Updates in the management of Hodgkin and T-cell lymphomas

Barbara Pro, MD
Professor of Medicine
Herbert Irving Comprehensive Cancer Center
Columbia University - Irving Medical Center

COLUMBIA
COLUMBIA UNIVERSITY
HERBERT IRVING COMPREHENSIVE
CANCER CENTER

Barbara Pro, MD

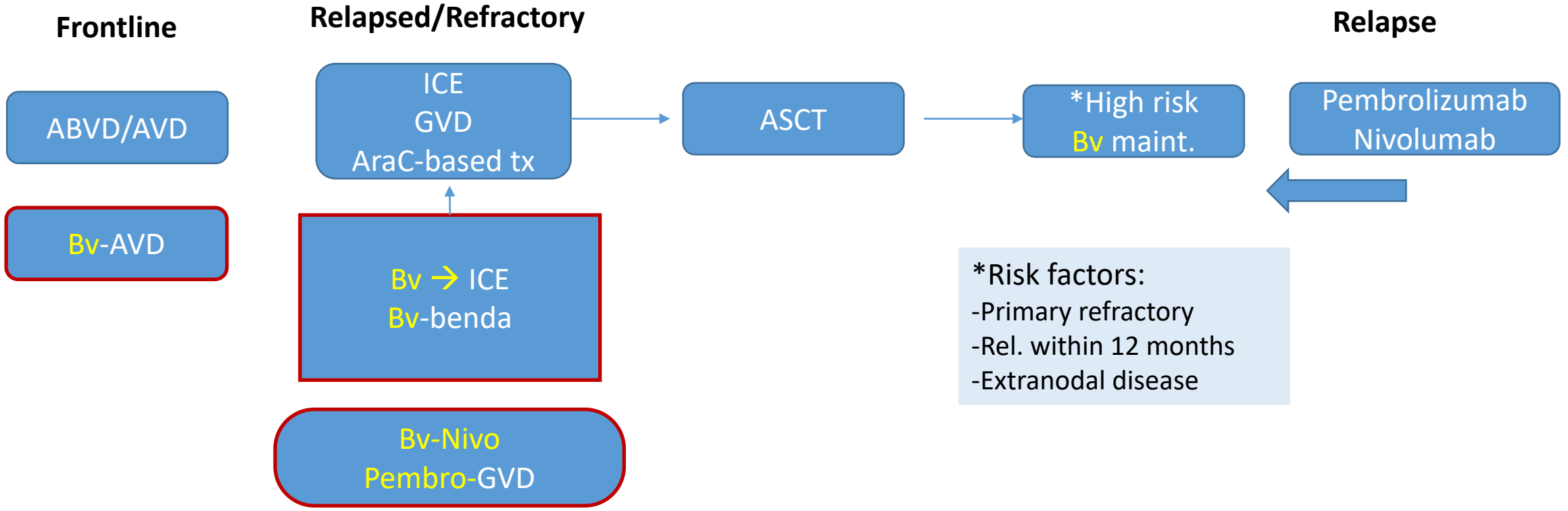
I have the following relevant financial relationship to disclose:

- **Honoraria: Takeda, Seattle Genetics, Secura Bio**
- **Research: Takeda , Seattle Genetics, Celgene, Verastem, Secura Bio, Astex Pharmaceuticals**

I will discuss off-label use in my presentation.

Hodgkin Lymphoma

- Estimated 8,830 cases in 2021
  - Stage at diagnosis: 53% Stage I/II, 42% Stage III/IV
- ~ 30% of patients relapse
  - Complete metabolic response predictive of PFS and OS
- Standard treatment approach

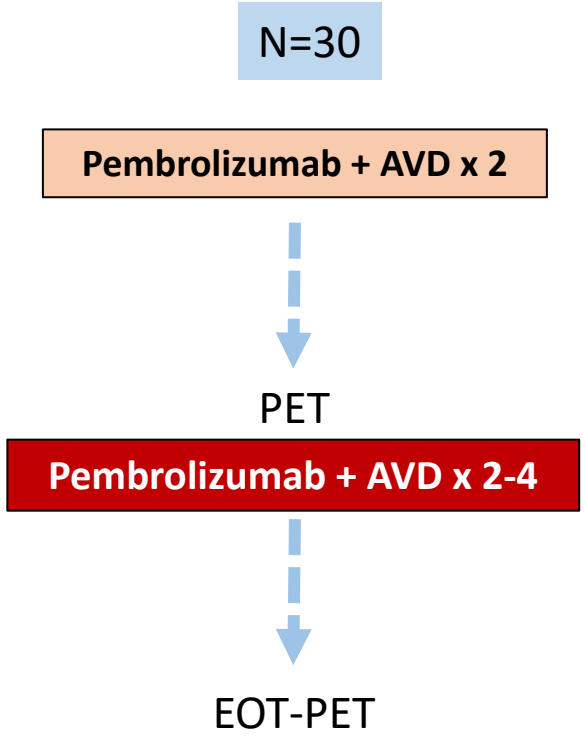


American Cancer Society. Cancer facts & figures 2021

Concurrent Pembrolizumab With AVD

- **Newly diagnosed - any stage**
- **ECOG 0-1**
- **Adequate organ function**
- **Measurable disease**

PEM 200 mg every 21 days
AVD standard dosing/schedule



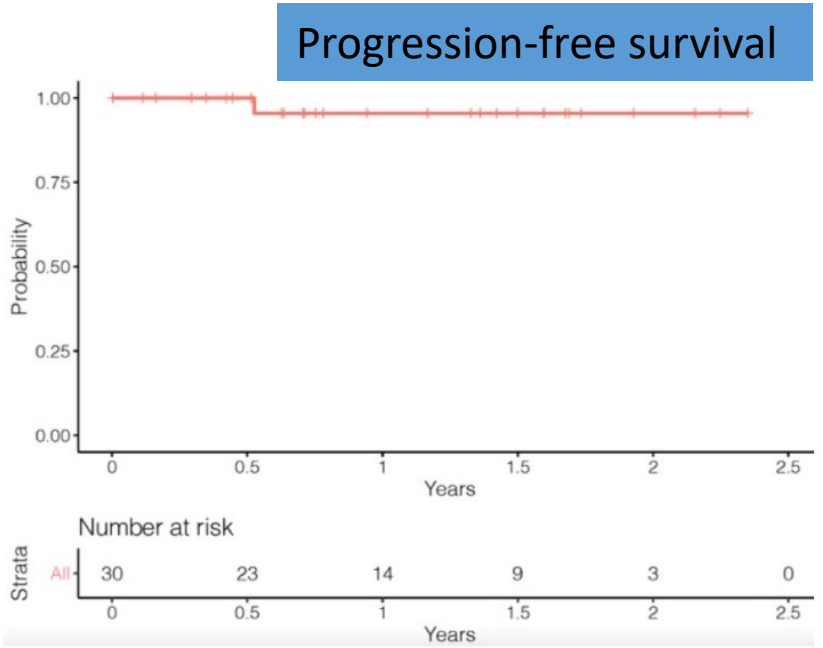
Primary Endpoint: > 85% of patients completing 2 cycles without delay
*role of PET scan, ctDNA

Lynch R et al. ASH 2021

Results

Efficacy

- Interim CMR 66%
- 1-year PFS 96%
- 1-year OS 100%
- 5 patients PET + EOT
  - 1 PD

