Advances in the Management of Hodgkin and non-Hodgkin Lymphomas

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Frontline Management of Hodgkin Lymphoma

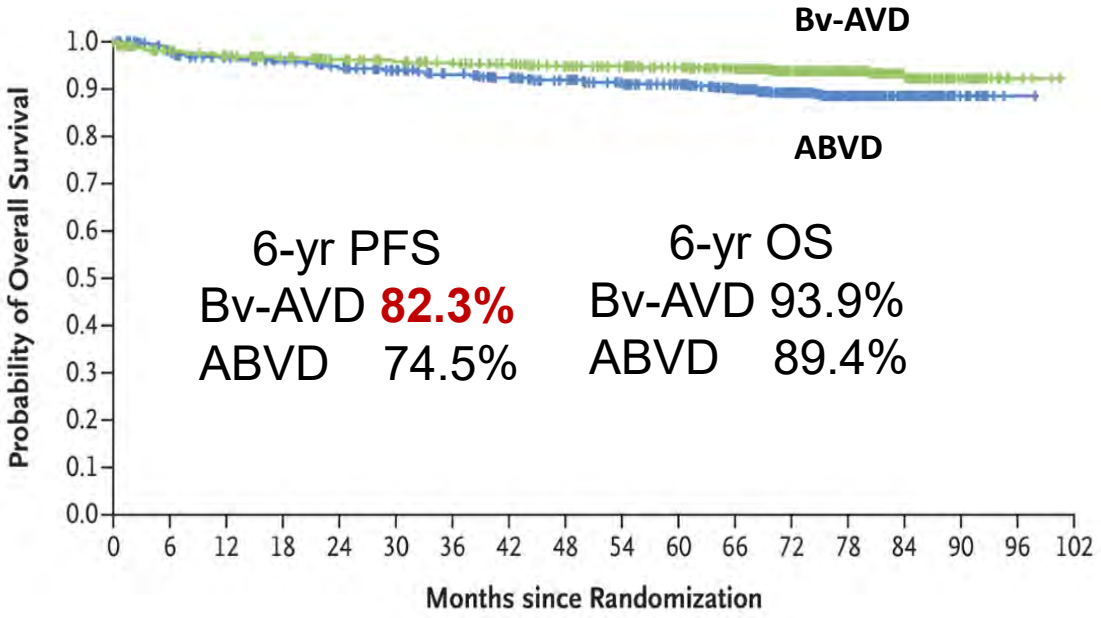
Approach to Advanced Stage Hodgkin Lymphoma- pre 2018

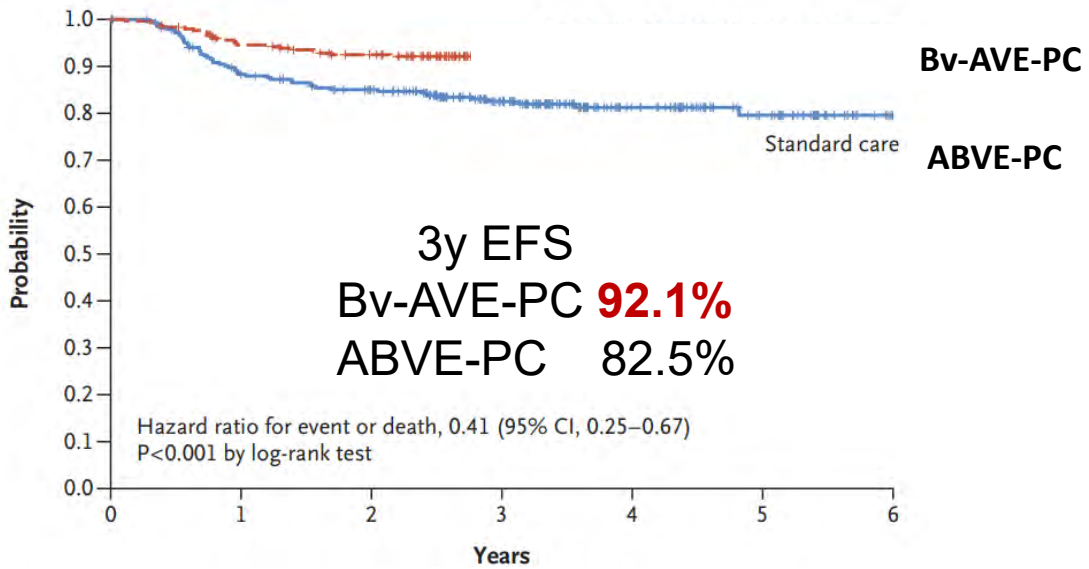
- PET-adapted combination chemotherapy has been the standard for cHL[1,2,3]
- Global, adult, and pediatric approaches differ
  - Consolidative radiation therapy (RT) is still delivered to 55-60% of pediatric patients
- Second-line treatment: high-dose chemo/autologous stem cell transplant

Herrera ASCO 2023, Stephens DM et al. Blood 2019. 2. Borchmann P. et al. Lancet 2017 3. Friedman DL et al. JCO 2014

Advanced Stage cHL: Current SOC

- Brentuximab vedotin (Bv): anti-CD30 antibody drug conjugate
- Bv in frontline treatment of advanced stage cHL improves outcomes in adult (OS) and pediatric (event-free survival) patients[4,5,6]

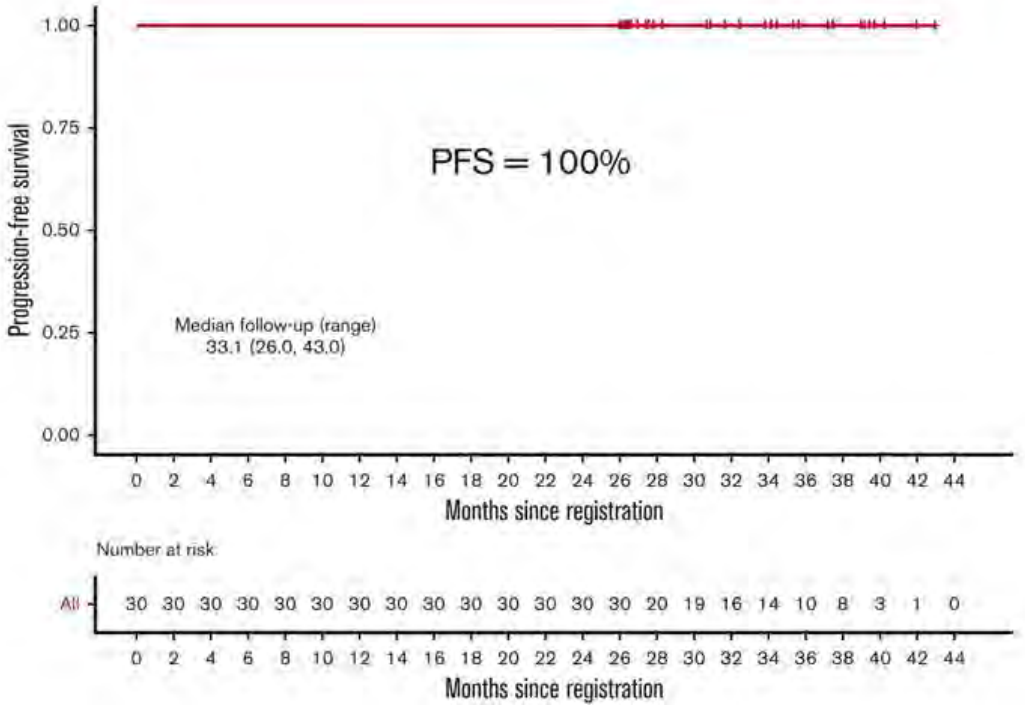


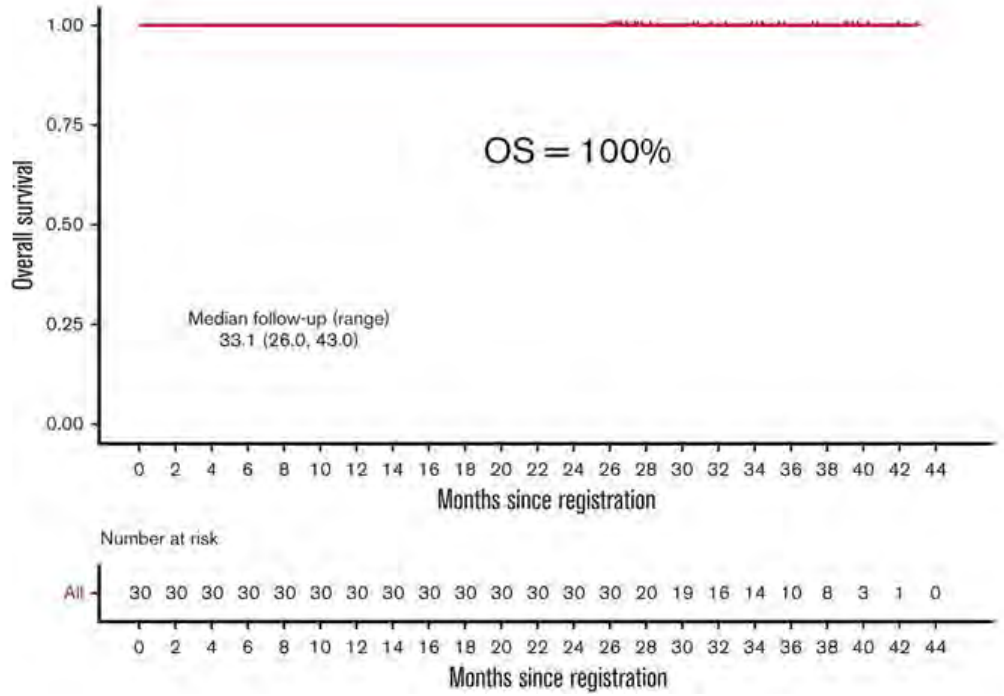


4. Ansell SM et al. NEJM 2022. 5. Castellino SM et al. NEJM 2022. 6. Borchmann P. et al. ISHL, ASH 2022.

Pembrolizumab- AVD

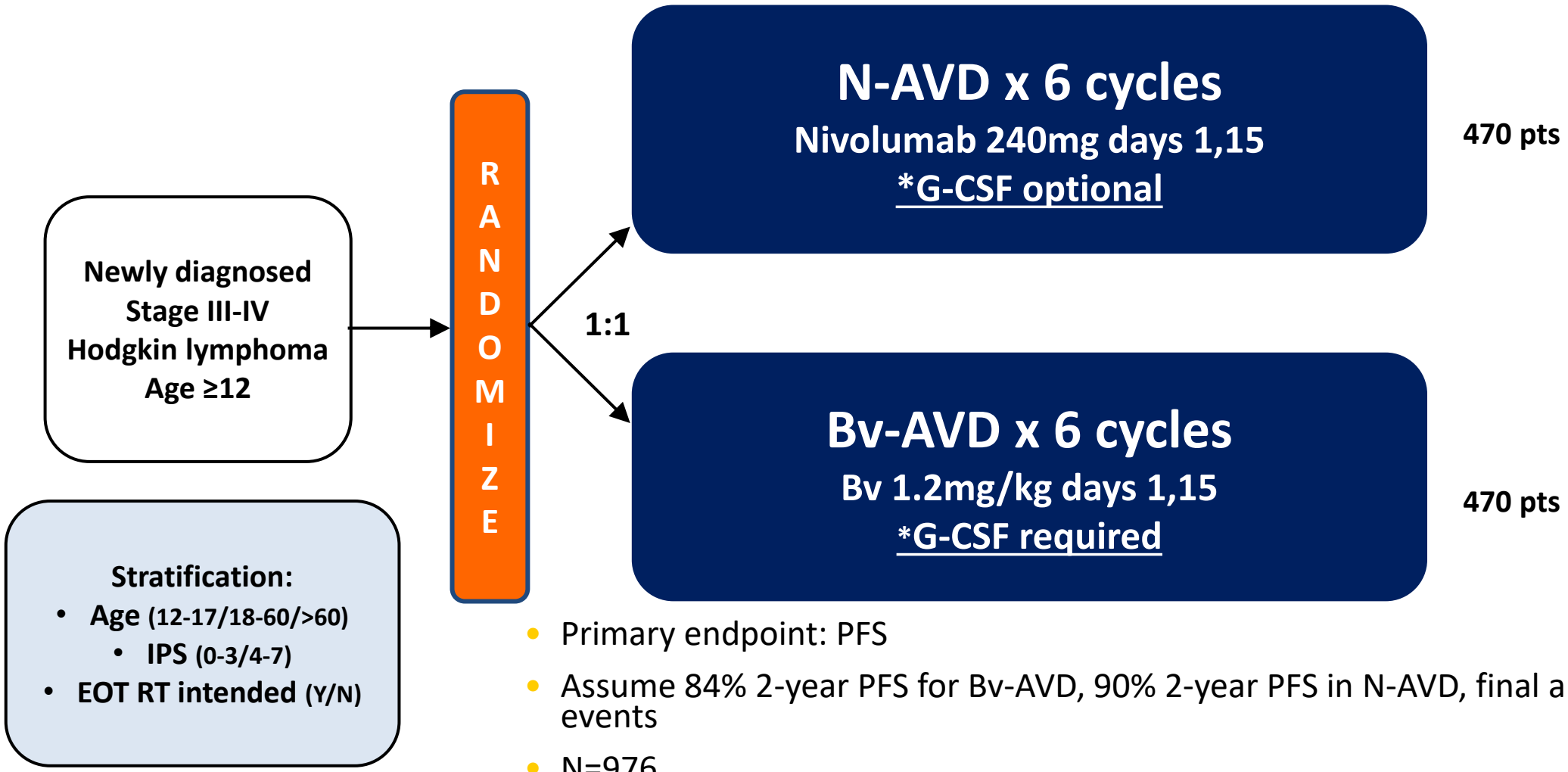
- Phase II study of sequential pembrolizumab (3 cycles)→AVD (4-6 cycles) N=30
- Median FU 33 mo





