

IN PURSUIT OF *YOUR CURE*.™

# Relapsed /Refractory Hodgkin Lymphoma 2024

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A Cancer Center Designated by the  
National Cancer Institute

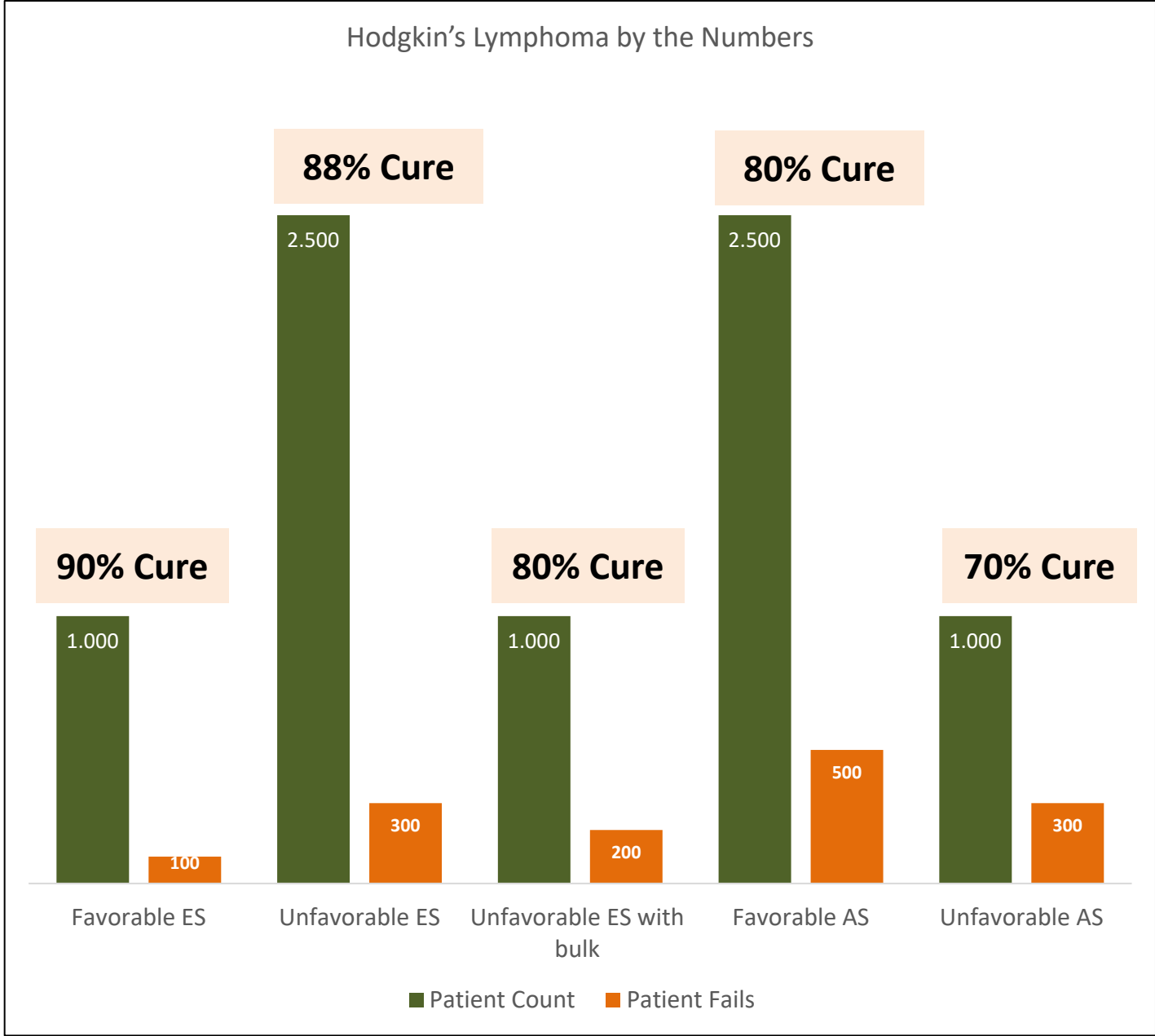
## Disclosures..

Research support-ADC therapeutics, Merck, Seattle Genetics, Astra Zeneca

Scientific Advisory Board-ADC therapeutics, Merck, Takeda, Merck, Seattle Genetics, Astra Zeneca. Incyte, Genmab

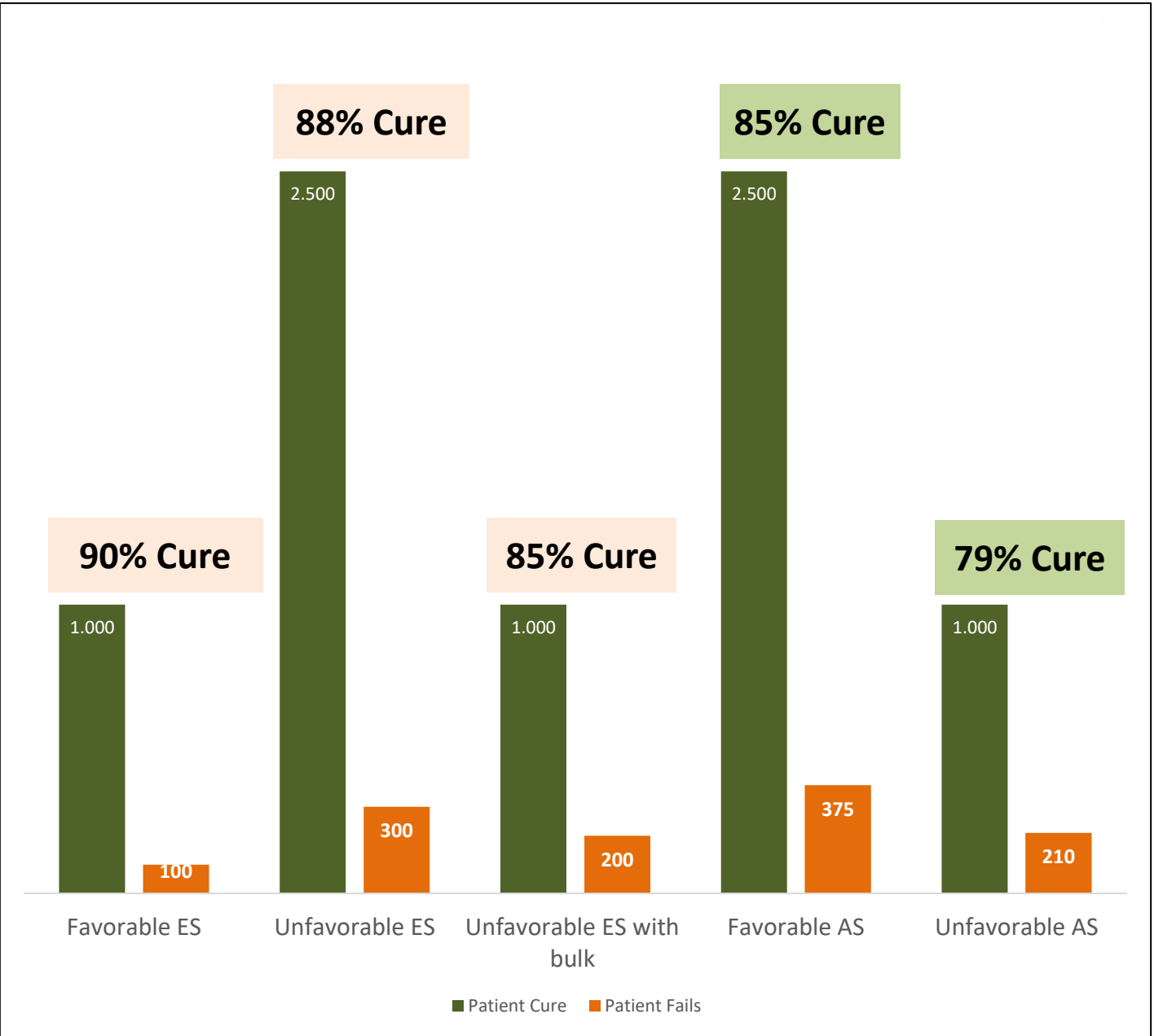
# Hodgkin Lymphoma by the Numbers

Optimal upfront treatment 8,500 patients (Pre BV)



