PTCL: Potential New Alternatives in Front Line Rx CHOP vs A-CHP

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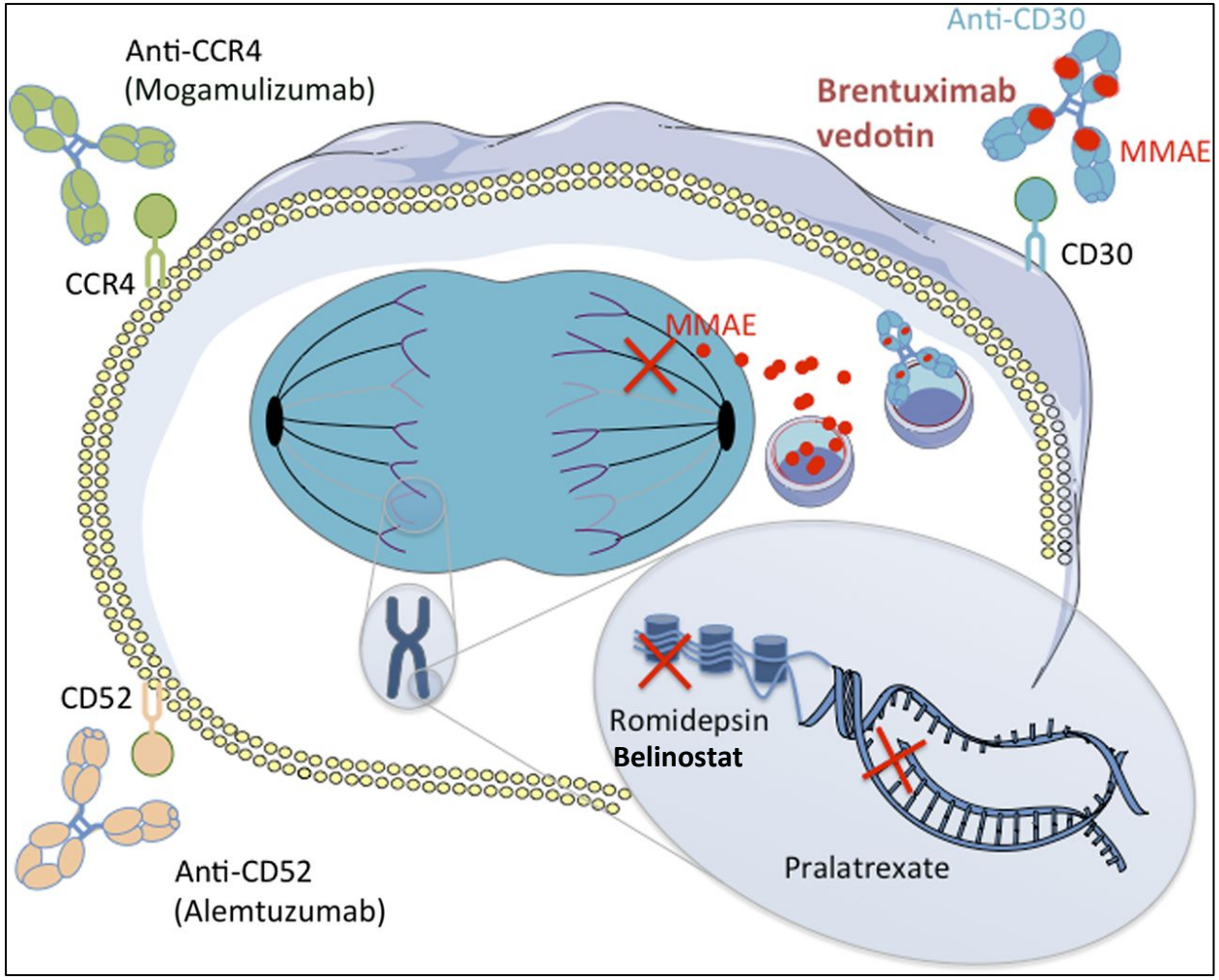
What to expect with CHOP in non ALCL PTCL

