



FRONTLINE HODGKIN LYMPHOMA TREATMENT IN 20256

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Disclosures



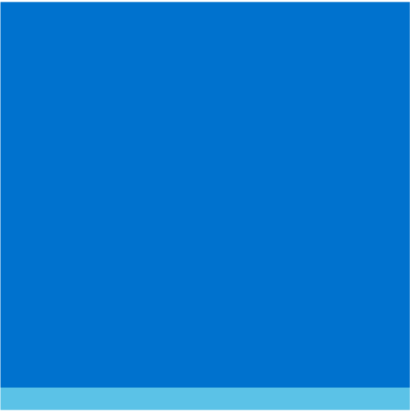
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Consultancy: Bristol Myers Squibb, Genentech, Merck, AstraZeneca, ADC Therapeutics, Takeda, Genmab, Pfizer, Abbvie, Allogene Therapeutics, Incyte, Lilly, Kite/Gilead

Presentation Outline

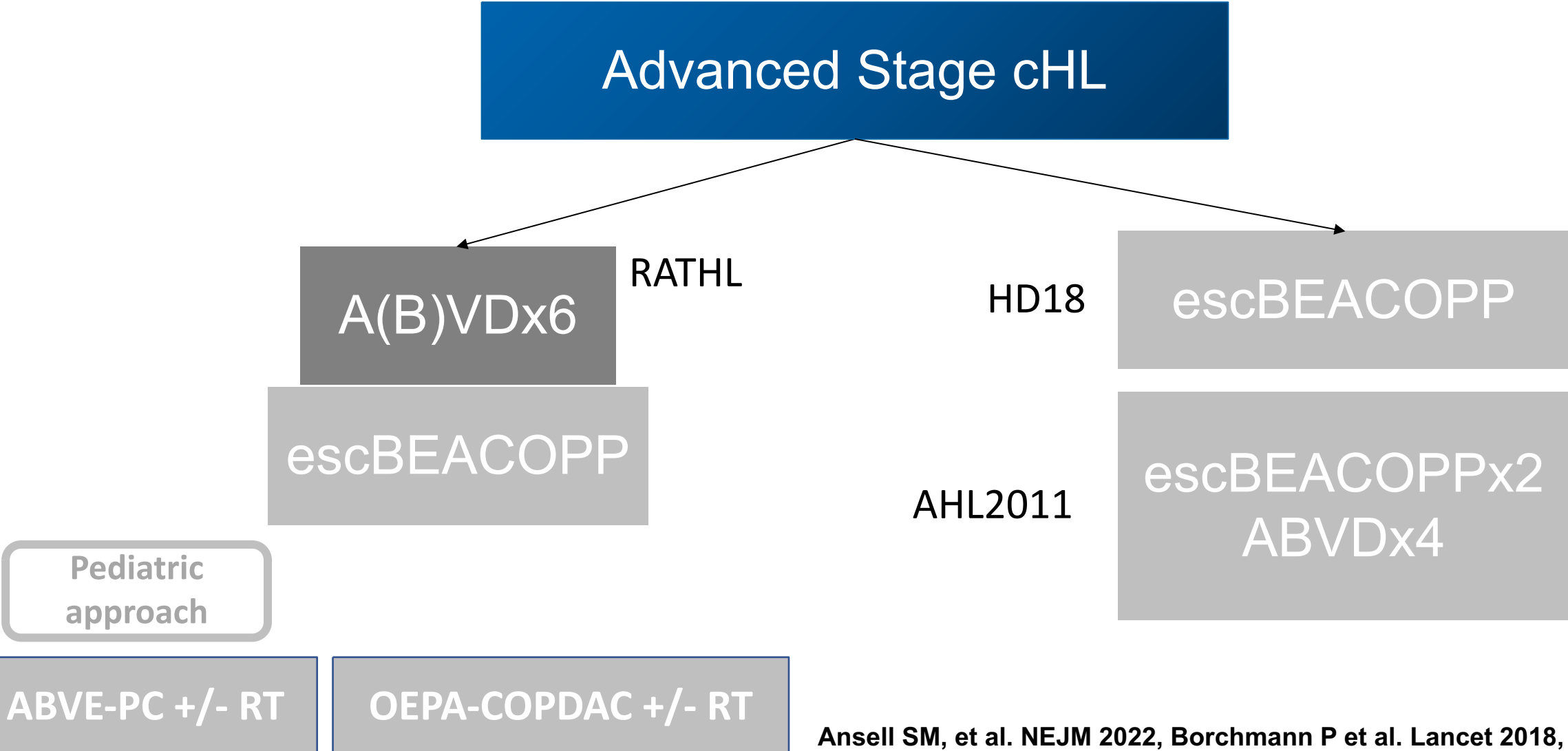


- Optimizing Frontline Treatment
 - Advanced Stage
 - ❖ BV-AVD
 - ❖ BrECADD
 - ❖ Nivolumab-AVD
 - ❖ How to choose?
 - Early Stage
 - ❖ Early studies incorporating BV and PD1 blockade



ADVANCED STAGE

Historical Management of Advanced Stage cHL



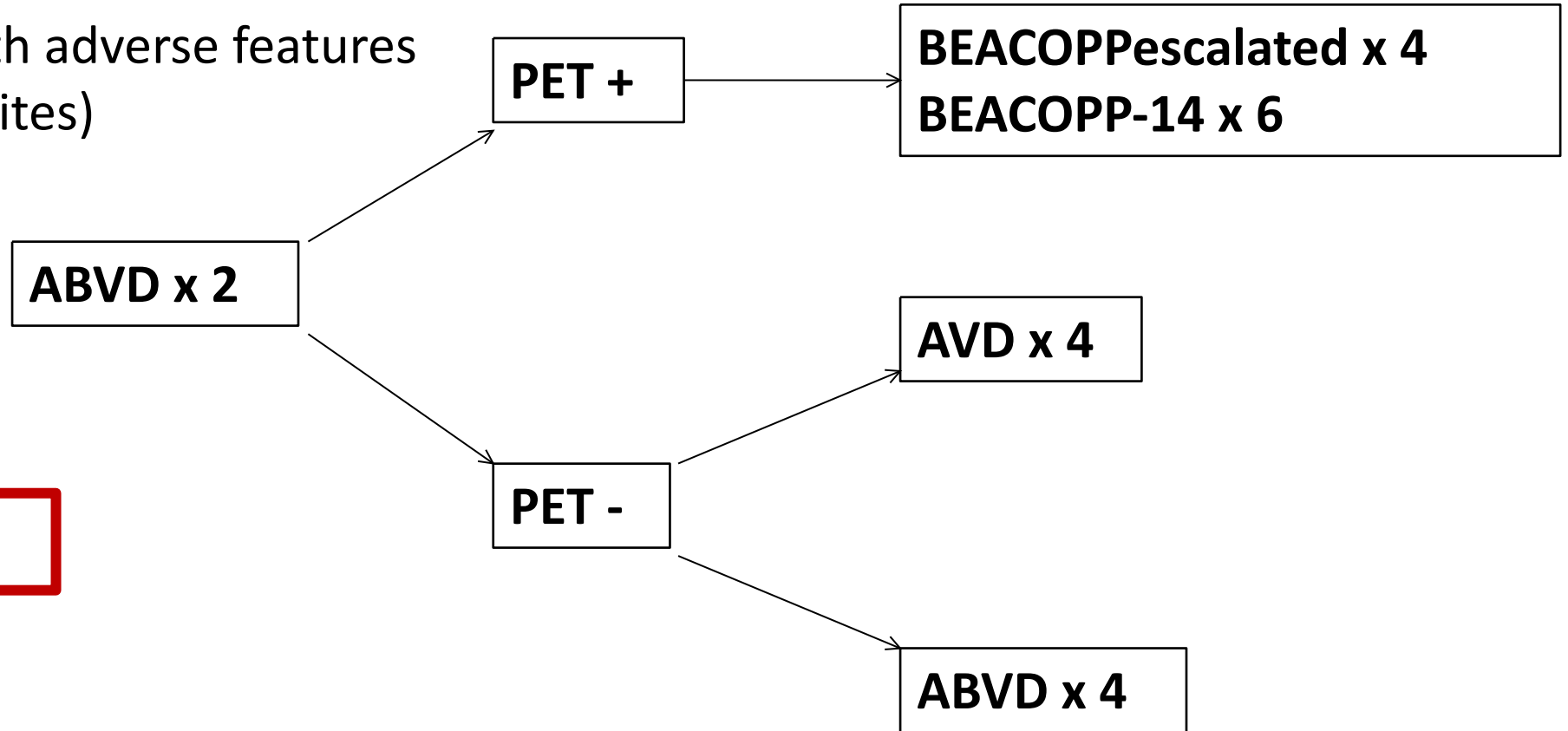
Ansell SM, et al. NEJM 2022, Borchmann P et al. Lancet 2018, Casasnovas O et al. Lancet Oncol 2019, Johnson P et al. NEJM 2016

PET-adapted RATHL study for advanced stage HL

- Stage III-IV untreated HL

or

- Stage IIA and IIB with adverse features (bulk, > 3 involved sites)

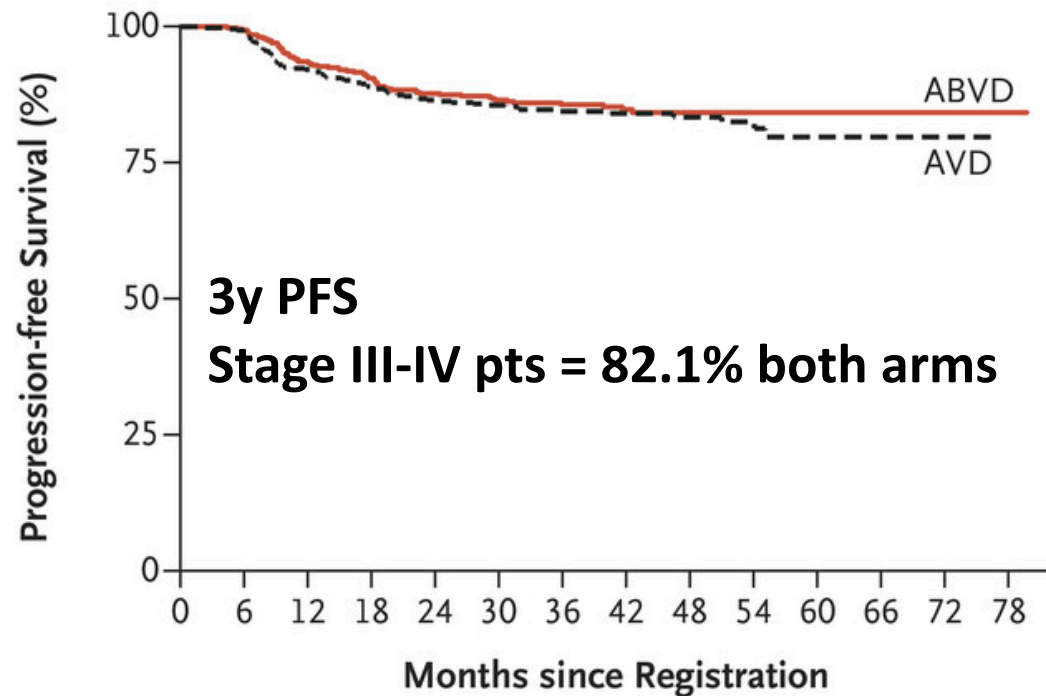


Stage II: 41.5%

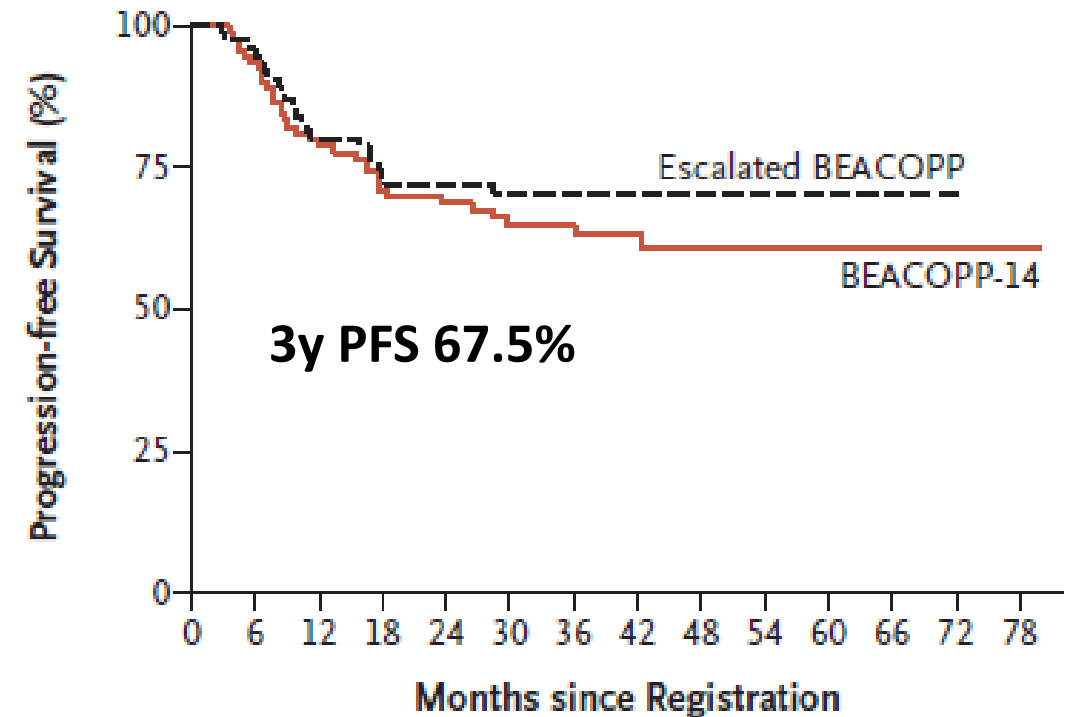
Stage III-IV: 58.5%

Omission of bleomycin is non-inferior in PET2-

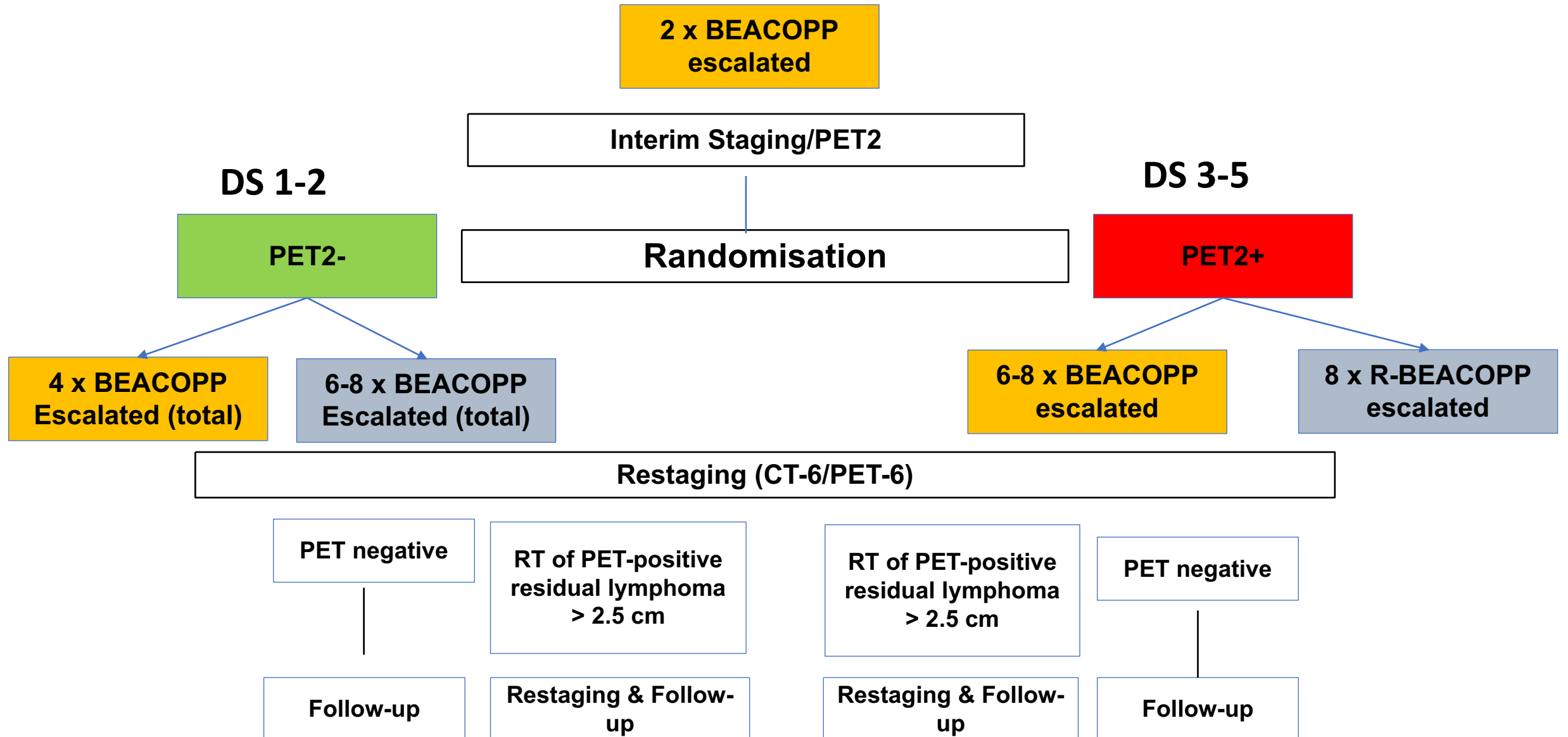
Progression-free Survival among Patients with Negative PET Findings