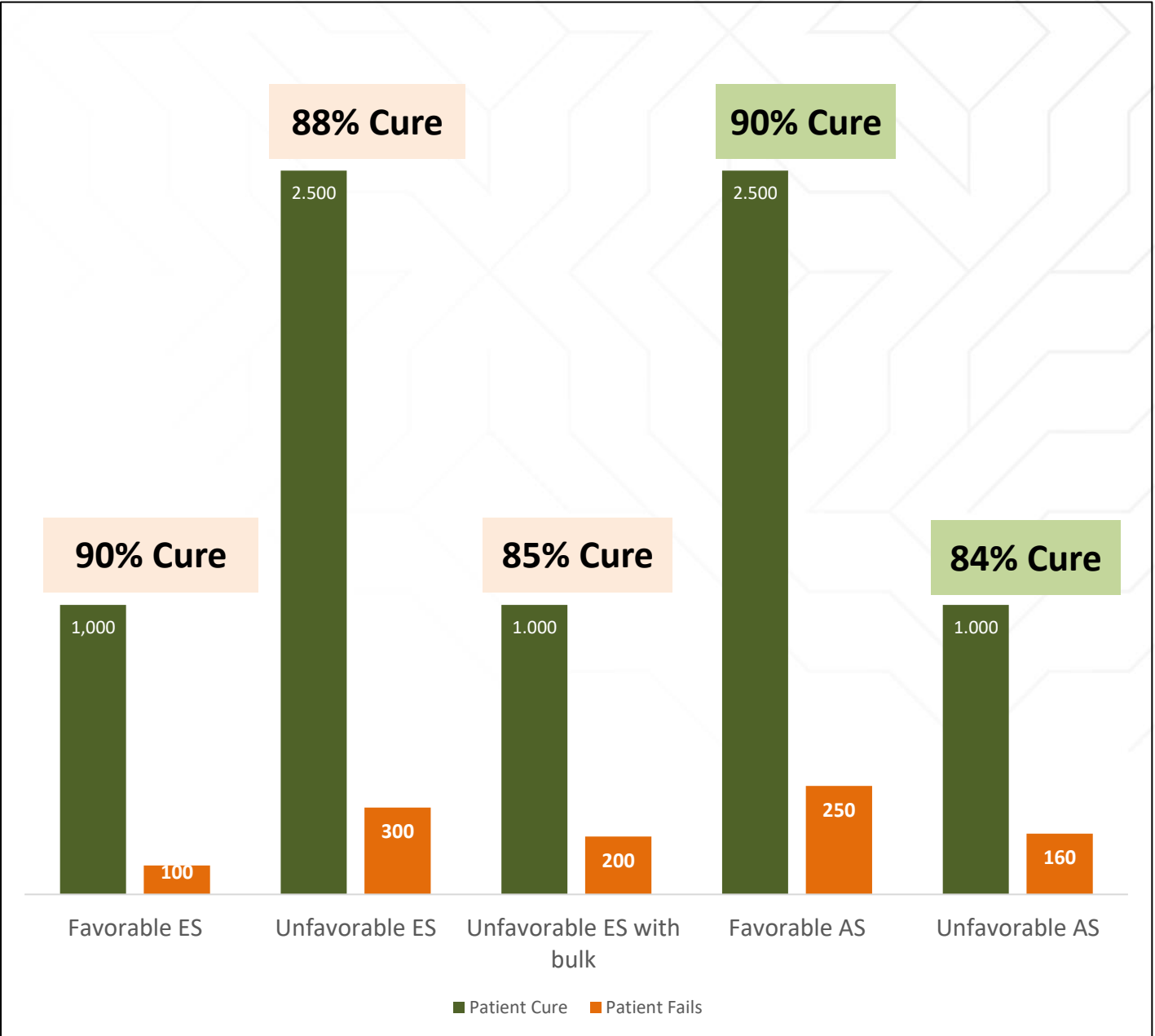
1400 pts need SLT

Optimal upfront treatment 8,500 patients (post BV)



1135 pts need SLT

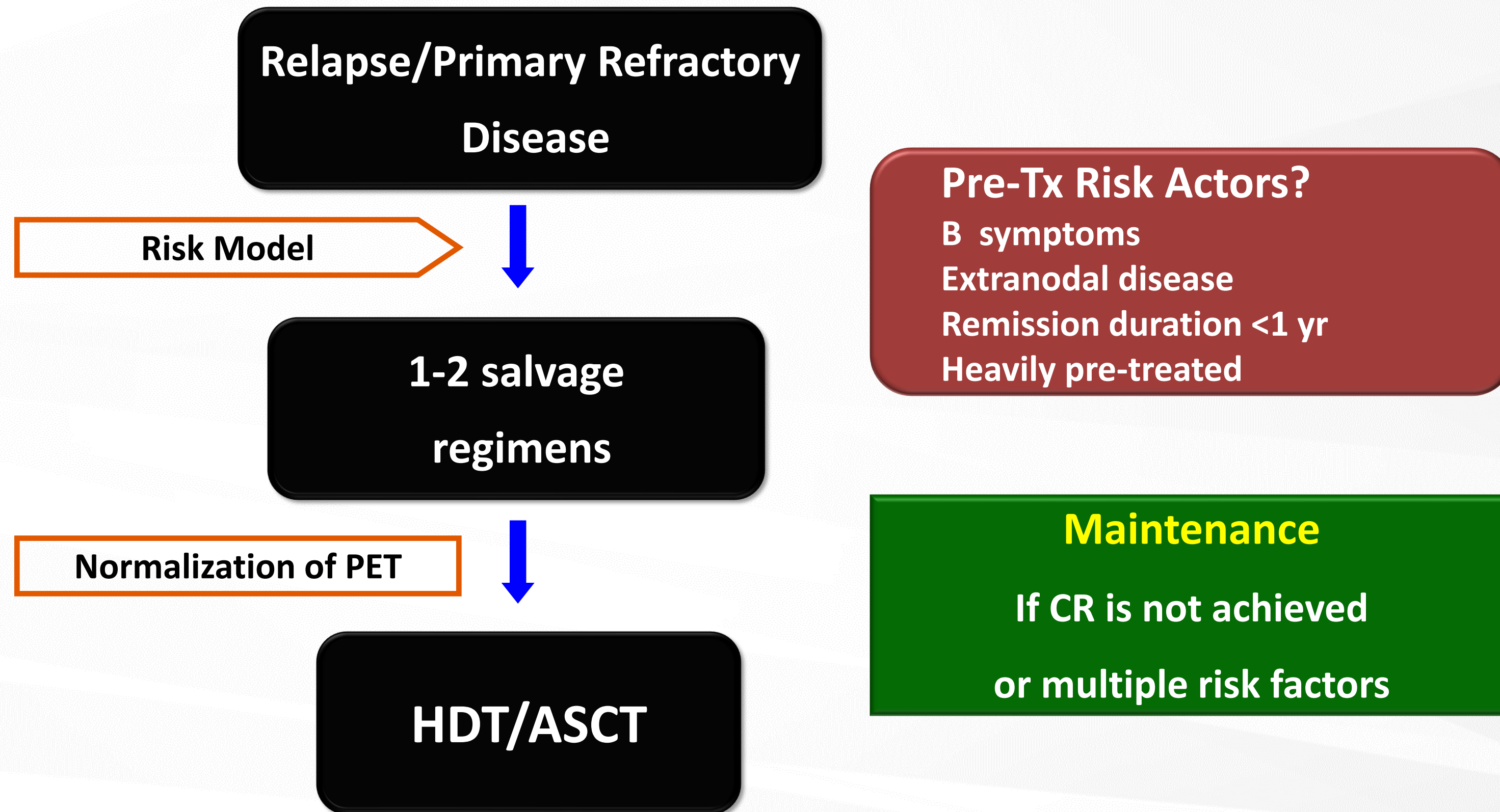
Optimal upfront treatment 8,500 patients (post CPI)