Allen et al Blood Advances 2023

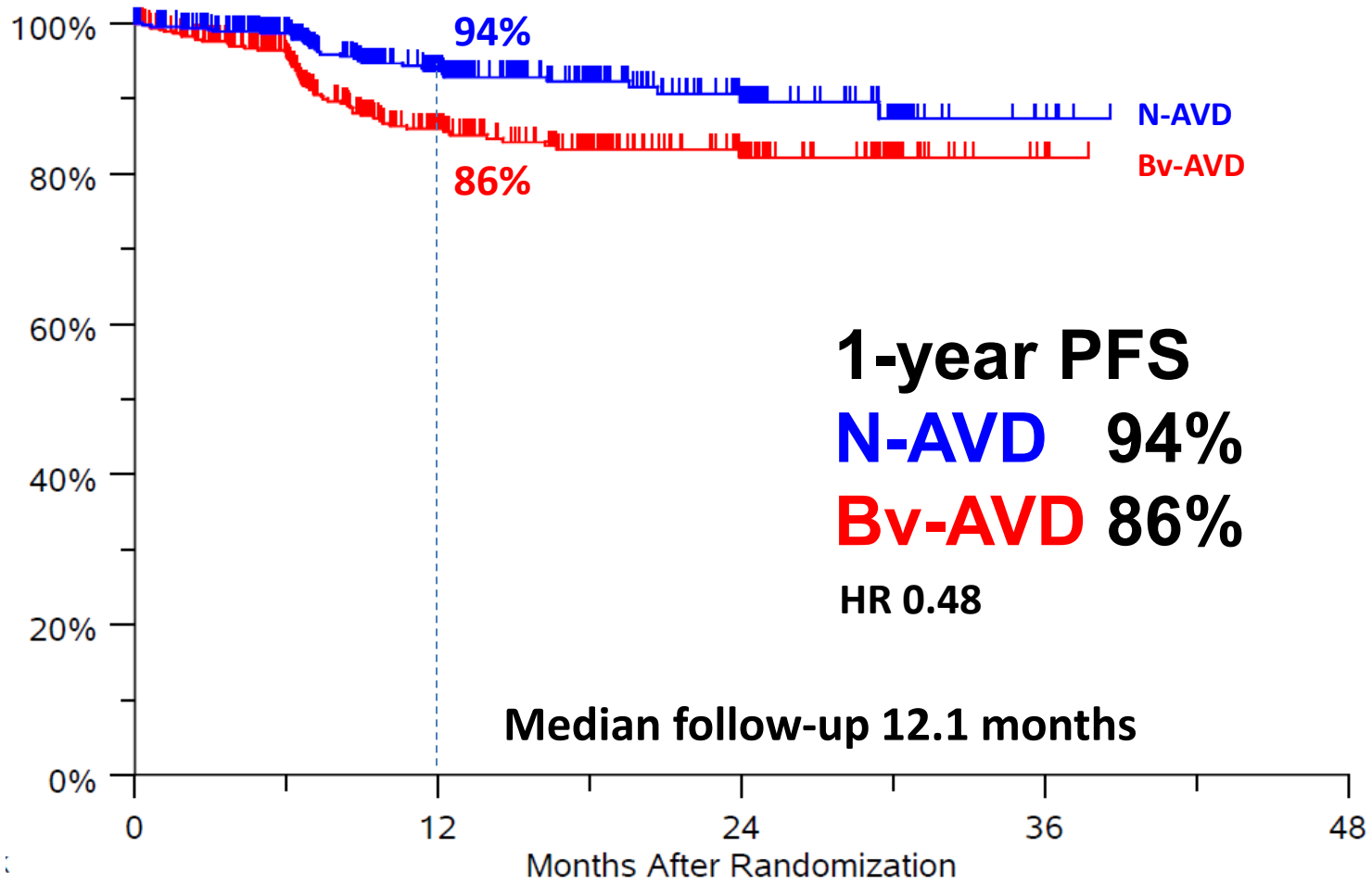
S1826: Nivo-AVD vs. BV-AVD



- Primary endpoint: PFS
- Assume 84% 2-year PFS for Bv-AVD, 90% 2-year PFS in N-AVD, final analysis @ 179 events
- N=976

N-AVD improves PFS compared to Bv-AVD

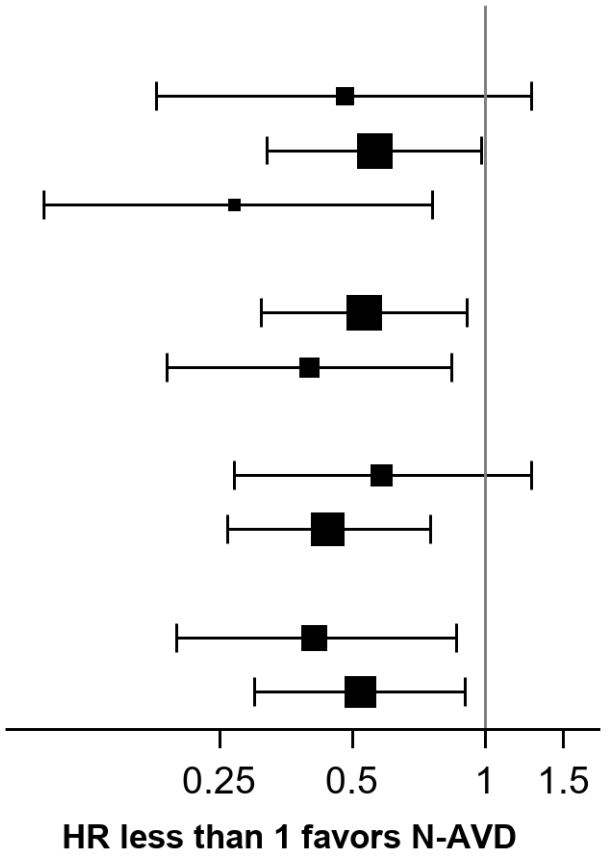
At *planned 2nd interim analysis* (50% of total PFS events), the SWOG DSMC recommended reporting the primary S1826 results because the *primary PFS endpoint crossed the protocol-specified conservative statistical boundary*



Herrera ASCO 2023

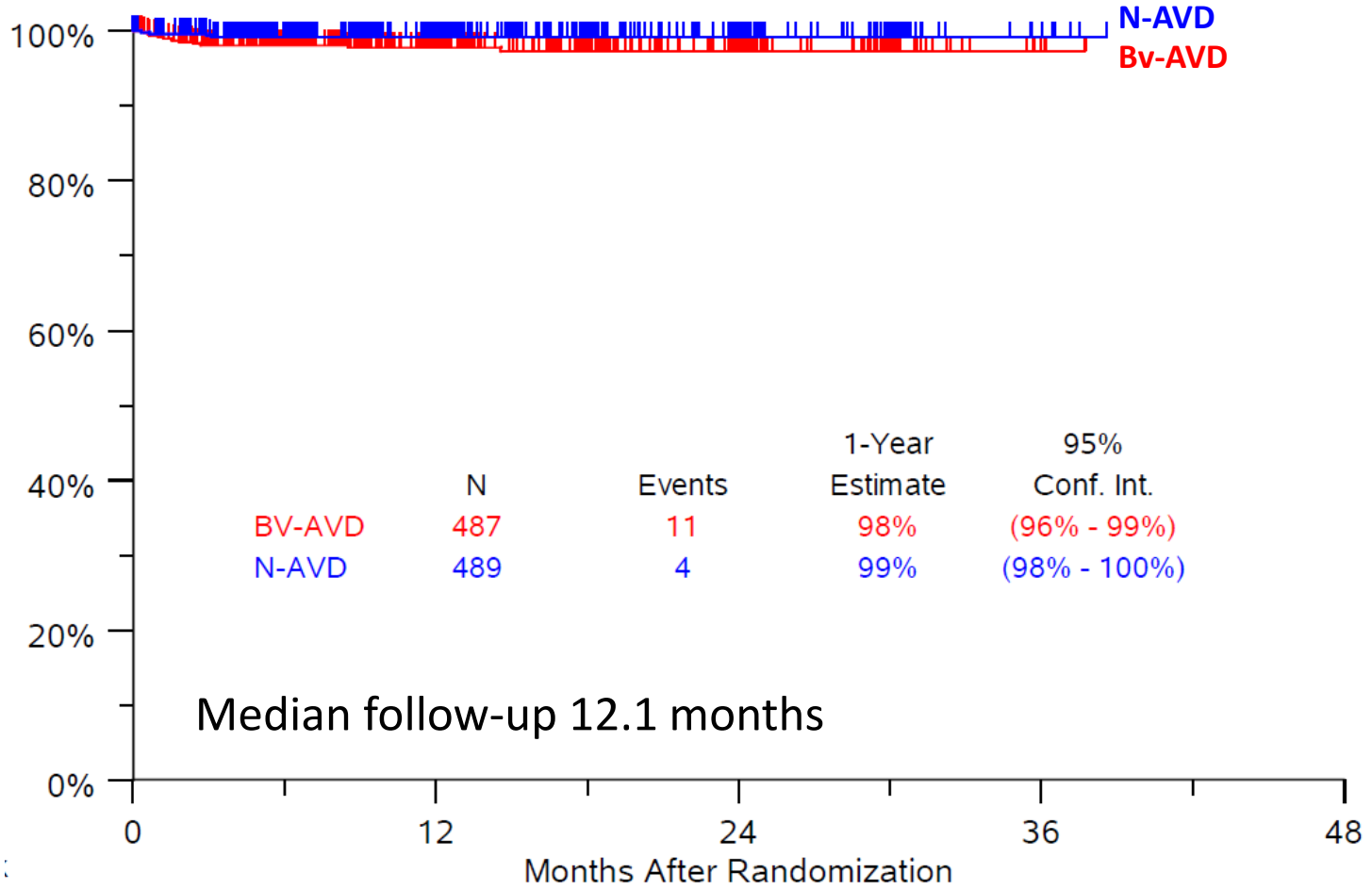
PFS benefit consistent across subgroups

Subgroup	N + AVD Events/N (%)	BV + AVD Events/N (%)	HR (95% CI)	P Value
Age				
12 - 17 y	6/120 (5.0)	12/117 (10.3)	0.48 (0.18, 1.27)	0.140
18 - 60 y	19/323 (5.9)	32/323 (9.9)	0.56 (0.32, 0.98)	0.042
> 60 y	5/46 (10.9)	14/47 (29.8)	0.27 (0.10, 0.76)	0.013
IPS				
0 - 3	20/331 (6.0)	36/330 (10.9)	0.53 (0.31, 0.91)	0.023
4 - 7	10/158 (6.3)	22/157 (14.0)	0.40 (0.19, 0.84)	0.015
Stage				
III	11/187 (5.9)	15/167 (9.0)	0.58 (0.27, 1.27)	0.176
IV	19/301 (6.3)	43/317 (13.6)	0.44 (0.26, 0.75)	0.003
Symptoms				
A	10/202 (5.0)	24/210 (11.4)	0.41 (0.20, 0.86)	0.017
B	20/286 (7.0)	34/274 (12.4)	0.52 (0.30, 0.90)	0.020



Herrera ASCO 2023

Overall Survival



Cause of death	N-AVD	Bv-AVD
Infection	2	4
Sepsis	1	2*
Cardiac arrest	0	1
Pneumonitis	0	1
Dehydration, vomiting, cHL	0	1
cHL	1**	0
Unknown	1	2
Total OS events	4 (3 =0.6%)	11 (2.3%)

* 1 death from COVID-19/sepsis
** never received treatment, ineligible on C1D1

Herrera ASCO 2023

More neutropenia with N-AVD
More growth factor use/bone pain with BV-AVD

Toxicity	N-AVD n = 483	Bv-AVD n = 473
	Gr ≥ 3, %	Gr ≥ 3, %
Neutropenia	47%	25%
Anemia	6%	9%
Thrombocytopenia	2%	3%
Received G-CSF	54%	95%
Bone pain	8%	20%