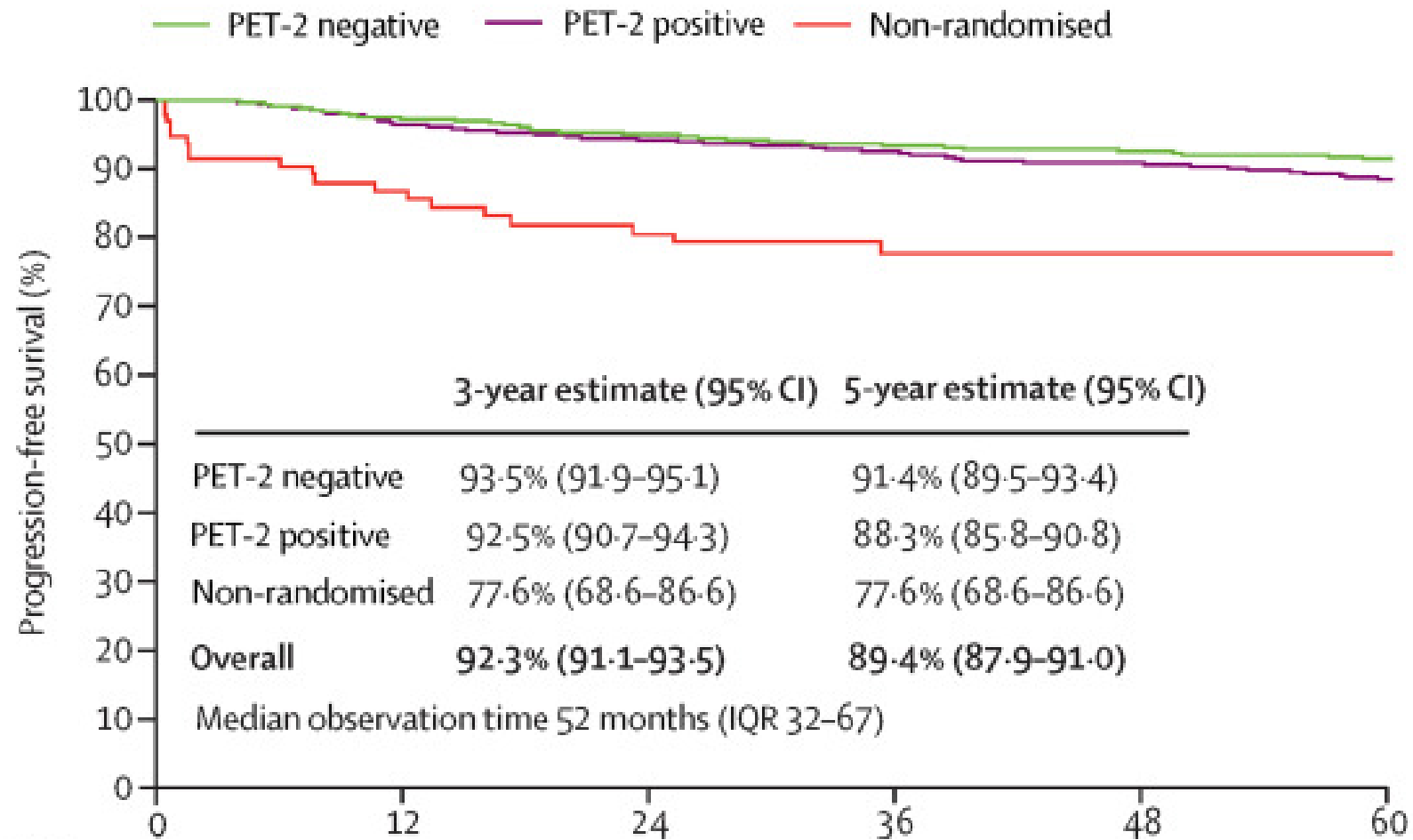
Progression-free Survival among Patients with Positive PET Findings



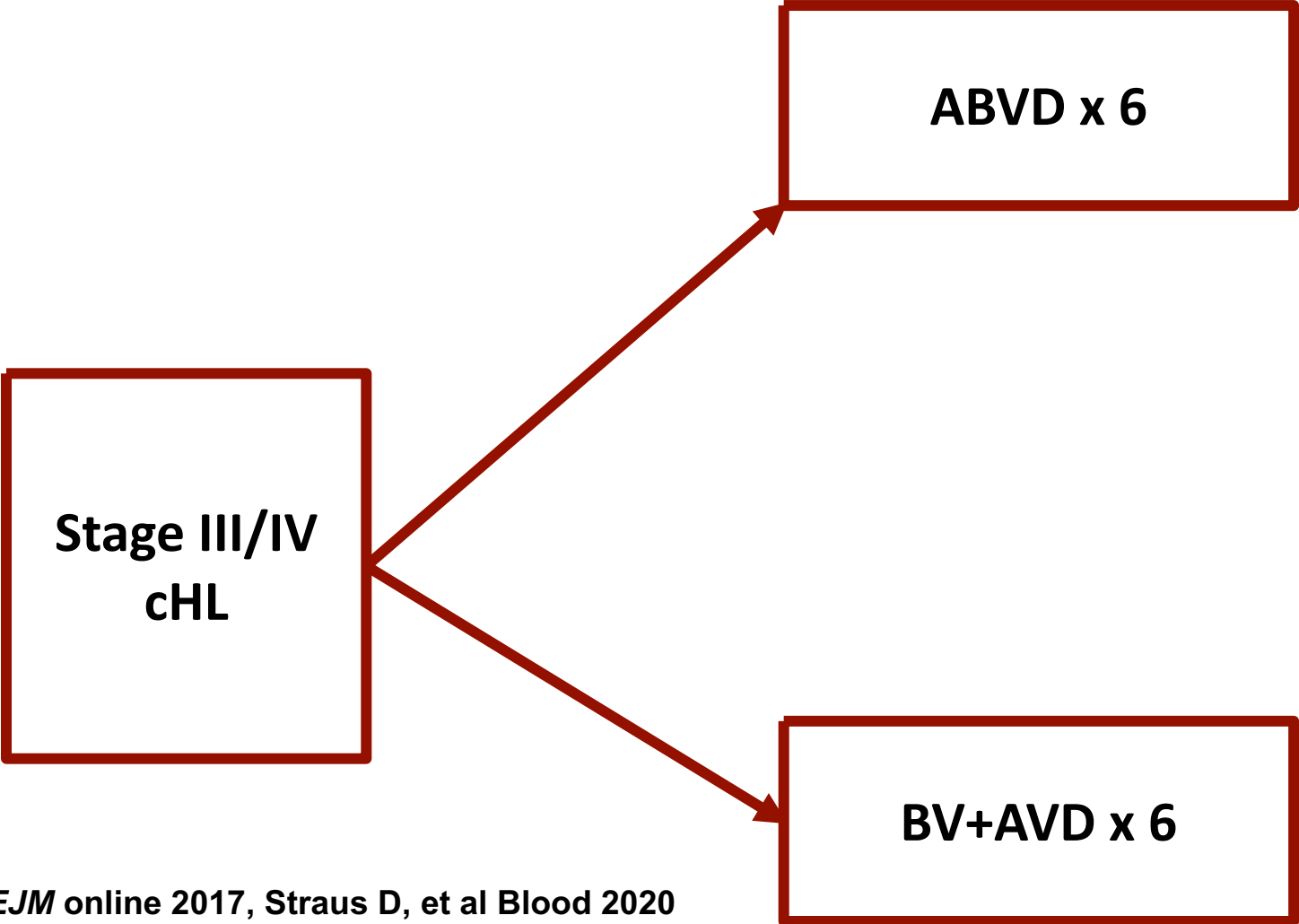
HD18: escBEACOPP in advanced stage HL



escBEACOPP: best disease control in advanced stage HL

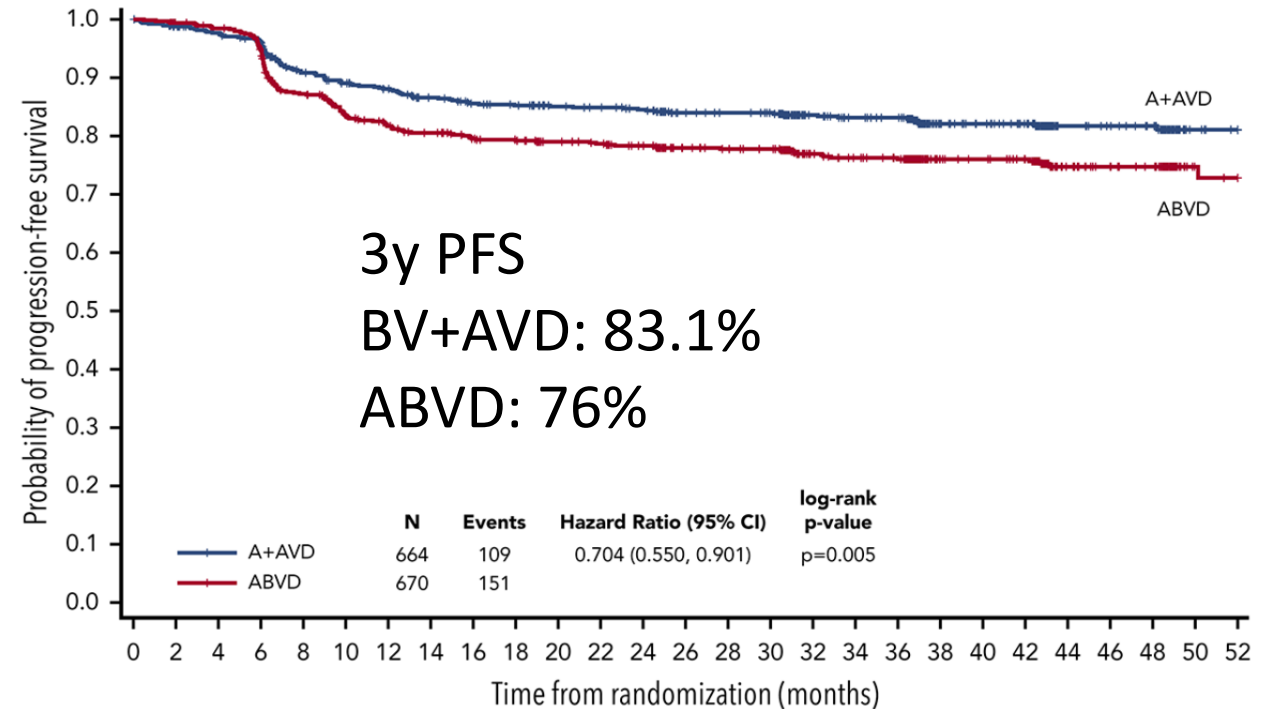
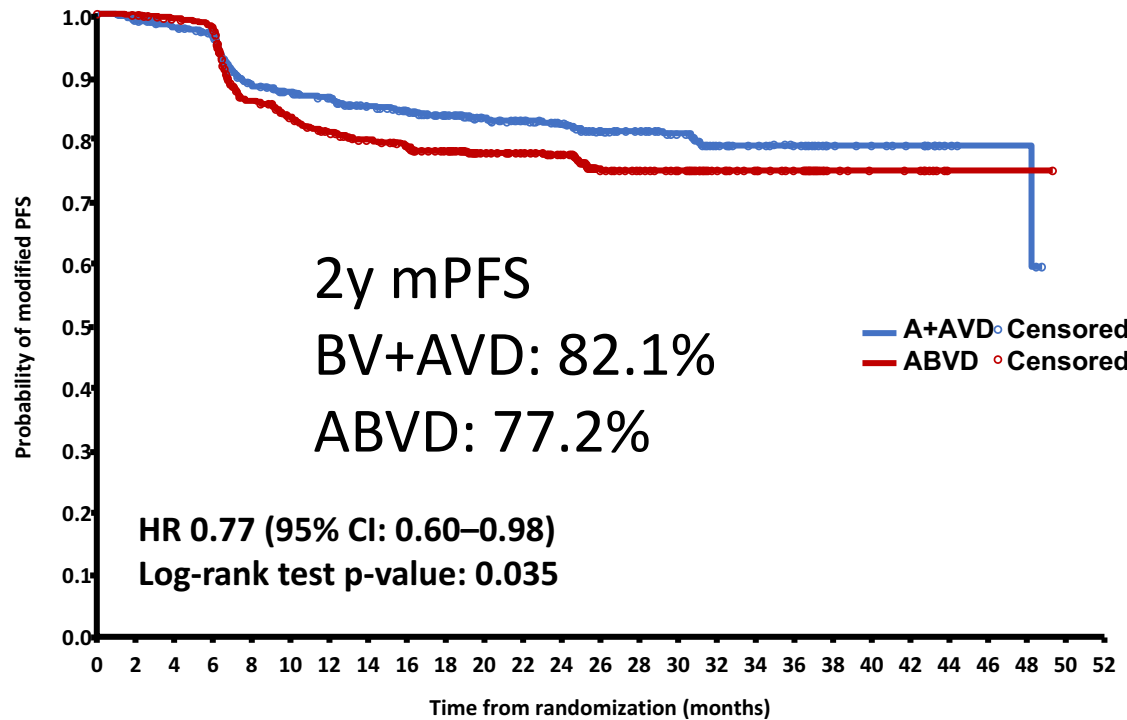