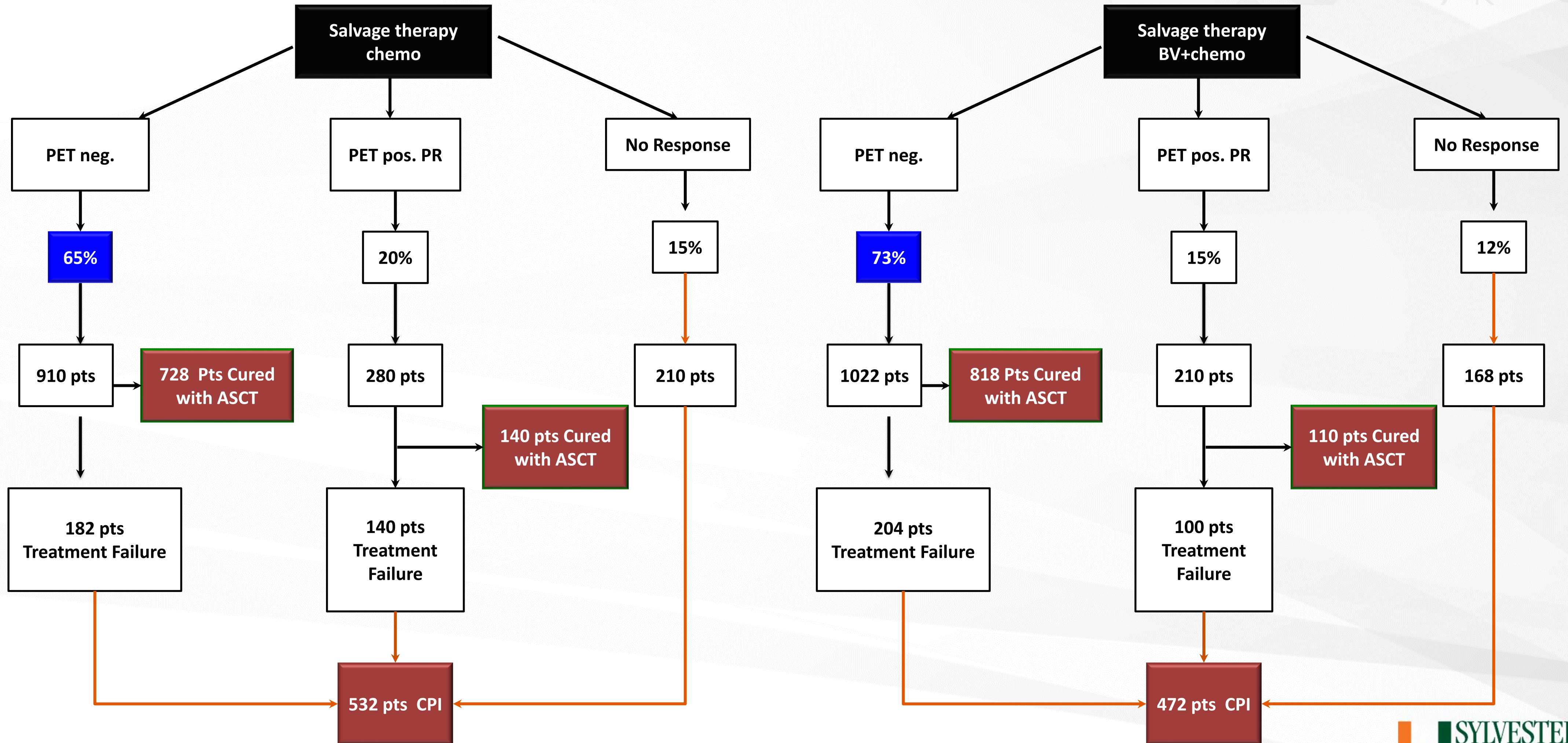
1010 pts need SLT

700 patients ≥70 excluded

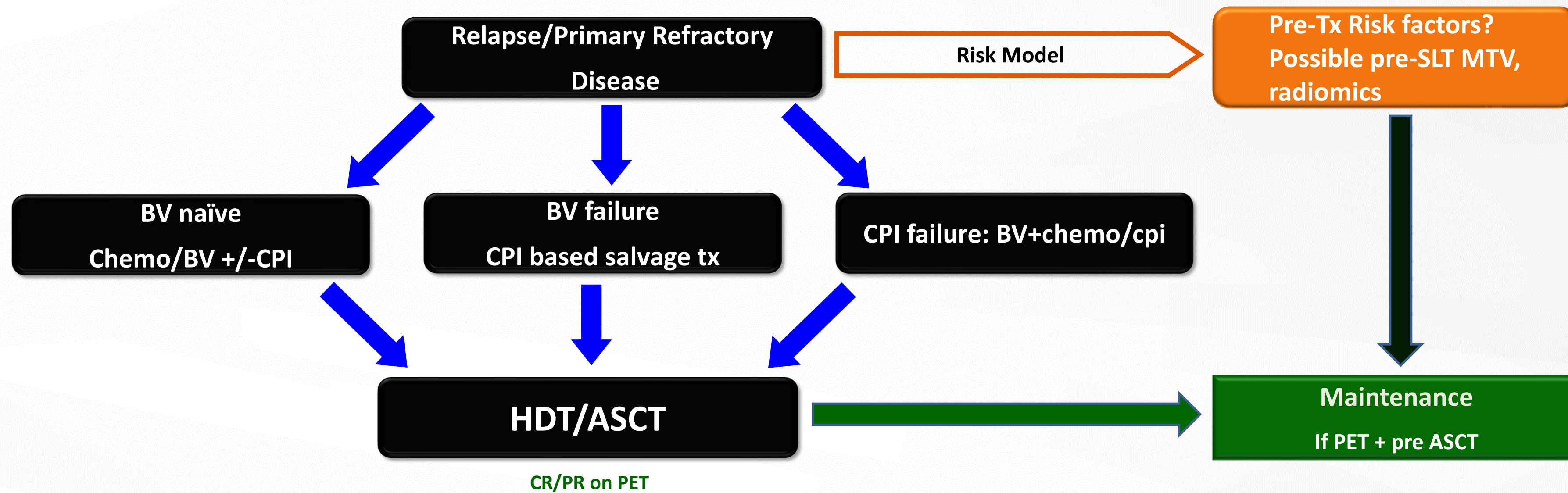
# A reasonable approach to relapsed/refractory Hodgkin lymphoma era of maintenance: 2014-2021