Herrera ASCO 2023

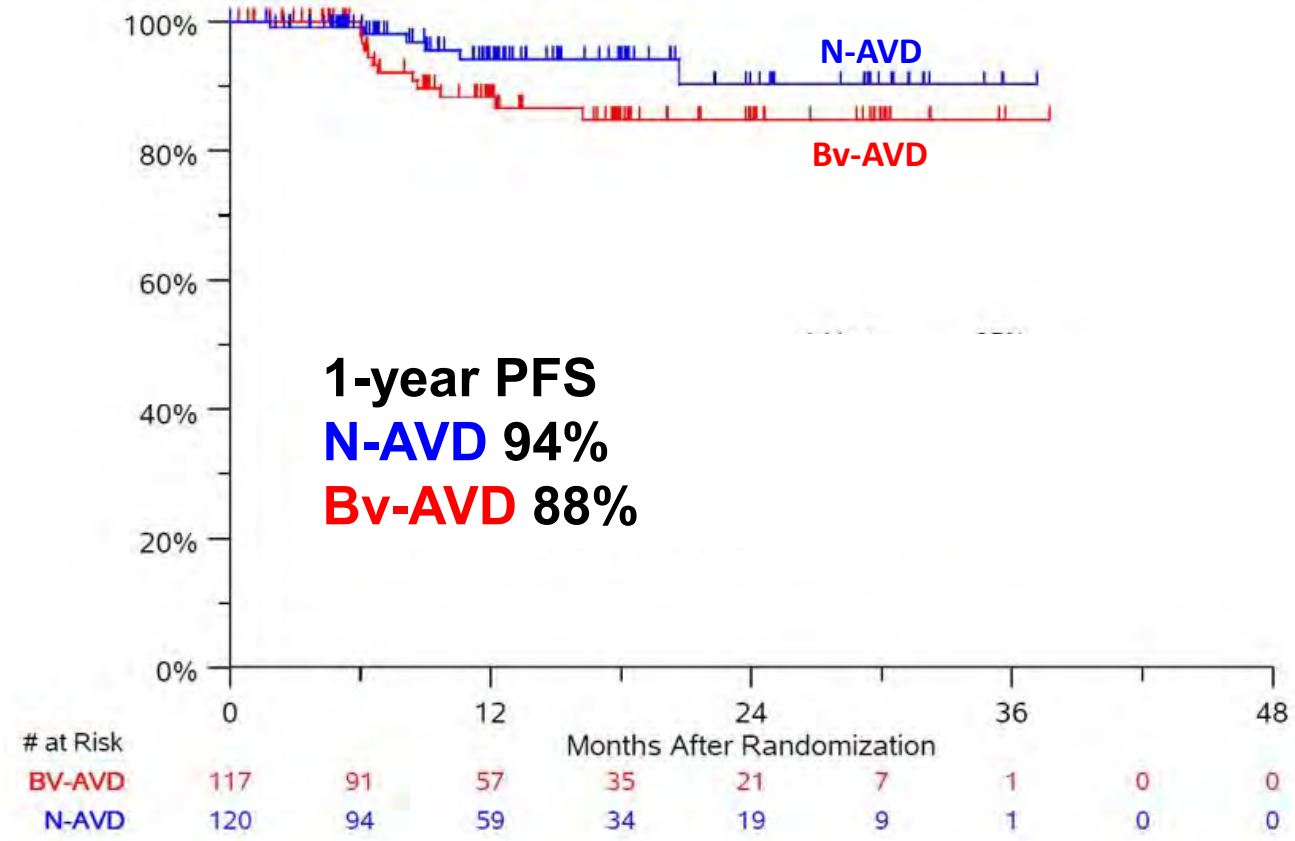
Toxicity Profile Favors Nivo-AVD

Toxicity	N-AVD n = 483	Bv-AVD n = 473
Febrile Neutropenia	5%	7%
Peripheral Neuropathy • All Grades • Grade ≥3	 29% 1%	 55% 8%
Discontinued Bv or Nivolumab	11%	22%

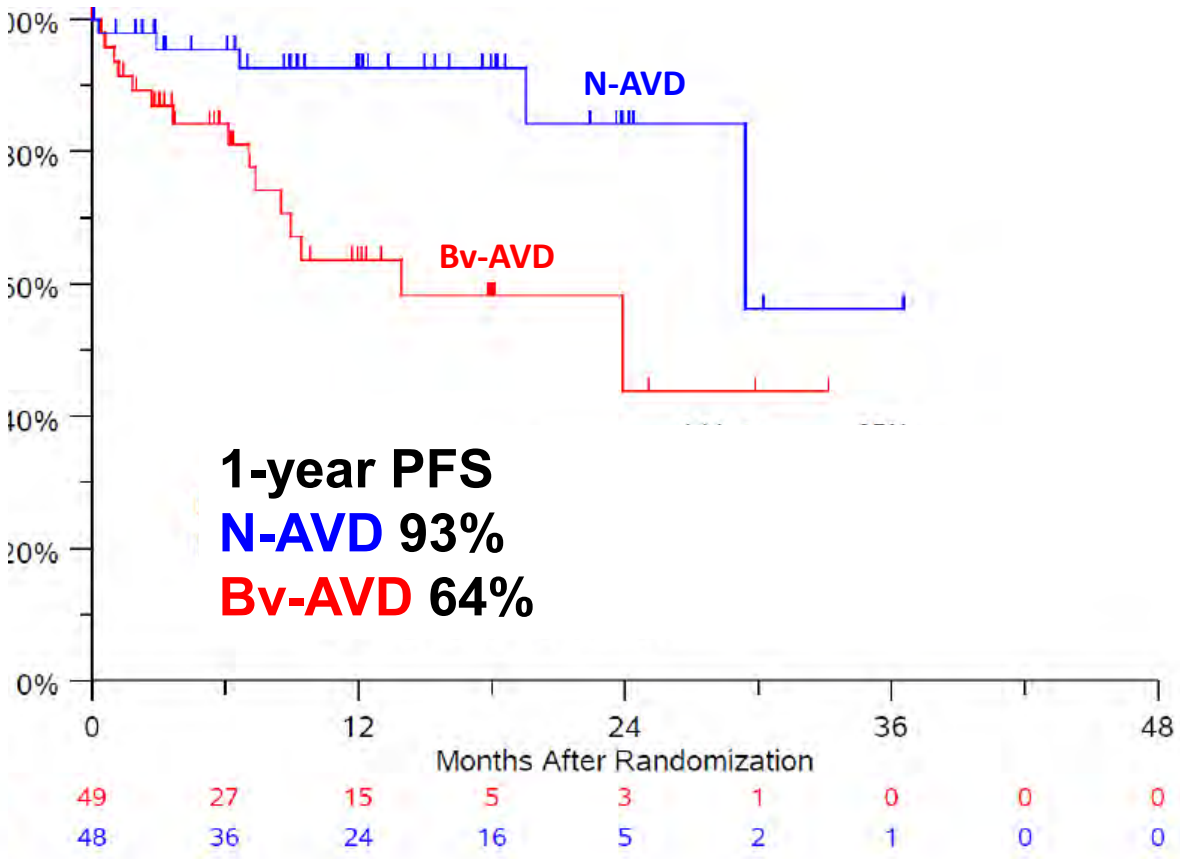
Herrera ASCO 2023

Ends of the Spectrum– the Young and the Old

Patients 12-17



Patients >60

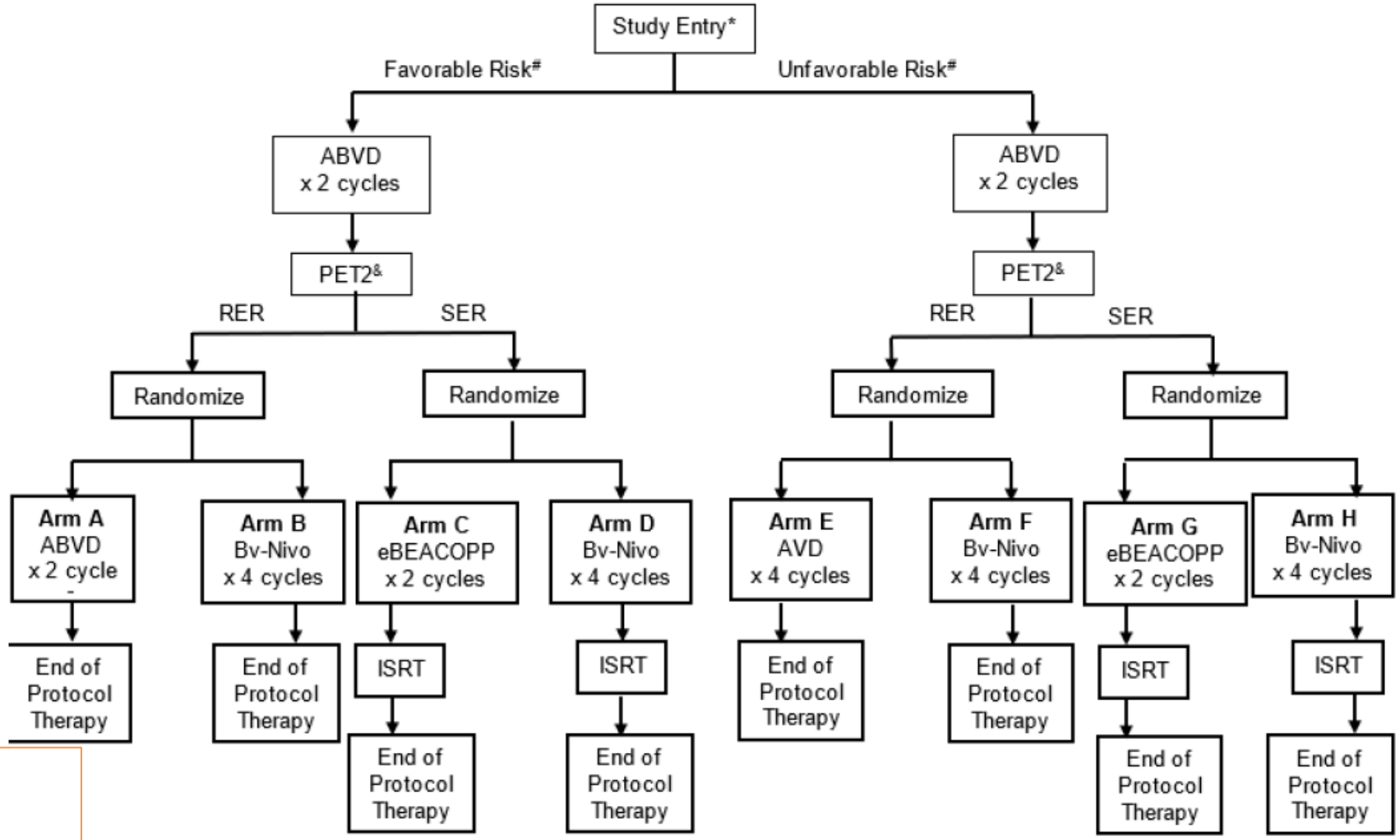


Rutherford ASH 2023, Kelly ASH 2023

S1826 Conclusions

- **N-AVD improved 1-yr PFS compared to Bv-AVD in advanced stage cHL**
- N-AVD was well-tolerated
  - Few immune-related adverse events
  - Growth factors NOT required
- Follow-up ongoing to confirm durability of PFS, long-term safety, OS, PROs
- Key step towards harmonizing pediatric and adult therapy of cHL
- **N-AVD is poised to be a new standard therapy for advanced stage cHL**

COG-AHOD2131: A Randomized Phase 3 Interim Response Adapted Trial Comparing Standard Therapy with Immuno-oncology Therapy for Children and Adults with Newly Diagnosed Stage I/II Classic Hodgkin Lymphoma



Ongoing:
NCT05675410

Mantle Cell Lymphoma

Frontline Therapy for Mantle Cell Lymphoma

- Intensive chemotherapy→ ASCT→ maintenance rituximab
- BTK based Regimens
- Elderly vs. Younger

Frontline Therapy for Mantle Cell Lymphoma

- Intensive chemotherapy→ ASCT→ maintenance rituximab
- BTK based Regimens
- Elderly vs. Younger

While significant progress is being made, frontline regimens for high risk patients remains an unmet need

Relapsed Therapy For Mantle Cell Lymphoma

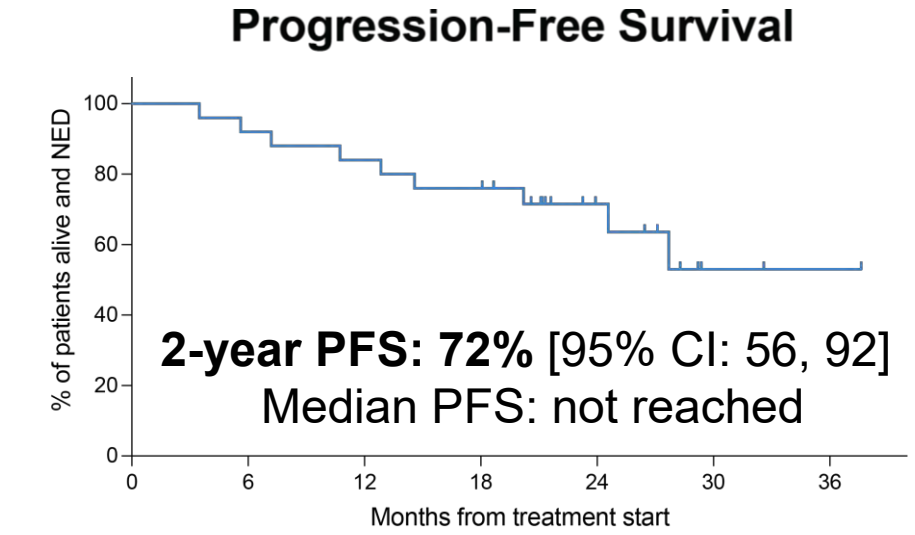
Agent	N	ORR	CR	PFS	Approval Year
Acalabrutinib	124	81%	48%	28.6 mo	2017
Zanubrutinib	86	84%	78%	33 mo	2019
Lenalidomide	134	25%	7%	4 mo	2013
(Ibrutinib)	*111*	*66%*	*21%*	*12.5 mo*	*2014*
Pirtobrutinib	90	58%	20%	7.4 mo	2019