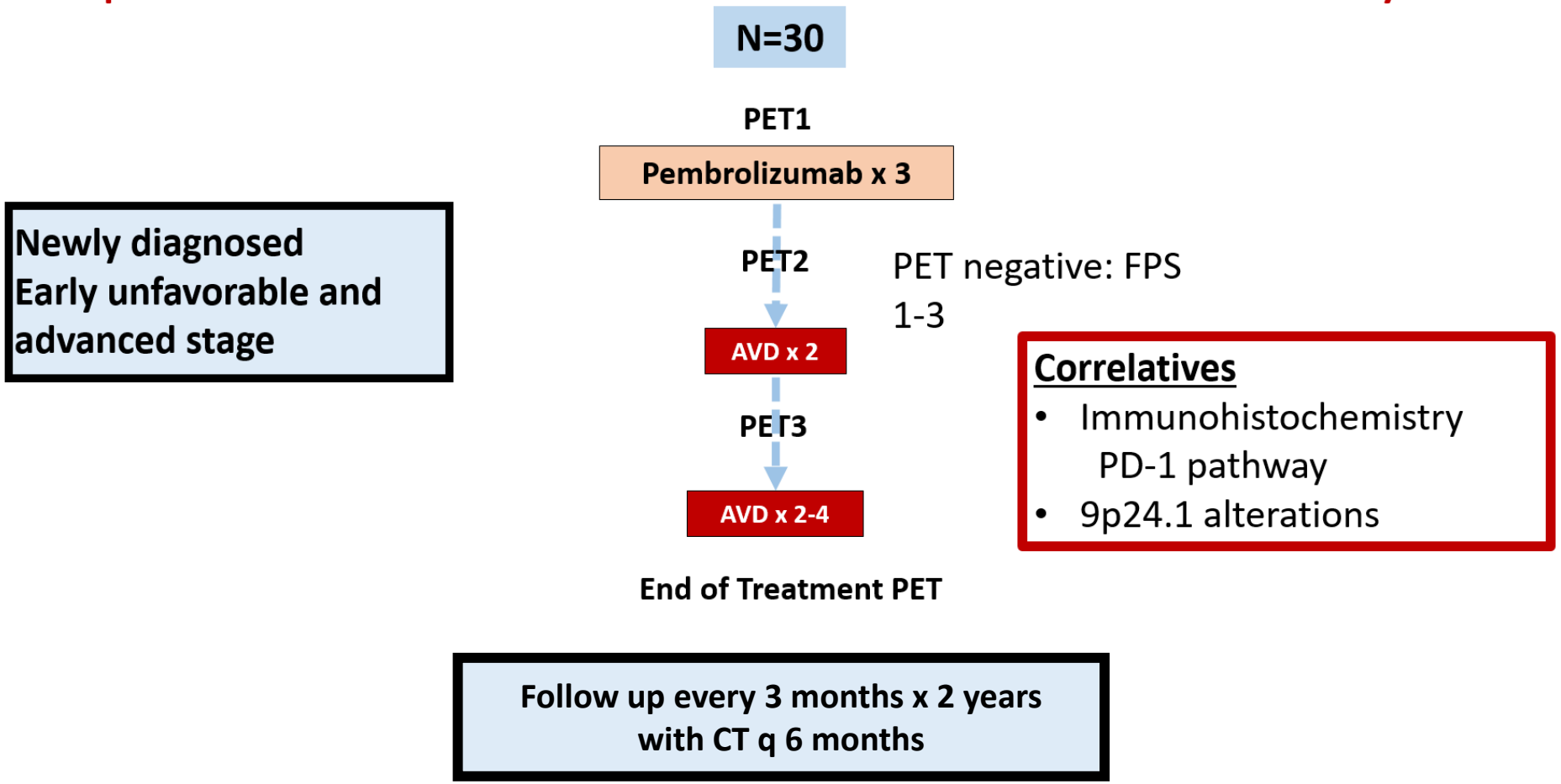


Toxicity

- Transaminitis grade ≥ 2 83%
- Febrile neutropenia 17%
- Hyponatremia 10%
- Syncope 10%

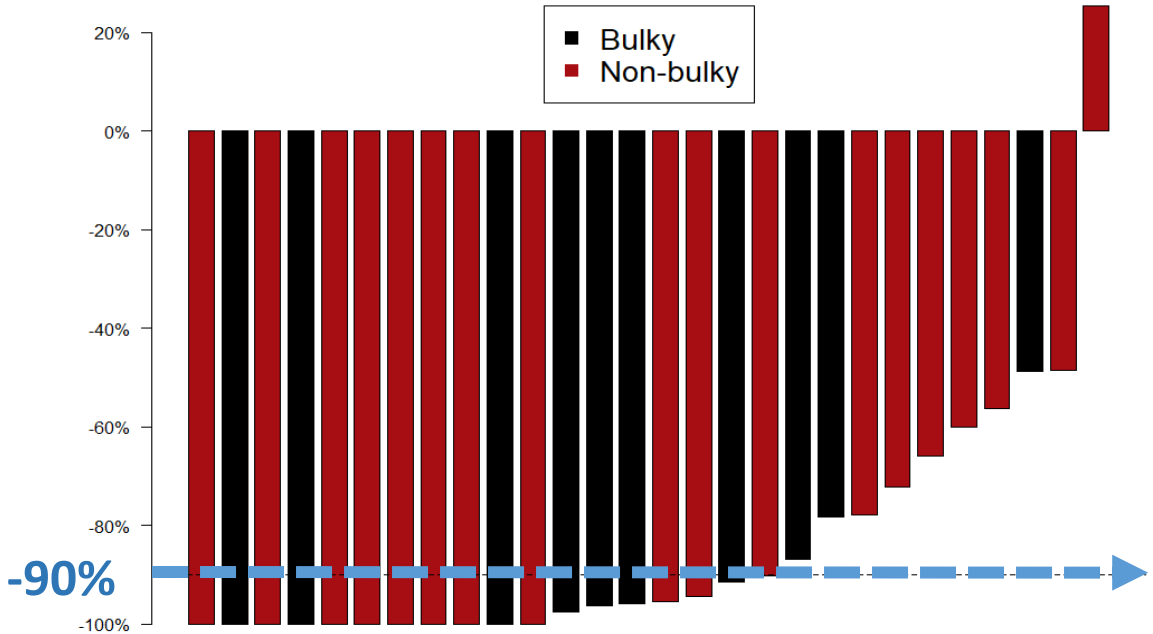
Lynch R et al. ASH 2021

Sequential Pembrolizumab and AVD : A Phase II Study

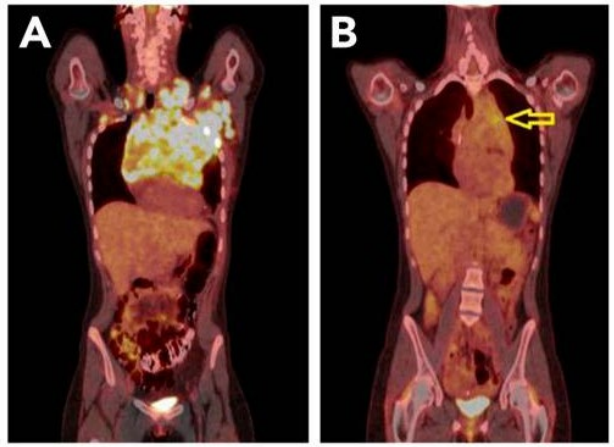


Allen PB et al. ASH 2021
Allen PB et al. *Blood* 2021.

