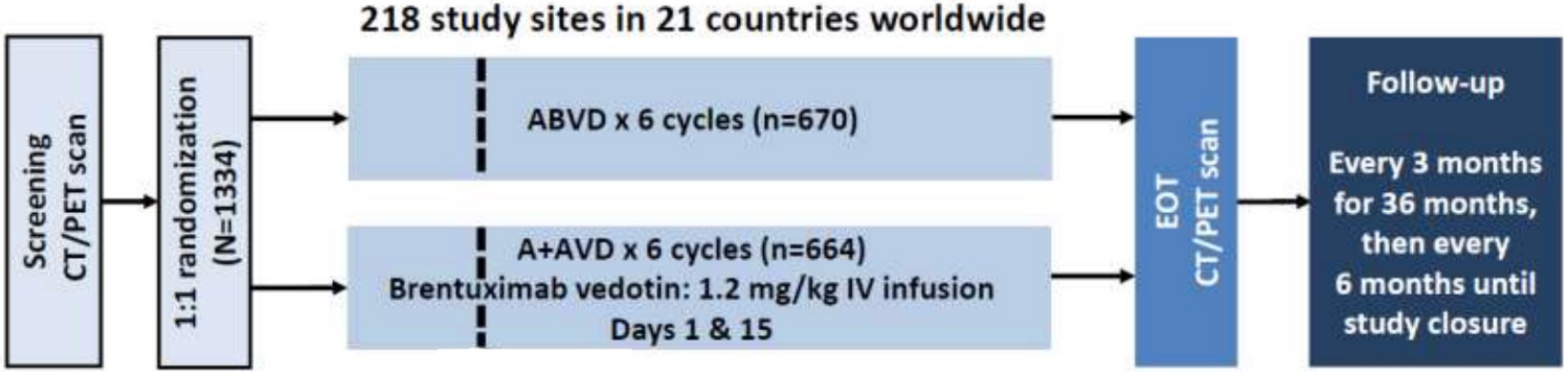
INITIAL THERAPY FOR STAGE III-IV CLASSICAL HODGKIN LYMPHOMA

- The ABVD chemotherapy regimen was developed in the 1970s, treatment leads to cure for most patients

- Until recently, limited improvements over ABVD
  - eBEACOPP improves disease control rate, but very toxic
  - Response-adapted treatments limit toxicity, but do not improve OS

- Brentuximab vedotin, a CD30-directed ADC, was approved by FDA in 2011 for R/R cHL. Efforts begin to move to earlier lines of therapy.

ECHELON-1 Study Design



Primary endpoint: Modified progression-free survival

Time to disease progression, death, or non-complete response and subsequent anti-cancer therapy

Primary endpoint – Modified PFS

TO THE EDITOR: ECHELON-1, the trial reported by Connors et al. (Jan. 25 issue),[1] shows advancement in the treatment of Hodgkin's lymphoma and introduces an effective regimen for patients who are unable to receive bleomycin. However, clinically meaningful outcomes in patients with curable cancers are reflected by overall survival, not modified progression-free survival (the time to progression, death, or noncomplete response and use of subsequent anticancer therapy). The authors state, "the results of the interim overall survival analysis . . . favored A+AVD [brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine]," but that statement is premature, and longer follow-up is required for validation. The