- CR ~ 35-39%
- Median EFS ~ 12 mo
- 2 y EFS rate 41-45%
  - Most events early
- 5 y OS ~ 40-50 %
- Pts with low/low int IPI have better outcomes
- Poor outcome at relapse

Unmet need

  - Achieving high CR rates
  - Translating these remissions into long-term survival

Mechanisms of action of new drugs in PTCL



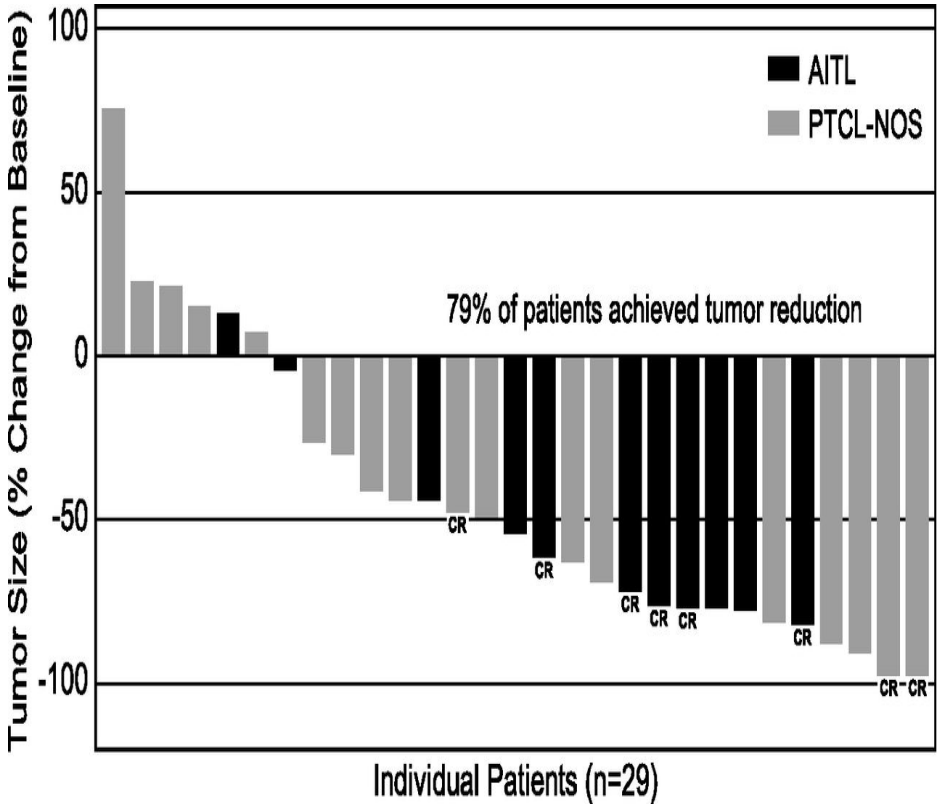
Bachy E , and Coiffier B Blood 2014

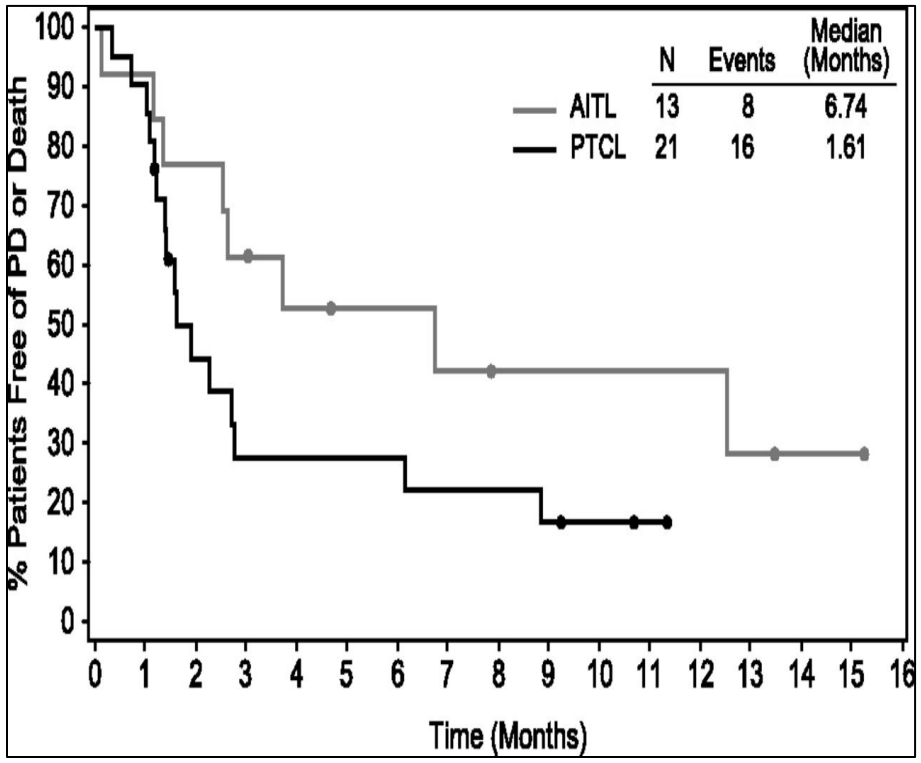
Relapsed/Refractory PTCL
FDA-Approved Agents

Agent	Regimen	N	ORR, %	CR, %	Response Duration, Mos