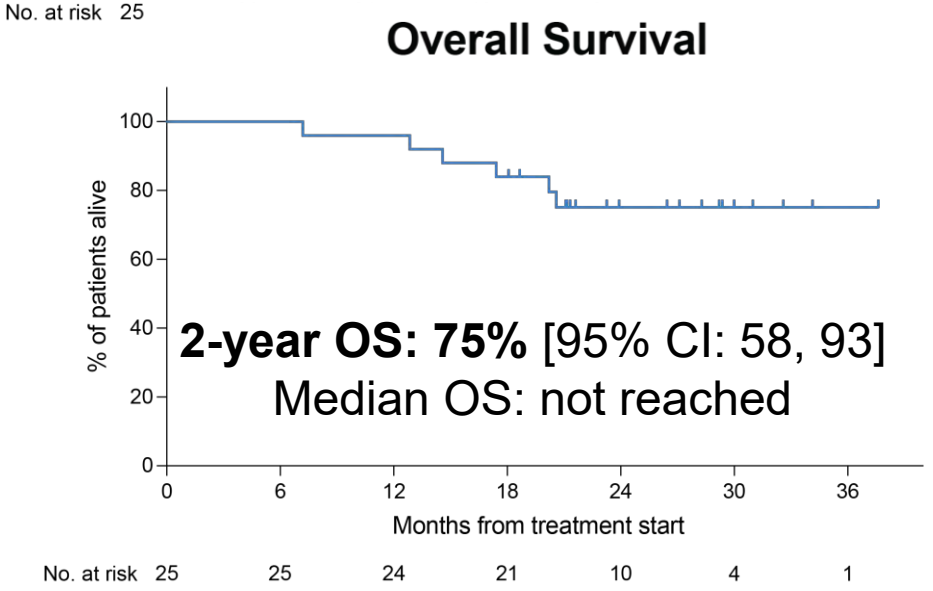
Le Gouill Haematologica 2024; Goy JCO 2013; Song Blood 2022; Wang NEJM 2013; Dreyling Hemasphere 2022; Wang JCO 2023; Shah JCO 2023

BOVen Results

- ORR: 96% (PR 88%, CR 8%)

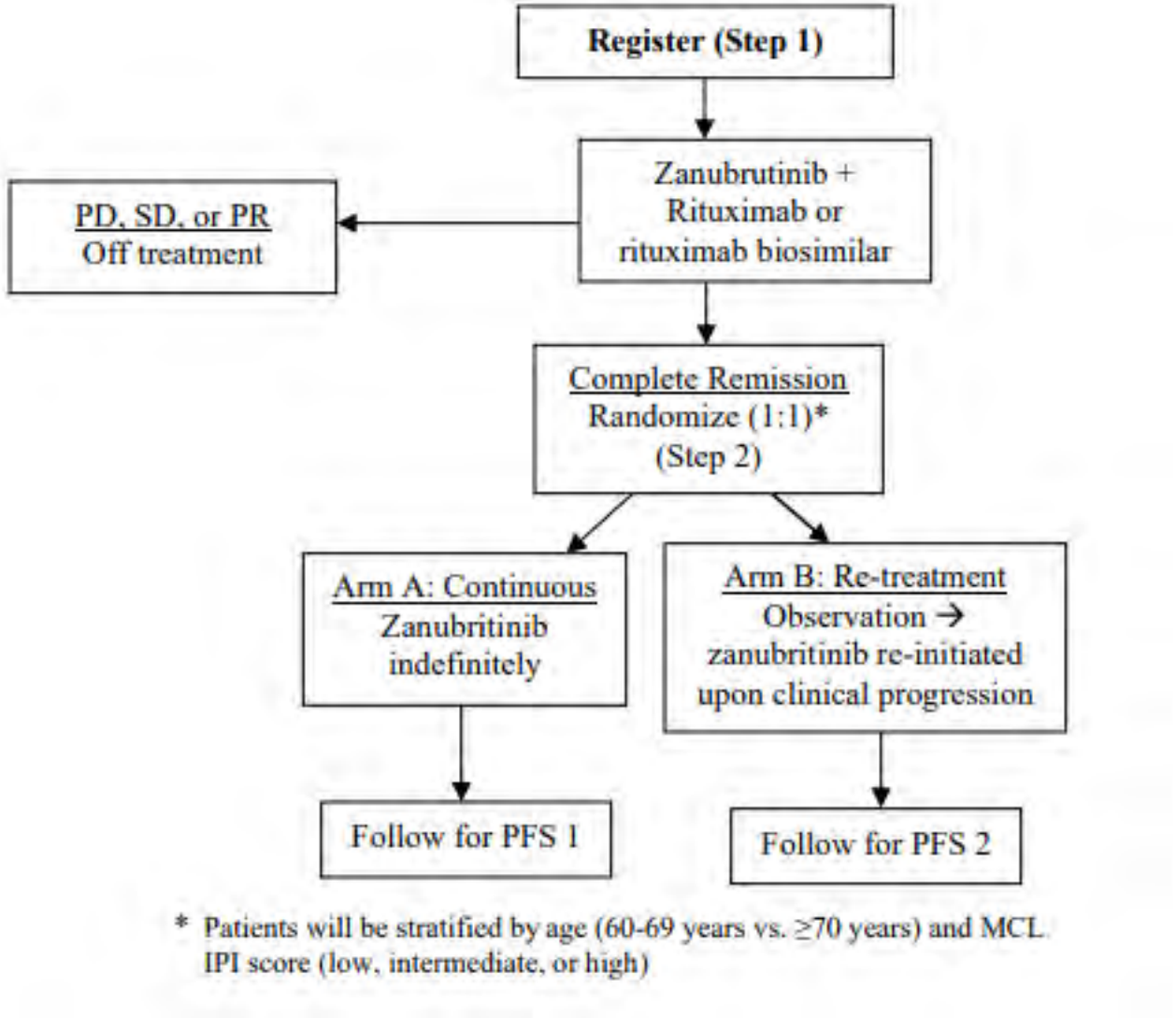
- 11/25 completed 24 mo of therapy
  - 100% achieved CR
  - 8/10 undetectable MRD→Stopped treatment
    - 2 had recurrent disease and resumed treatment





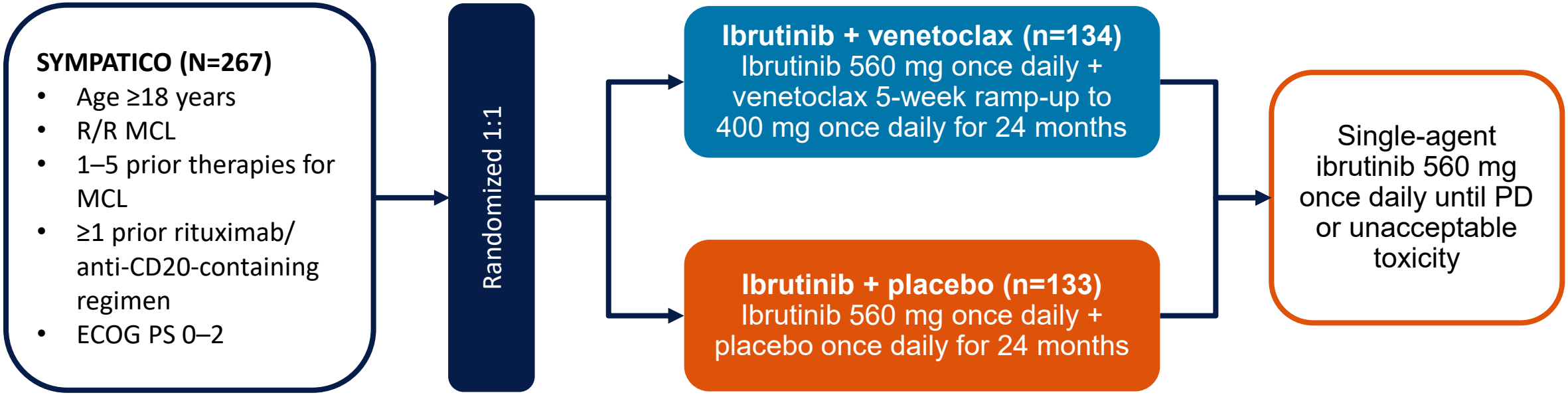
Kumar et al ASH 2023

A052101: Randomized Phase III study of Continuous vs Intermittent Maintenance in untreated, older patients with Mantle cell lymphoma



NCT05976763

SYMPATICO



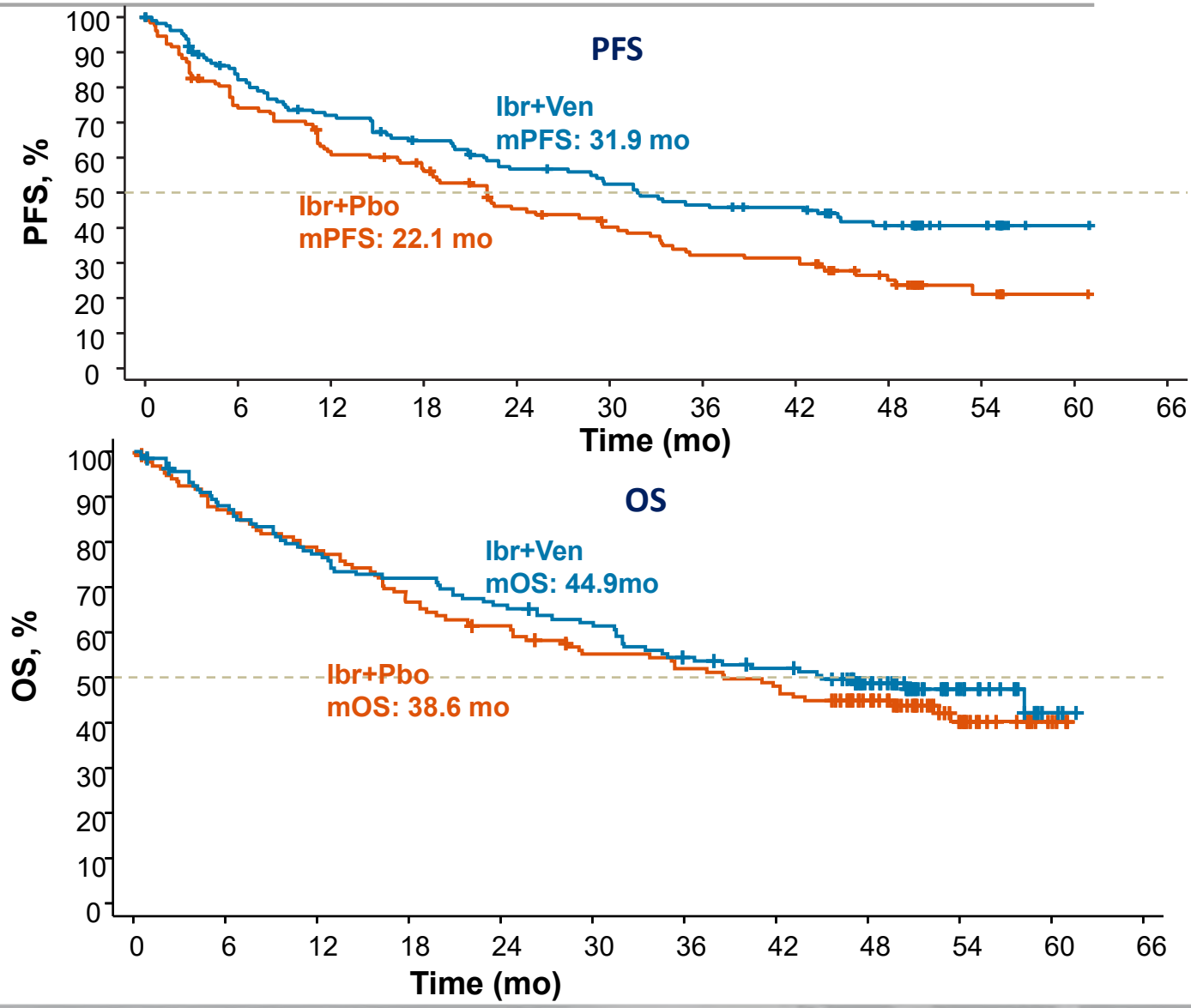
Stratification: ECOG PS, prior lines of therapy, TLS risk[a]