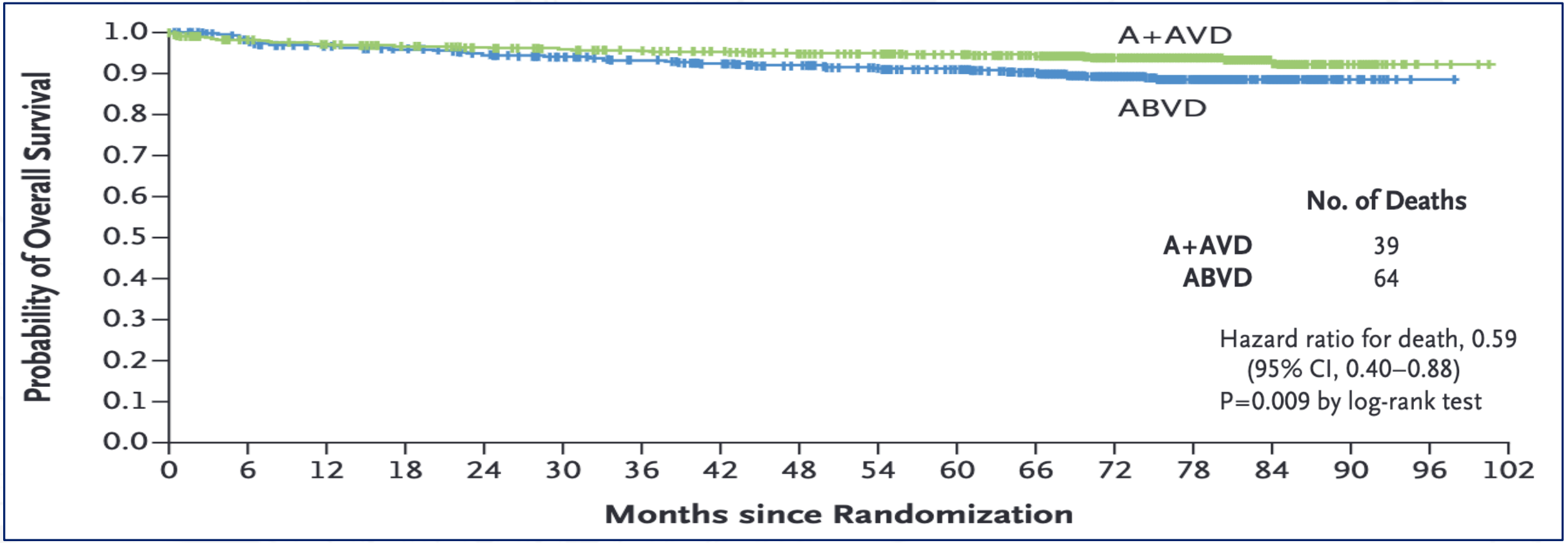
TO THE EDITOR: Connors et al. report the results of a clinical trial comparing A+AVD with ABVD in advanced-stage Hodgkin's lymphoma. Is there a rush to judgment here with respect to the conclusions of this trial? The investigators claim victory without adequate follow-up. A difference of only 4.9 percentage points in 2-year progression-free survival with A+AVD, with increased toxicity and a substantially higher cost than ABVD, cannot be construed as a triumph.

The results of the ECHELON-1 trial are not yet practice changing. Much longer follow-up than that described in the article by Connors et al. will be required to assess the true value of brentuximab added to chemotherapy in the treatment of advanced Hodgkin's lymphoma.

TOXICITY WITH BV-AVD

Peripheral neuropathy	**More in BV-AVD arm, but improves with time** 71% had complete resolution, 13% had significant improvement at last follow-up
Febrile neutropenia	**More with BV-AVD, but risk mitigated with G-CSF primary ppx** 10.8% incidence in BV-AVD group vs 7.9% ABVD
Fertility	**Does not seem to impact more than ABVD** 114 pregnancies in BV-AVD group vs. 81 in ABVD
Secondary malignancy	**Fewer in BV-AVD group** 3.5% BV-AVD group vs. 4.9% ABVD group