# Relapsed/Refractory HL: 1400 pts/year: and 65% are cured at time of AETHERA publication

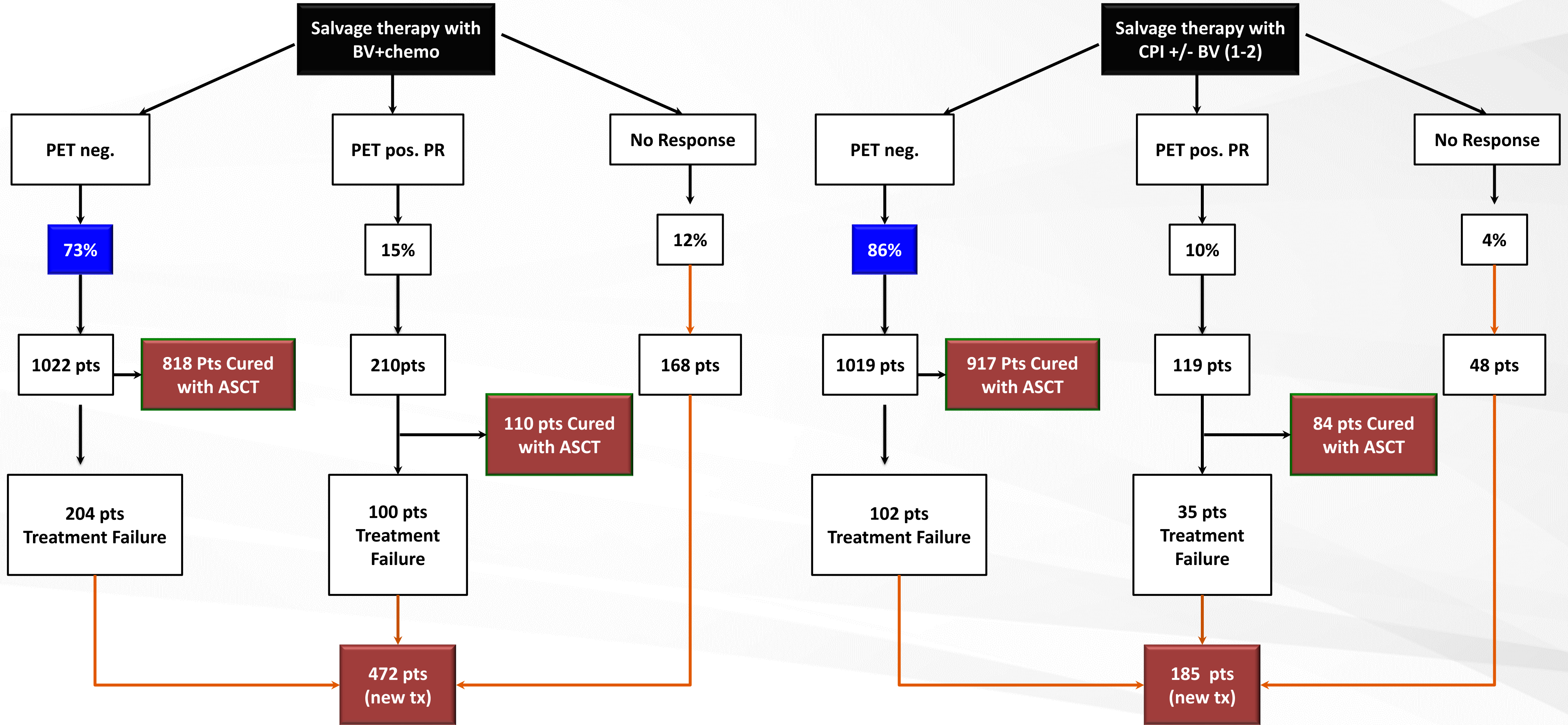


# A reasonable approach to relapsed/refractory Hodgkin lymphoma-2024

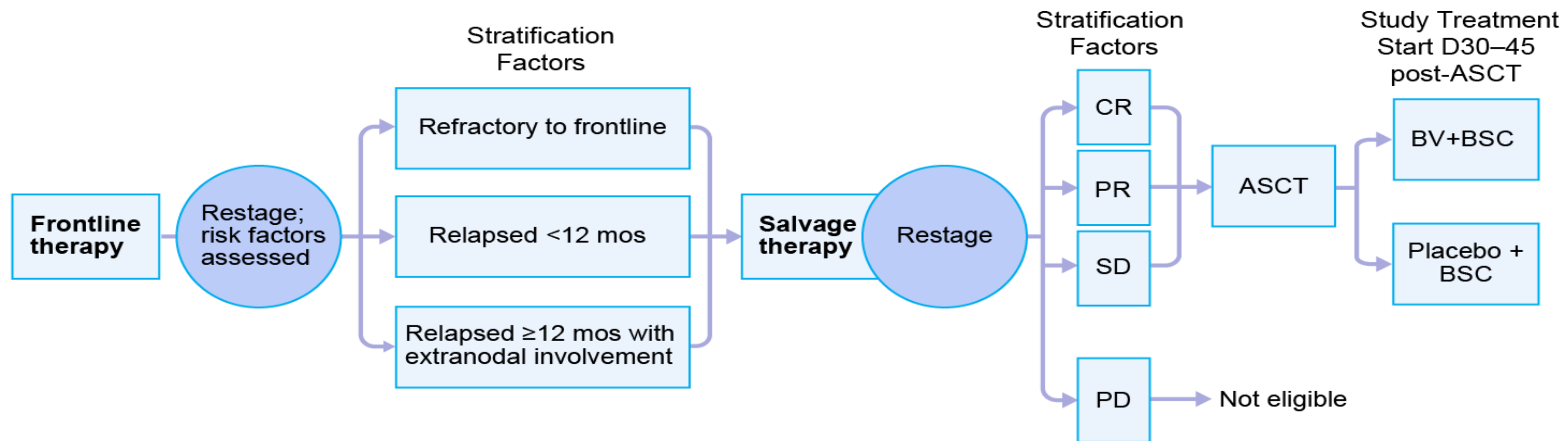


1400 pts/year vs

1185 pts/yr



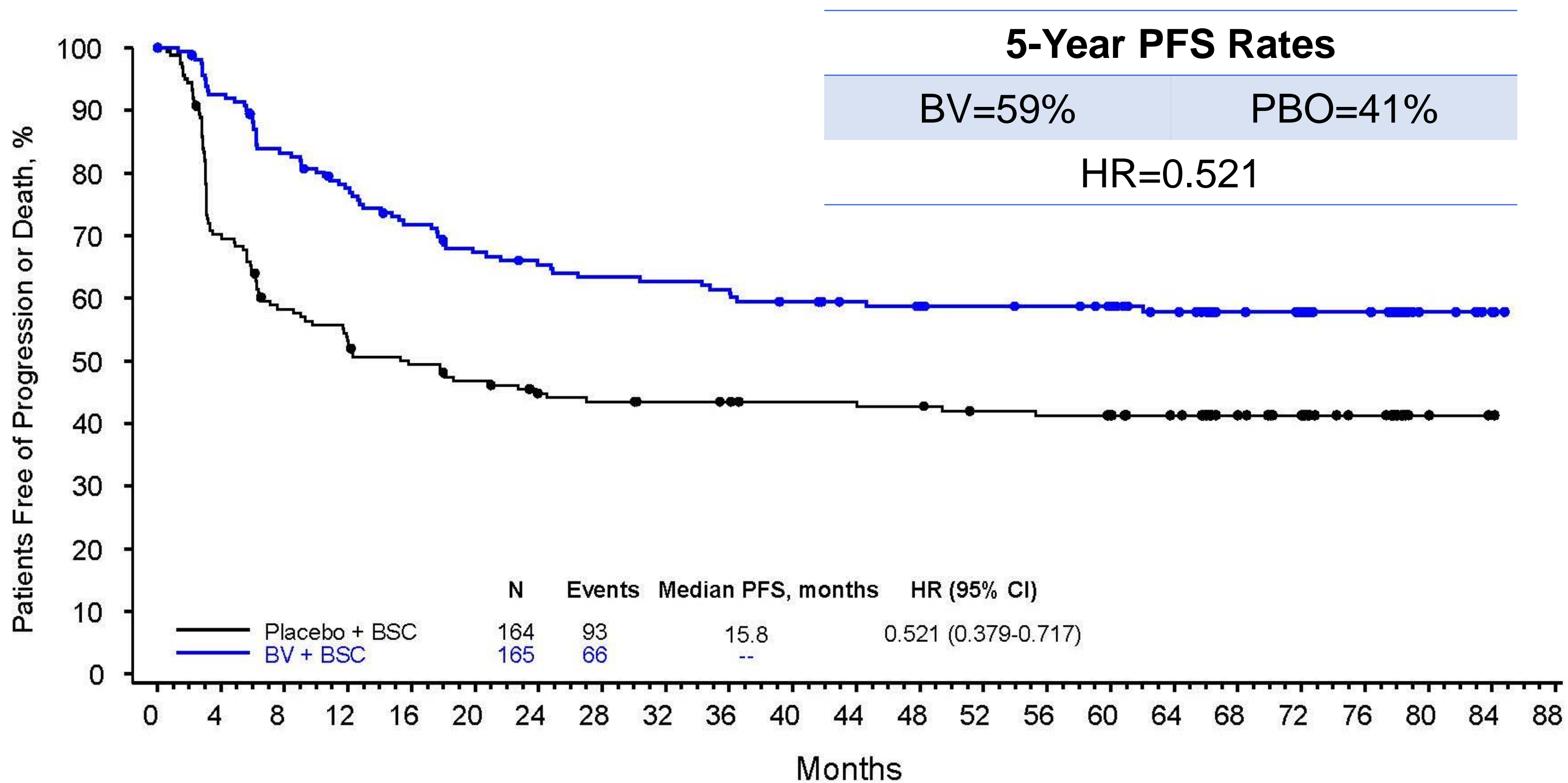
# AETHERA Trial Design



- Randomization was stratified by:
  - Risk factors after frontline therapy
  - Best clinical response to salvage therapy before ASCT
- 329 patients randomized to BV 1.8 mg/kg IV and BSC or PBO + BSC for up to 16 cycles, starting 30–45 days after ASCT
- Patients on the PBO+BSC arm with progressive disease had access to BV subsequent therapy on a separate study



# 5-Year PFS per Investigator: All Patients (N=329)



No. at risk (events)

Pla+BSC	164 (0)	113 (48)	92 (67)	83 (76)	77 (81)	72 (85)	66 (88)	64 (90)	62 (90)	61 (90)	59 (90)	58 (91)	58 (91)	55 (92)	54 (93)	52 (93)	44 (93)	32 (93)	27 (93)	17 (93)	2 (93)	1 (93)	0 (93)
BV+BSC	165 (0)	149 (12)	133 (27)	122 (36)	112 (45)	104 (52)	100 (55)	97 (58)	96 (59)	94 (61)	90 (64)	87 (64)	84 (65)	83 (65)	82 (65)	78 (65)	66 (66)	47 (66)	43 (66)	26 (66)	7 (66)	3 (66)	0 (66)