- **Primary endpoint:**
  - PFS by investigator assessment using Lugano criteria
- **Secondary endpoints (tested hierarchically in the following order):**
  - CR rate by investigator assessment
  - TTNT[b]
  - OS (interim analysis)
  - ORR by investigator assessment

Wang ASH 2023

SYMPATICO

- High risk population
  - 1/3 patients TP53 mutated
  - 1/3 patients high risk MIPI
- Ibrutinib+Venetoclax favored in all prespecified subgroups
  - Improved time to next treatment
- Higher grade ≥3 AEs with ibrutinib+venetoclax
  - 84% vs. 76%
  - Diarrhea, pneumonia higher



Wang ASH 2023

SYMPATICO

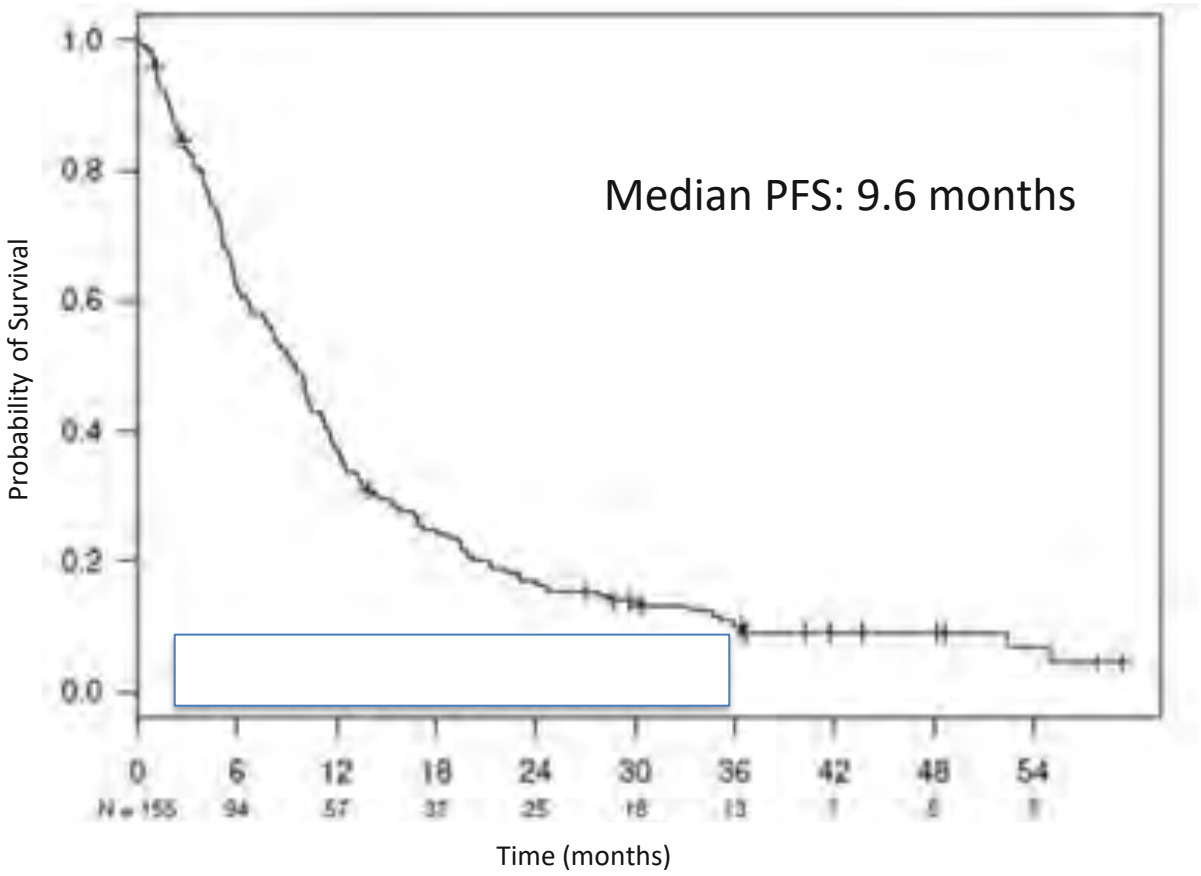
- Ibrutinib+venetoclax improved PFS over ibrutinib alone
  - Expected increase in toxicity
- Ibrutinib no longer approved in the US
- Ibrutinib appears less effective than other available BTKi

Wang ASH 2023

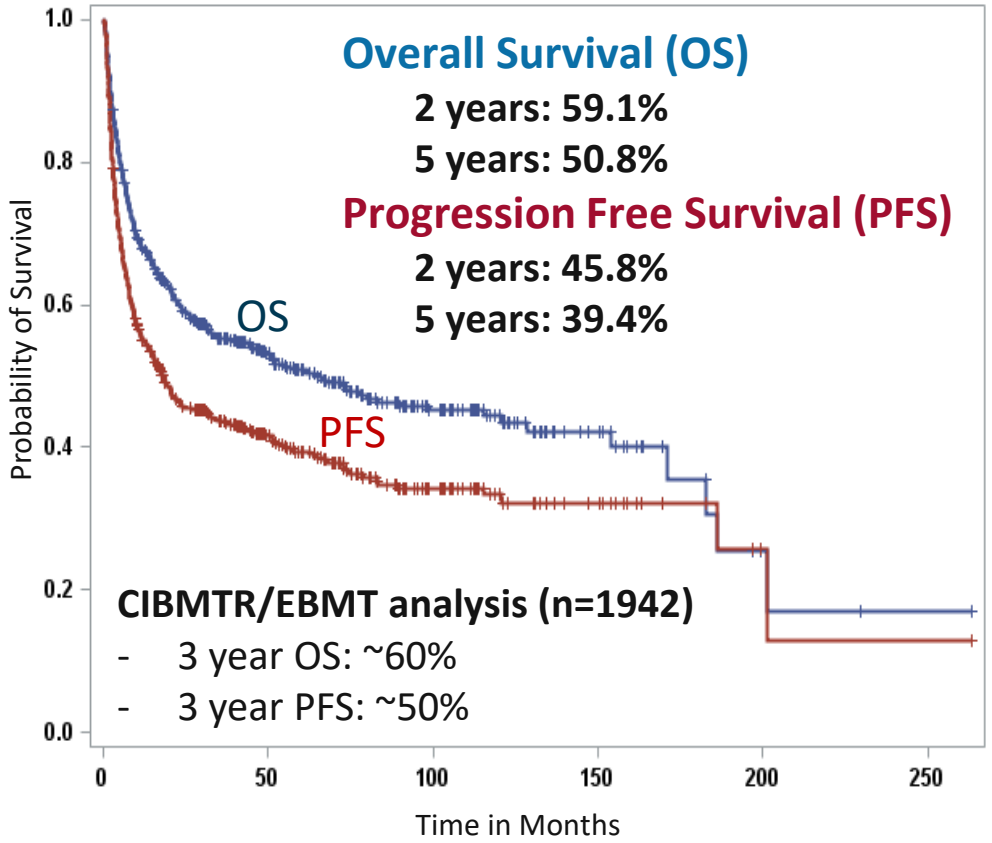
Relapsed/Refractory T-cell Lymphomas

Outcomes in Relapsed/Refractory PTCL

PFS in Relapsed/Refractory PTCL (n=499)



Outcomes of Allogeneic Transplant for T-cell Lymphomas (n=508)



Lansigan ACTA Hematol epub 2019; Mehta-Shah ASH 2017; Dreger et al ICML 2021

Clinical Activity of Standard Chemotherapy in R/R PTCL

Regimen	N	ORR/CR%	DOR
ICE	40	70% / 35%	mPFS: 6 months
GemDexCis	51	80% / 47%	mPFS: 4 months
ESHAP	22	32% / 18%	mPFS: 2.5mo
Gemcitabine	20	55% / 30%	mDOR: 34 mo
Bendamustine	60	50% / 28%	mDOR: 3.5 mo
Romidepsin	45	25% /15%	mDOR: 8.9 mo
Bellinostat	57	26% / 11%	mDOR: 8.3 mo
Pralatrexate	111	29%/ 15%	mDOR: 7.6 mo
Brentuximab vedotin	34	69% / 44%	mPFS: 6.7 mo

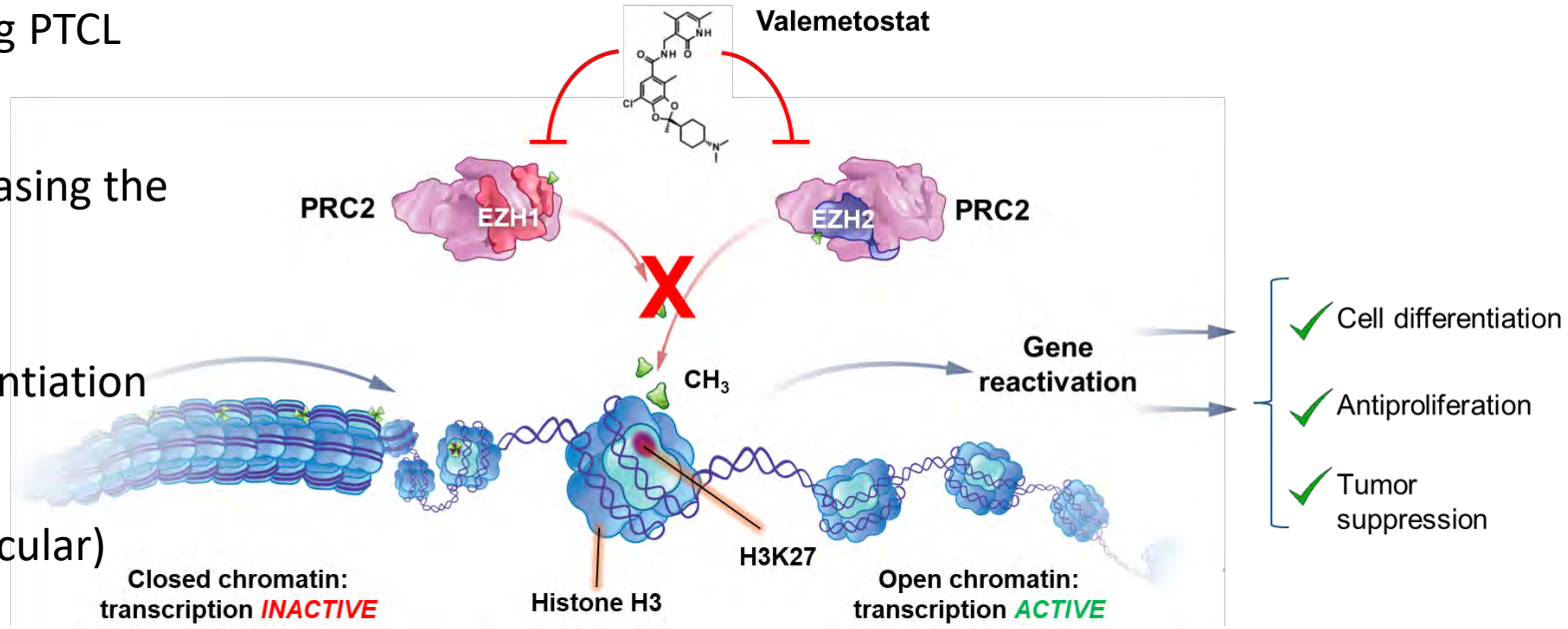
Damaj et al JCO 2013; Zinzani et al Ann Oncol 2012; Kogure et al Ann Hematol 2014; Arkenau et al heamtologica 2007; Parkin et al Blood 2013; Horwitz et al Blood 2005; Mehta-Shah, ASH Education Book 2019

New Kids on the Horizon

- EZH2 inhibitors
- JAK/STAT Inhibitors
- PI3K inhibitors

EZH2 inhibitors Background

- EZH2 overexpression drives the development and progression of many types of cancer, including PTCL
  - *EZH2* mutations are rare in PTCL
- EZH 1/2 inhibitors inhibit H3K27me3→ increasing the expression
  of genes associated with
  the regulation of cell proliferation and differentiation
- EZH2 inhibitors generally well tolerated
  - Tazemetostat (approved in US for R/R Follicular)
  - Valemetostat (approved in Japan for R/R ATLL)
- Two EZH2 inhibitors presented



Horwitz ASH 2023

VALENTINE-PTCL01: global, multicenter, open-label, single-arm, phase 2 trial of valemetostat in R/R PTCLs

Eligibility Criteria

- ≥ 18 years
- Confirmed PTCL diagnosis (WHO 2016 classification[1])
- ECOG PS score ≤ 2
- ≥ 1 prior line of systemic therapy
  - Patients with ALCL received prior brentuximab vedotin treatment
- Prior Allo and ASCT permitted

→

R/R PTCL
N = 133
N = 119 with PTCL histology confirmed by central pathology

→

Valemetostat
200 mg/day
Continuous 28-day cycles until PD or unacceptable toxicity