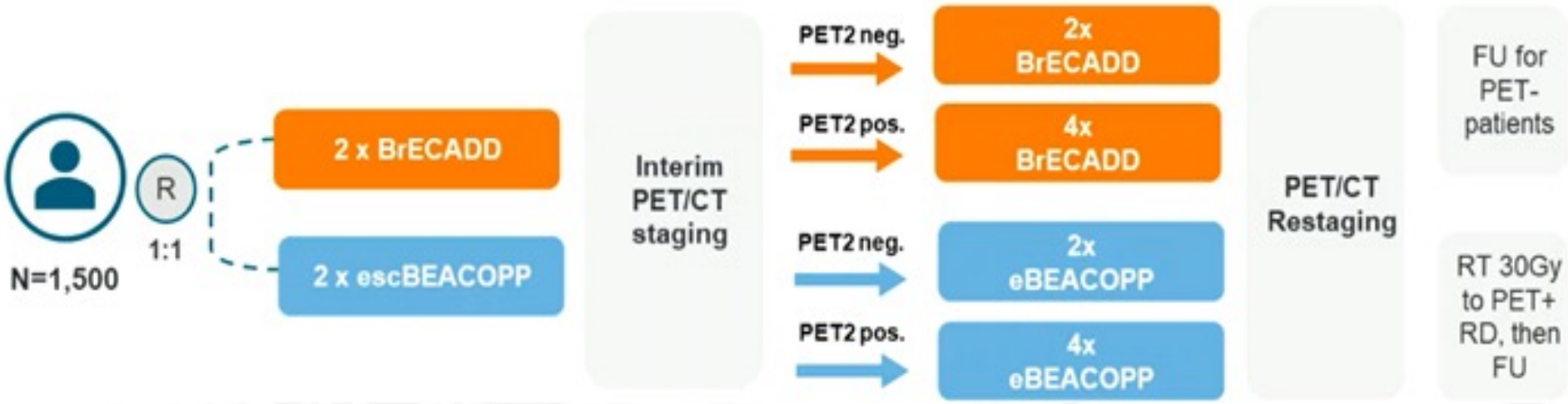
Overall survival benefit finally demonstrated



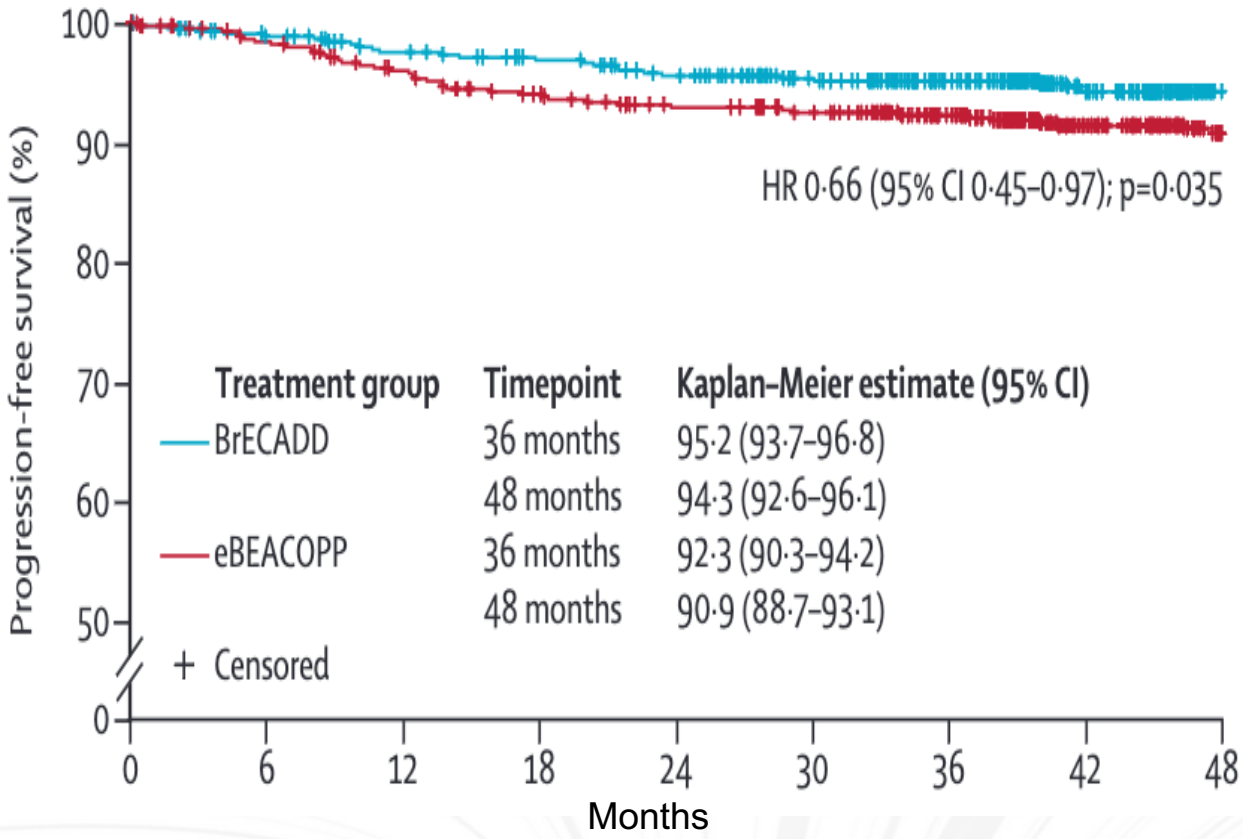
Now more than 6 years of follow-up
BV-AVD is associated with both a PFS and OS benefit compared to ABVD
Category 1 recommendation in NCCN guidelines