# When evaluating patients for SLT/ASCT in 2024 the most important issues are

- Did the patient receive BV-AVD
- Did the patient receive N/P-AVD
- If the patient had ESHL was short course chemo alone administered?
  - Does the patient have low volume stage I/II nodal disease
- Did the patient achieve a PET neg response after salvage chemotherapy
  - Was BV-based salvage chemotherapy used
  - Was CPI-based salvage chemotherapy used
  - Was BV/nivo salvage therapy used
  - Was standard platinum-based salvage chemotherapy used



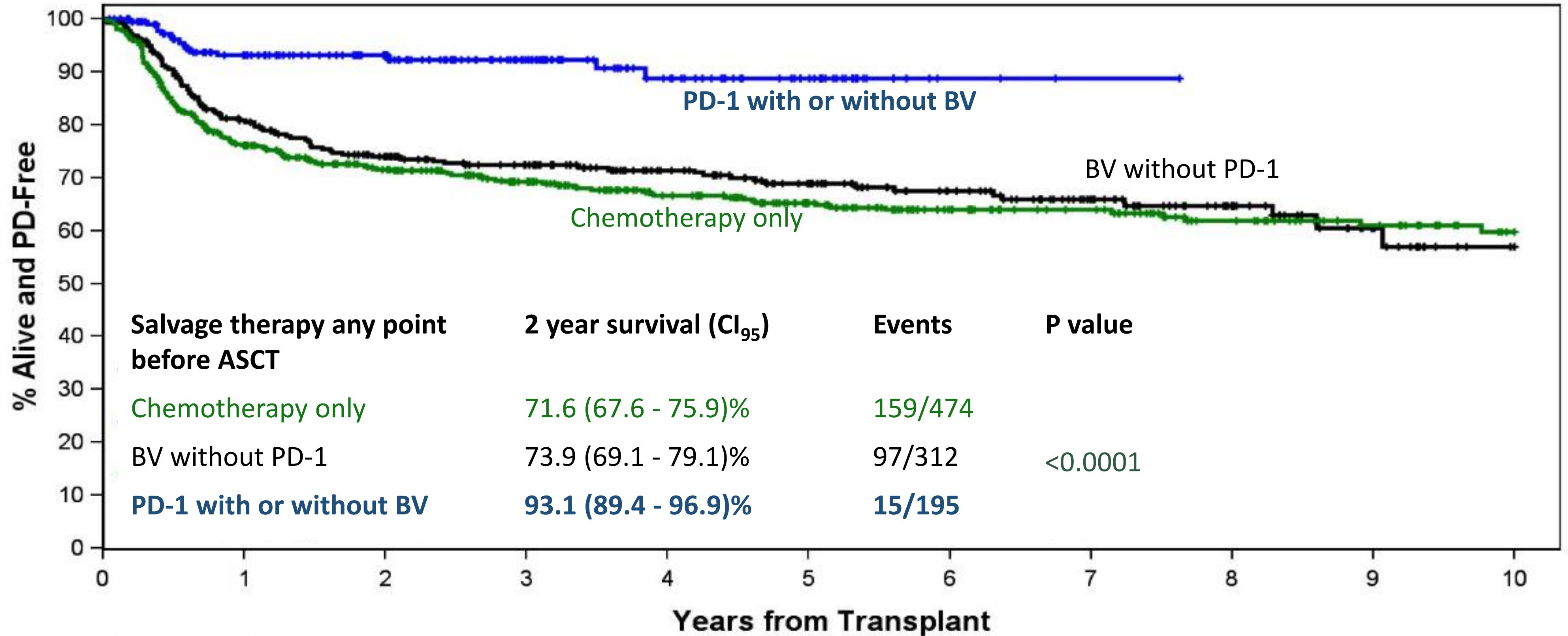
American Society of Hematology

Helping hematologists conquer blood diseases worldwide

# #182: PD-1 Blockade before Autologous Stem Cell Transplantation Improves Outcomes in Relapsed/Refractory Classic Hodgkin Lymphoma: Results from a Multicenter Cohort

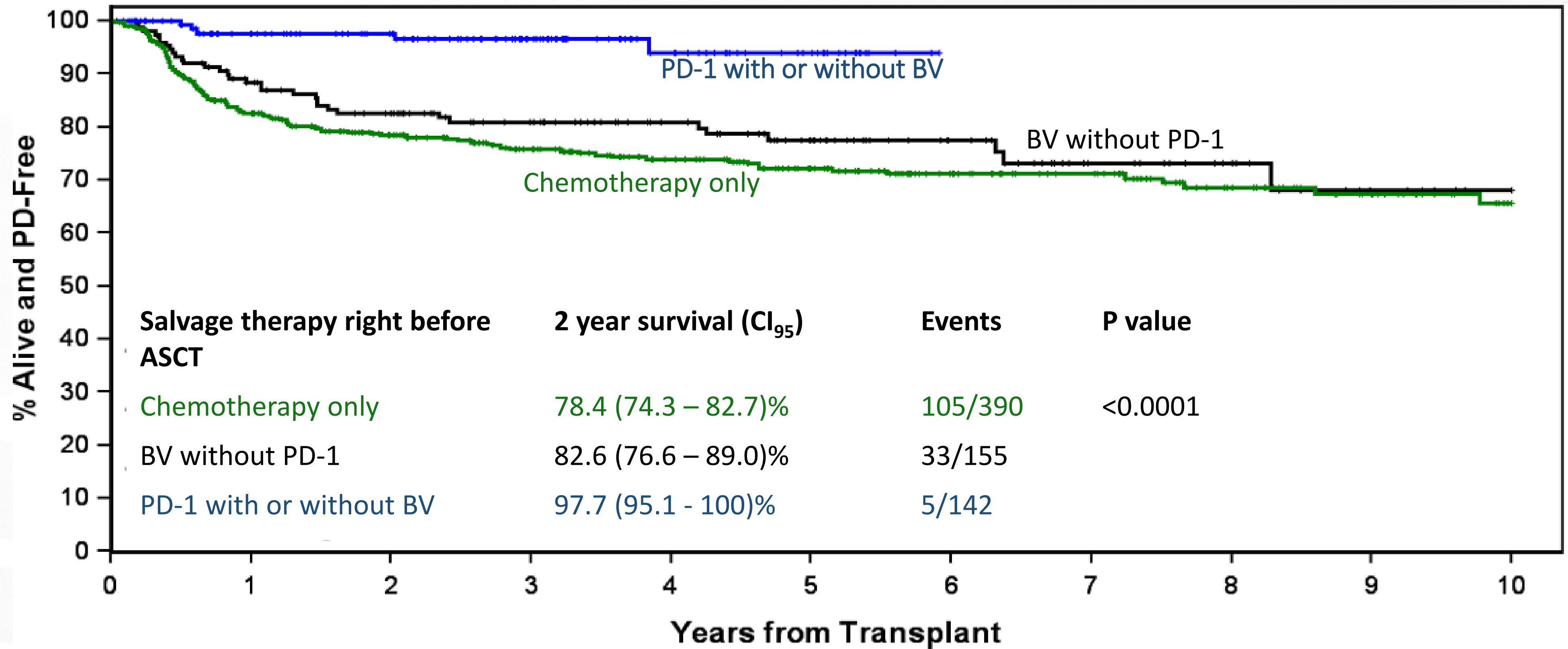
**Sanjal H. Desai, MBBS<sup>1,2</sup>**, Reid W. Merryman, MD<sup>3</sup>, Harsh Shah, DO<sup>4\*</sup>, Levi D. Pederson, MS<sup>2\*</sup>, Susan M. Geyer, PhD<sup>2</sup>, Nivetha Ganesan<sup>5\*</sup>, Tiffany Chang, MS<sup>5\*</sup>, Tamer Othman, MD<sup>6</sup>, Ayo S Falade, MD, MBA<sup>3</sup>, Gunjan L. Shah<sup>5</sup>, Urshila Durani, MD, MPH<sup>7</sup>, Kelsey Baron, MD<sup>4</sup>, Shin Yeu Ong, MD, FRCPath<sup>8\*</sup>, Stephen M Ansell<sup>7</sup>, Philippe Armand, MD, PhD<sup>9</sup>, Siddharth Ivengar, MD<sup>10\*</sup>, Ivana Micallef, MD<sup>2\*</sup>, Alison Moskowitz, MD<sup>5</sup>, Alex F. Herrera, MD<sup>11</sup>, Robert Stuver, MD<sup>5</sup> and Matthew Genveh Mei, MD<sup>11\*</sup>