Primary endpoint: ORR (CT-based BICR assessment; ≥ 10 months follow-up[b])

Key secondary endpoints: DOR, DOCR, CR rate, PR rate, PFS (CT-based BICR assessment and investigator assessment), OS, safety and tolerability

Key exploratory endpoint: PET-CT–based clinical response (BICR)

Lugano 2014 response criteria[2]

133 patients with PTCL (53 TFH phenotype; 41 PTCL NOS; 9 ALCL) with 119 evaluable for efficacy
Median age 69; median 2 lines of prior therapy
Required central path review for evaluability

Horwitz ASH 2023

Valemetostat Efficacy

CT–based assessment

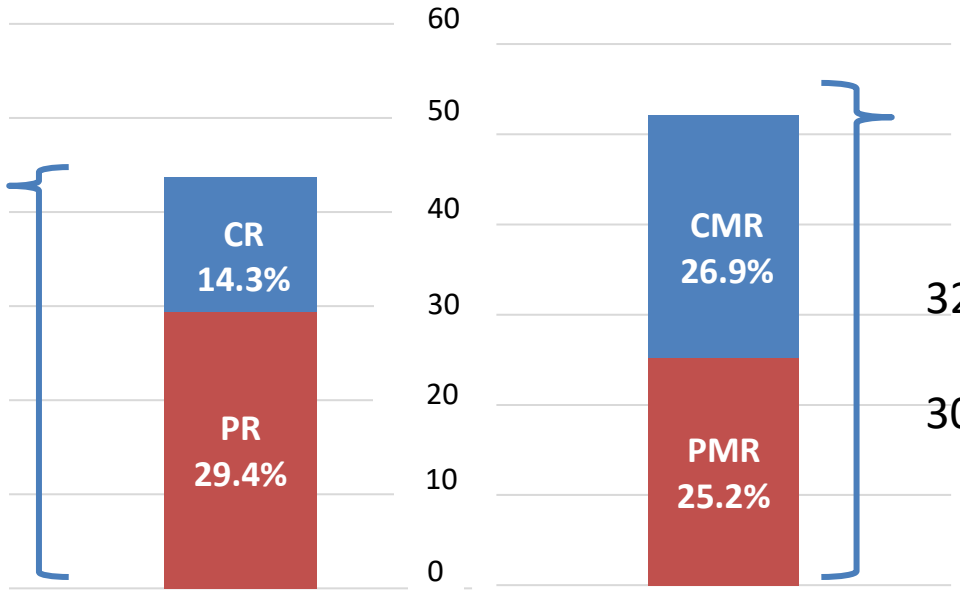
(Primary endpoint)

ORR was **43.7%**
(n = 52; 95% CI, 34.6–53.1)

17 patients **(14.3%)** achieved a **CR**

35 patients **(29.4%)** achieved a **PR**

Efficacy-evaluable population (N = 119)



PET-CT–based assessment

(Exploratory endpoint)

ORR was **52.1%**
(n = 62; 95% CI, 42.8–61.3)

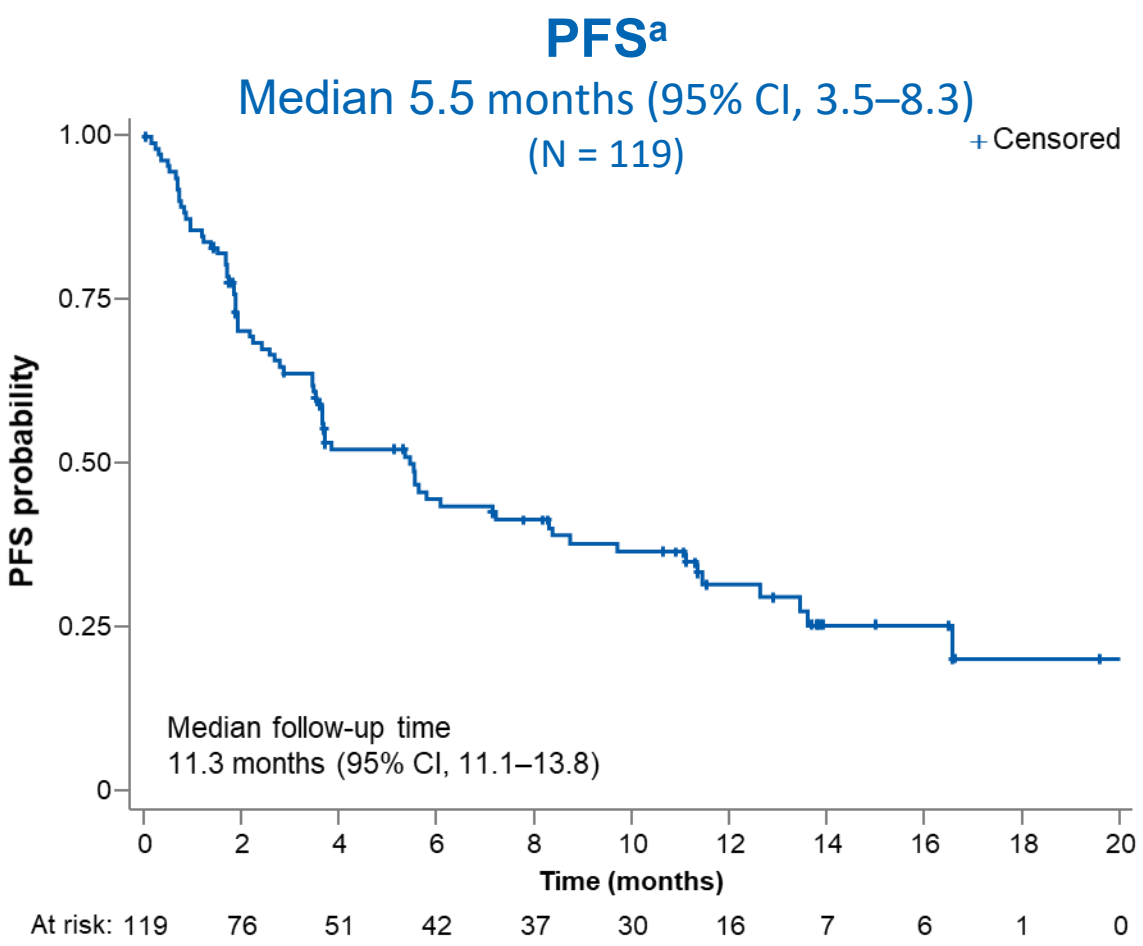
32 patients **(26.9%)** achieved a **CMR**

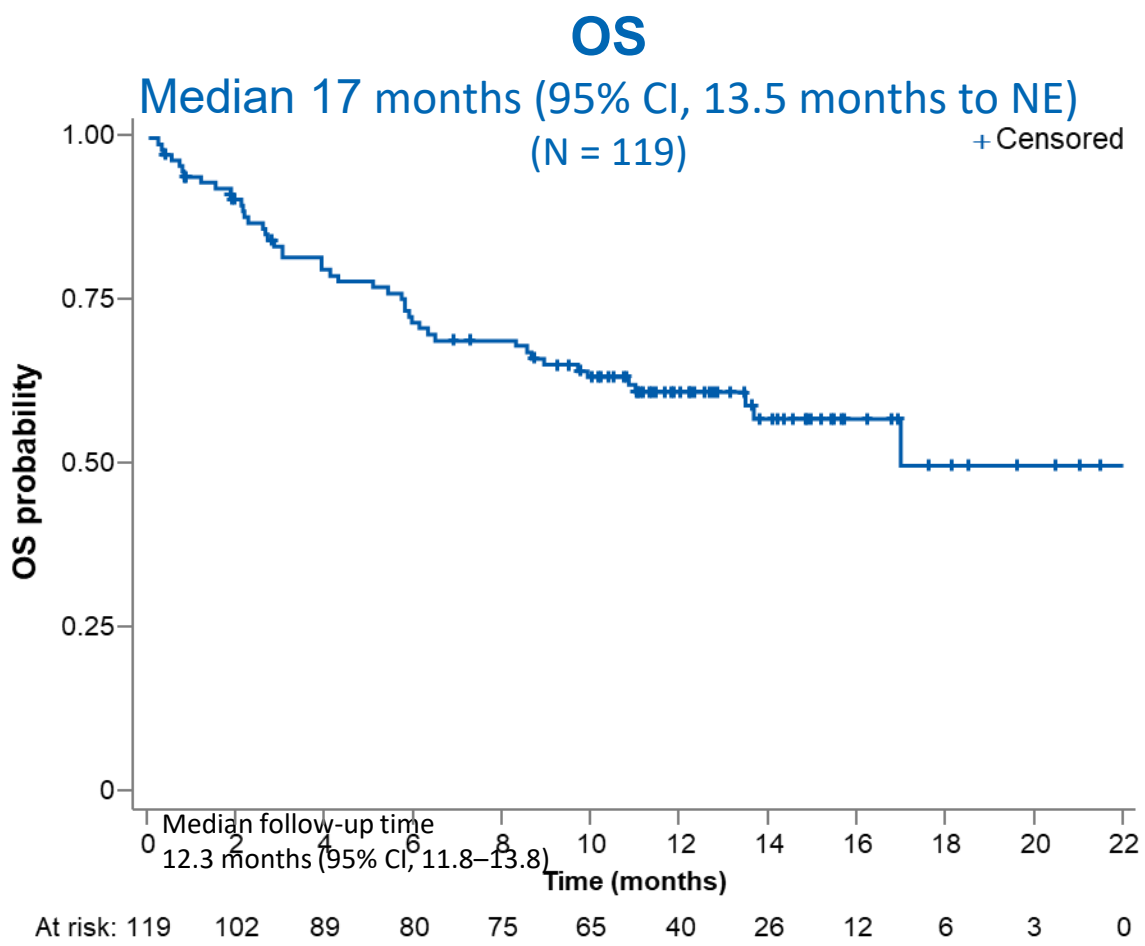
30 patients **(25.2%)** achieved a **PMR**

- Ten (8.4%) patients treated with valemetostat proceeded to allo-HCT, including 8 patients (6.7%) with a CR[a] and 2 patients with an unknown response
  - The median time from first dose of valemetostat to subsequent allo-HCT was 6.9 months

Horwitz ASH 2023

Progression-Free Survival and Overall Survival



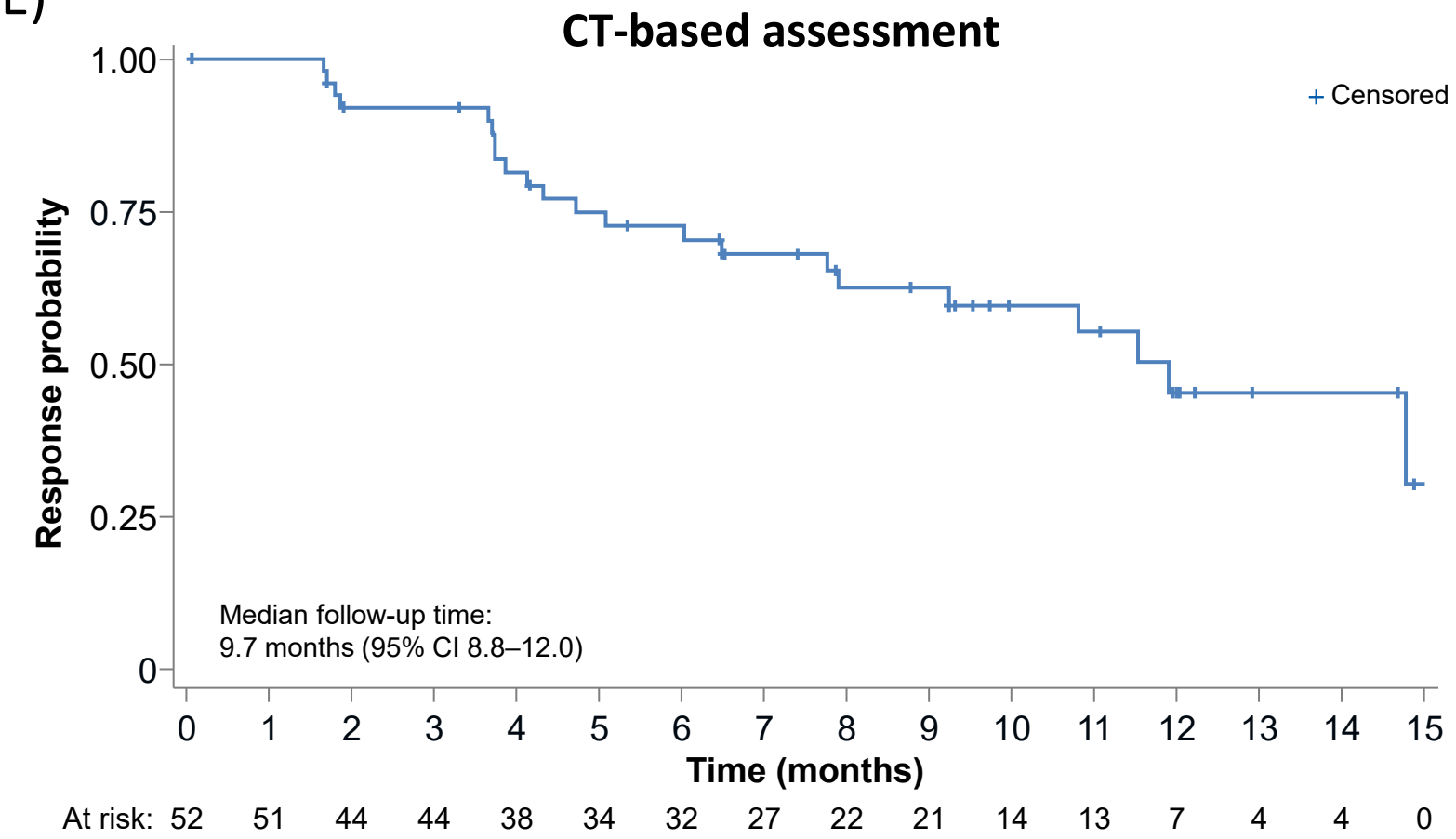


- Median **TTR** was **8.1 weeks** (range, 5–37) and median **DOR** was **11.9 months** (95% CI, 7.8 months to NE)