ECHELON-1: BV+AVD in advanced stage HL



Connors et al. *NEJM* online 2017, Straus D, et al *Blood* 2020

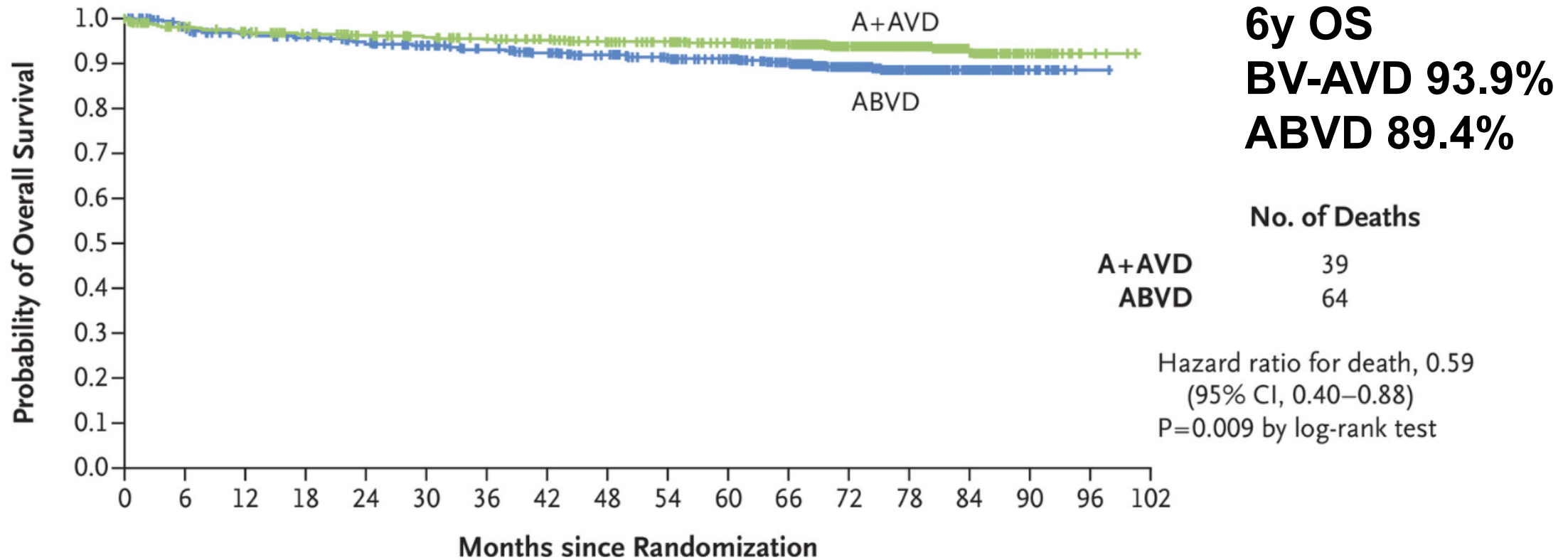
ECHELON-1: BV+AVD in advanced stage HL



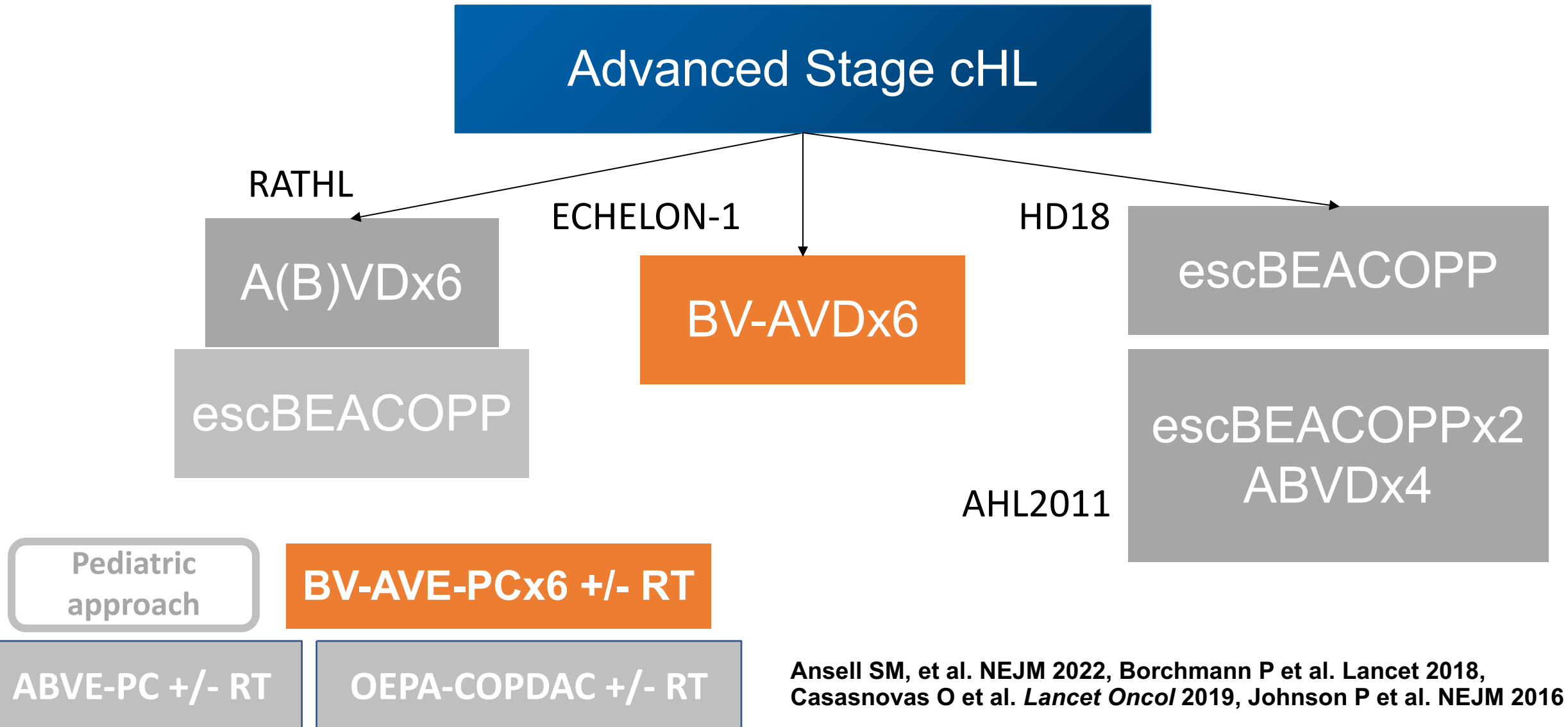
BV-AVD: more febrile neutropenia and neuropathy

| | BV+AVD | ABVD |
|---|---|--|
| Grade ≥ 3 AE | 549 (83%) | 343 (66%) |
| SAE | 284 (43%) | 178 (27%) |
| PN all grades | 55% | 30% |
| PN grade ≥ 3 | 9% | 1% |
| SAE of febrile neutropenia, sepsis, infection, neutropenia | 33% no G-CSF ppx 24% G-CSF ppx | 17% no G-CSF ppx 9% G-CSF ppx |

The end of ABVD: BV-AVD improves OS



Standard Management of Advanced Stage cHL

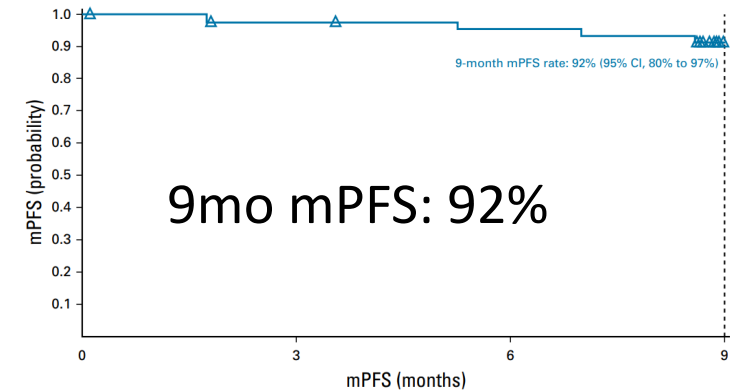


Incorporating PD-1 blockade into initial cHL therapy is well-tolerated and highly effective

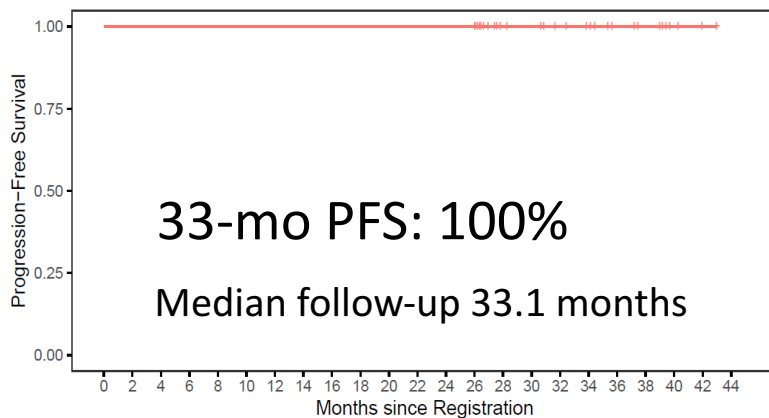
Studies of frontline PD-1 blockade in cHL have been promising^{10,11,12,13}

- N-AVD well-tolerated
- Excellent PFS

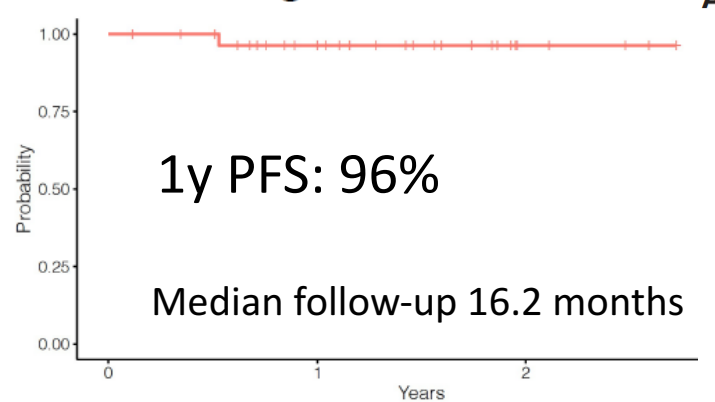
1L Nivolumab-AVD in advanced stage cHL



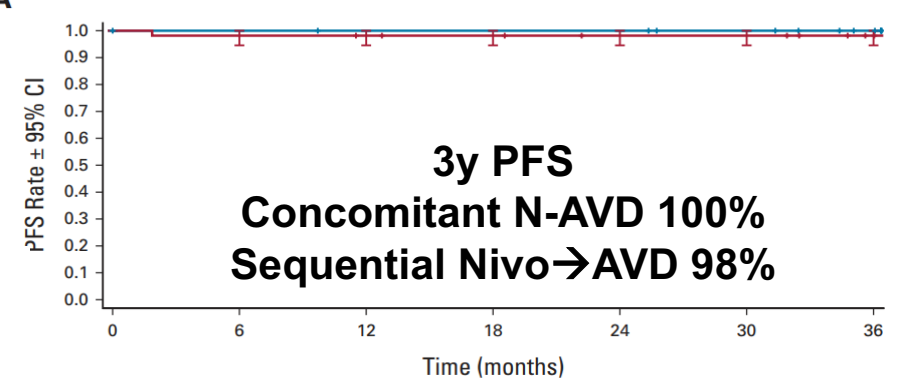
Sequential Pembro-AVD in cHL



Concurrent Pembro-AVD in cHL Progression-free survival

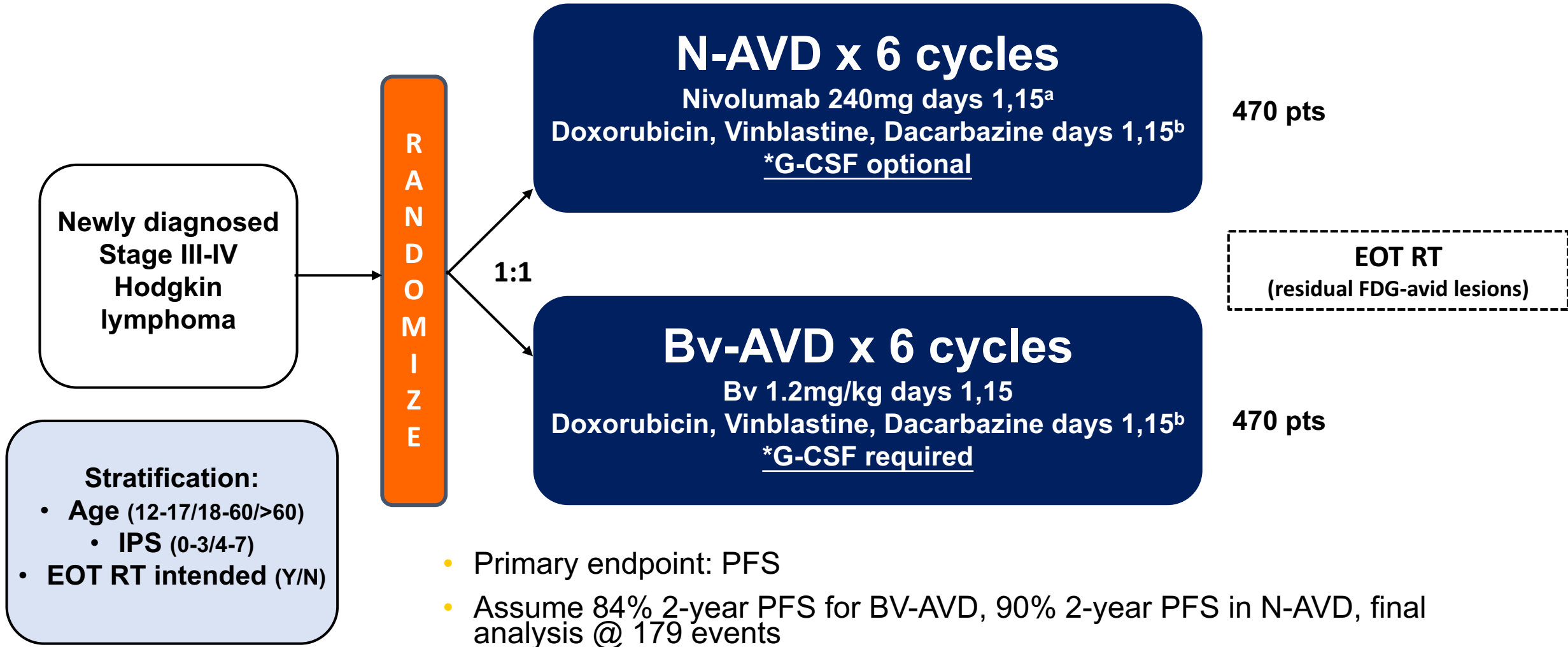


1L Nivolumab-AVD in early stage cHL



10. Bröckelmann PJ et al JCO. 2023 11. Ramchandren R et al JCO 2019 12. Allen PB, et al Blood. 2021 13. Lynch RC et al Blood 2023

S1826 Study Design



^a Nivolumab 3mg/kg for ages ≤ 17, max 240mg

^b Conventional doses of AVD: Stephens DM et al Blood 2019, Ansell SM et al NEJM 2022

S1826 Baseline Characteristics

| Baseline characteristics | N-AVD n=487 N (%) | Bv-AVD n=483 N (%) |
|----------------------------|-------------------------|--------------------------|
| Age, median (range) | 27 (12-83) | 26 (12-81) |
| 12-17 years | 118 (24%) | 118 (24%) |
| 18-60 years | 321 (66%) | 318 (66%) |
| ≥ 61 years | 48 (10%) | 47 (10%) |
| Female Sex | 216 (44%) | 210 (43%) |
| Race | | |
| White | 372 (76%) | 361 (75%) |
| Black | 58 (12%) | 56 (12%) |
| Asian | 11 (2%) | 17 (4%) |
| Other/Unknown | 46 (9%) | 49 (10%) |
| Hispanic | 66 (14%) | 58 (12%) |

| Baseline characteristics | N-AVD n=487 N (%) | Bv-AVD n=483 N (%) |
|--------------------------------|-------------------------|--------------------------|
| Stage | | |
| III | 185 (38%) | 168 (35%) |
| IV | 302 (62%) | 315 (65%) |
| B symptoms present | 288 (59%) | 273 (57%) |
| IPS Score | | |
| 0-3 | 332 (68%) | 328 (68%) |
| 4-7 | 155 (32%) | 155 (32%) |
| Bulky disease > 10cm | 156 (32%) | 127 (26%) |
| HIV+ | 11 (2%) | 5 (1%) |