# Progression free survival



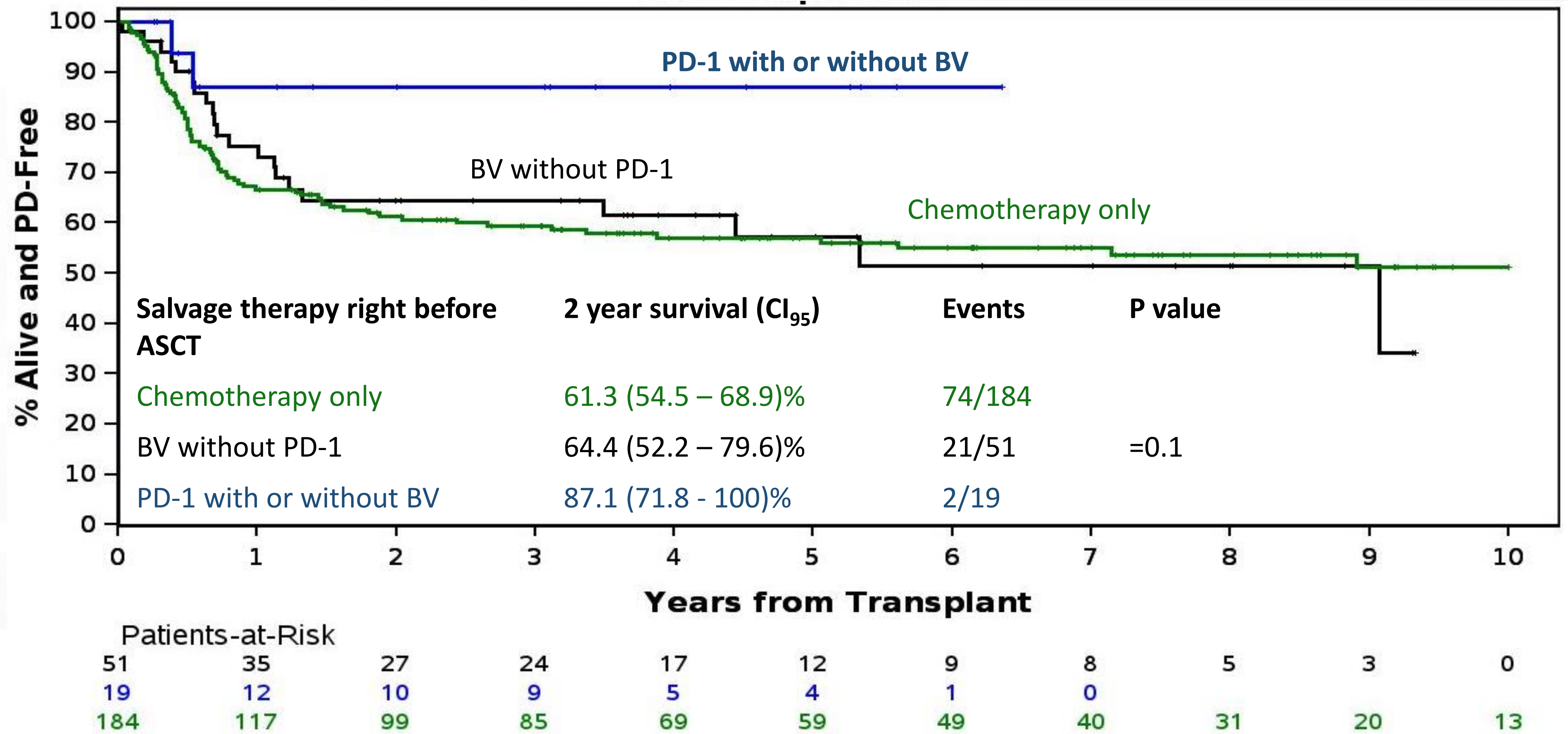
Patients-at-Risk										
0	1	2	3	4	5	6	7	8	9	10
312	236	201	176	144	117	90	65	42	18	4
195	147	120	77	45	27	3	1	0		
474	339	286	244	199	159	123	106	84	64	45

# PD-1 inhibitors improve PFS in PET- pts

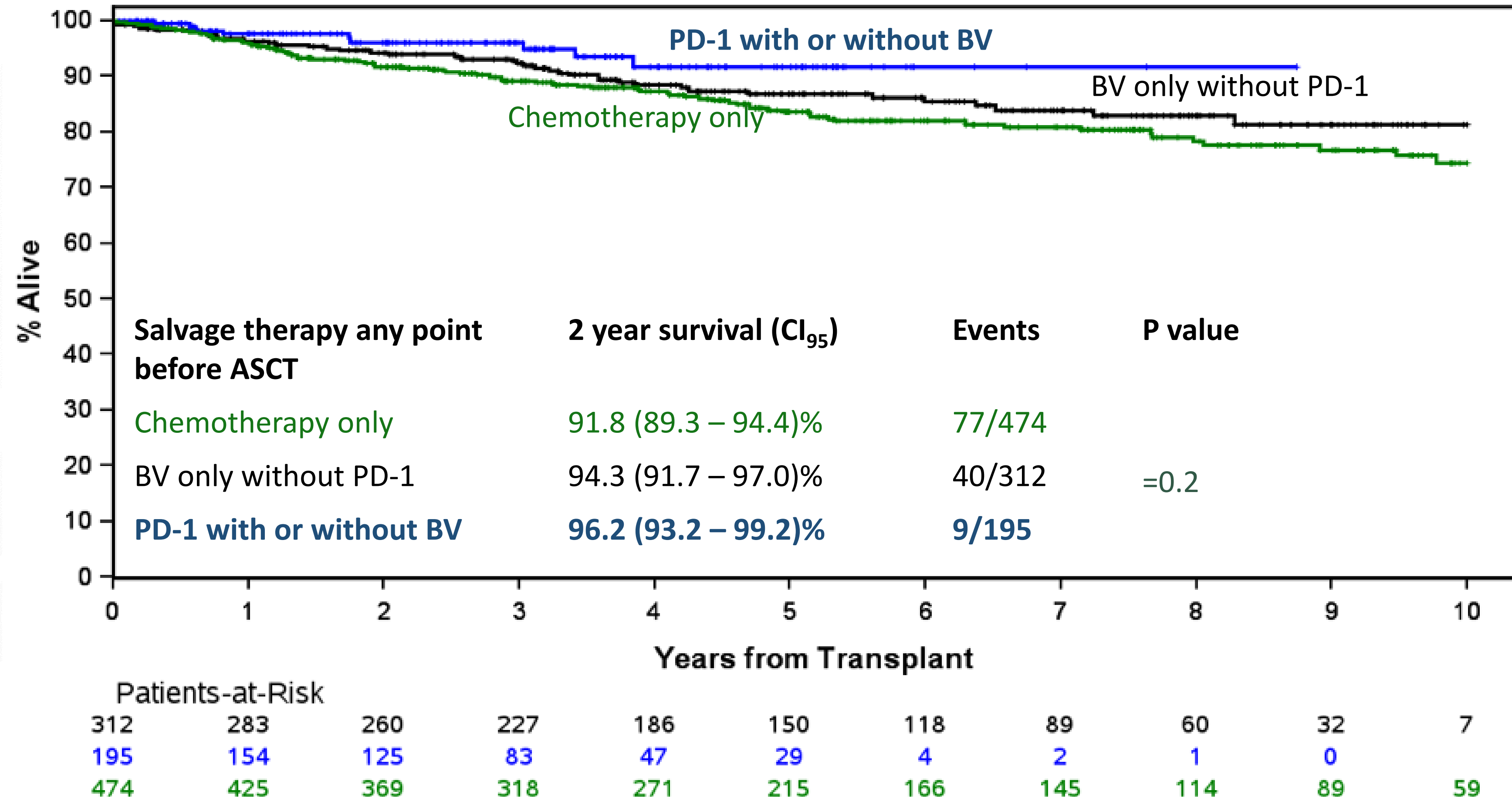


Patients-at-Risk										
0	1	2	3	4	5	6	7	8	9	10
155	124	108	90	73	57	40	24	17	8	3
142	113	94	60	33	18	0				
390	303	255	221	185	152	116	99	72	51	33