Pralatrexate O'Connor , et al. JCO 2011	30 mg/m^2 weekly x 6 of 7 wks	111	29	11	10.1
Romidepsin Coiffier , et al. JCO 2012	14 mg/m^2 weekly x 3 every 28 days	131	25	14	17.0
Brentuximab vedotin (ALCL) **Pro, et al. JCO 12**	**1.8 mg/kg every 21 days**	**58**	**86**	**57**	**12.6**
Belinostat Oconnor ASCO 2013	1000 mg/m2 1-5 every 21 days	129	26	10.8	8.3

Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin

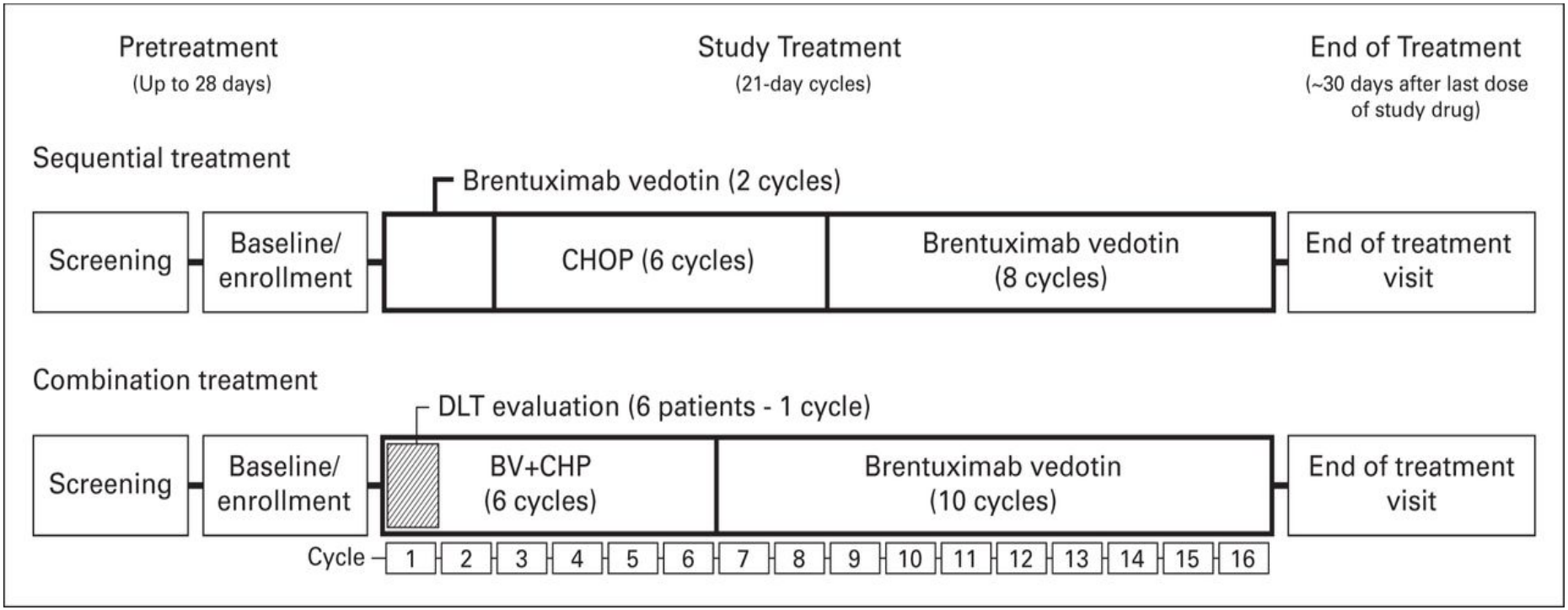
Response did not correlate with level of CD 30 expression