Representative study, inclusive of high-risk pts

N-AVD better tolerated than BV-AVD

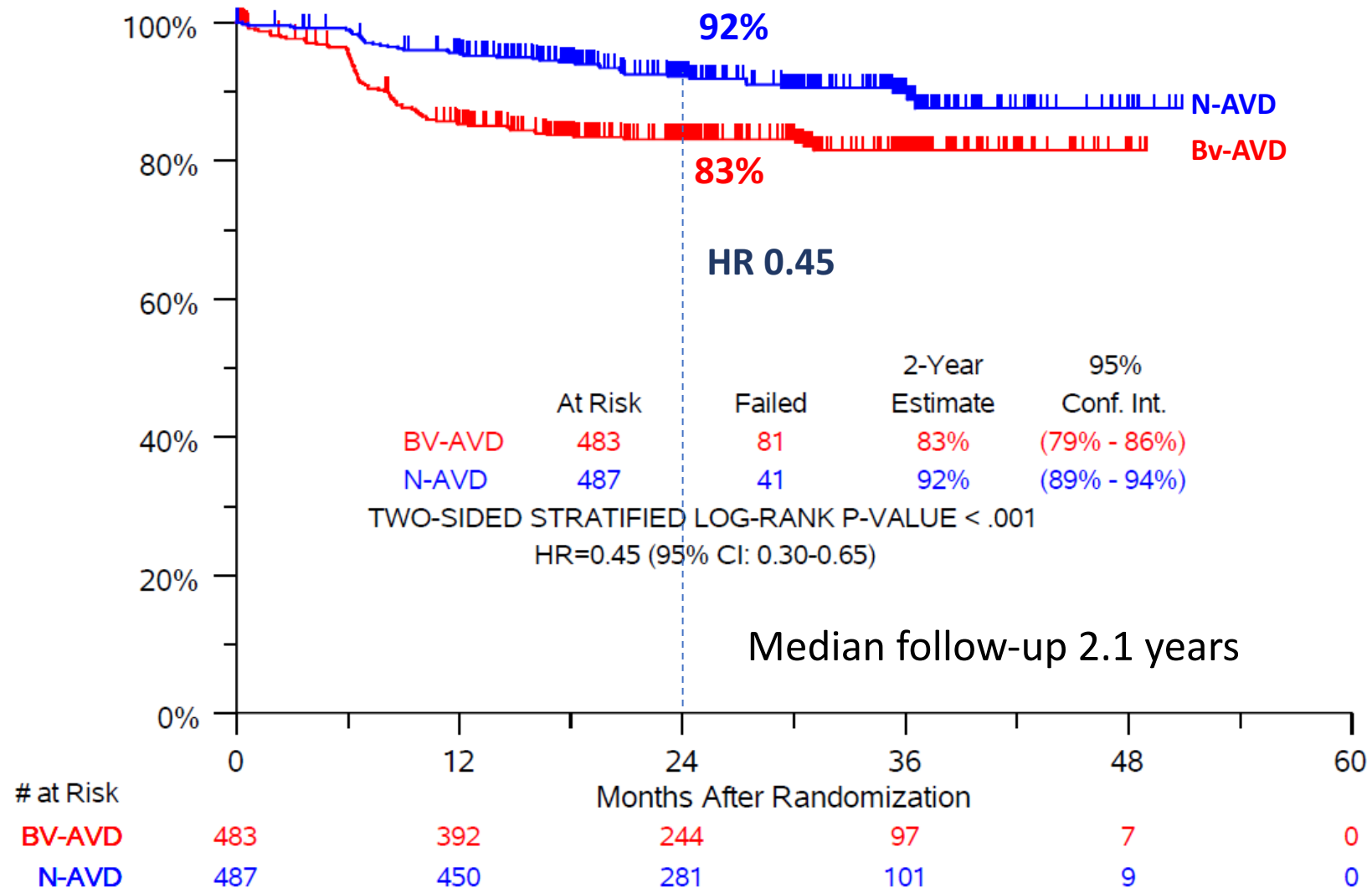
| | Received G-CSF | Gr \geq 3 neutropenia | Febrile neutropenia | Gr \geq 3 infections, infestations | Sepsis | Bone pain |
|------------------|----------------|-------------------------|---------------------|--------------------------------------|--------|-----------|
| N-AVD (n = 482) | 56% | 48% | 6% | 5% | 2% | 8% |
| BV-AVD (n = 476) | 97% | 26% | 7% | 7% | 3% | 20% |

| | Peripheral sensory Neuropathy All Gr/Gr 2+ | Peripheral motor neuropathy All Gr/Gr 2+ | Thyroid dysfunction | ALT increased | Pneumonitis | Colitis |
|------------------|--|--|---------------------|---------------|-------------|---------|
| N-AVD (n = 482) | 29%/9% | 4%/1% | 10% | 33% | 2% | 1% |
| BV-AVD (n = 476) | 56%/32% | 7%/5% | 1% | 42% | 3% | 1% |

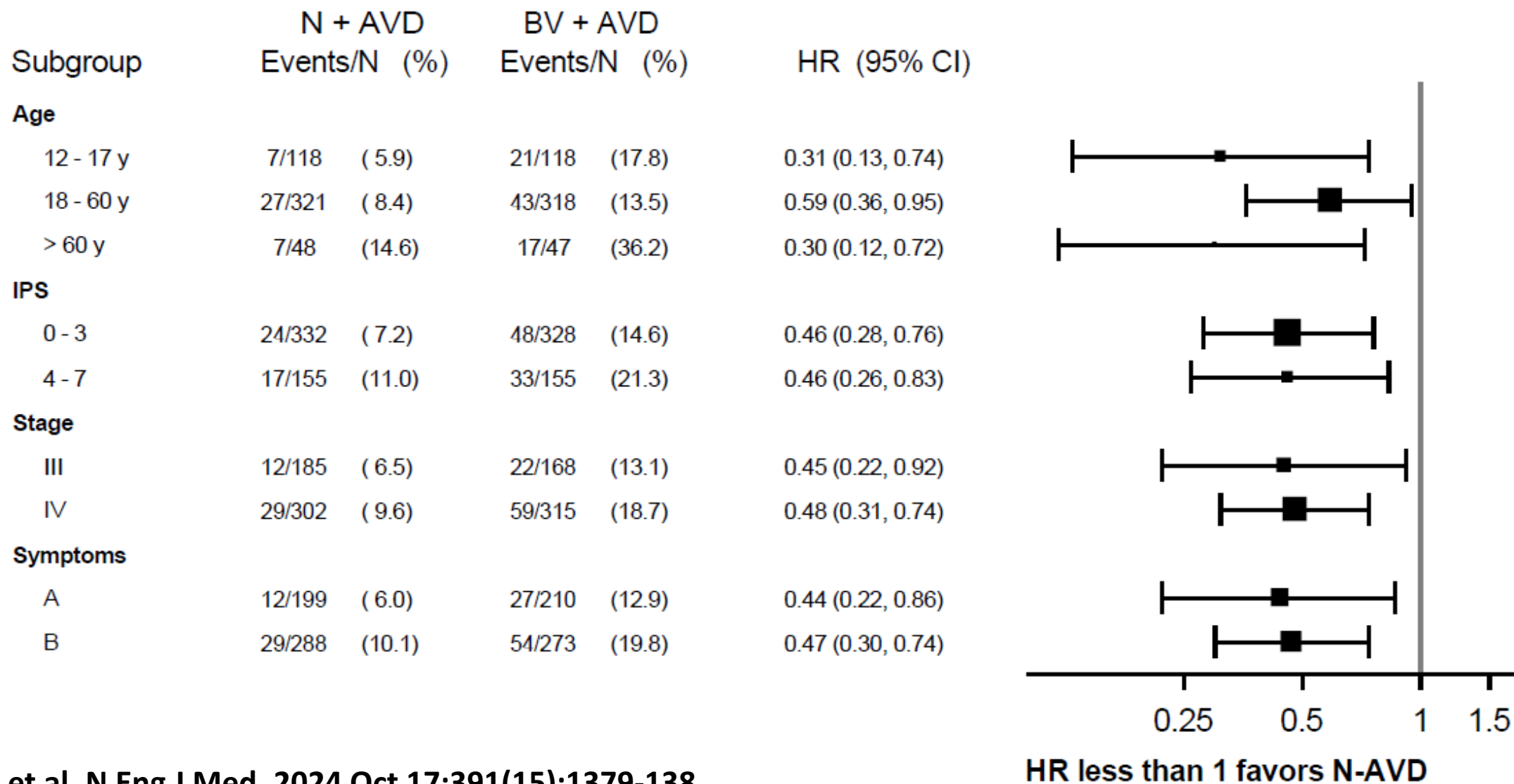
Treatment Discontinuation and Deaths

| Disposition | N-AVD (n=487) N (%) | Bv-AVD (n=483) N (%) |
|--|---------------------------|----------------------------|
| Completed treatment | 450 (92.4%) | 425 (88%) |
| Discontinued all treatment early | 37 (7.6%) | 58 (12%) |
| Adverse event | 20 (4.1%) | 20 (4.1%) |
| Refusal unrelated to AE | 9 | 13 |
| Progression/relapse | 0 (0%) | 9 (1.9%) |
| Death on treatment | 3 (0.6%) | 8 (1.7%) |
| Other – not protocol specified | 5 | 8 |
| Any discontinuation Bv or Nivolumab | 46 (9.4%) | 107 (22.2%) |
| Dose reduction | NA | 129 (26.7%) |
| Received radiotherapy | 3 (0.6%) | 4 (0.8%) |