Summary of Response to Single-Agent Pembrolizumab



Decline in Metabolic Tumor Volume



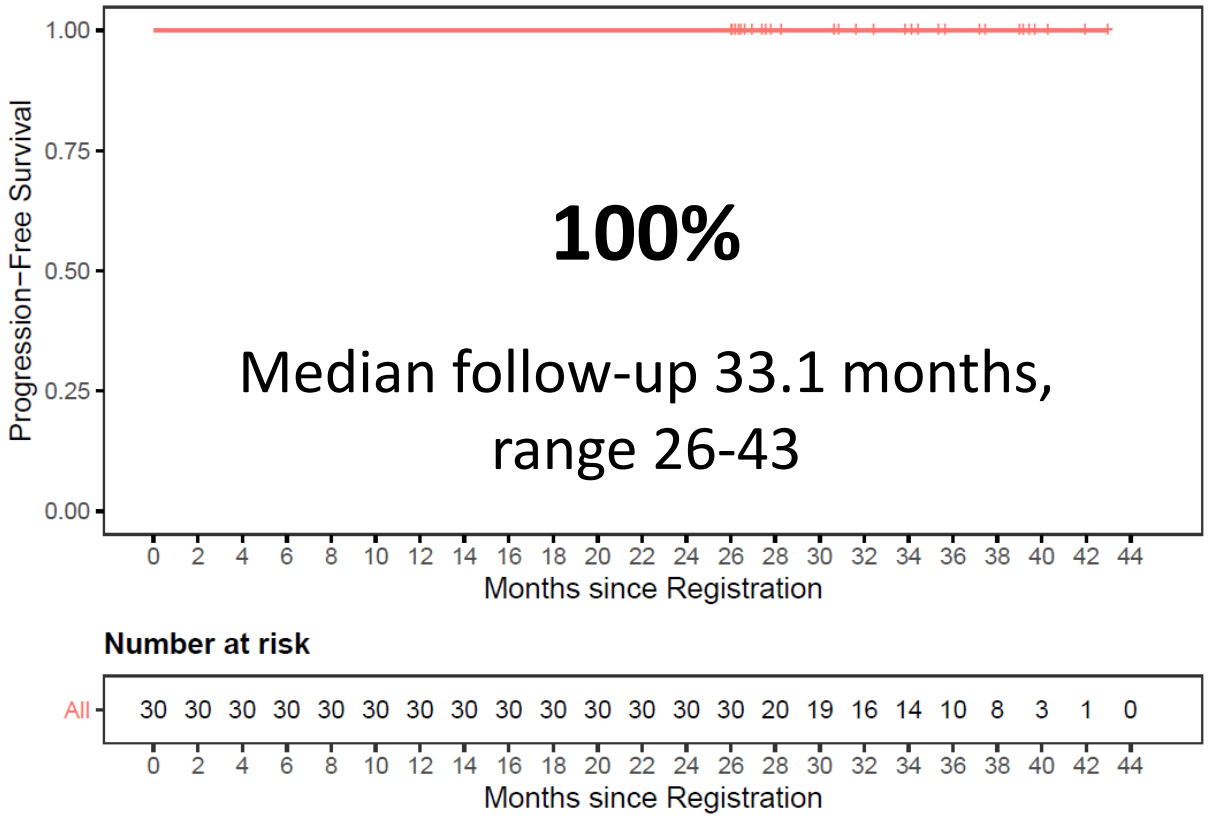
Response to single-agent pembrolizumab

***Near-CMR ≥ 90% reduction in metabolic tumor volume**

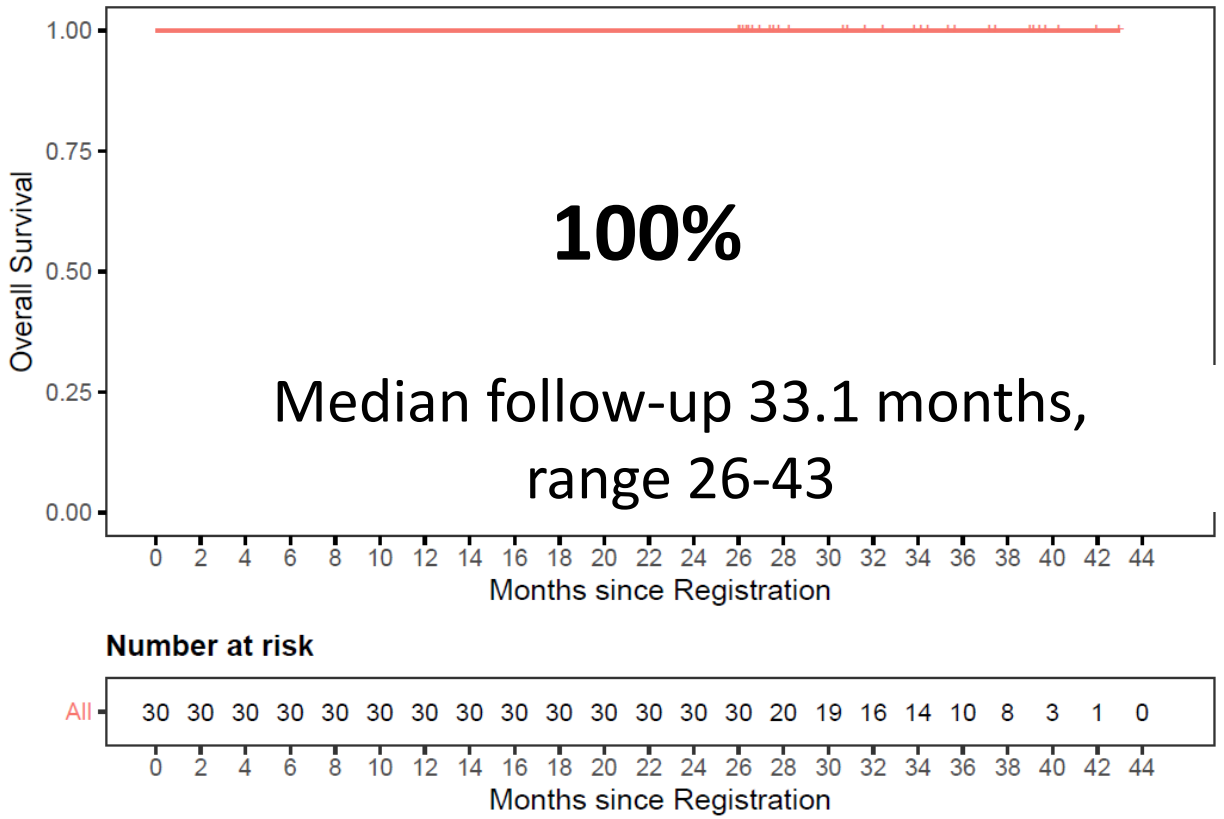
Allen P et al. ASH 2021

Sequential Pembrolizumab and AVD

Progression-Free Survival



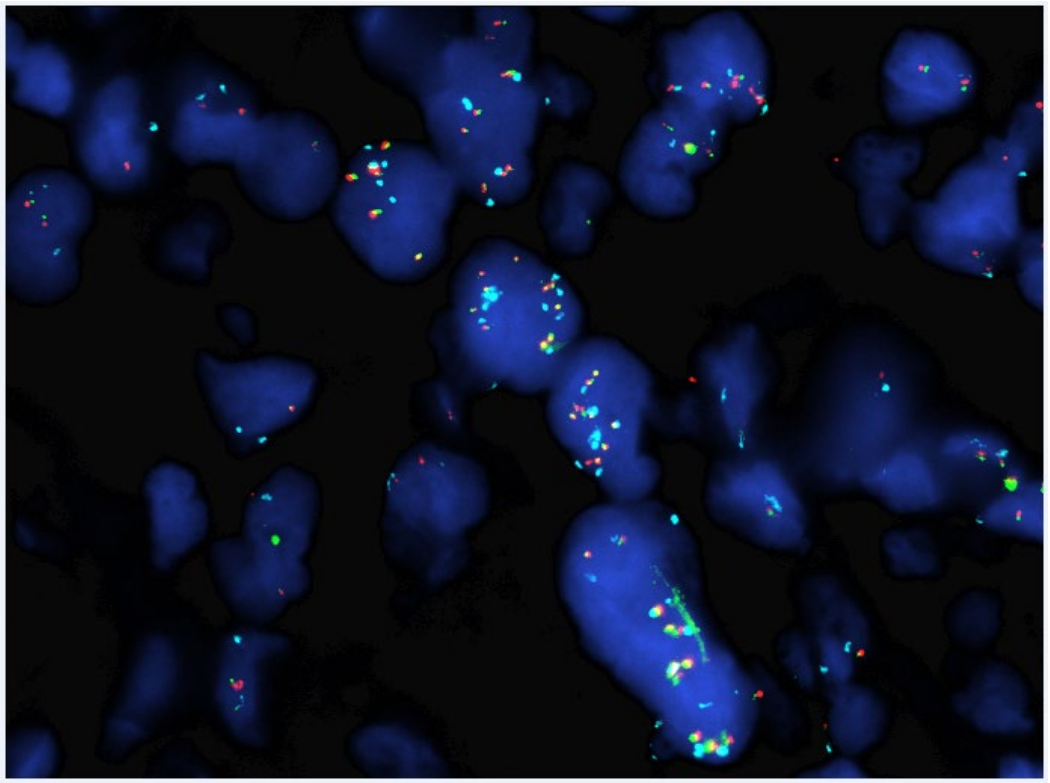
Overall Survival



Allen P et al. ASH 2021

Correlative Summary

Biomarker	N = 30
9p24.1 alteration (highest level)	29, 21-77
Disomy	0 (0%)
Copy number gain	14 (50%)
Amplification	14 (50%)
PD-L1 H score (median, range)	215 (20-300)
PD-L2 H score (median, range)	20 (0-180)
pSTAT3 H score	300 (60-300)



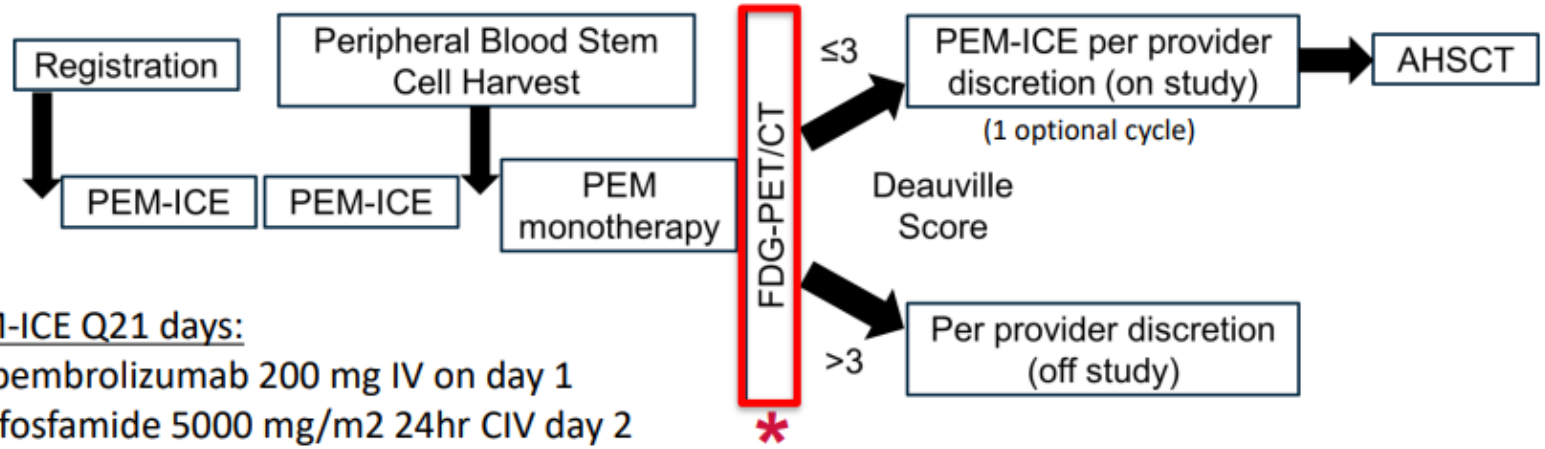
*No correlation between PD-1 pathway markers and response

Allen P et al. ASH 2021.

Pembrolizumab Added to ICE Chemotherapy: A Multi-Institutional Phase 2 Trial

Trial Schema:

<u>Key enrollment criteria:</u>
Age >18 years
Medically fit for AHSCT
Relapsed/refractory classic Hodgkin lymphoma
Exclusions: >2 prior regimens, prior PD-1 inhibitor exposure, history of autoimmune disease, known CNS involvement.



<u>PEM-ICE Q21 days:</u>

- pembrolizumab 200 mg IV on day 1
- ifosfamide 5000 mg/m2 24hr CIV day 2
- carboplatin AUC 5 IV day 2
- etoposide 100 mg/m2 IV days 1-3

NCT03077828

Primary endpoint: Improve CMR to 70%.