GHSG HD21 – MORE BRENTUXIMAB-BASED THERAPY

***BrECADD	eBEACOPP
Brentuximab vedotin	Bleomycin
Etoposide	Etoposide
Cyclophosphamide	Doxorubicin
Doxorubicin	Cyclophosphamide
Dacarbazine	vincristine
Dexamethasone	Procarbazine
	Prednisone



HD21 Results



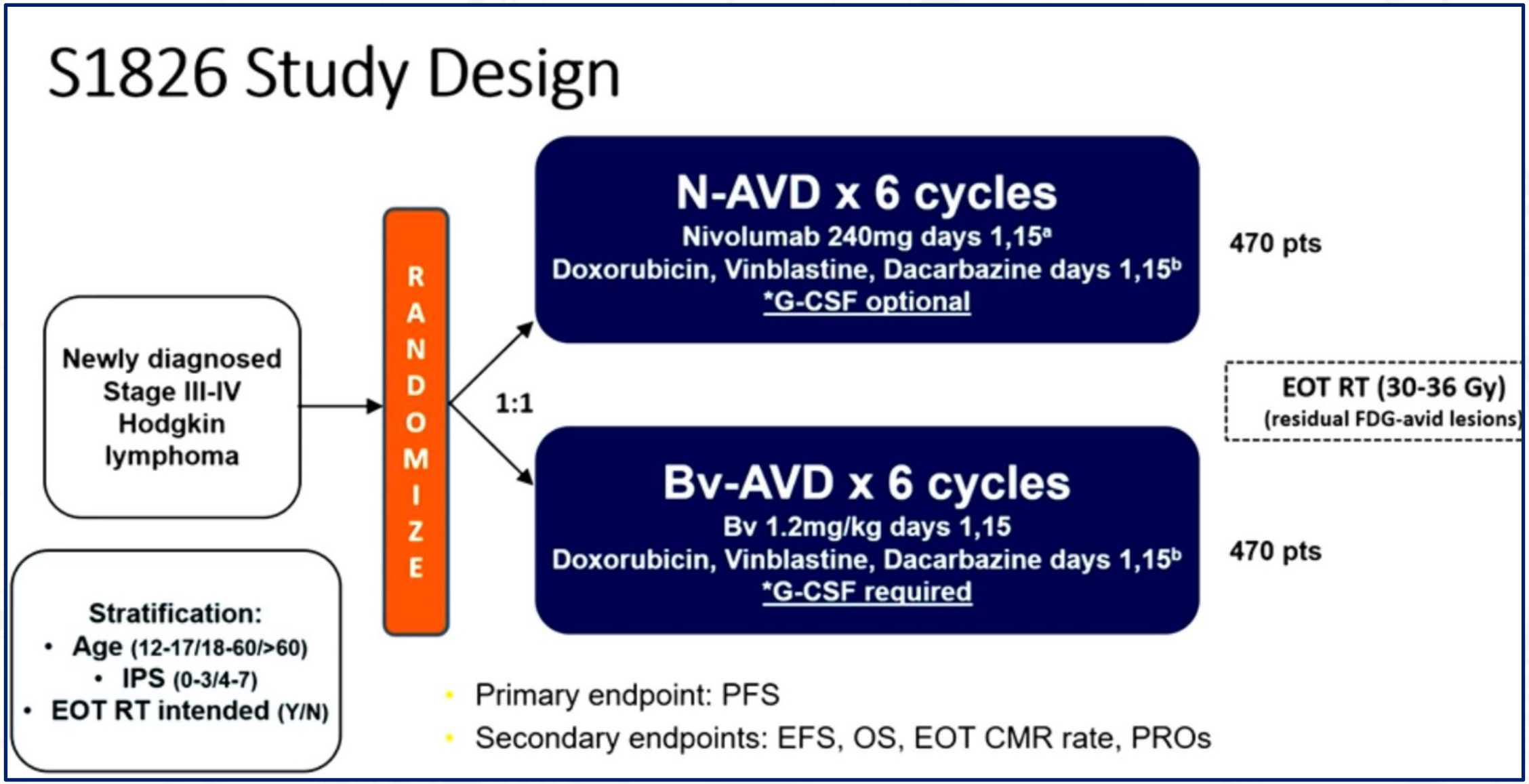
Enrolled patients 18-60 years old

Median follow-up 48 months

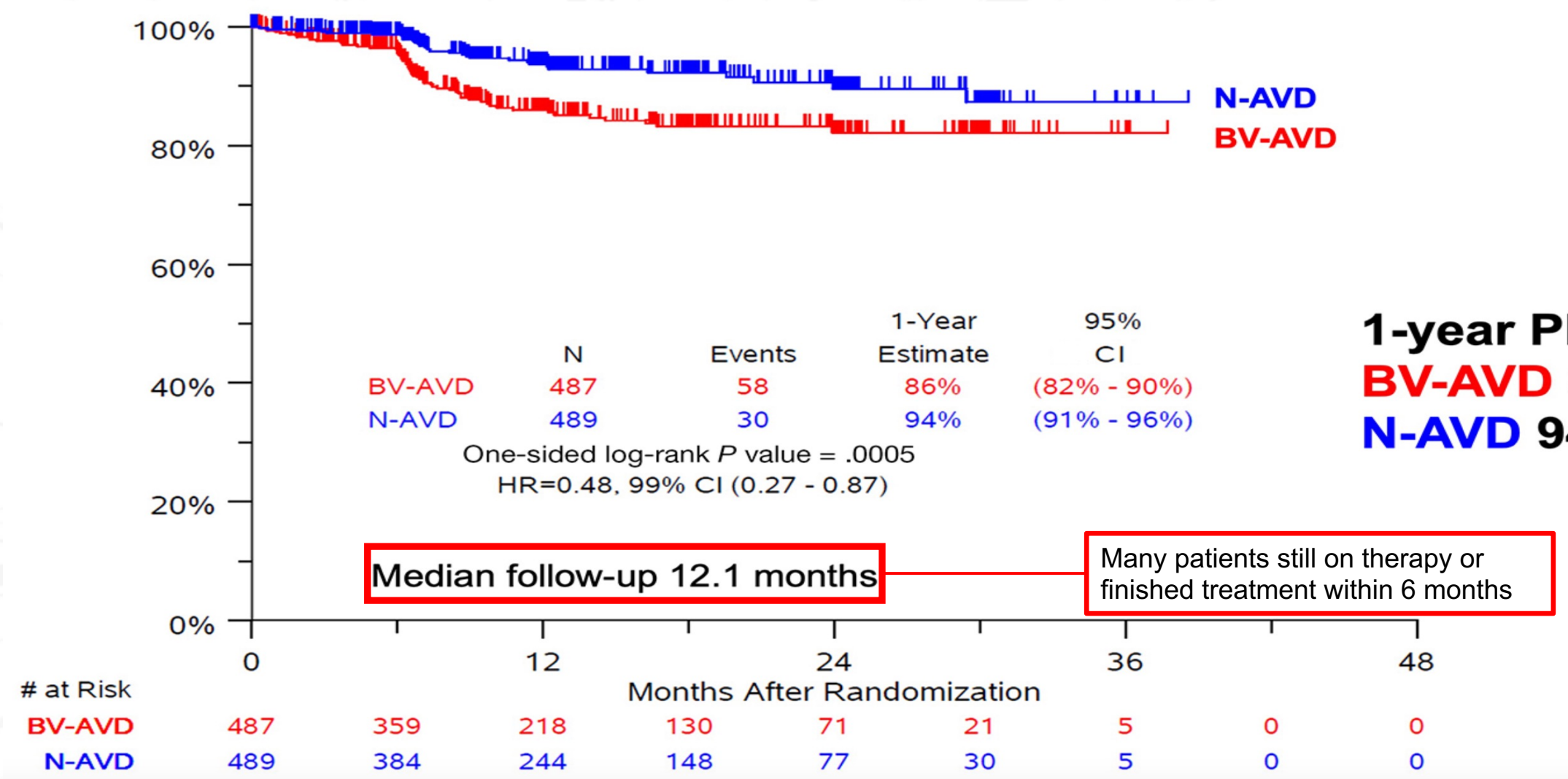
More acute toxicity with BrECADD compared with ABVD-based regimen, but all organ toxicities improved to Grade ≤ 1 by 12 months