Horwitz et al Blood 2014

Brentuximab Vedotin Administered Concurrently or Sequentially with Multi-Agent Chemotherapy as Frontline Treatment of ALCL and other CD30-Positive Mature T-Cell and NK-Cell Lymphomas
Phase 1 Trial



CD 30 defined as positive if $\geq$ 1% on central review for non ALCL subtypes

Fanale M A et al. JCO 2014

Demographics and Baseline Characteristics

Parameter	Total N=39
Age* , years	57 (21–82)
Gender, n	20 M / 19 F
IPI score ≥2, n (%)	26 (67)
Stage III/IV disease, n (%)	26 (67)
Baseline B symptoms	18(46)
Diagnosis	
sALCL, n (%)	32 (82)
ALK – / +, n	26 /6
Other CD30+ T- and NK-cell neoplasms, n (%)	7 (18)
Peripheral T-cell lymphoma NOS, n	2
Angioimmunoblastic T-cell lymphoma, n	2
Adult T-cell leukemia/lymphoma, n	2
Enteropathy-associated T-cell lymphoma, n	1

* Median (range)

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Preferred Term*	Sequential Treatment (n = 13)		Combination Treatment (n = 26)	
	No.	%	No.	%
Any event	8	62	19	73
Febrile neutropenia	2	15	8	31
Neutropenia	2	15	6	23
Anemia	2	15	4	15
Peripheral sensory neuropathy	2	15	2	8
Leukopenia	1	8	2	8
Pulmonary embolism	0		3	12
Septic shock	1	8	2	8
Syncope	1	8	2	8
Cardiac failure	0		2	8
Constipation	2	15	0	
Fatigue	2	15	0	
Respiratory failure	0		2	8

2/3 unrelated

PSN only AE that led to discontinuation in > 1 patient (n =2, 12%)

Response After Sequential or Combination Treatment

Response	Sequential ALCL (n = 13)		Combination					
			ALCL (n = 19)		Non-ALCL (n = 7)		Total (n = 26)	
	No.	%	No.	%	No.	%	No.	%
Objective response	11	85	19	100	7	100	26	100
Complete remission	8	62	16	84	7	100	23	88
Partial remission	3	23	3	16	0		3	12
Stable disease	0		0		0		0	
Progressive disease	2	15	0		0		0	

NOTE. Response assessment per investigator (Cheson[9]) at cycle 8 (sequential treatment), cycle 6 (combination treatment), or at last available response assessment for patients who discontinued treatment before these time points.

Abbreviation: ALCL, anaplastic large-cell lymphoma.