Bryan et al. ASH 2021

Patient Characteristics

45 patients enrolled
-8 inevaluable

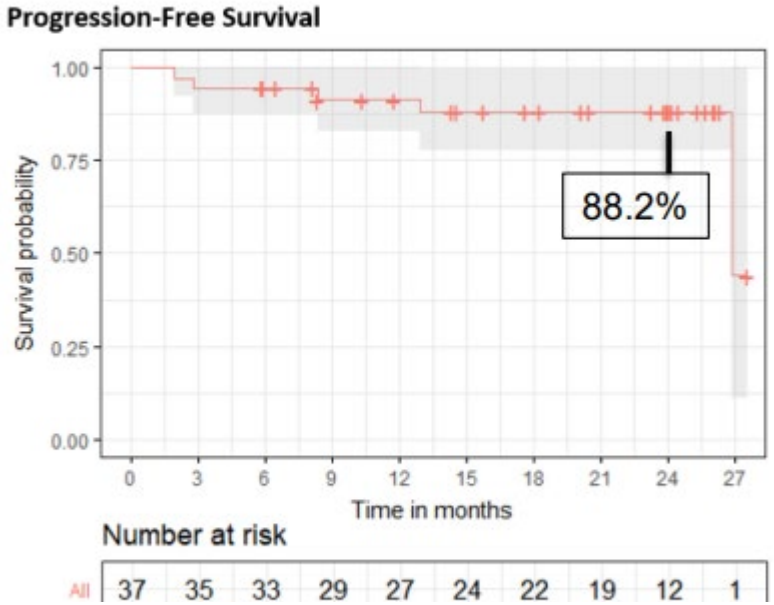
Patient Characteristics (n = 37)	n	(%)
Age: median age (range)	37	(19-70)
Sex		
Female	25	(68)
Male	12	(32)
Race		
White	26	(70)
African American	6	(16)
Asian	1	(3)
Not Reported / Unknown	4	(11)
Treatment History		
Received ABVD as Front-line Therapy	34	(92)
Primary Refractory Disease	14	(39)
Relapsed Disease within 1 yr	12	(32)
Bulky Disease (>10 cm) at Enrollment	6	(16)

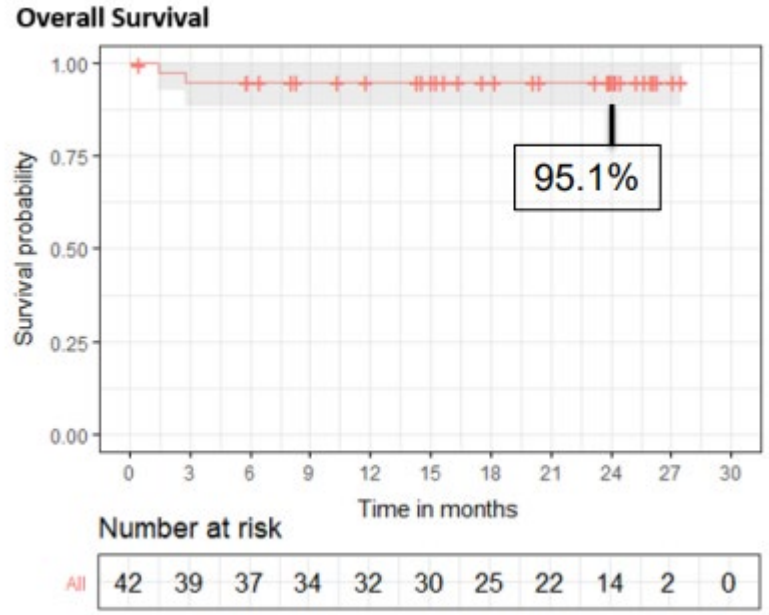
Bryan et al. ASH 2021.

Results

PET/CT Response Assessment (n = 37)		
Complete Response Rate	**86.5%**	(71 - 96)
PET2 Response	n	(%)
Deauville Score 1	17	(45)
Deauville Score 2	10	(27)
Deauville Score 3	3	(8)
Deauville Score 4	*5	(14)
Deauville Score 5	*2	(5)

* 2 cases with follow up biopsies confirmed noncaseating granuloma and EBV positive cells without evidence of lymphoma





Bryan et al. ASH 2021

Toxicity

Safety and Tolerability (n = 42)	n	(%)
Grade 3-4 Hematologic Toxicity		
Thrombocytopenia	39	(93)
Anemia	32	(76)
Febrile Neutropenia	12	(29)
Grade 3-4 Non-hematologic Toxicity		
Hypokalemia	15	(36)
Hypophosphatemia	11	(26)
Oral Mucositis	10	(24)
Attribution to PEM		
PEM-related Autoimmune Events	1*	

Grade 5 Toxicities
Cardiac arrest during stem cell collection
*ARDS following autoSCT – engraftment syndrome

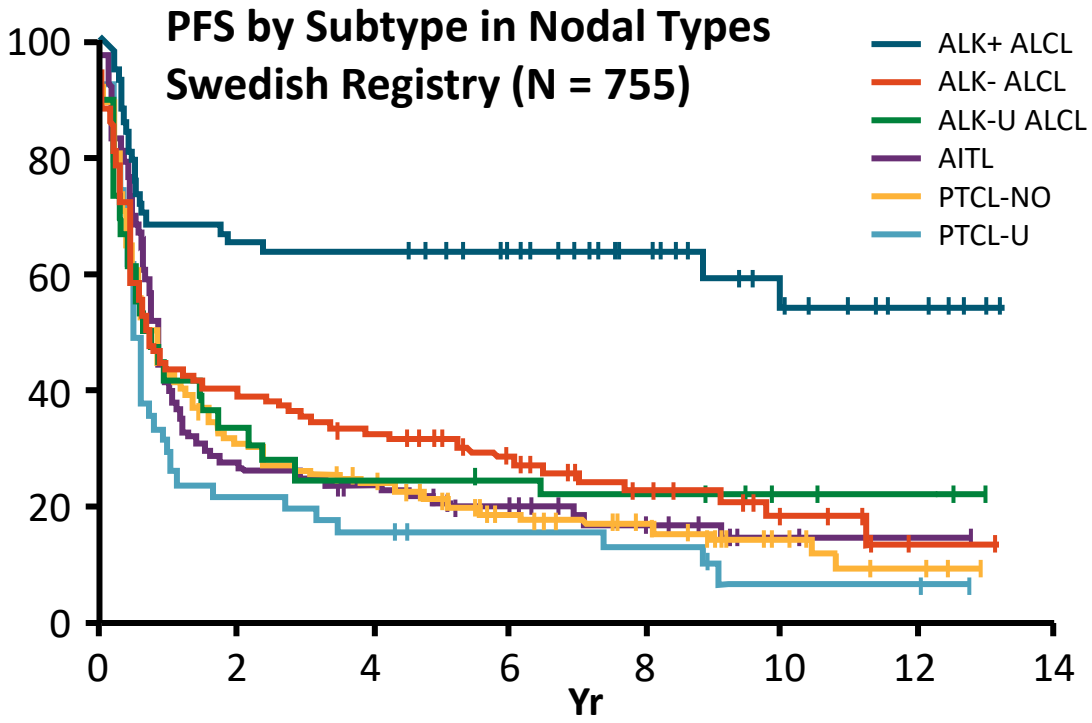
Bryan et al. ASH 2021.