Unprecedented 4-yr PFS rate for advanced stage cHL
64% of patients only required 4 cycles of BrECADD
BrECADD is less toxic than eBEACOPP

S1826 Study Design



S1826 – PROGRESSION FREE SURVIVAL



1-year PFS
BV-AVD 86%
N-AVD 94%

S1826 INTERIM ANALYSIS

- Nivo-AVD improved PFS compared to BV-AVD at an early timepoint
- So far, info limited to 1-page abstract, oral presentation, and word-of-mouth
- Not possible to fully assess risk/benefit profile of this regimen currently

LBA4 **Plenary Session**

SWOG S1826, a randomized study of nivolumab(N)-AVD versus brentuximab vedotin(BV)-AVD in advanced stage (AS) classic Hodgkin lymphoma (HL).

Alex Francisco Herrera, Michael Leo LeBlanc, Sharon M. Castellino, Hongli Li, Sarah C. Rutherford, Andrew M. Evens, Kelly Davison, Angela Punnett, David C. Hodgson, Susan K. Parsons, Sairah Ahmed, Carla Casulo, Nancy L. Bartlett, Joo Y Song, Richard F. Little, Brad S. Kahl, John Paul Leonard, Kara M Kelly, Sonali M. Smith, Jonathan W. Friedberg; City of Hope National Medical Center, Duarte, CA; Southwest Oncology Group Statistical Center, Seattle, WA; Emory University School of Medicine, Atlanta, GA; SWOG Cancer Research Network, Seattle, WA; Weill Cornell Medicine, New York, NY; Rutgers Cancer Institue of New Jersey, New Brunswick, NJ; Research Institute of McGill University Health Centre, Montreal, QC, Canada; SickKids Hospital, Toronto, ON, Canada; Princess Margaret - University Health Network, Toronto, ON, Canada; Tufts Medical Center/Tufts University, Boston, MA; University of Texas MD Anderson Cancer Center, Houston, TX; University of Rochester, Rochester, NY; Washington University School of Medicine, St. Louis, MO; Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD; Roswell Park Comprehensive Cancer Center and University at Buffalo Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY; University of Chicago, Chicago, IL; University of Rochester Medical Center, Rochester, NY