Horwitz ASH 2023

Duration of Response (CT-Based BICR Assessment)

- Median **TTR** was **8.1 weeks** (range, 5–37) and median **DOR** was **11.9 months** (95% CI, 7.8 months to NE)



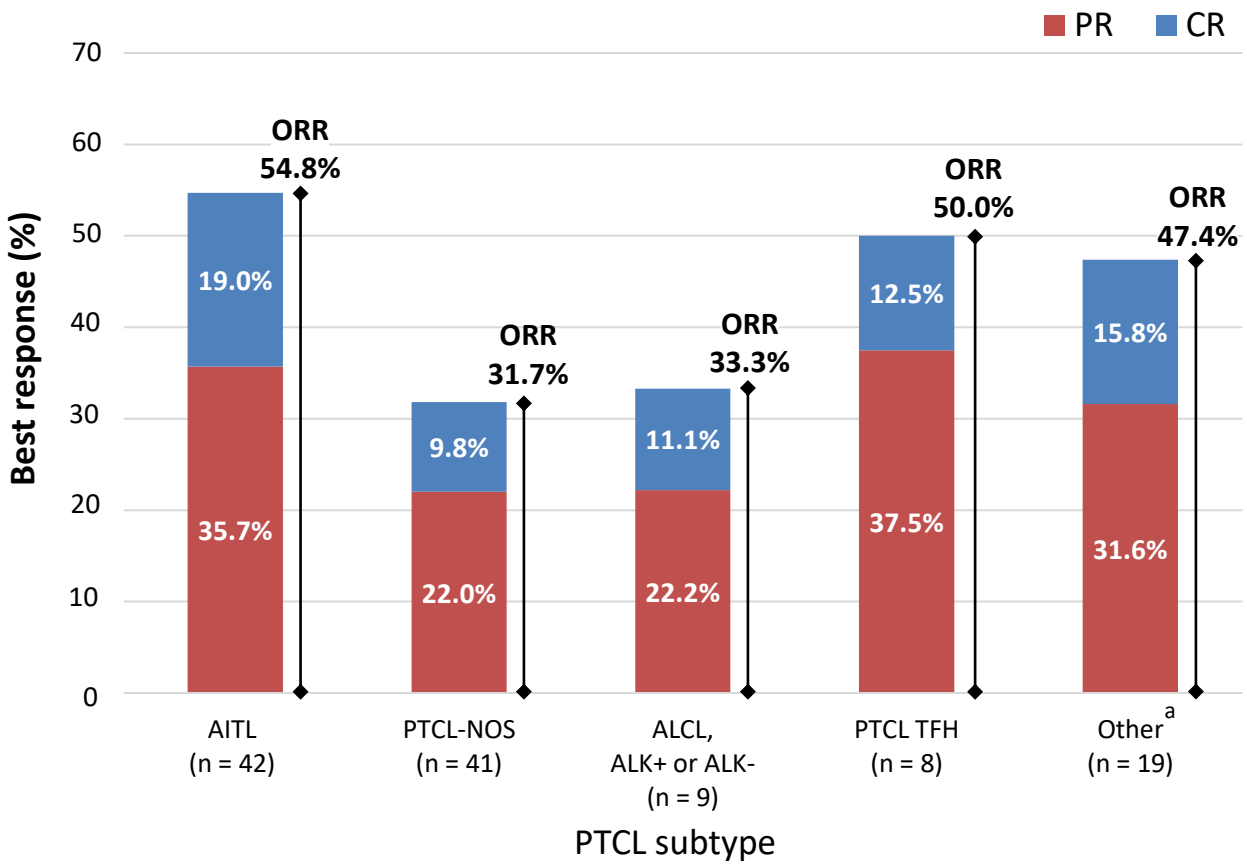
Horwitz ASH 2023

- Data cutoff: May 5, 2023.
- NE, not evaluable; TTR, time to response.

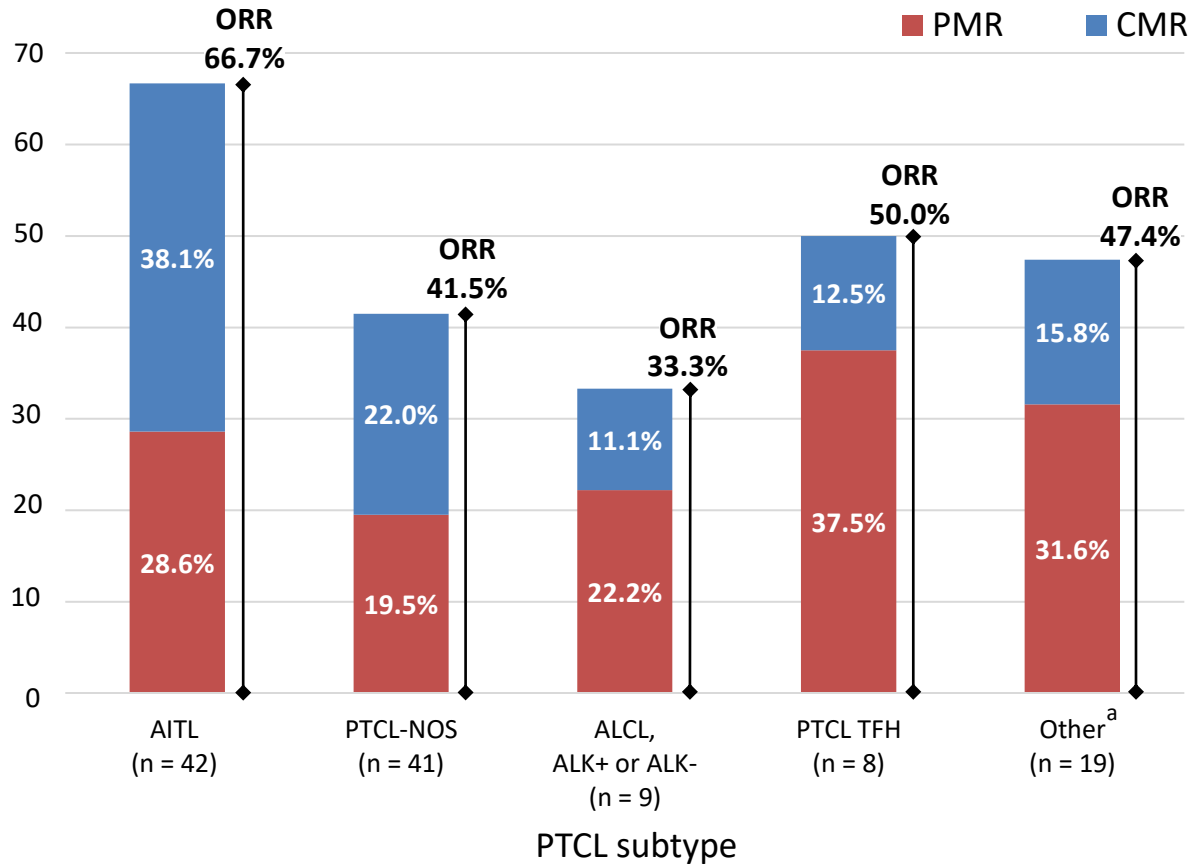
Responses Seen Across PTCL Subtypes

Responses were observed across all PTCL subtypes

CT-based assessment
(N = 119)



PET-CT-based assessment
(N = 119)



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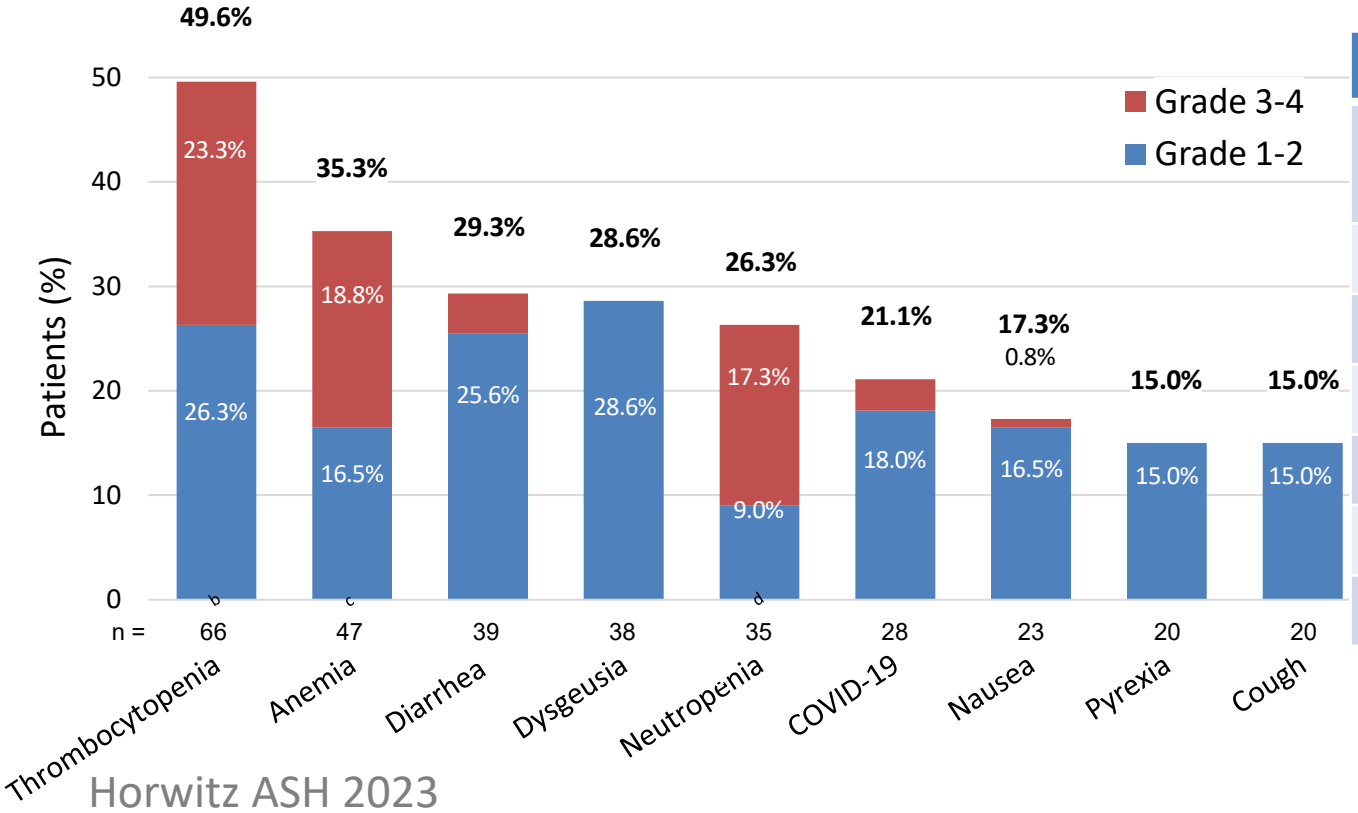
Data cutoff: May 5, 2023.

[a] Other TCLs include 3 patients with FTL, 1 with PCGTL, 1 with CD8+ PCAECTCL, 1 with MEITL, and 13 with other eligible, but undetermined PTCL subtypes.