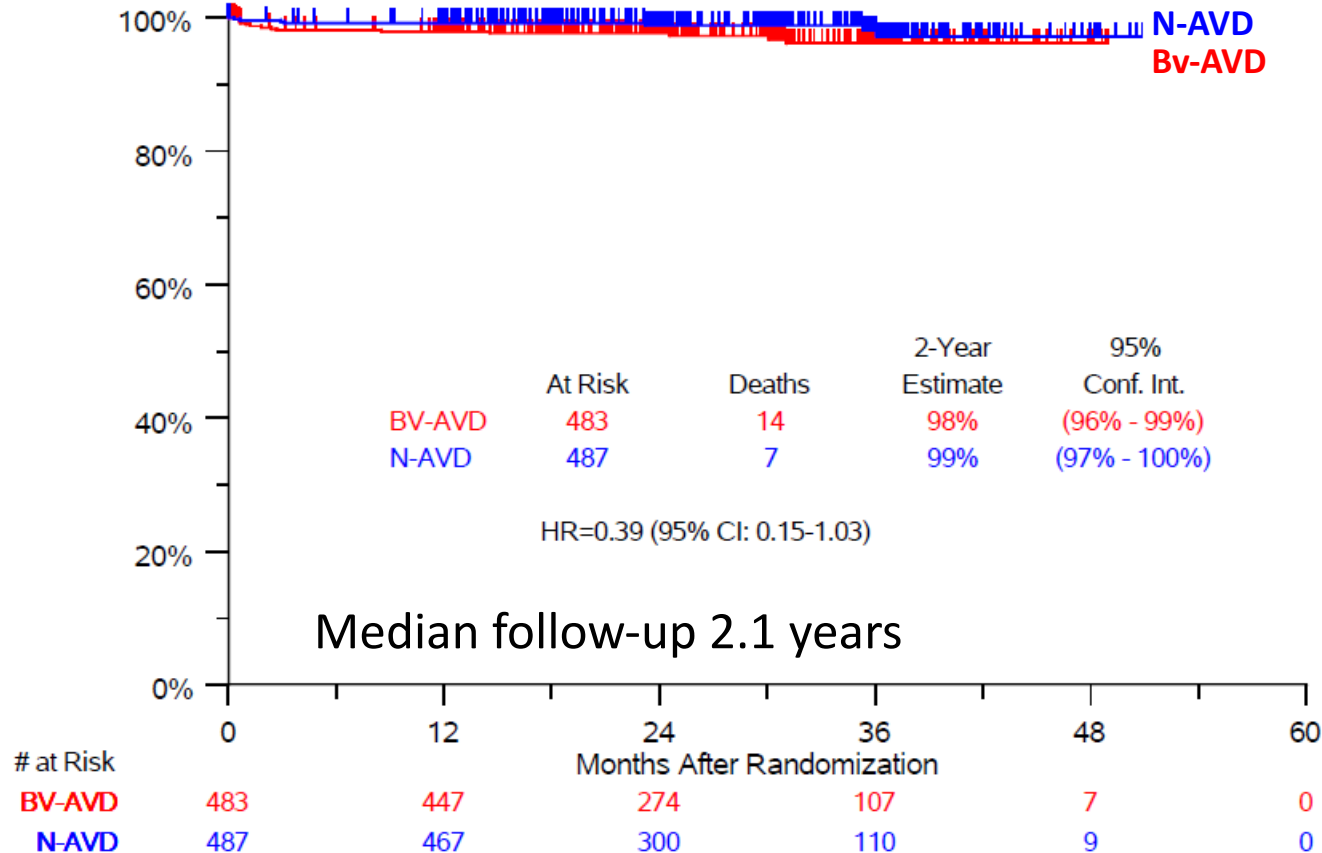
N-AVD improves PFS compared to Bv-AVD



PFS benefit with N-AVD consistent across subgroups

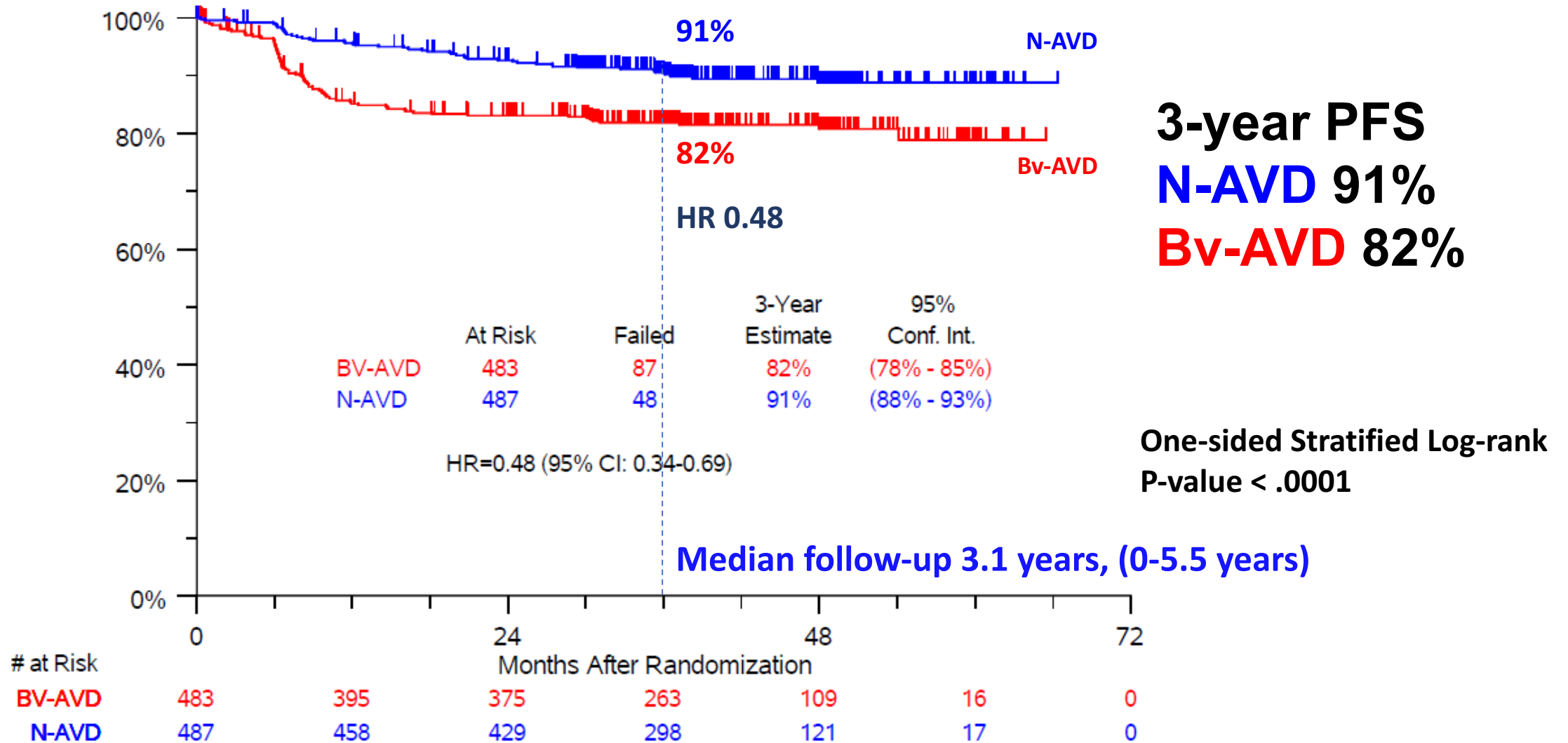


Overall Survival

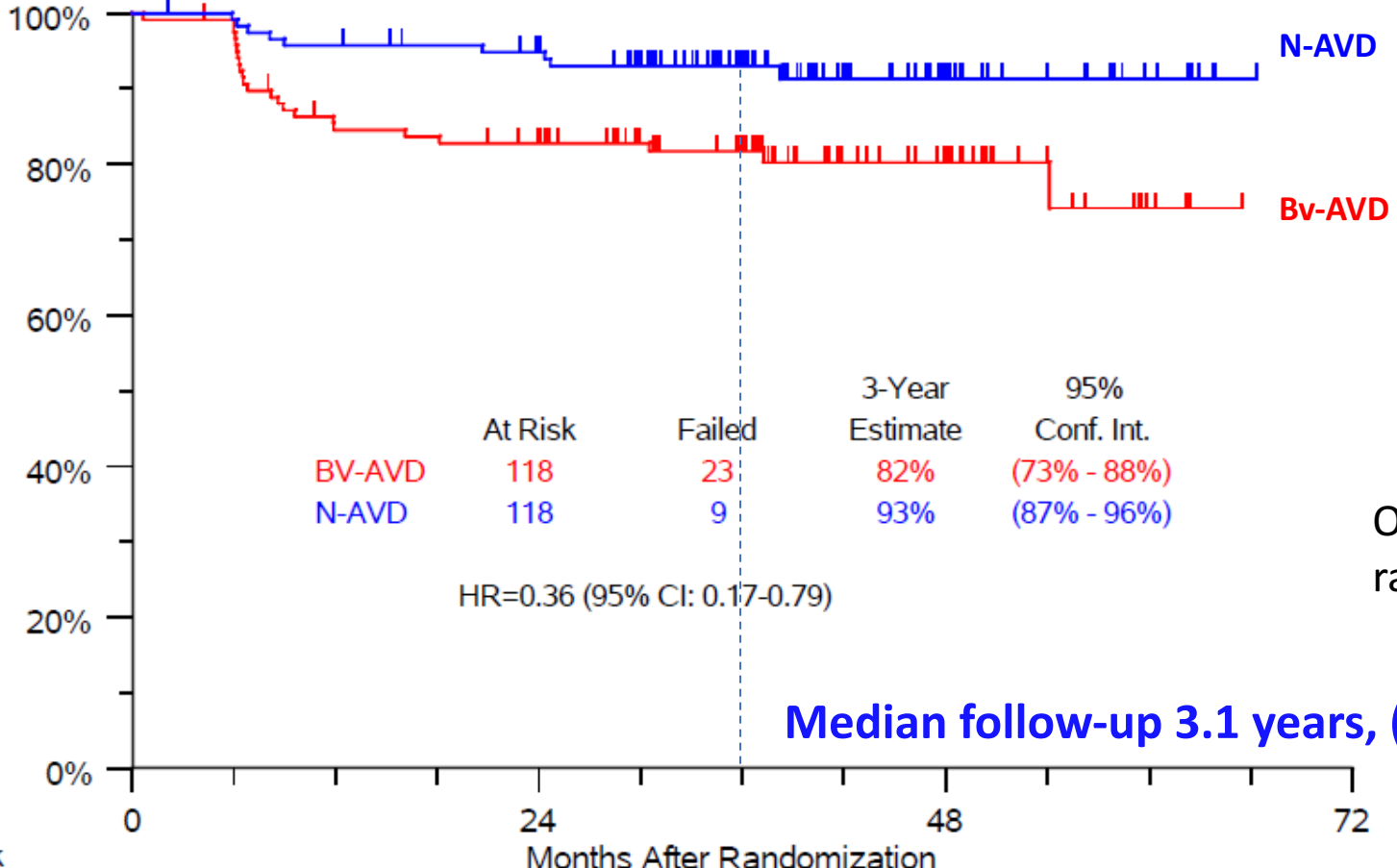


| Cause of Death | N-AVD N=487 | BV-AVD N=483 |
|----------------------------------|----------------|-----------------|
| Infection/Sepsis | 4 | 6 |
| Lymphoma | 1 | 2 |
| Medical issues other than cancer | 2 | 4 |
| New primary malignancy | 0 | 1 |
| Unknown | 0 | 1 |
| Total | 7 | 14 |

PFS benefit of N-AVD sustained with 3y follow-up



N-AVD prolongs PFS in adolescents

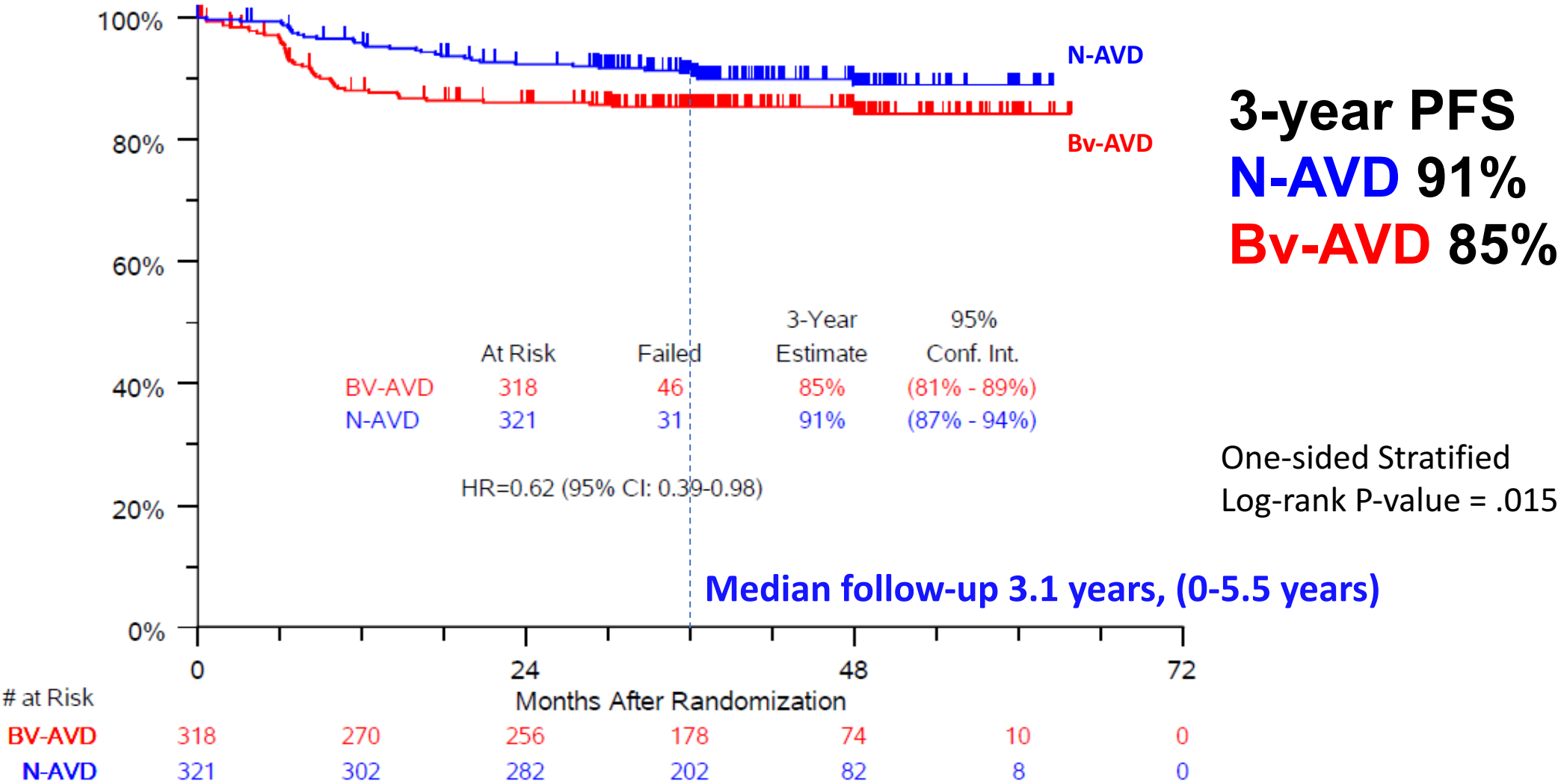


3-year PFS
N-AVD 93%
BV-AVD 82%

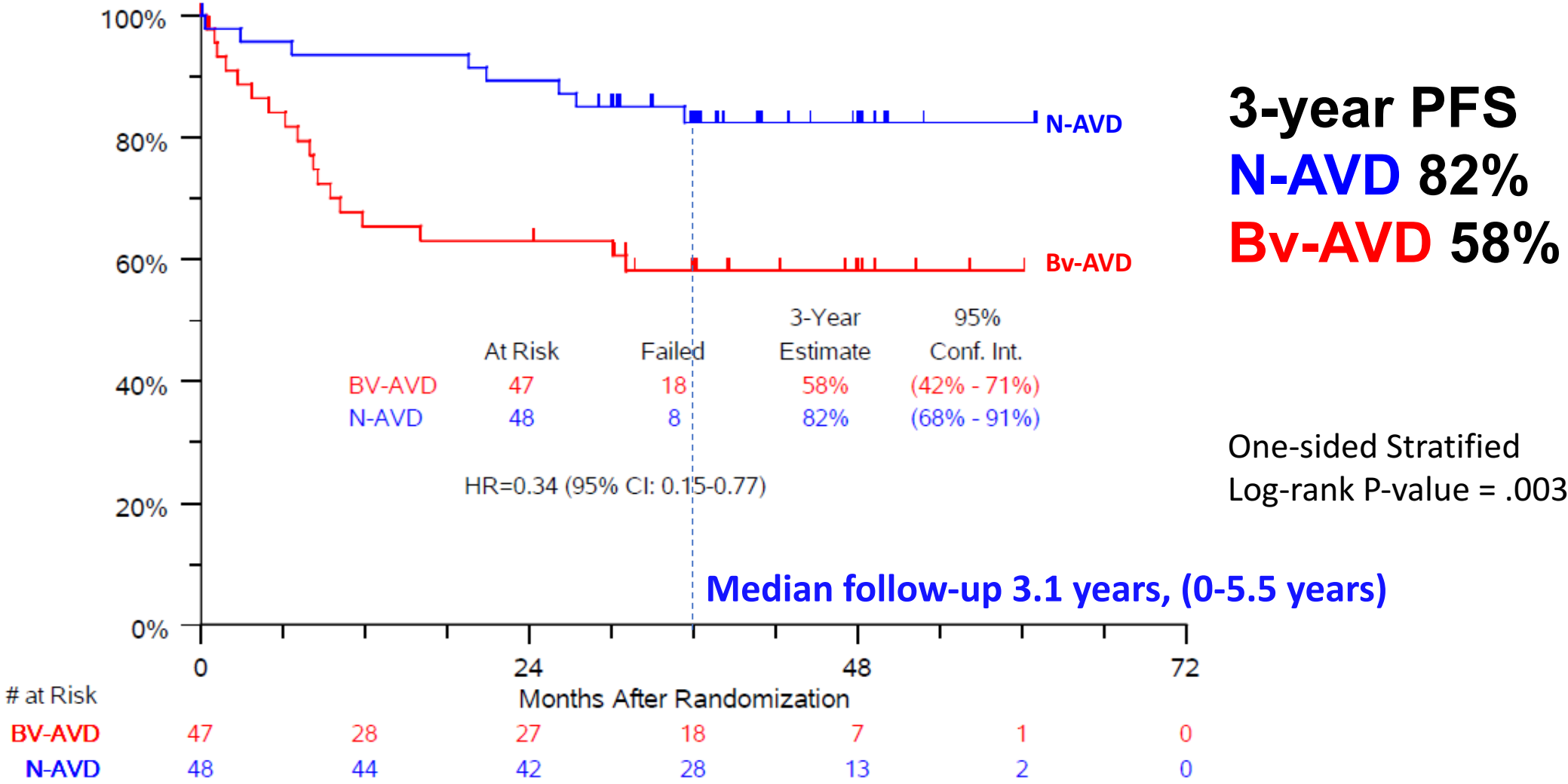
One-sided Stratified Log-rank P-value = .004

| # at Risk | 0 | 24 | 48 | 72 | | | |
|---------------|-----|-----|-----|----|----|---|---|
| BV-AVD | 118 | 97 | 92 | 67 | 28 | 5 | 0 |
| N-AVD | 118 | 112 | 105 | 68 | 26 | 7 | 0 |

N-AVD prolongs PFS in 18-60 year-old adults

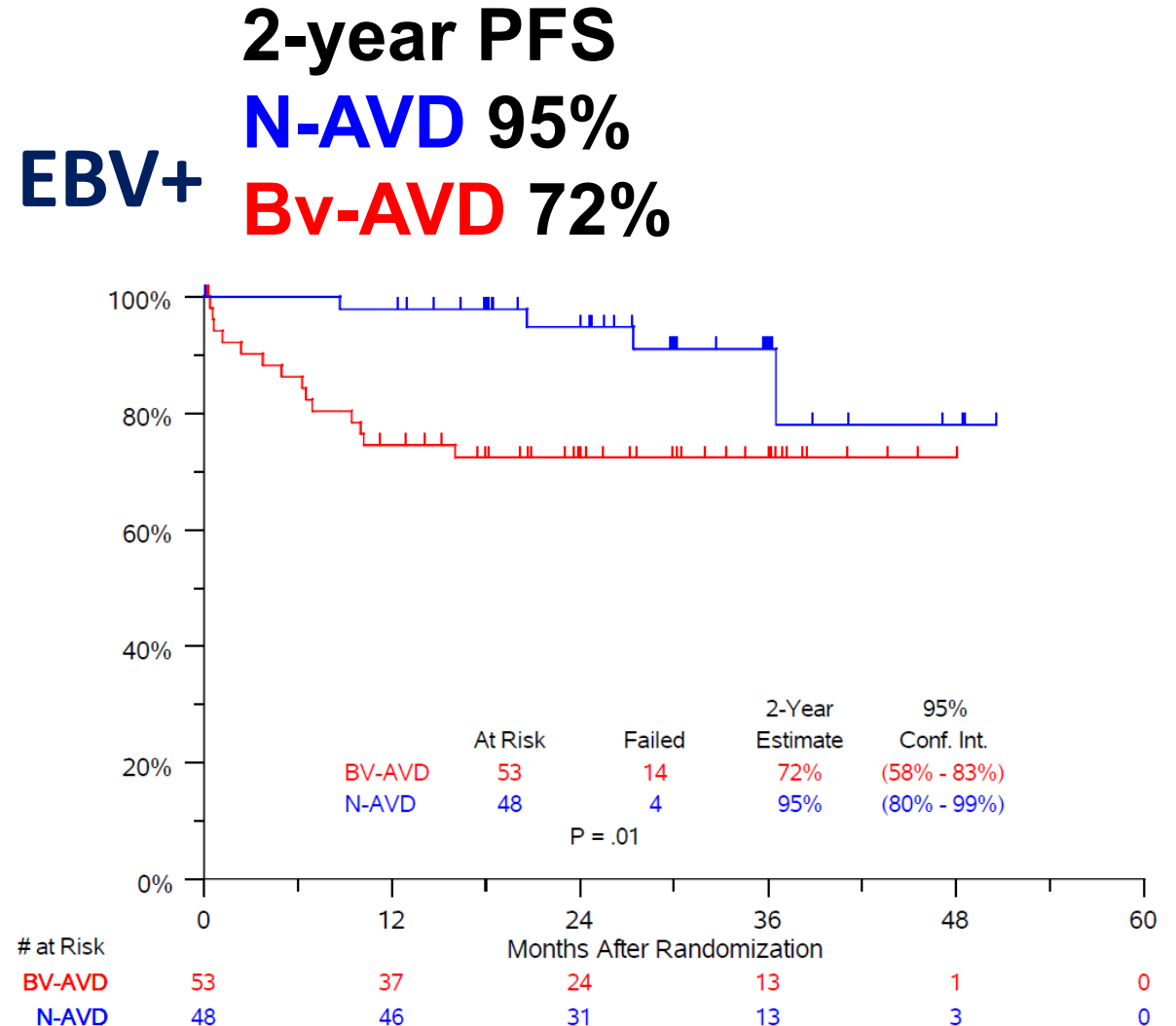
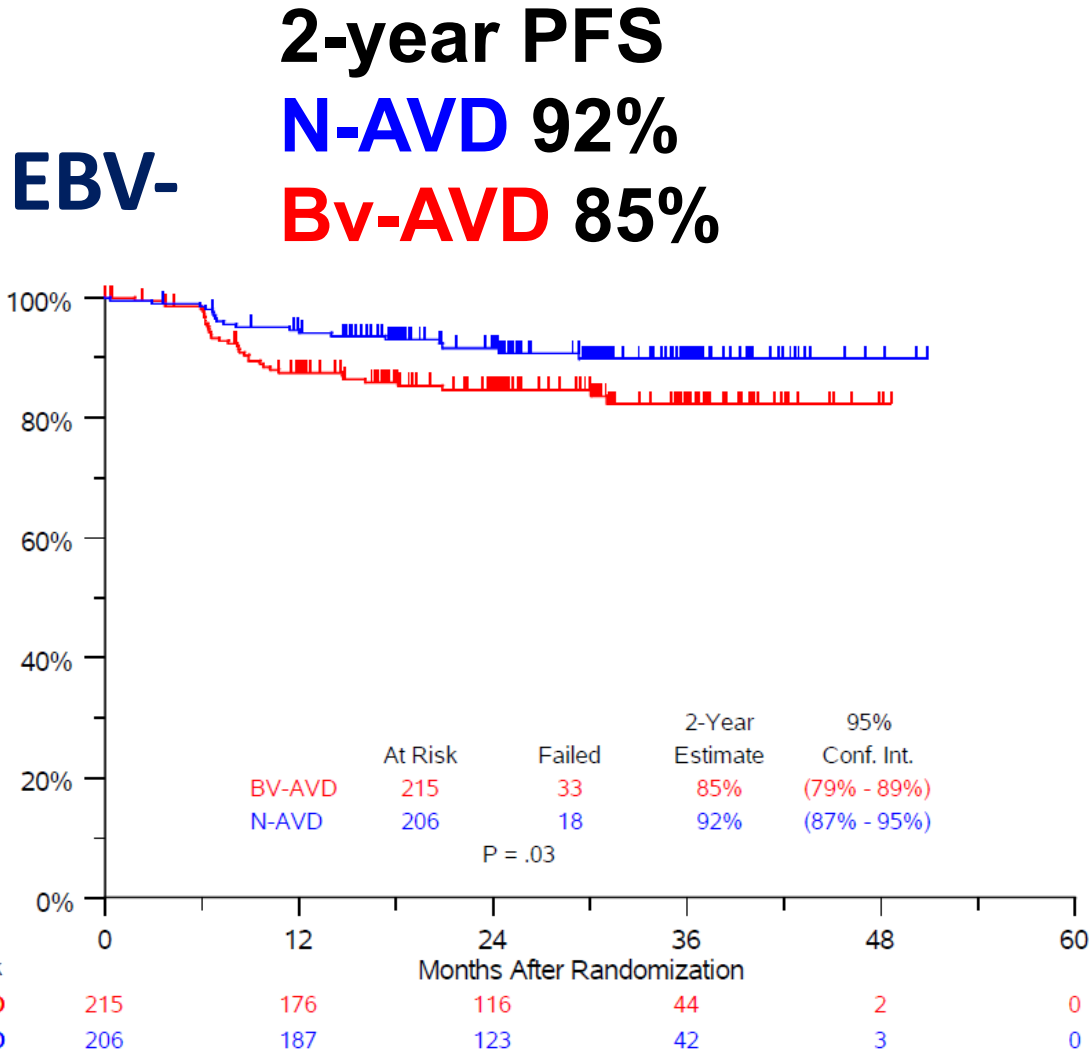