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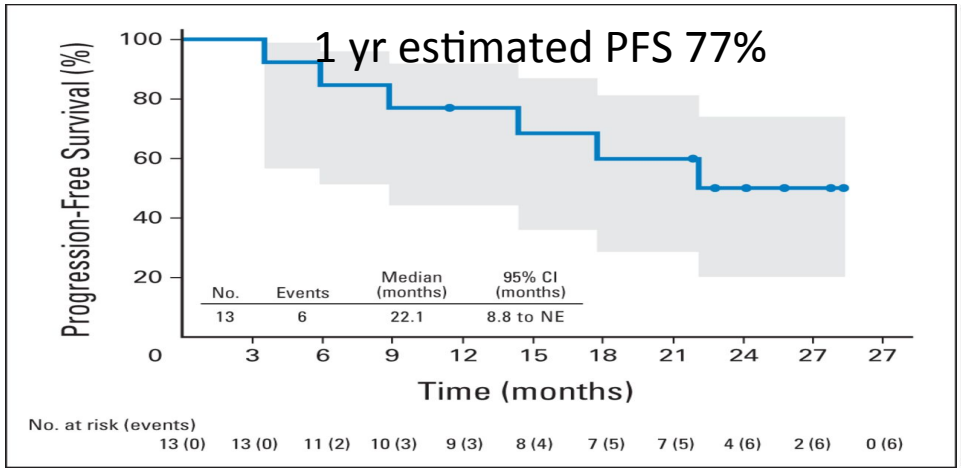
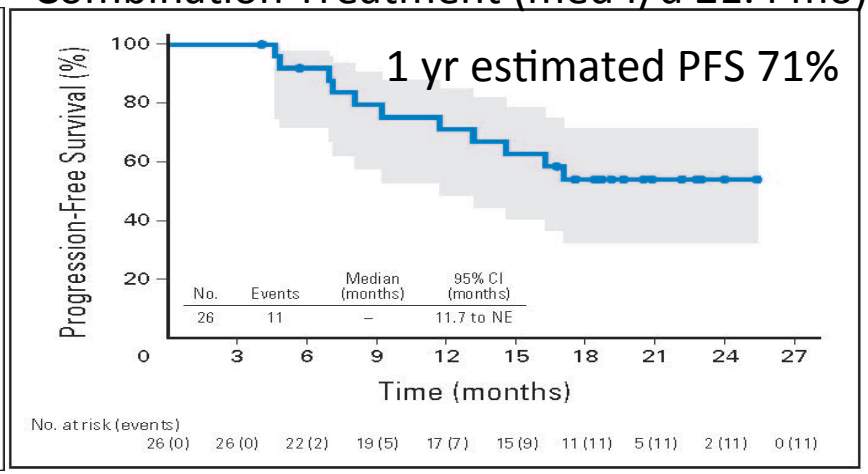
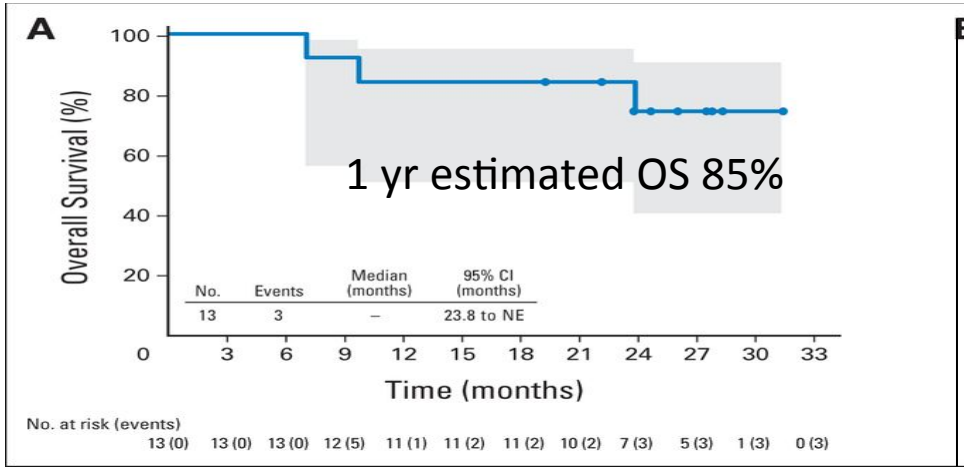
Outcomes