Background: The addition of BV to initial chemotherapy improves overall survival (OS) in adults and PFS in pediatric patients (pts) with AS HL. However, frontline BV adds toxicity, most pediatric pts receive radiation therapy (RT), and 7-20% of pts still develop relapsed/refractory (RR) HL. The PD-1 pathway is central to the pathogenesis of HL and PD-1 blockade is effective in RR HL. The adult and pediatric cooperative groups of the National Clinical Trials Network (NCTN) conducted the randomized, phase 3 S1826 trial to evaluate N-AVD vs BV-AVD in pts with newly diagnosed AS HL. **Methods:** Eligible pts were ≥12 years (y) with stage 3-4 HL. Pts were randomized 1:1 to either 6 cycles of N-AVD or BV-AVD. Recipients of BV-AVD were required to receive G-CSF neutropenia prophylaxis vs optional with N-AVD. Pre-specified pts could receive RT to residually metabolically active lesions on end of treatment PET. Pts were stratified by age, international prognostic score (IPS), and intent to use RT. Response and disease progression were assessed by investigators using 2014 Lugano Classification. The primary endpoint was PFS; secondary endpoints included OS, event-free survival, patient-reported outcomes (PROs), and safety. **Results:** 994 pts were enrolled from 7/9/19 to 10/5/22; 976 were eligible and randomized to N-AVD (n=489) or BV-AVD (n=487). Median age was 27y (range, 12-83y), 56% of pts were male, 76% were white, 12% were black, and 13% were Hispanic. 24% of pts were < 18y, 10% were > 60y, and 32% had IPS 4-7. So far, < 1% of pts received RT. At the planned 2nd interim analysis (50% of total PFS events) the SWOG Data and Safety Monitoring Committee recommended to report the primary results because the primary PFS endpoint crossed the protocol-specified conservative statistical boundary. 30 PFS events occurred after N-AVD vs 58 events after BV-AVD. With a median follow-up of 12.1 months, PFS was superior in the N-AVD arm [HR 0.48, 99% CI 0.27-0.87, one-sided p=0.0005); 1y PFS: N-AVD, 94%, BV-AVD, 86%. 11 deaths (7 due to adverse events, AE) were observed after BV-AVD compared to 4 after N-AVD (3 due to AE). The rate of grade (gr) ≥ 3 hematologic AE was 48.4% (45.1% gr ≥ 3 neutropenia) after N-AVD compared to 30.5% (23.9% gr ≥ 3 neutropenia) after BV-AVD. Rates (any gr) of febrile neutropenia (5.6% N vs 6.4% BV), pneumonitis (2.0% N vs 3.2% BV), ALT elevation (30.7% N vs 39.8% BV), and colitis (1% N vs 1.3% BV) were similar. Hypo/hyperthyroidism was more frequent after N-AVD (7%/3% N vs <1% BV) while peripheral neuropathy (any gr) was more common after BV-AVD (sensory: 28.1% N vs 54.2% BV; motor: 4% N vs 6.8% BV). **Conclusions:** N-AVD improved PFS vs BV-AVD in pts with AS HL. Few immune AEs were observed and < 1% of pts received RT. Longer follow-up is needed to assess OS and PROs. S1826, the largest HL study in NCTN history, is a key step towards harmonizing the pediatric and adult treatment of AS HL. Funding provided by: National Cancer Institute of the National Institutes of Health U10CA180888 and U10CA180819 and Bristol-Myers Squibb. Clinical trial information: NCT03907488. Research Sponsor: U.S. National Institutes of Health; Bristol Myers Squibb; NIH/NCI/NCTN: U10CA180888 and U10CA180819).

CONCLUSION

- Long follow-up, established efficacy of BV-based therapy for advanced stage HL
- Just because long-term survival results bore out for BV-AVD does not mean the same will be true for Nivo-AVD – only time will tell
- Nivo-AVD is not yet ready to be the new standard regimen for advanced cHL

Thank you!