N-AVD prolongs PFS in older adults



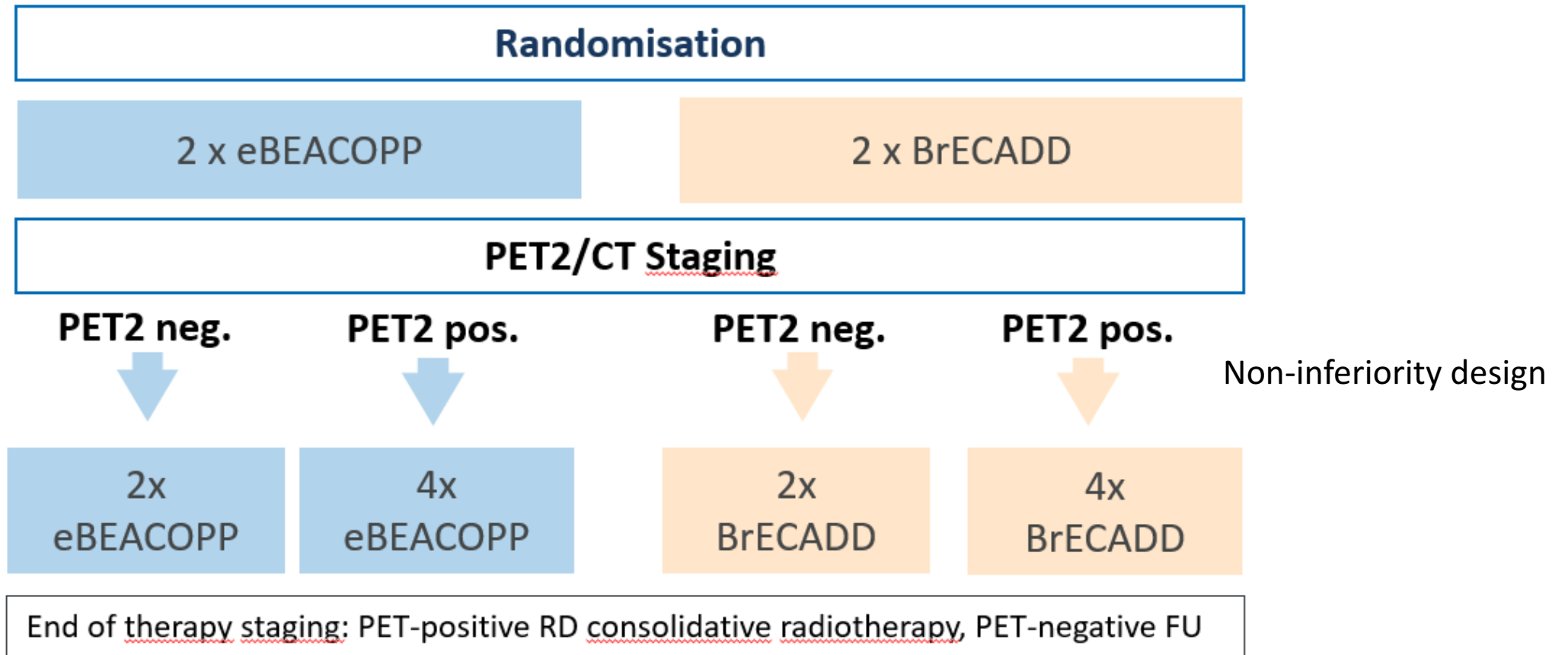
One-sided Stratified
 Log-rank P-value = .003

N-AVD > BV-AVD in EBV- and EBV+ cHL



HD21: Reducing toxicity of escBEACOPP

- Advanced stage cHL < 60y



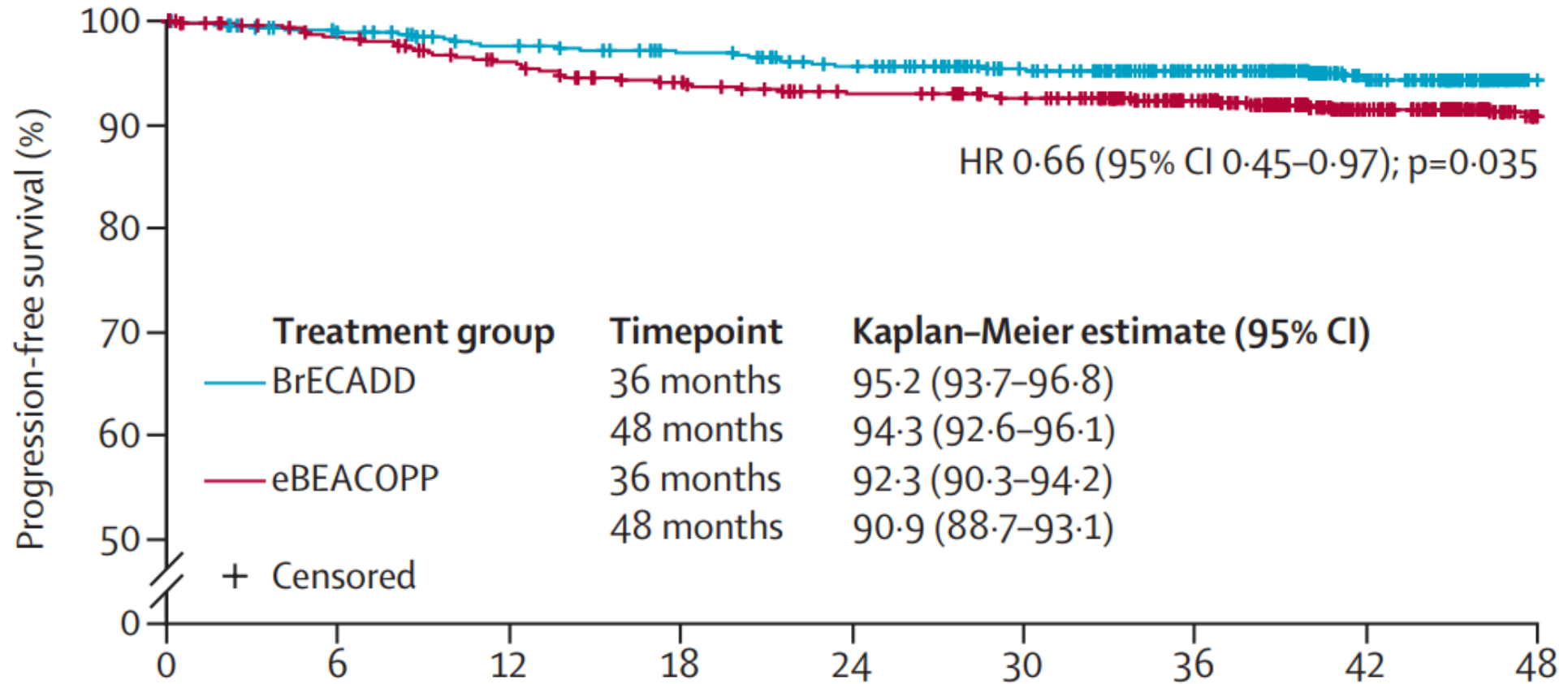
HD21: Reducing toxicity of escBEACOPP

| Drug | Day | BEACOPP ¹ Dose (mg/m ²) | BrECADD Dose (mg/m ²) | Potential <u>improvement</u> |
|-------------------------|------|---|--------------------------------------|---------------------------------------|
| Bleomycin | 8 | 10 | - | <u>lung tox</u> |
| Etoposide | 1-3 | 200 | 150 | <u>hem tox, transfusion frequency</u> |
| <u>Doxorubicin</u> | 1 | 35 | 40 | |
| <u>Cyclophosphamide</u> | 1 | 1250 | 1250 | |
| <u>Vincristine</u> | 8 | 1.4 | - | neuropathy |
| Brentuximab vedotin | 1 | - | 1.8 mg/kg | |
| Procarbazine | 1-7 | 100 | - | gonadal tox, sAML/MDS |
| <u>Prednisone</u> | 1-14 | 40 | - | weight, bone, infections |
| Dacarbazine | 2-3 | - | 250 | |
| Dexamethasone | 1-4 | - | 40 | |

BrECADD better tolerated than escBEACOPP

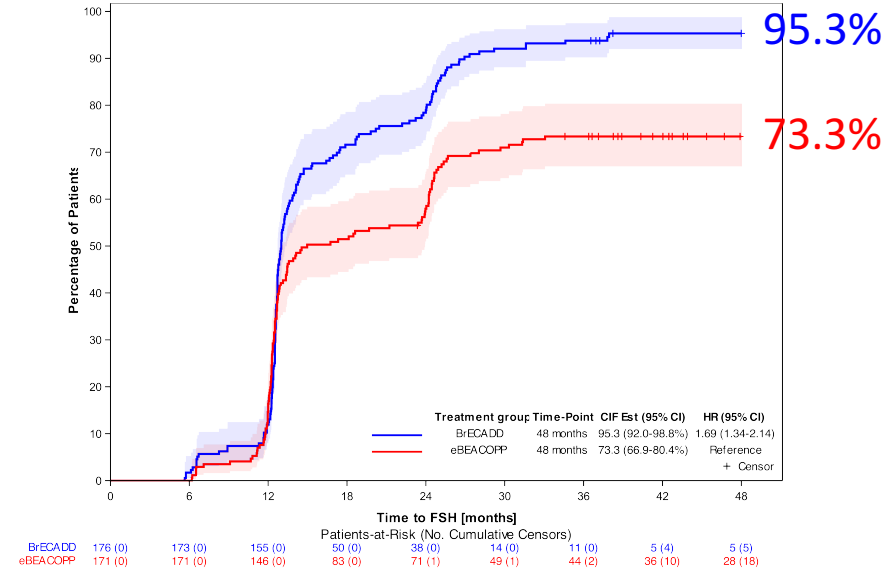
| Adverse event, n (%) | BrECADD (n=738) | | escBEACOPP (n=732) | |
|---|--------------------|----------|-----------------------|----------|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Neutropenic fever | 194 (28) | 193 (28) | 144 (21) | 141 (21) |
| Infection | 358 (49) | 150 (20) | 335 (46) | 138 (19) |
| Peripheral sensory neuropathy | 287 (39) | 10 (1) | 360 (49) | 17 (2) |
| Peripheral motor neuropathy | 28 (4) | 3 (<1) | 31 (4) | 1 (<1) |
| Respiratory, thoracic, and mediastinal disorders | 282 (38) | 24 (3) | 347 (47) | 34 (5) |
| Treatment related morbidity | | | | |
| Anemia, thrombocytopenia, or infection of CTCAE grade 4 | 231 (31) | | 382 (52) | |
| Organ toxicity of CTCAE grade 3–4 | 139 (19) | | 126 (17) | |
| Treatment-related morbidity | 312 (42) | | 430 (59) | |

HD21: BrECADD >> escBEACOPP

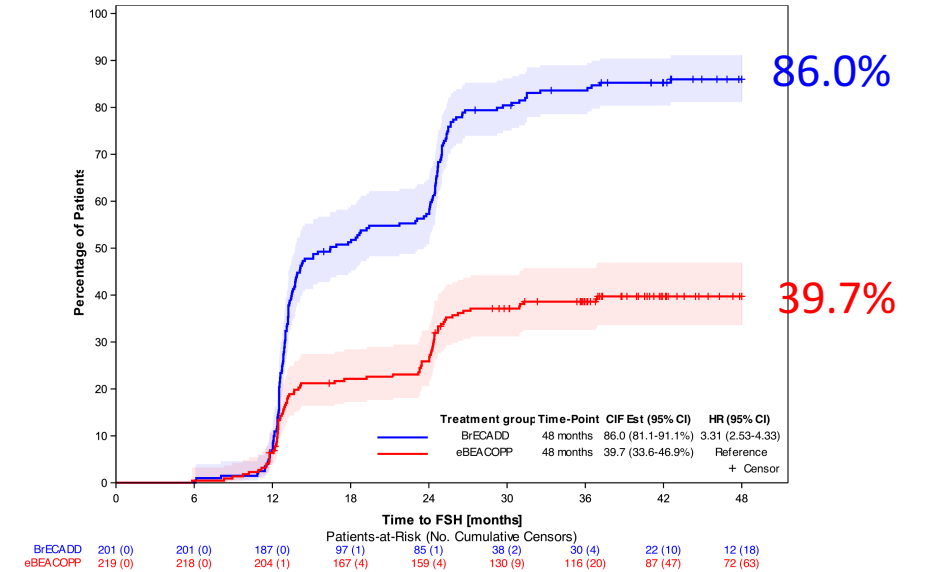


GHSB HD21 gonadal function and fertility

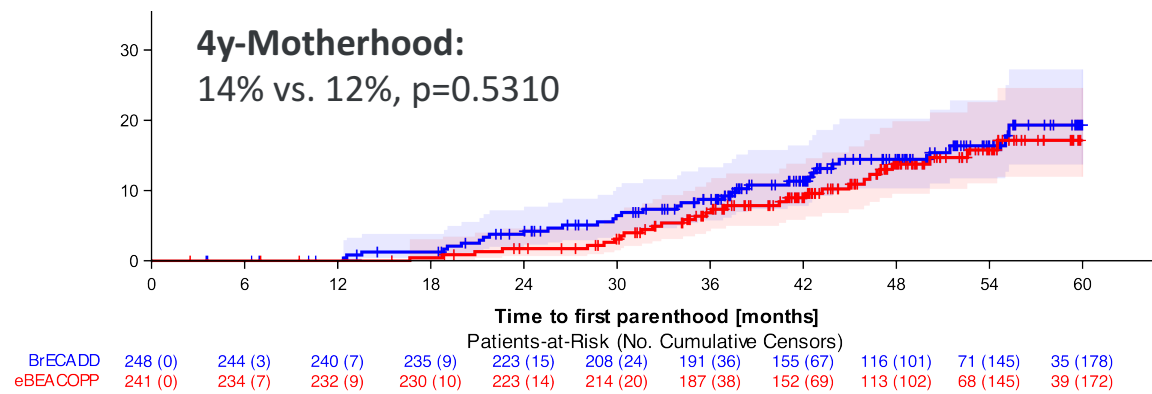
Women up to 40



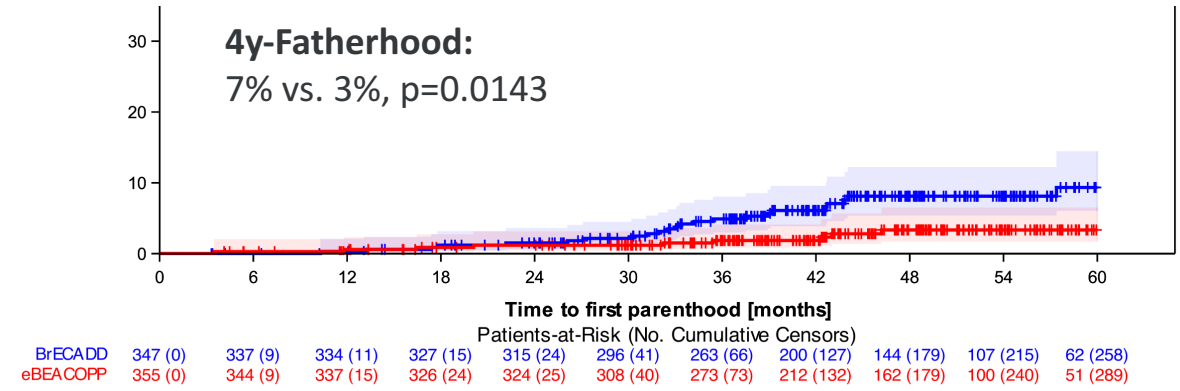
Men up to 50



4y-Motherhood:
14% vs. 12%, p=0.5310



4y-Fatherhood:
7% vs. 3%, p=0.0143





HOW TO CHOOSE?