# PD-1 inhibitors improve PFS in PET+ pts



# Overall survival

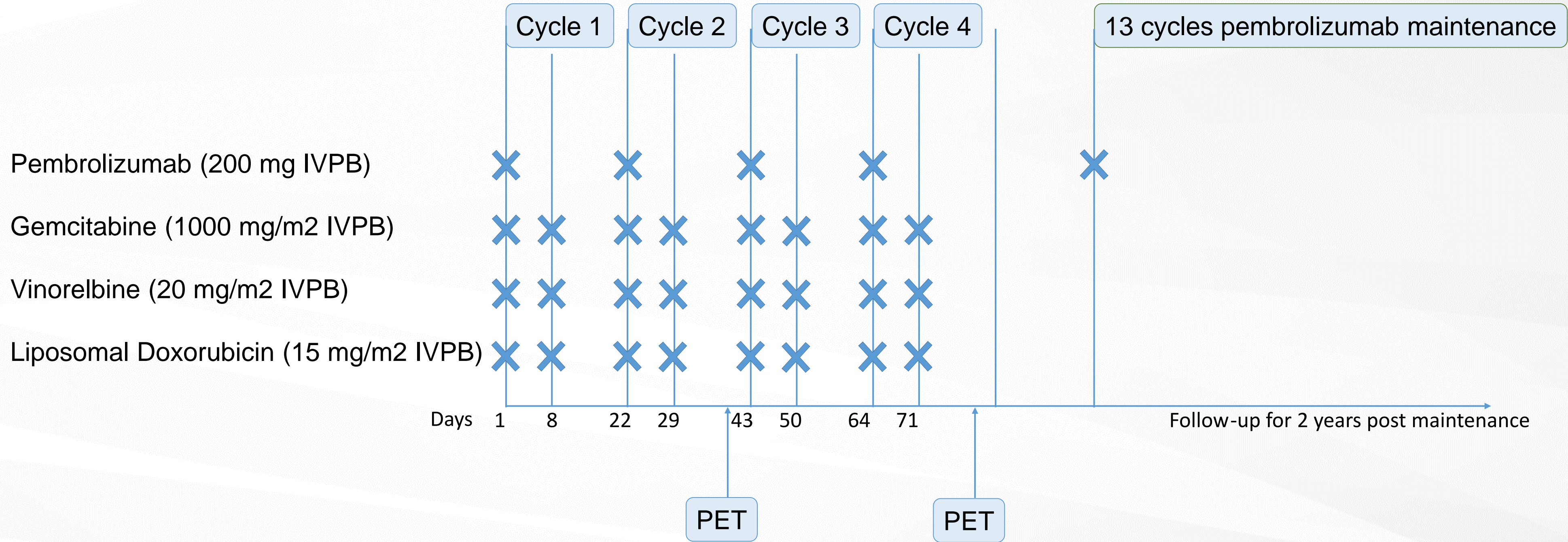


Do relapsing patients require HDT/ASCT  
as part of second-line therapy?



# Next cohort: Pembro-GVD -> maintenance

Patients with CR after pembro-GVD x 4



**Exploratory: cytokines, immune-cell subsets, metabolic tumor volume, ctDNA, 9p24.1 amplification, IHC staining for MHC-I, MHC-II, pd-1, pd-l1, pd-l2, beta-2 microglobulin**

# Pembro-RT

## Eligibility

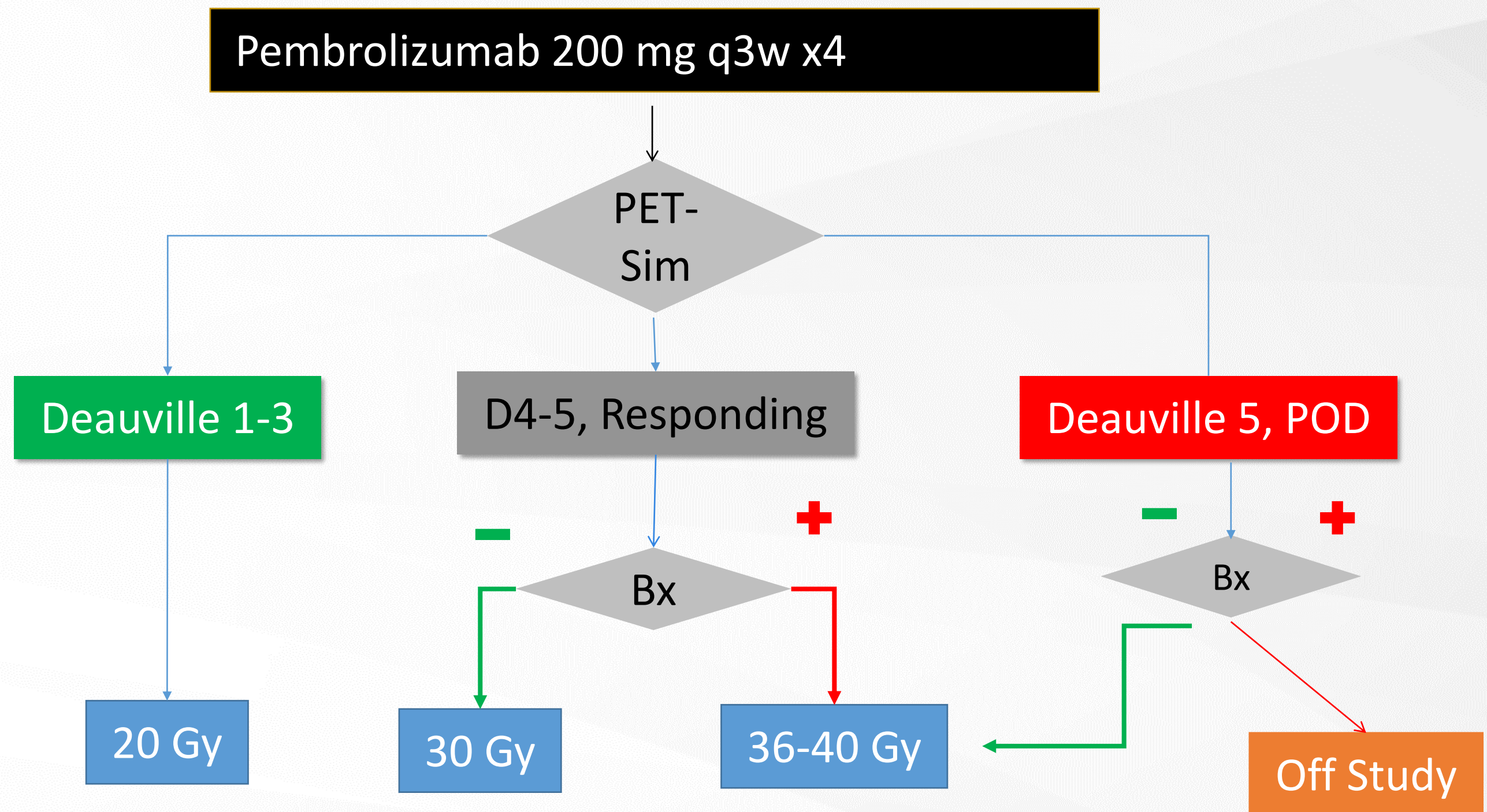
Initial stage: I-IIA

Prior therapy: Chemo only or  
CMT with relapse outside field

Relapse stage: I-II

No bulk > 10 cm

ECOG 0-1



Exploratory: cytokines, metabolic tumor volume, ctDNA, 9p24.1 amplification, IHC staining for MHC-I, MHC-II, pd-1, pd-l1, pd-l2, beta-2 microglobulin

# Can the treatment paradigm be changed

- Not all salvage regimens are the same; consider efficacy, toxicity, easy of administration and cost
- Post-ASCT, BV should be standard for patients with multiple risk factors in BV naive pts or pts that have had a CR to BV based salvage but not 16 doses
- Research studies need to explore non-ASCT programs for favorable disease
- Off study I am in favor of withholding the salvage therapy/ASCT program until second relapse if patients have early-stage disease that relapses as early stage, if all the disease can be encompassed into a reasonable RT field using a novel agent and RT consolidation
- Excluding ASCT for any other pt group should not be done off study!