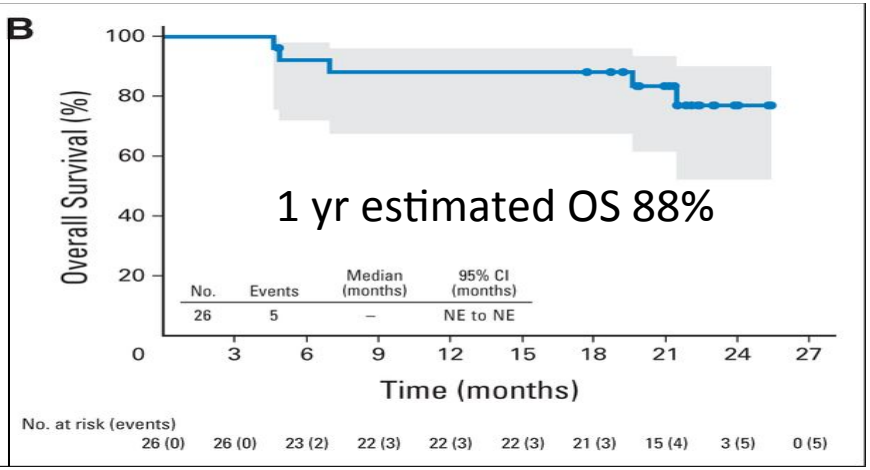
Sequential Treatment (med f/u 23.8 mo)



Combination Treatment (med f/u 21.4 mo)







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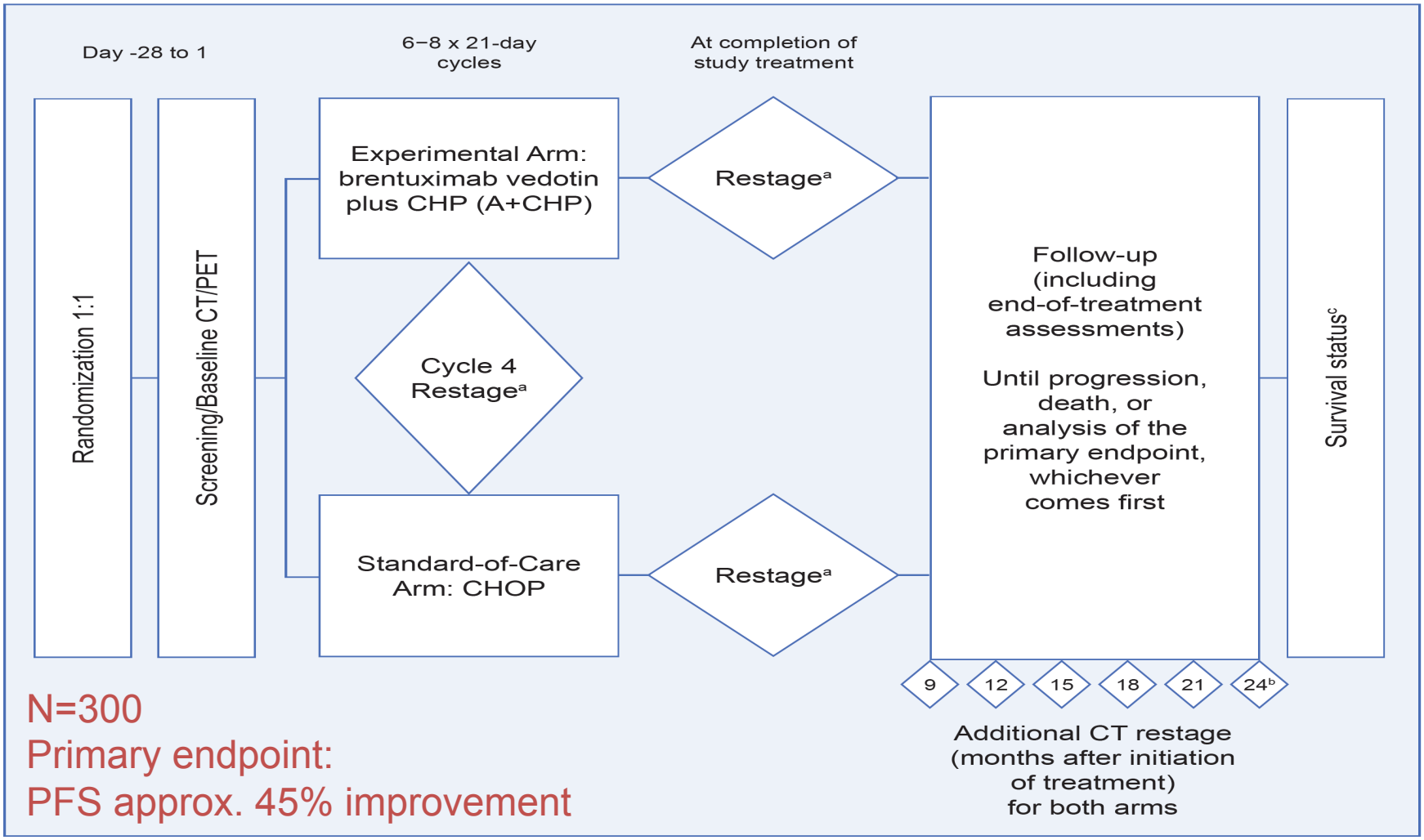
No pt recd BMT