HD21 BrECADD vs S1826 Baseline Characteristics



- HD21: Ages 18-60 only (separate 60+ cohort)
- HIV+ included S1826, excluded in HD21
- Stage IIB (+ extranodal and/or bulky) included in HD21
 - Stage IV = 45% in HD21 vs 63% in S1826
- IPS 4-7 = 21% in HD21 vs 32% in S1826

BrECADD vs N-AVD hematologic toxicity



| Toxicity | Frequency (%) |
|------------------------------|---------------|
| Gr \geq 3 anemia | 30% (vs 6%) |
| PRBC transfusion | 24% |
| Gr \geq 3 thrombocytopenia | 55% (vs 2%) |
| Platelet transfusion | 17% |
| Gr \geq 3 leukopenia | 87% (vs 47%) |
| Febrile neutropenia | 28% (vs 5%) |
| Gr \geq 3 infection | 20% (vs 5%) |

BrECADD vs N-AVD – additional considerations



- Use of consolidative radiation: BrECADD 14% vs S1826 < 1%
- 2/3 of patients in HD21 BrECADD arm – 4 cycles of therapy

Pros/Cons of N-AVD vs BrECADD



Nivo-AVD

- Tolerability
 - Pros: less heme/infectious/GI tox; older pts can tolerate
 - Cons: Immune tox, more anthracycline
- Efficacy
 - No direct comparison, no clear difference
- Duration
 - 24 wks, longer than BrECADD, esp PET2 neg
- Logistics
 - Familiarity globally with PD1 blockade
 - Q2 week dosing

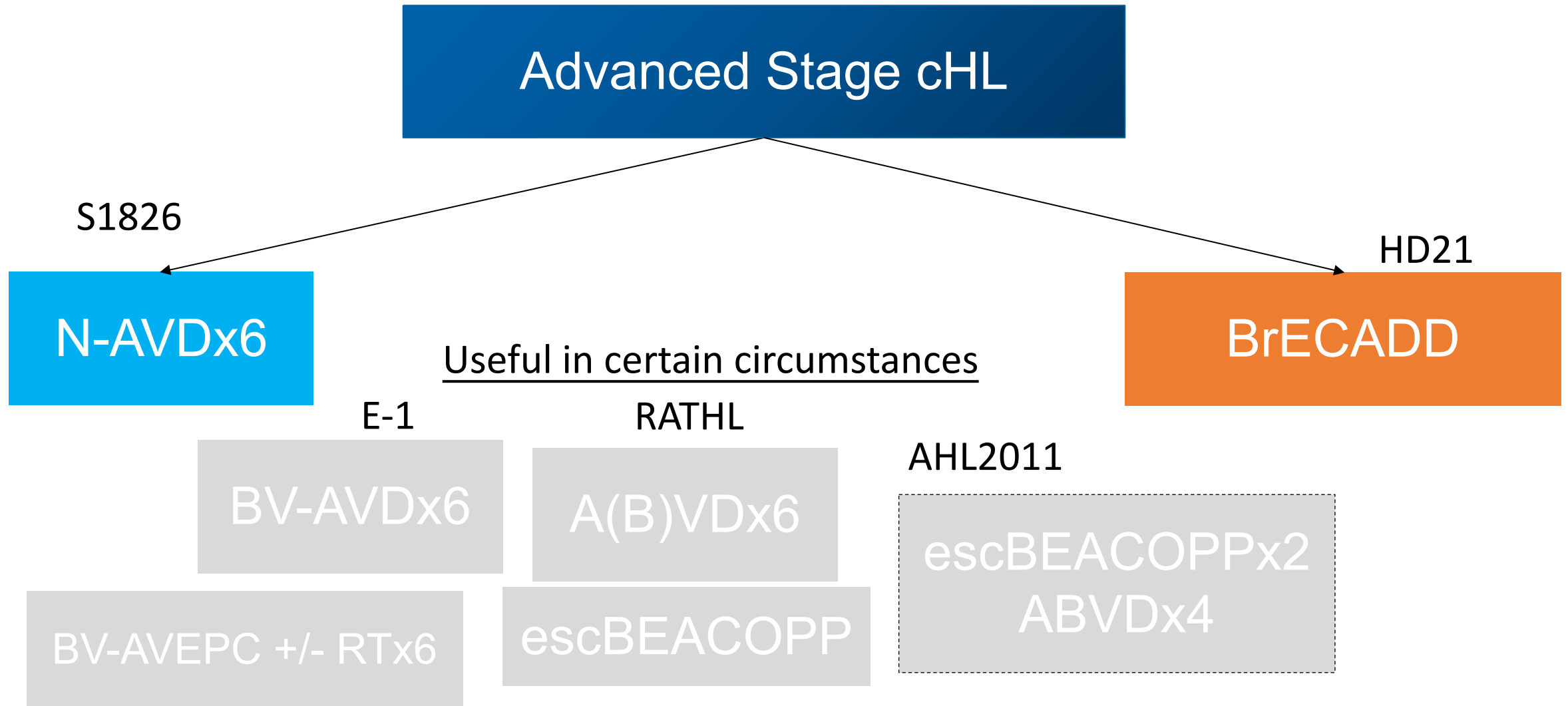


Adobe Stock | #1468432760

BrECADD

- Tolerability
 - Pros: no immune tox, less anthracycline
 - Cons: more heme/infectious/GI tox, toxic in older pts
- Efficacy
 - No direct comparison, no clear difference
- Duration
 - 12-18 wks, shorter than N-AVD, esp PET2 neg (2/3)
- Logistics
 - Daily dosing x 3-4 days
 - Transfusions, ~30% febrile neutropenia

Current Management of Advanced Stage cHL



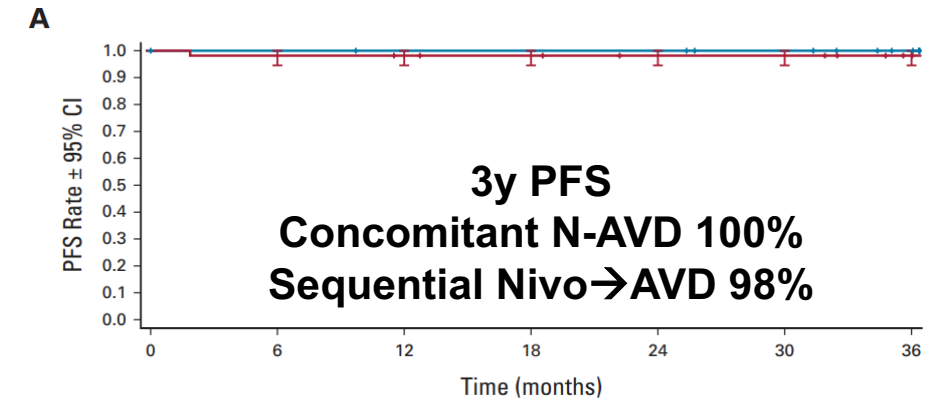


EARLY STAGE

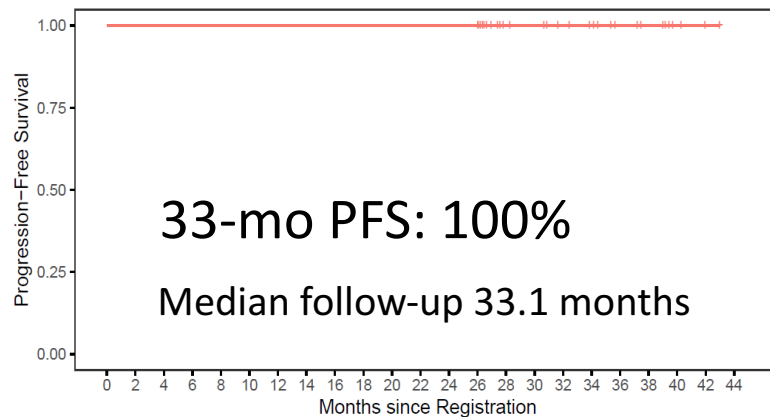
PD-1 blockade in early stage cHL safe and effective

- Studies of frontline PD-1 blockade in cHL have been promising^{10,11,12,13}
 - N-AVD well-tolerated
 - Excellent PFS

1L Nivolumab-AVD + RT in early stage cHL

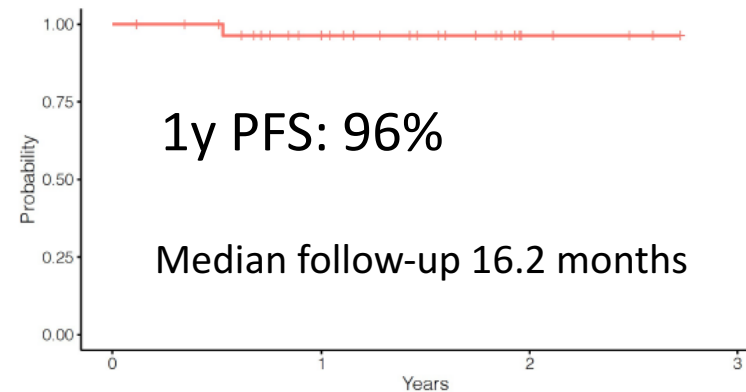


Sequential Pembro-AVD in cHL



Concurrent Pembro-AVD in cHL

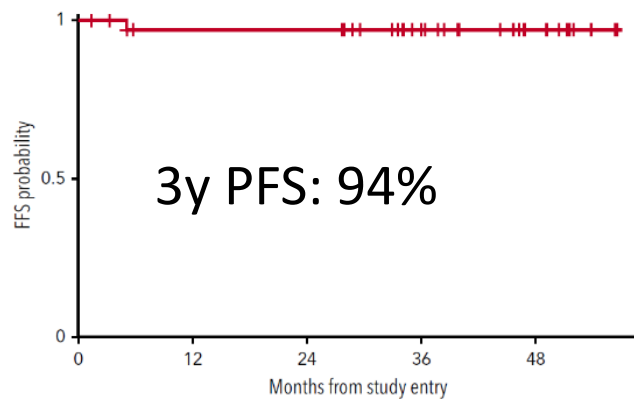
Progression-free survival



BV in early stage is safe and effective

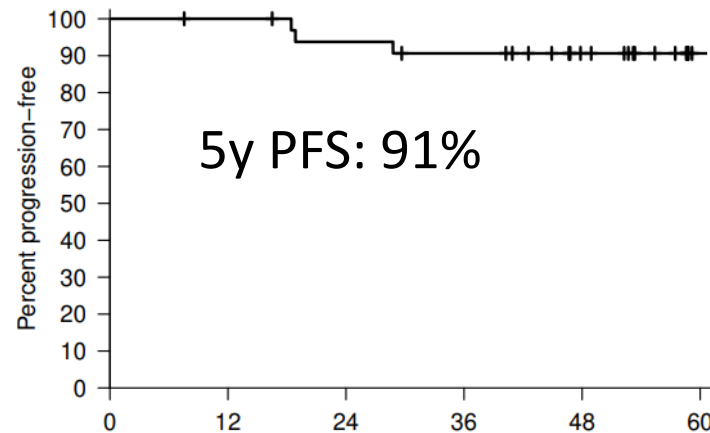
- Studies of frontline BV in cHL have been promising
 - Well-tolerated
 - Excellent PFS

BV-AVD in early stage non-bulky cHL

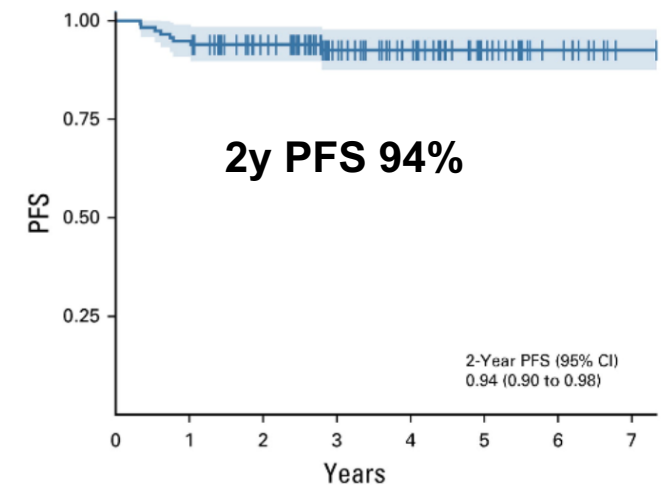


Abramson J, et al Blood 2019; Abramson J, et al. Blood Adv 2022; Kumar A, et al JCO 2021.