PTCL: Frontline Treatment

PTCL-NOS
AITL
ALK- ALCL
ALK+ ALCL

→ **CHOP/CHOP-like** → **CR or PR** → **ASCT**

Low-risk ALK+ ALCL → observe

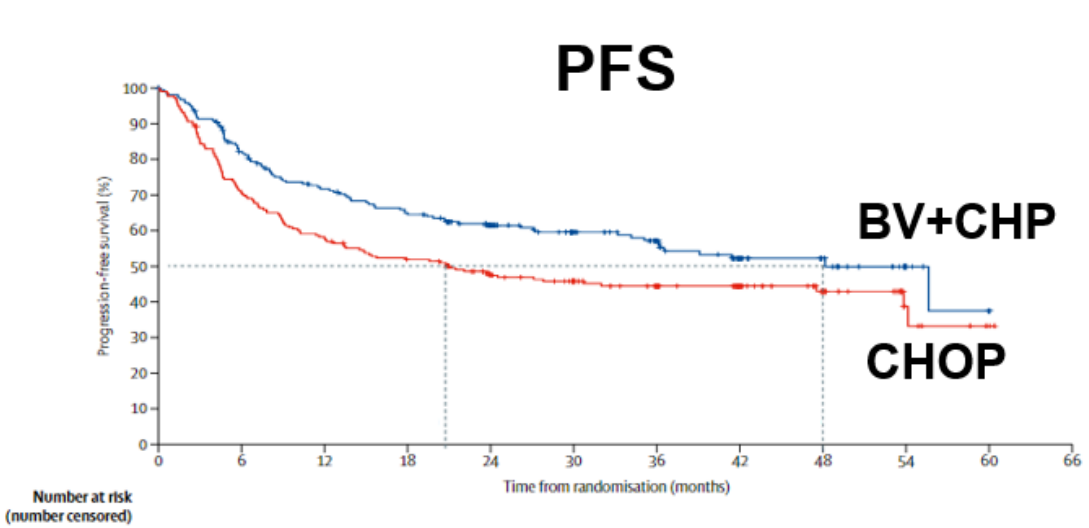


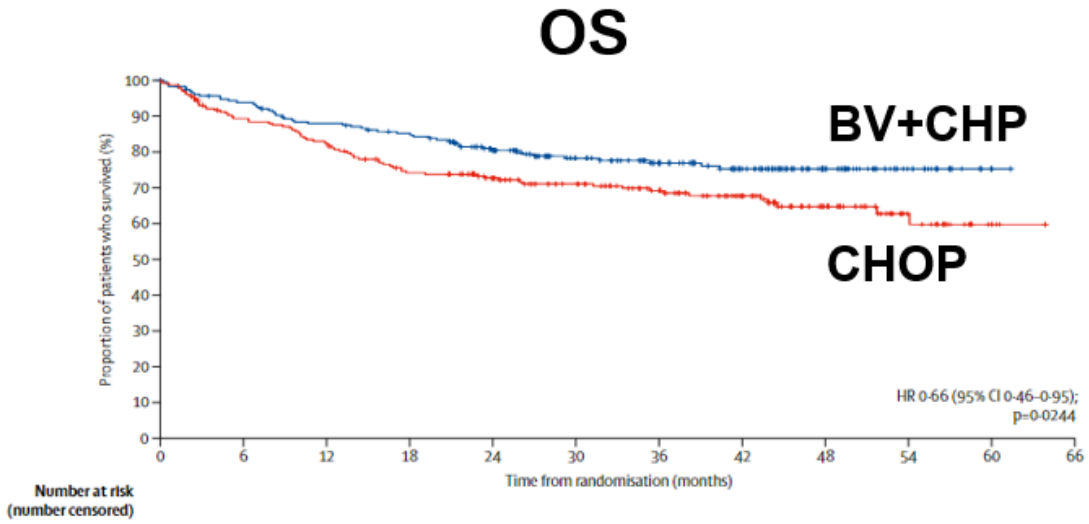
	ASCT	Non-ASCT	CHOEP	CHOP
	(n = 128)	(n = 124)	(n = 145)	(n = 107)
5-yr OS, %	48	26	47	30
5-yr PFS, %	41	20	40	23

Ellin. *Blood*. 2014;124:1570.

PTCL: CD30-targeted therapy

- CD30 expression universal in ALCL, ~50% in other PTCL subtypes
- Brentuximab vedotin + CHP as frontline therapy for CD30+ (≥10%) PTCLs improved PFS and OS compared to CHOP





Horwitz S, et al. Lancet 2019.

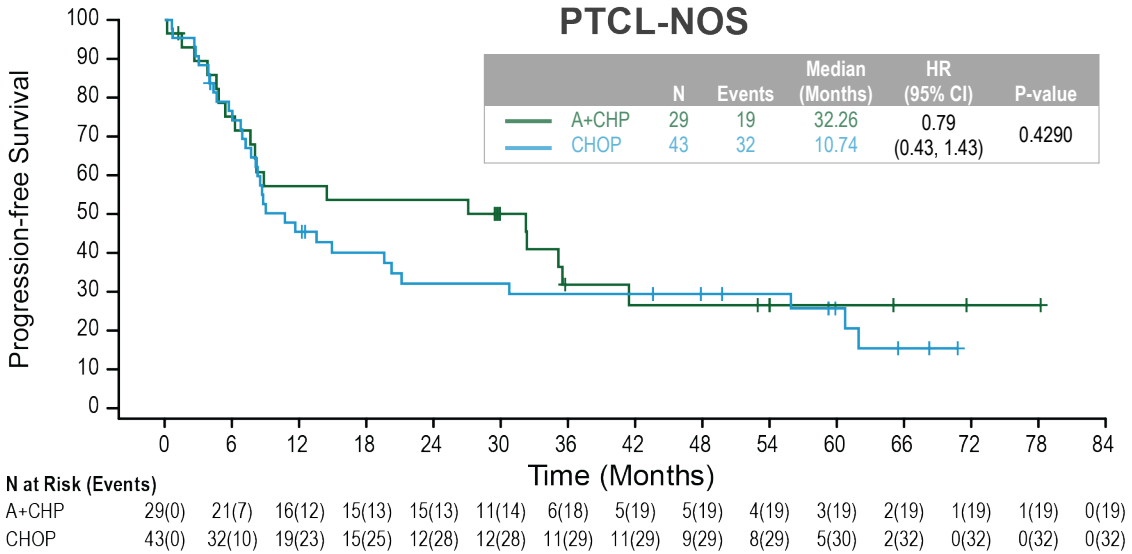
Echelon-2: Analysis by subtypes
Estimated 5-year PFS and OS rates in prespecified subgroups

Subgroup	Estimated 5-year PFS rate		HR (95% CI)	P-value	Estimated 5-year OS rate		HR (95% CI)	P-value
	A+CHP	CHOP			A+CHP	CHOP		
PTCL subtype								
PTCL-NOS, % (n)	26.5 (29)	25.7 (43)	0.79 (0.43, 1.43)	0.4	46.2 (29)	35.9 (43)	0.75 (0.37, 1.48)	0.4003
AITL, % (n)	26.6 (30)	48.1 (24)	1.41 (0.64, 3.11)	0.3958	67.8 (30)	62.5 (24)	1.01 (0.40, 2.55)	0.9855
sALCL								
Overall, % (n)	60.6 (162)	48.4 (154)	0.55 (0.39, 0.79)	0.0009	75.8 (162)	68.7 (154)	0.66 (0.43, 1.01)	0.0529
ALK+ % (n)	87 (49)	67 (49)	0.40 (0.17, 0.98)	0.0372	91.5 (26)	79.6 (27)	0.48 (0.16, 1.40)	0.1688
ALK– % (n)	49 (113)	39 (105)	0.58 (0.40, 0.86)	0.0054	68.7 (50)	63.3 (41)	0.71 (0.44, 1.12)	0.1373
sALCL, IPI Score								
0–1, % (n)	59.5 (41)	47.6 (32)	0.42 (0.18, 0.94)	0.0301	87.0 (41)	86.2 (32)	0.73 (0.20, 2.73)	0.6411
2–3, % (n)	68.5 (95)	50.9 (100)	0.57 (0.35, 0.90)	0.0158	80.6 (95)	68.7 (100)	0.57 (0.32, 1.01)	0.0496
4–5, % (n)	27.2 (26)	36.4 (22)	0.73 (0.35, 1.50)	0.3839	38.0 (26)	43.2 (22)	0.89 (0.42, 1.89)	0.7606

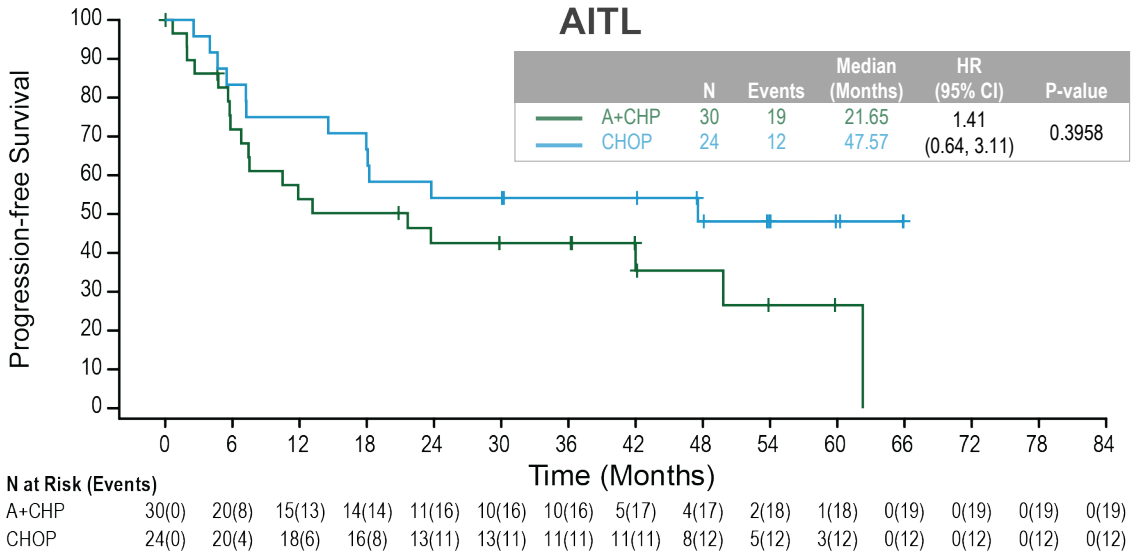
IPI, International Prognostic Index.