Valemetostat Tolerability

- Cytopenias were common and manageable with dose modifications and/or supportive care
  - Thrombocytopenia was the most frequent any grade (49.6%) and grade ≥ 3 (23.3%) TEAE
  - Thrombocytopenia often transient
- 2 patients developed secondary AML and discontinued treatment



TEAEs leading to dose modifications[a] (N = 133)			
	Treatment discontinuation	Dose reduction	Dose interruption
Preferred term	%	%	%
Any TEAE	9.8	15.8	49.6
Thrombocytopenia	2.3	5.3	16.5
Anemia	0	3.8	9.8
COVID-19	0	1.5	8.3
Neutropenia	0	2.3	5.3

Horwitz ASH 2023

Valemetostat Conclusions

- Valemetostat is a well tolerated oral EZH1/2 inhibitor with high ORR
  - ORR: 52% by PET, 44% by CT
  - Durable responses seen
- Compares favorably to available agents (belinostat, pralatrexate, romidepsin) which have ORR ~25% and not as well tolerated
- Need confirmatory study

Horwitz ASH 2023

Other EZH2 Inhibitors

- HH2853 (EZH 1/2 Inhibitor)
  - 34 R/R PTCL patients with ORR 65%, CR 22%
  - Median duration of response NR

  - Tulmimetostat (EZH 1/2 inhibitor)
    - 3/7 ORR (2 CR, 1 PR)

Drescher ASCO 2023; Hong ASH 2023

JAK/STAT Inhibition in T-cell Lymphoma

- JAK/STAT upregulated in 25-90% TCL
- Cerdulatinib (JAK/SYK)
  - ORR 35% (7/20)
- Ruxolitinib:
  - ORR 23%
    - If with JAK/STAT activation: ORR 29%
- Golidicitinib: oral JAK1 selective inhibitor
  - Single arm phase II study (n=112)
  - **ORR by CT: 44% (CR 24%)**
  - Median follow-up 6 mo, median duration of response not reached
  - Promising activity in AITL and PTCL-NOS
    - AITL: 9/16 responders
    - PTCL: 23/50 responders

Horwitz SM et al. ASH 2019; Cai ASCO 2023, Moskowitz *Blood* 2021

Golidicitinib Study Design

Key eligibility criteria

Patients with r/r PTCLs

- PTCLs diagnosed locally
- Relapsed or refractory/intolerant to prior systemic therapy
- For ALCL patients, the prior systemic treatment should include CD30-targeted therapy (brentuximab vedotin) Measurable disease
- Age ≥ 18 y (for Korean ≥ 19 y)
- ECOG PS ≤ 2
- Adequate organ/system functions

Golidocitinib 150 mg QD
1 cycle = 21 days

Tumor assessment

Day 1 of Cycle 3, and then every 3 cycles until disease progression or intolerance or withdrawal from the study

- **Primary endpoint:** IRC assessed ORR **based on CT** per Lugano 2014 criteria
- **Secondary endpoints:** IRC assessed CRR, DoR, PFS and TTR, and safety investigator assessed ORR, CRR, DoR, PFS, TTR

104 patients with PTCL (51 PTCL NOS; 16 AITL; 11 ALCL) with 119 evaluable for efficacy

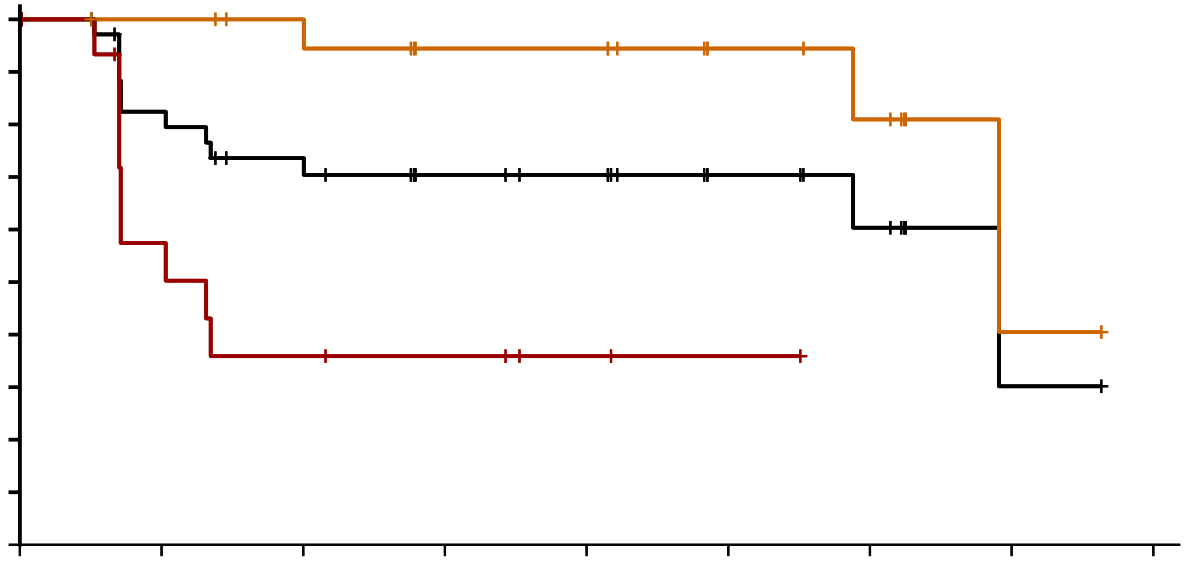
Median age 58; median 2 lines of prior therapy

Required central path review for evaluability (n=88)

Song ASH 2023

Golidicitinib Results

Tumor Response	n = 88
ORR, n (%)	39 (44.3)
Overall response, n (%)	
Complete response	21 (23.9)
Partial response	18 (20.5)
Stable disease	17 (19.3)
Progressive disease	20 (22.7)
Not evaluable	12 (13.6)



- The most common (incidence >10%) Grade≥3 TRAEs included thrombocytopenia, leukopenia, neutropenia
- mDoR was 20.7 months (53.8% still responding);
- patients with CRs achieved longer DoR compared with those with PRs;
- mPFS was 5.6 months; mOS was 19.4 months (52.3% still surviving).

Song ASH 2023

Conclusion

- Goliditicinib shows efficacy with ORR 44% and CR 24% by CT
- Median DOR 20.7 mo
- Toxicity is manageable
- Did not report response by JAK/STAT or by PET

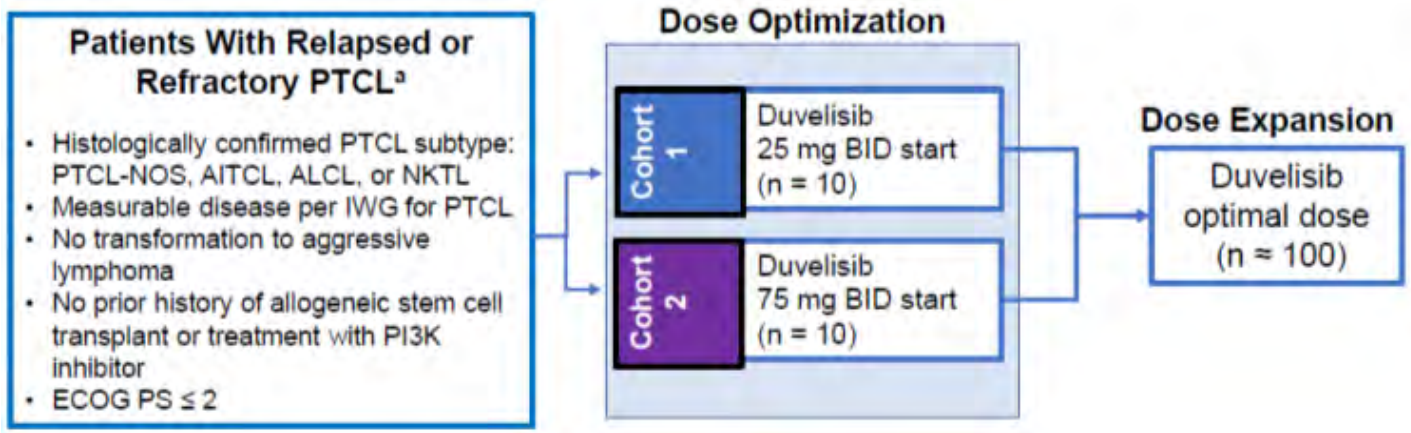
- Again, promising potential new addition to the armamentarium
  - Likely will need confirmatory study

Song ASH 2023

PI3K Inhibitors in PTCL

- Duvelisib is an oral gamma/delta phosphoinositide 3-kinases (PI3K) inhibitor

- Studied in single agent phase II study (PRIMO)
  - 75mg BID x 2 cycles→ 25mg BID unless progression/intolerance
  - ORR 49%, CR 34%
    - Median duration of response 7 mo
  - Grade ≥3 transaminitis 23%



- In combination study of duvelisib 75mg BID and romidepsin (n=66):
  - ORR 55%, CR 34%
  - Grade ≥3 transaminitis 14%

- Multiple other PI3 kinase inhibitors in development
  - Tenalisib: ORR 46% (n=35)
  - Linperlisib: *ongoing @ WUSTL*

Characteristic	PRIMO-EP (N=101)	
	ORR (%)	mPFS (range)
Overall	**49/101 (49%)**	**3.6 mo (3.2-8.1)**
PTCL-NOS	25/52 (48%)	6 mo (1.8- 8.1)
AITL	**20/30 (67%)**	**9.2 mo (3.8- NC)**
ALCL	2/15 (13%)	1.5 mo (0.4 - 1.8)

Mehta-Shah EHA 2023; Horwitz ASH 2021; Cheun et al Cancers 2020

CAR T-cells in T-cell Lymphomas

CD 5 CAR (Baylor; NCT03081910)

- CRs seen in PTCL, AITL

CD30 CAR

- Baylor: NCT02917083
- UNC: NCT02690545
- UNC: NCT03602157

CD7 CAR

- Baylor NCT 03680011

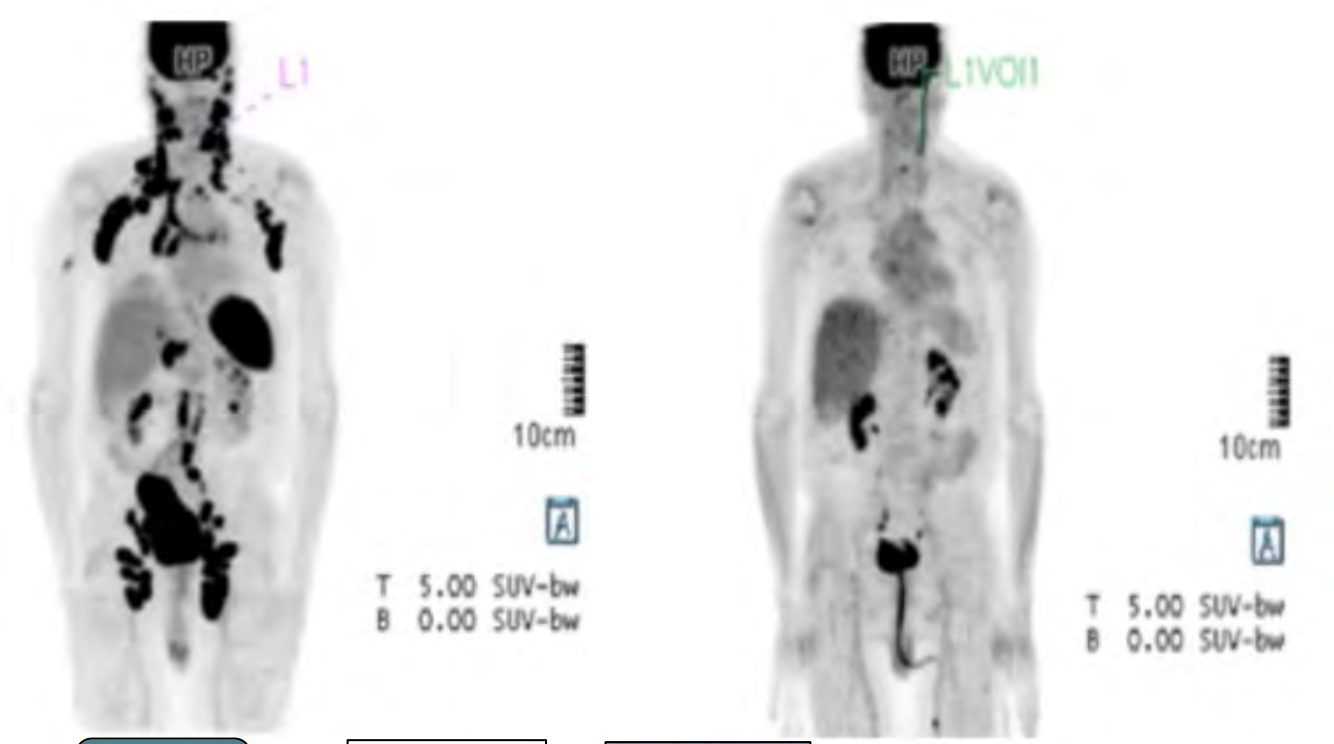
CD70 Allo CAR

- NCT04502446
- At MTD, ORR 75% PTCL (n=7), 67% CTCL (n=8)

CD7 Allo CAR

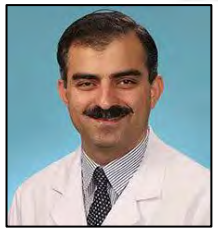
- WUSTL NCT 05377827
- CR rate 58% in T-ALL (n=12)

Pre-CD5 CAR T => CR @ 4 wk post CD5 CAR-T




Michael Kramer, MD, PhD


John DiPersio, MD, PhD


Armin Ghobadi, MD

Iyer EHA 2022; Ghobadi ASH 2023

Thank you!

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Thank you!

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NCCN National Comprehensive Cancer Network