BV-AD in early stage non-bulky cHL



BV-AVD+/-RT in early unfavorable cHL



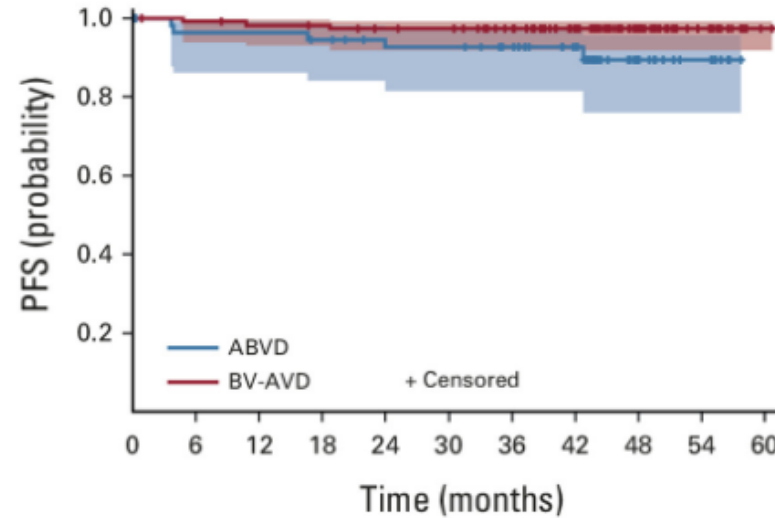
BREACH: BV-AVD + RT higher EOT CR vs ABVD + RT



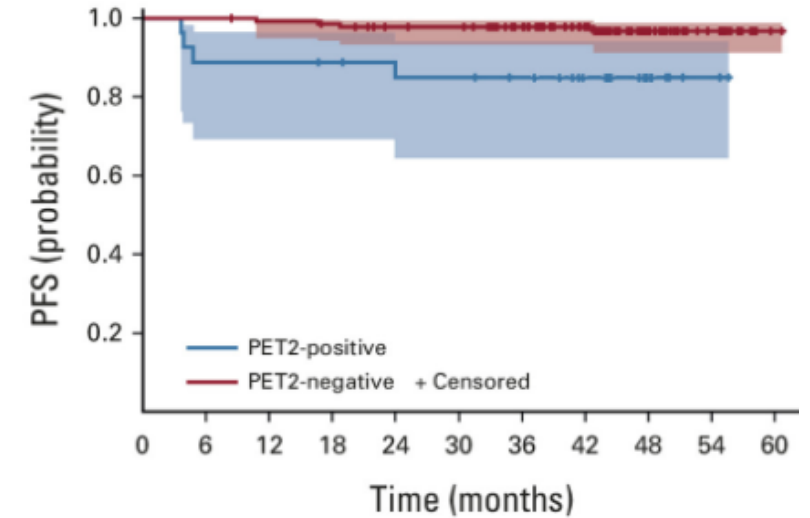
EOT CR
 BV-AVD+RT: 88%
 ABVD+RT: 77%

2y PFS PET2-
 97.8% vs 97.7%

2y PFS PET2+
 BV-AVD 93.8%
 ABVD 71.6%



| No. at risk: | | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 | 60 |
|--------------|--|-----|-----|-----|-----|-----|-----|----|----|----|----|----|
| ABVD | | 57 | 53 | 53 | 51 | 47 | 47 | 42 | 33 | 15 | 7 | 0 |
| BV-AVD | | 113 | 111 | 109 | 108 | 105 | 104 | 97 | 80 | 44 | 17 | 2 |



| No. at risk: | | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 | 60 |
|---------------|--|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|
| PET2-positive | | 27 | 24 | 24 | 23 | 21 | 21 | 19 | 14 | 7 | 2 | 0 |
| PET2-negative | | 136 | 136 | 134 | 132 | 127 | 126 | 116 | 95 | 50 | 21 | 1 |

AHOD2131: PET-adapted BV-Nivo in early stage cHL

n=1782

ABVD
x 2 cycles

PET2

Neg

Randomize

A(B^F)VD x 2^F – 4^U cycles

Bv-Nivo x 4 cycles

Pos

Randomize

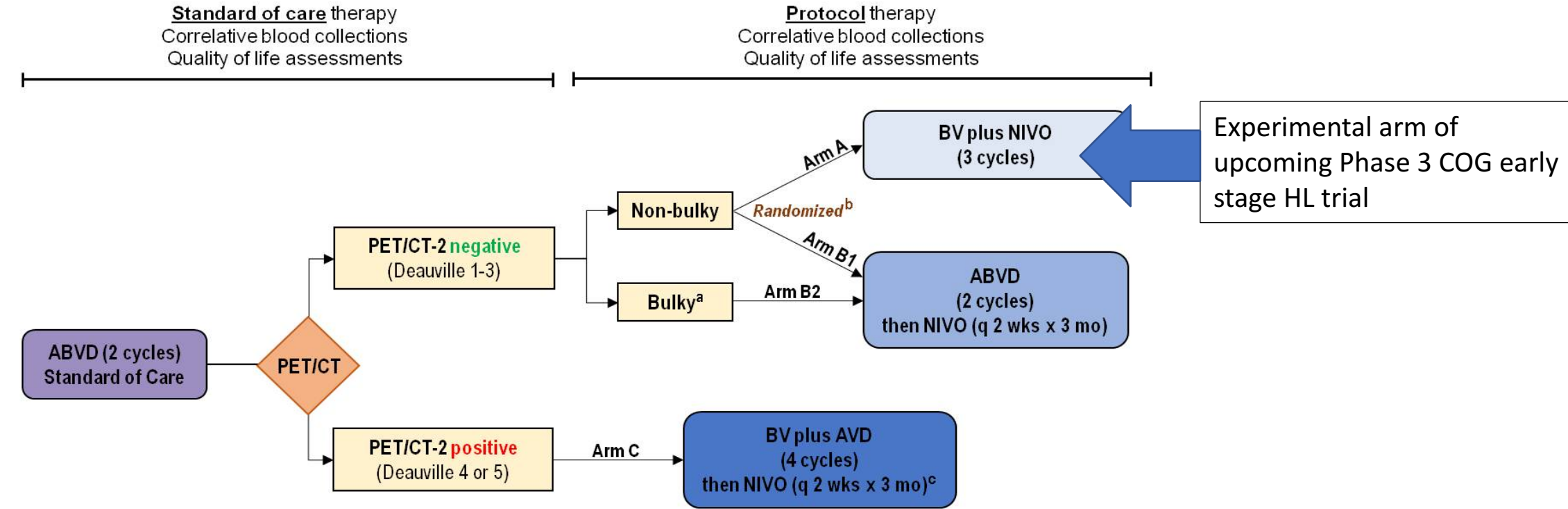
**eBEACOPP x 2 cycles +
ISRT**

Bv-Nivo x 4 cycles + ISRT

^a 1 cycle = 28 days

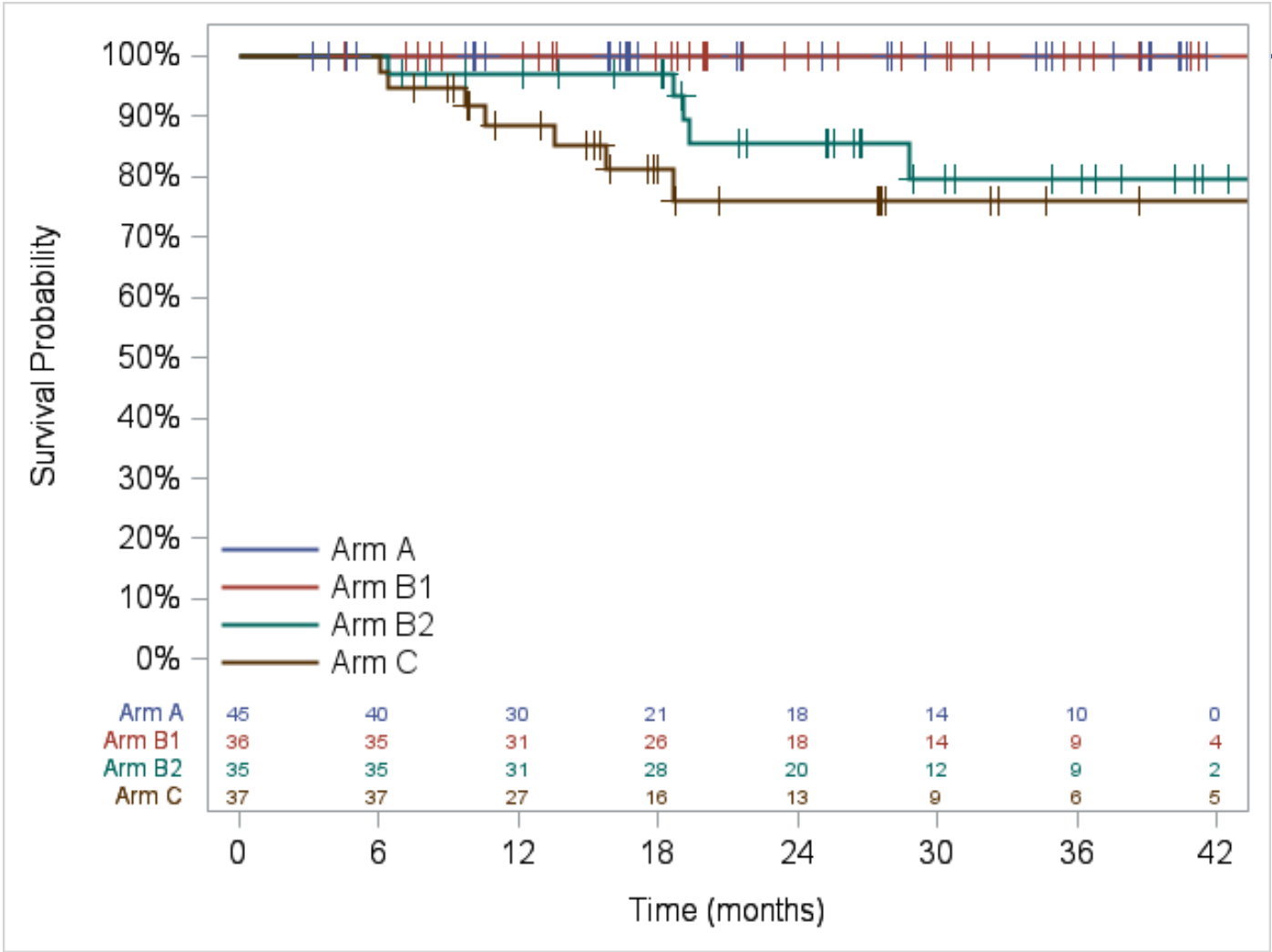
^b PET2 positive defined as Deauville 4 or 5

COH IIT 18157: A Phase 2 Study of PET-Adapted Incorporation of BV and Nivolumab into Radiation-Free Frontline Management of Early Stage HL



↑ Patients may enroll before or anytime after the start of standard of care ABVD as long as they can start protocol therapy (Arms A, B1, B2, or C) within timelines specified by the trial (See Section 10)*

Incorporating Nivo +/- BV in PET2-negative early stage cHL highly effective



← PET2 negative arms

PET2 Negative Arms

Arm A: ABVDx2 → BV-Nivo x 3

Arm B1: ABVDx2 → ABVD x 2, Nivo x 6

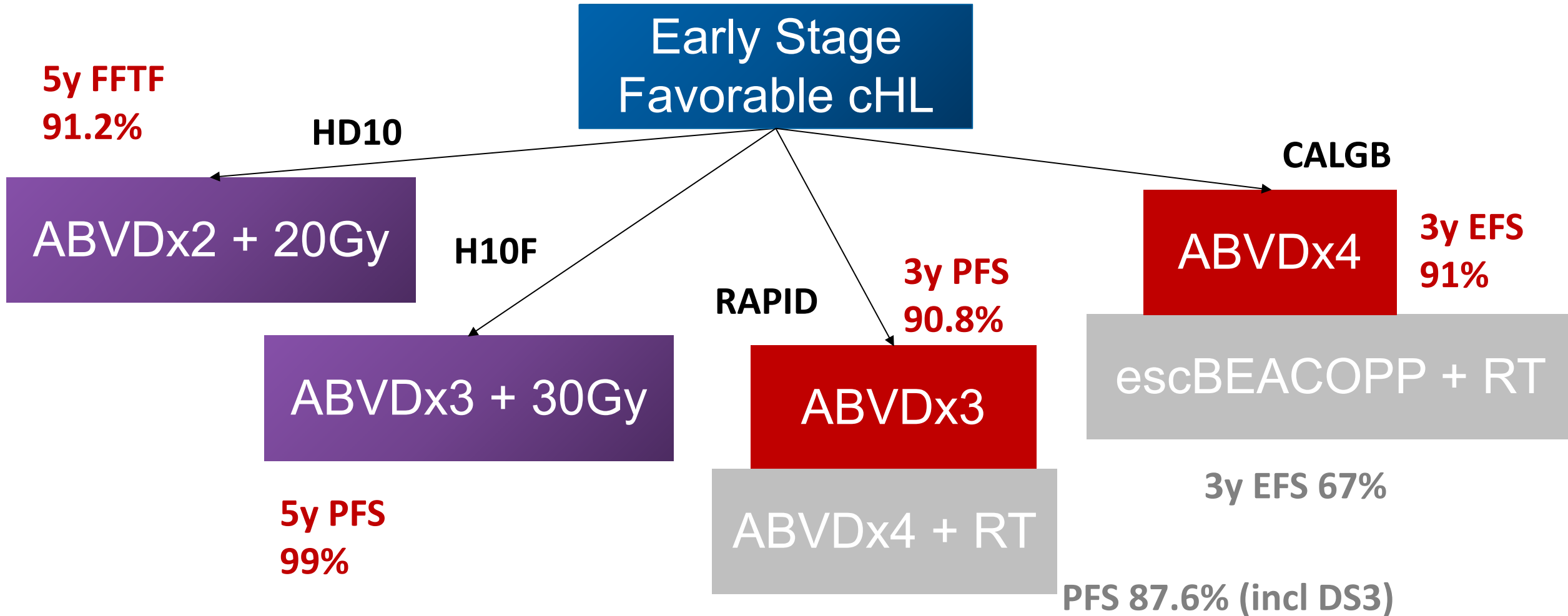
Arm B2 (bulky) ABVDx2 → ABVD x 2, Nivo x 6

PET2 Positive

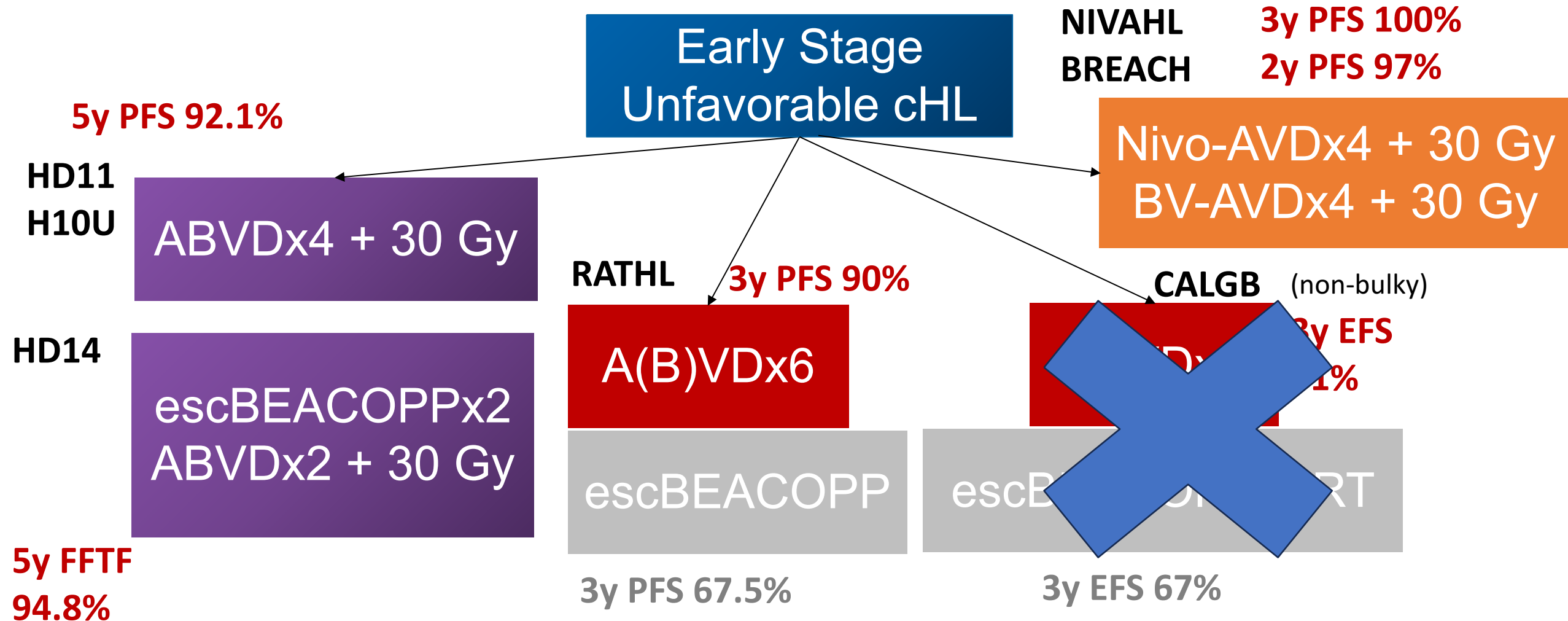
Arm C: ABVDx2 → BV-AVD x 4, Nivo x 6

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Standard Management of Early Stage cHL



Standard Management of Early Stage cHL



Eich HT et al. JCO 2011, von Tresckow B et al. JCO 2012, Straus D et al. Blood. 2018, Johnson P et al. NEJM 2016

Optimizing Initial Treatment of cHL: Conclusions

- Moving PD-1 blockade into earlier lines of cHL treatment has been promising and established a new paradigm of immunotherapy-based treatment of cHL
- Advanced Stage
 - **N-AVD**
 - N-AVD improved PFS compared to Bv-AVD in advanced stage cHL
 - N-AVD better tolerated than Bv-AVD
 - < 1% of patients received consolidative RT
 - May reduce late effects
 - **N-AVD is a new standard therapy for advanced stage cHL**
 - **BrECADD**
 - Improved PFS compared to escBEACOPP in advanced stage cHL
 - BrECADD was better tolerated than escBEACOPP
 - No adverse impact on gonadal function
 - **BrECADD is a new standard therapy for advanced stage cHL**
- Early Stage
 - CMT and PET-adapted chemotherapy remain the standard
 - Consider novel agents in unfavorable, high risk disease

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