Horwitz S et al. ASH 2021

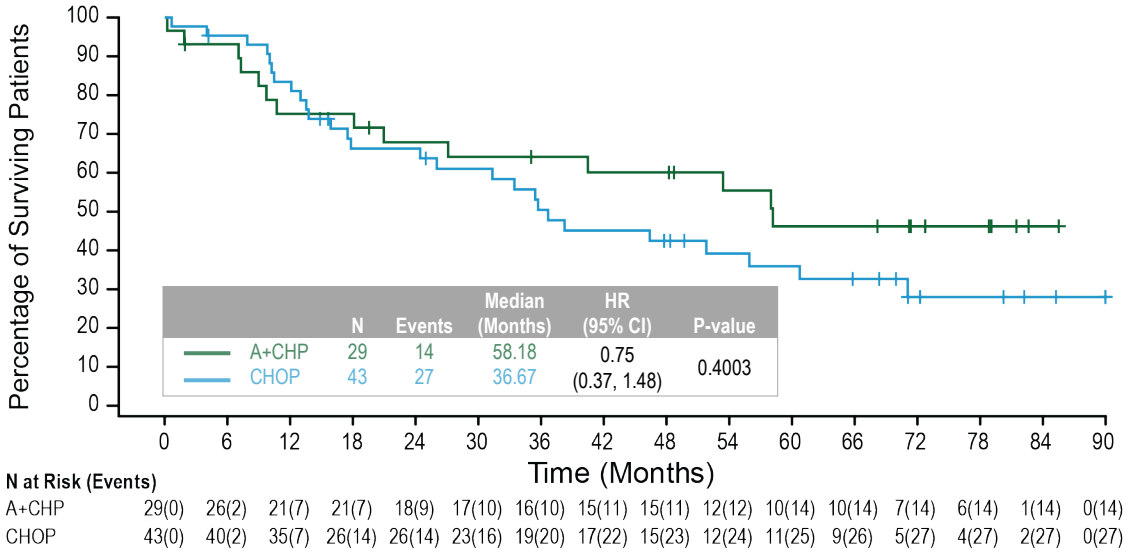
Summary of OS and PFS per Investigator (PTCL-NOS and AITL)



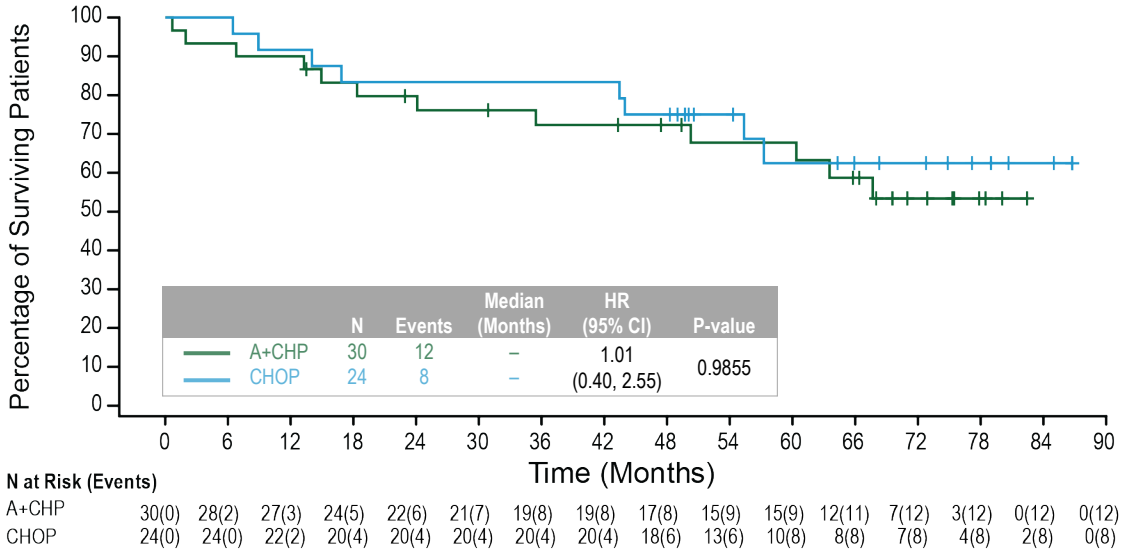
	N	Events	Median (Months)	HR (95% CI)	P-value
A+CHP	29	19	32.26	0.79 (0.43, 1.43)	0.4290
CHOP	43	32	10.74		



	N	Events	Median (Months)	HR (95% CI)	P-value
A+CHP	30	19	21.65	1.41 (0.64, 3.11)	0.3958
CHOP	24	12	47.57		



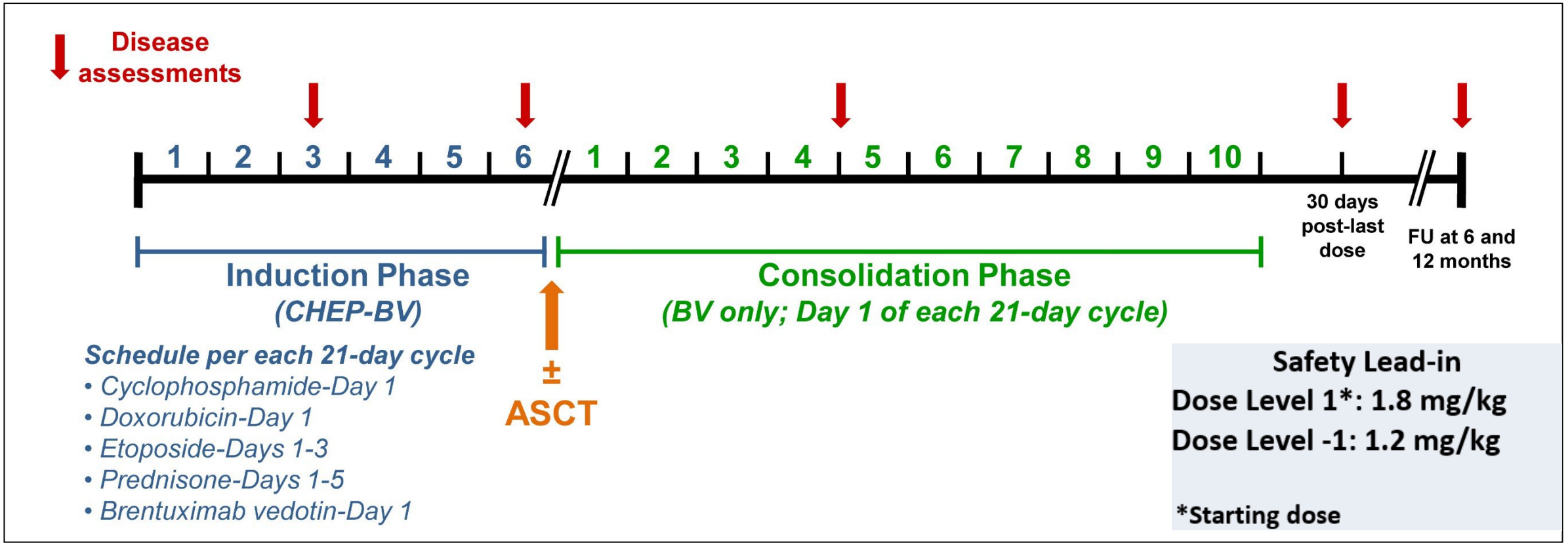
	N	Events	Median (Months)	HR (95% CI)	P-value
A+CHP	29	14	58.18	0.75 (0.37, 1.48)	0.4003
CHOP	43	27	36.67		



	N	Events	Median (Months)	HR (95% CI)	P-value
A+CHP	30	12	–	1.01 (0.40, 2.55)	0.9855
CHOP	24	8	–		

Horwitz S et al. ASH 2021.

CHEP-BV Followed by BV Consolidation Study Schema

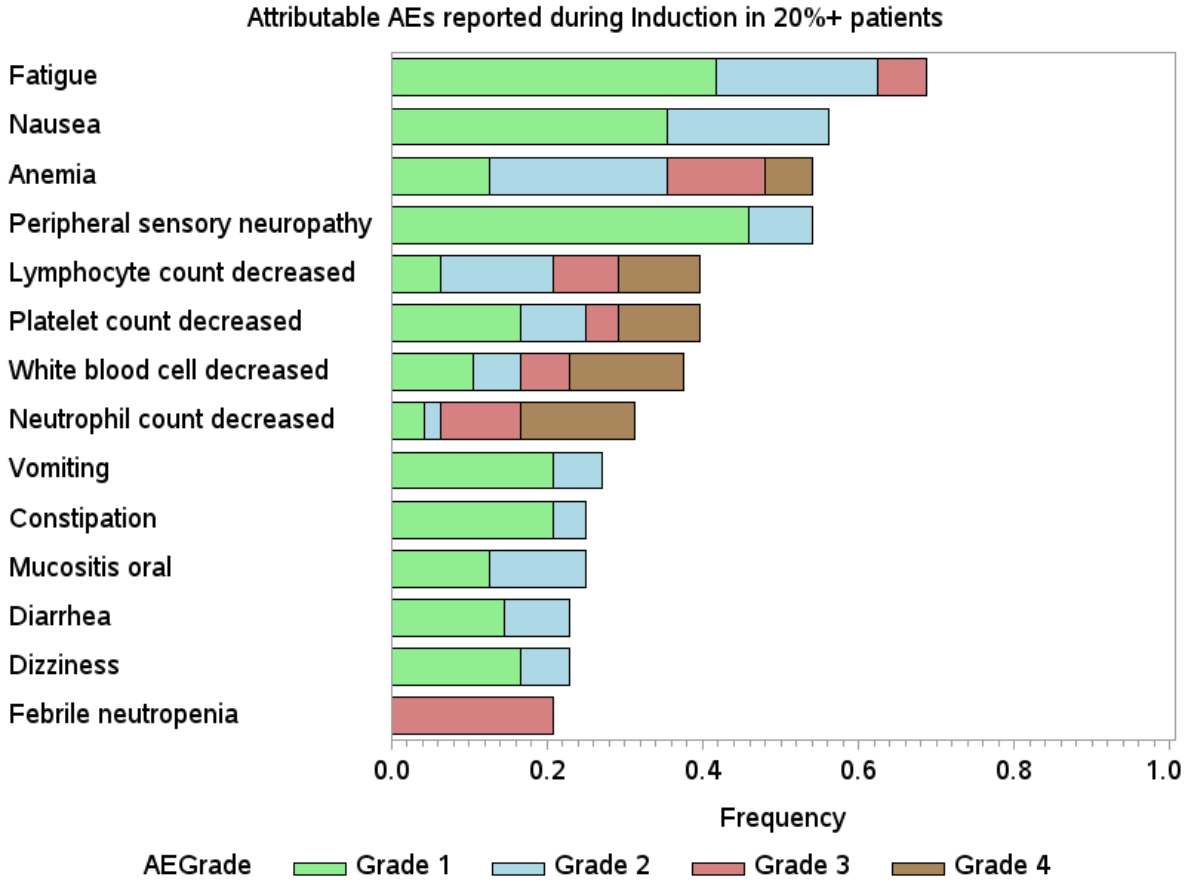


*CD30-positivity ≥ 1% on tumor cells by IHC (local review)
Response assessment by investigators: 2014 Lugano classification