Echelon-2 Trial

PTCL-CD30+ (≥ 10%), If ALK+ ALCL IPI ≥2



a CT and PET scans required
b Additional CT scans every 6 months thereafter until progression per investigator, death, or analysis of the primary endpoint, whichever comes first
c For patients with documented progression, continued follow-up for survival every 6 months until death or study closure, whichever comes first

Key Eligibility

- Eligible histology:
  - ALK-positive sALCL IPI score >/= 2
  - ALK-negative sALCL, PTCL-NOS, AITL
  - Adult T-cell leukemia/lymphoma if HTLV 1 +
  - Enteropathy-associated T-cell lymphoma (EATL)
  - Hepatosplenic T-cell lymphoma
- CD30 positivity by immunohistochemistry.
  - CD30 detected in 10% or >of neoplastic cells
    - if enumeration of neoplastic cells not possible, total lymphocytes may be used
  - CD30 staining any intensity above background.
  - Membranous, cytoplasmic, and/or golgi pattern of expression of the CD30 antigen.
- FDG-avid disease by PET and measurable disease of at least 1.5 cm by CT.
- Age >/= 18, ECOG </=2, Adequate lab parameters, LVEF > 45%
- No PML, other co morbidities
- Baseline peripheral neuropathy ≥ Grade 2 or demyelinating form of Charcot-Marie-Tooth syndrome.

Study Endpoints Definitions

- Primary Endpoint:
  - PFS per IRF
- Secondary Efficacy Endpoints:
  - PFS per IRF in Patients with sALCL
  - Complete Remission Rate per IRF
  - Objective Response Rate per IRF
  - Overall Survival

- Additional Endpoints:
  - Incidence of ATA
  - Medical Resource Utilization
  - Quality of Life

Statistical Plan

- ~ 300 patients (~150 patients per treatment arm) will be randomized.
- Target proportion of patients with sALCL per central pathology assessment will be 75% (+/-5%)
  - ~ 225 (+/-15) patients.
  - Central monitoring to ensure that the enrollment targets are reached and not exceeded.
- ~ 238 events (progression or death due to any cause) required for final analysis
  - to detect a hazard ratio of 0.6895
  - 23.9 months median PFS for the A+CHP arm versus 16.5 months for the CHOP arm)
  - log-rank test with >80% power and an overall one-sided alpha level of 0.025.

Current Status: Echelon 2 trial

- Non ALCL accrual goal met
- Study open only for sALCL