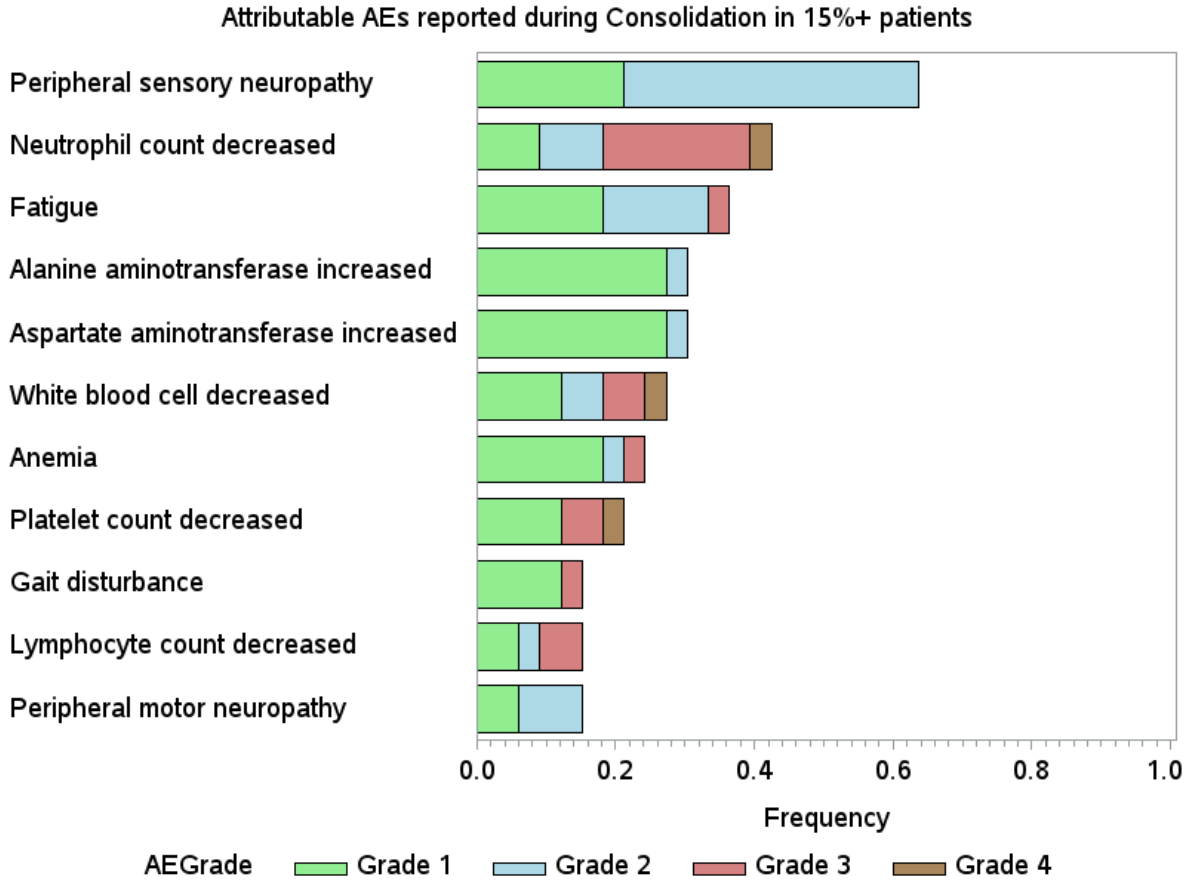
Herrera AF et al. ASH 2021.

Most Common Adverse Events

CHEP-BV



BV consolidation

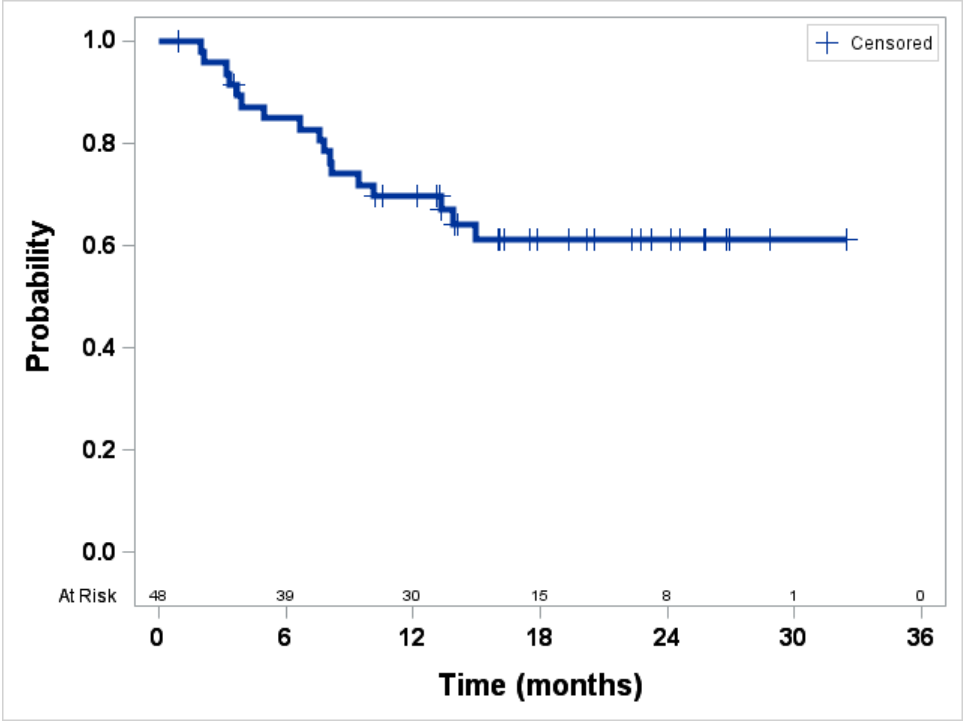


**5 deaths on study: 4 due to PD, 1 due to COVID-19 during C3 of CHEP-BV

Herrera AF et al. ASH 2021

End of CHEP-BV Response: PTCL Subtypes

Response	ALCL (n=16)	Non-ALCL (n=30)	AITL (n=17)	PTCL NOS (n=11)	PTCL TFH (n=2)
Overall response (ORR)	**15 (94%)**	**27 (90%)**	**16 (94%)**	**9 (82%)**	**2 (100%)**
Complete response (CR)	**15 (94%)**	**22 (73%)**	**14 (82%)**	**6 (55%)**	**2 (100%)**
Partial response (PR)	0	5	2	3	0
Stable disease (SD)	0	0	0	0	0
Progressive disease (PD)	1	3	1	2	0



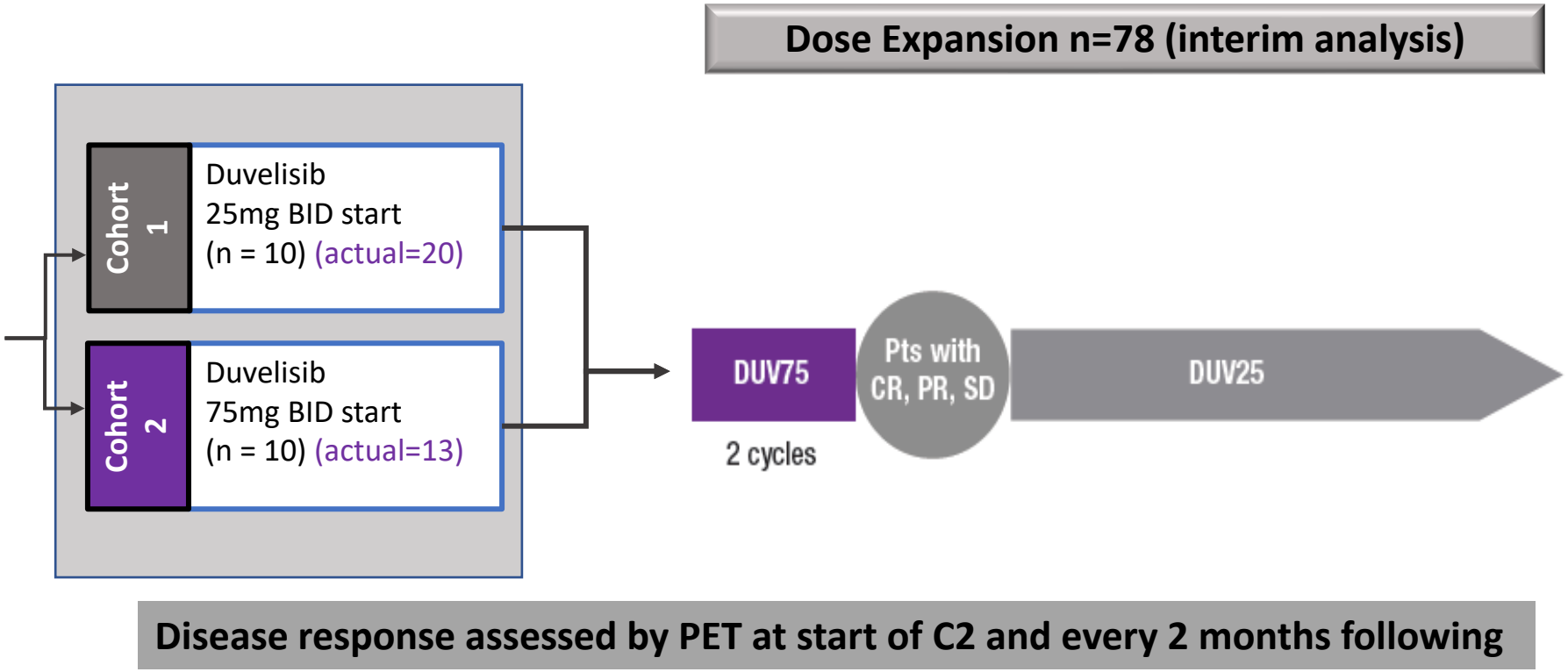
Median follow-up 16.1 months
18-month PFS 61%

Herrera AF et al. ASH 2021.

PRIMO: Phase 2 Study of Duvelisib Monotherapy in R/R PTCL

Patients with Relapsed or Refractory PTCL[a]

- Histologically confirmed PTCL subtypes: PTCL-NOS, AITCL, ALCL, SPLTCL, MEITL, and NKTL
- Measurable disease per IWG for PTCL
- No prior history of allogeneic stem cell transplant or treatment with PI3K inhibitor
- ECOG PS ≤2



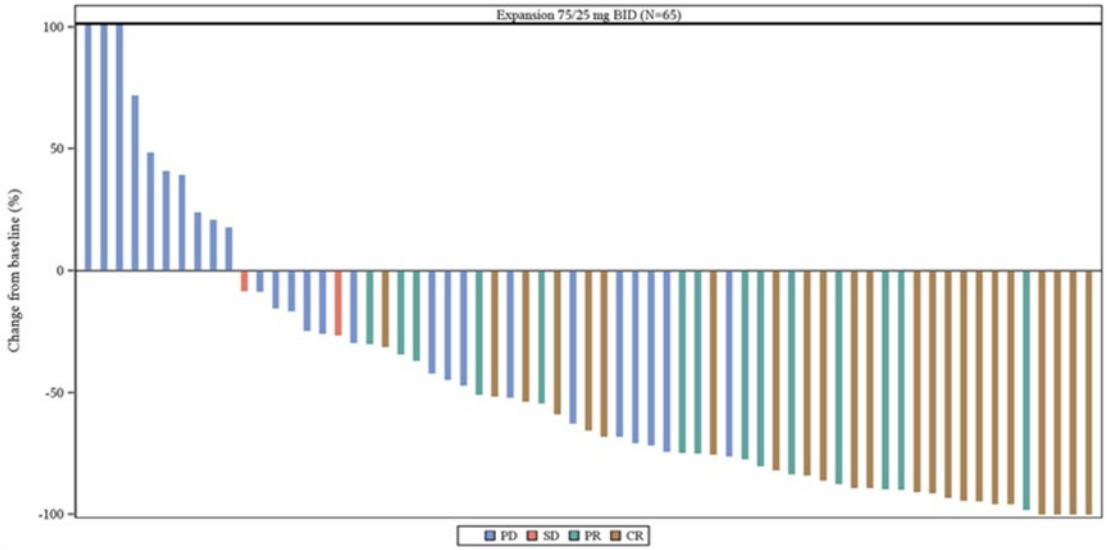
Objectives

Primary Objective	IRC assessed ORR
Secondary Endpoints	Safety, DOR, PFS, DCR (i.e., CR + PR + SD ≥ 8 weeks), OS
Exploratory Endpoints	PK/PD markers

[a] Received ≥ 2 cycles of 1 prior regimen administered with curative intent and failed to achieve PR or better after ≥ 2 cycles, or failed to achieve CR after ≥ 6 cycles, or progressed after initial response.

Dose Expansion: Results

Best percent change from baseline in target lesions (n=65)*



*65 out of 78 subjects had both best overall response (CR, PR, SD, PD) and data available to compute percent change from baseline sum of target lesions

Number of patients dosed	78
Summary of responses, by IRC Number of Responders (Lugano Criteria), n (%) CR PR	39 (50) 25 (32.1) 14 (17.9)
Duration of response in days Median (95% CI) Range	233 (90, NC) (1+, 420+)
Number of patients discontinued from treatment, n (%) Disease progression Death Transplant Adverse Event Other	64 (82.1) 34 (43.6) 4 (5.1) 5 (6.4) 14 (17.9) 7 (8.9)
Median time to response, days (range)	53 (15,114)
Number of patients continued on treatment, n (%)	14 (18)
Minimum follow up, months	6

Brammer JA et al. ASH 2021

Conclusions

- **cHL**

Use of PD-1 inhibitors in the frontline setting appears very promising

- Ongoing US intergroup Phase 3 study evaluating BV or nivolumab in combination with AVD
- Multicenter trial of sequential pembrolizumab and AVD planned

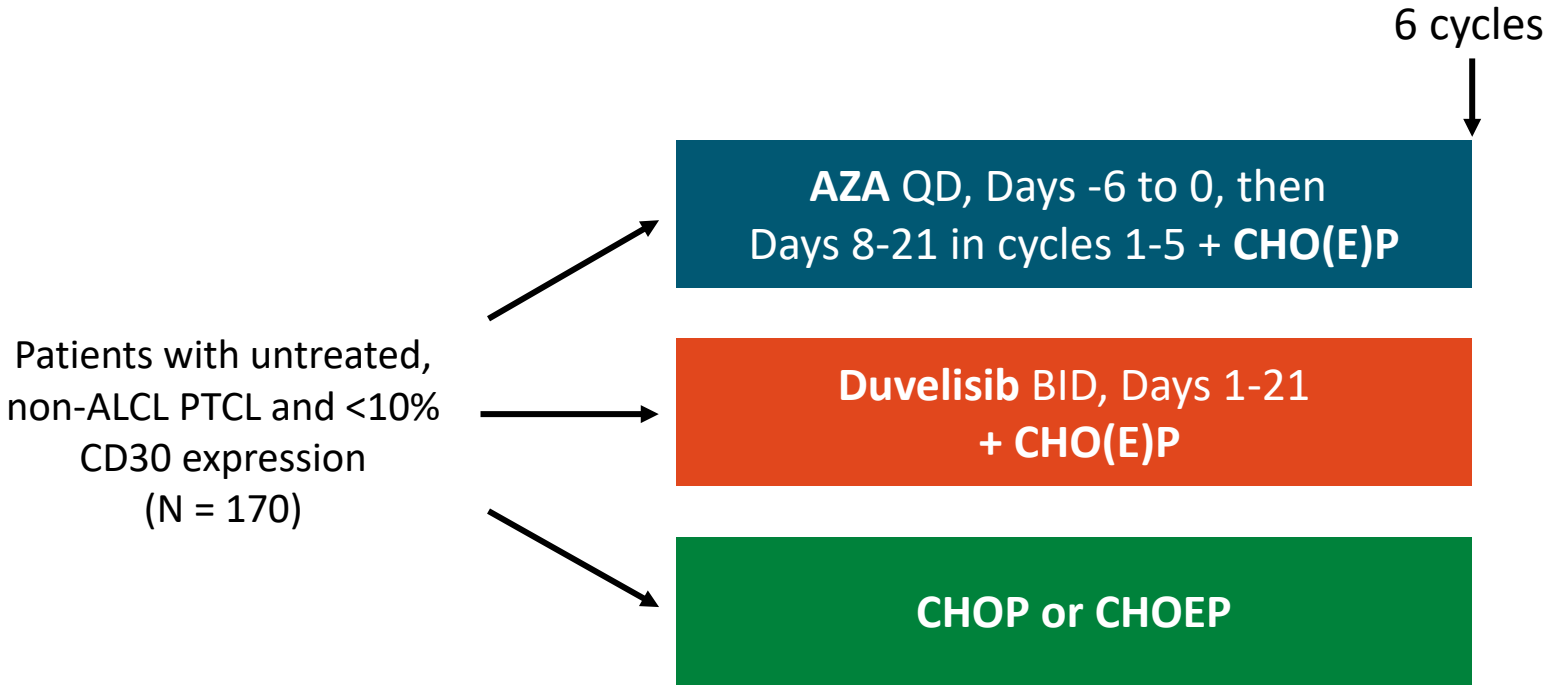
Novel combinations in the R/R setting very effective

- **PTCL**

sALCL: BV + CHP has a PFS and OS benefit over CHOP

Alternative therapies for AITL/TFH-PTCL , PTCL-NOS, CD30- cases are needed

Phase II A051902: Azacitidine + CHO(E)P vs Duvelisib + CHOEP vs CHOP or CHOEP in CD30- Untreated PTCL



- Primary endpoint: CR rate per PET/CT (goal: 25% difference)
- Secondary endpoints: safety/tolerability, ORR, DoR, PFS, EFS, OS, PROs

ClinicalTrials.gov. NCT04803201.