Risk-adapted approach

Low risk

Pembro-GVD x 2

High risk

Pembro-GVD x 2

CR

randomization

SOC  
Pembro-GVD x 2  
*plus* ASCT

Experimental  
Pembro-GVD x 2  
*plus* ISRT

SOC  
Pembro-GVD x 2  
*plus* ASCT

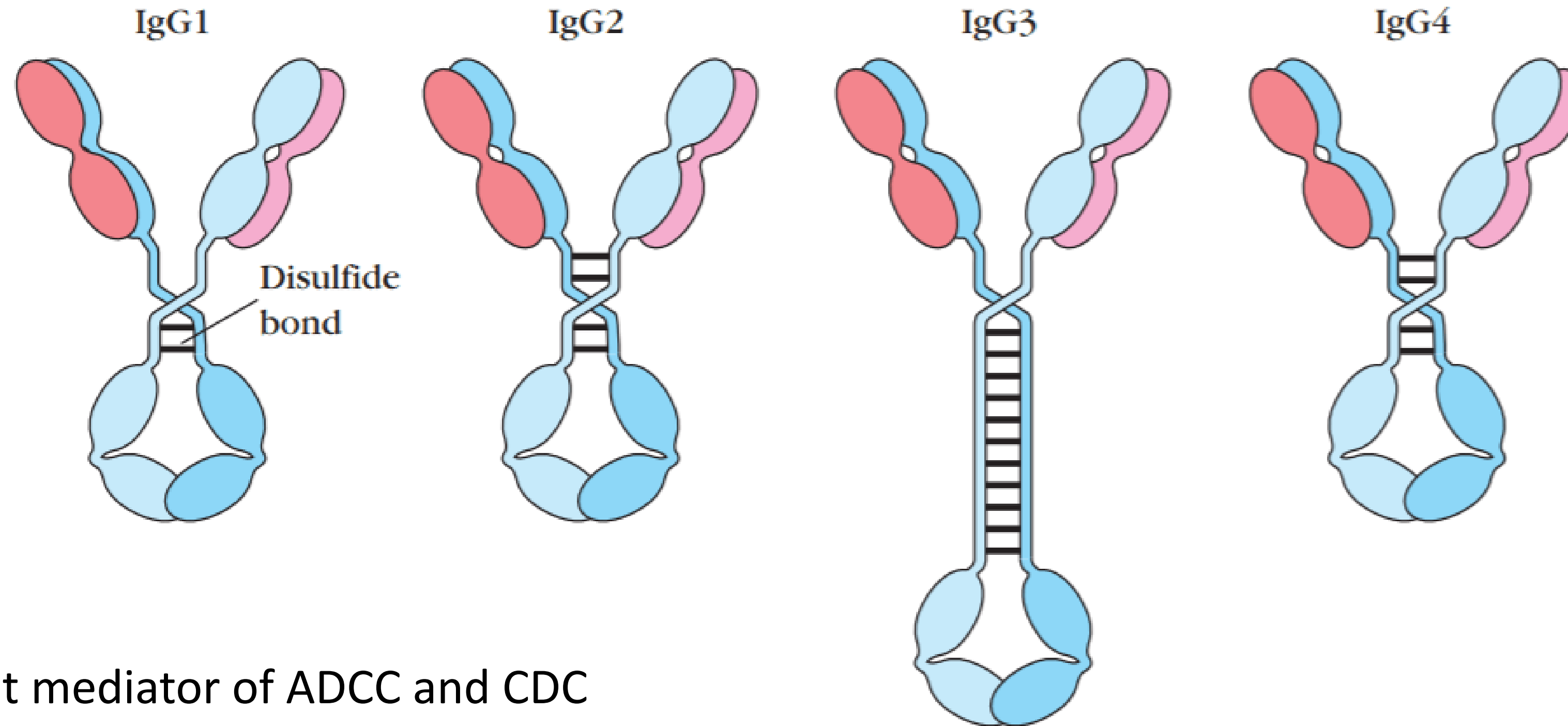
Experimental  
Pembro-GVD x 2  
*plus* pembro  
maintenance

Are there options when ASCT fails?

# Checkpoint Inhibitors

Are they all the same?

# IgG isotypes



IgG1: potent mediator of ADCC and CDC

IgG2 & IgG4: almost no ADCC or CDC

IgG3: large immunogenic hinge region (not used for therapeutics)

IgG4: disulfide bond arrangement can lead to Fab switching – S228P mutation abolishes this

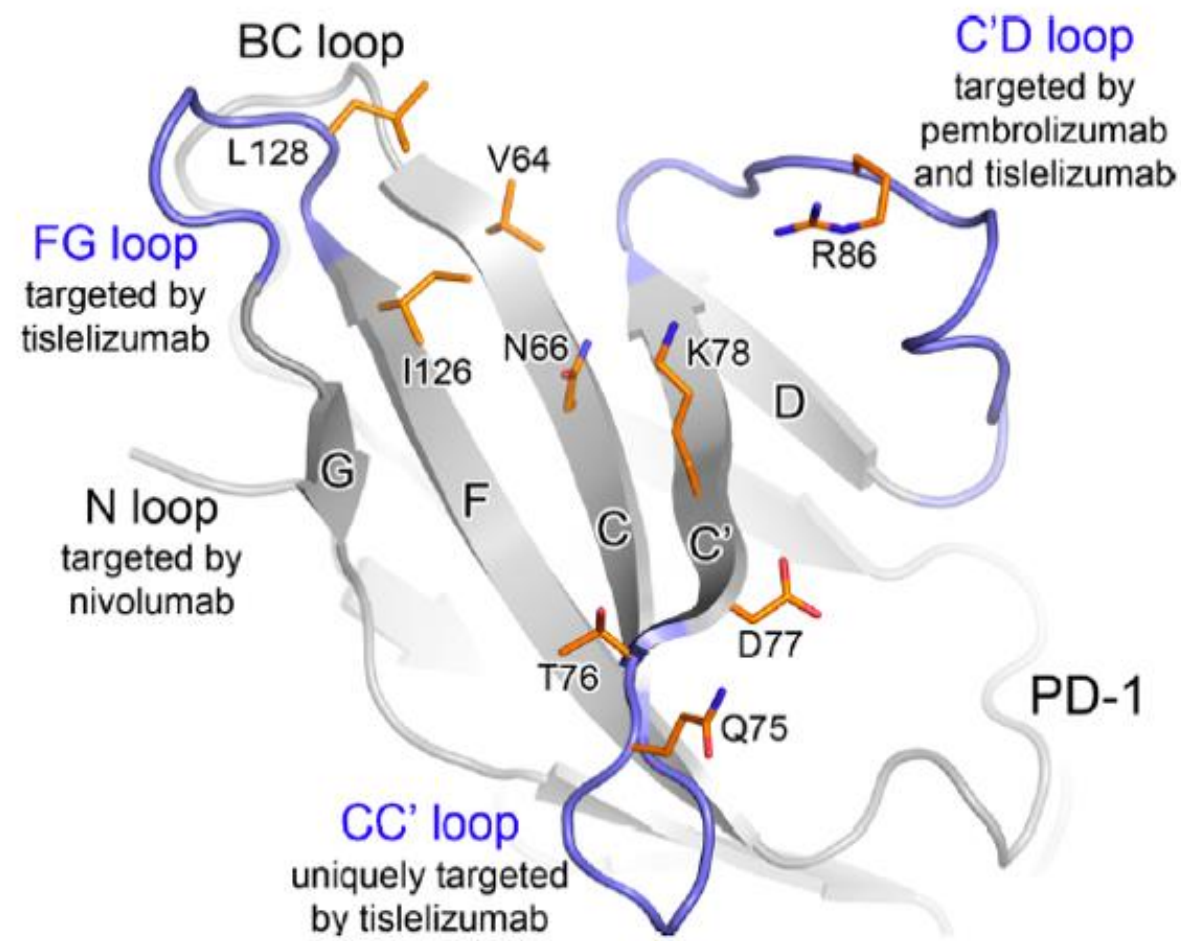
# IgG isotypes and Fc engineering

**TABLE 2** | Select PD-1 and PD-L1 antibodies under development for cancer treatment.

Target	Company	mAb	Clinical stages	IgG isotype or mutant with effector function nullified
PD-1	Bristol-Myers Squibb	Nivolumab	Approved	IgG4 S <sub>228</sub> P
PD-1	Merck	Pembrolizumab	Approved	IgG4 S <sub>228</sub> P
PD-1	Regeneron/Sanofi	Cemiplimab	Approved	IgG4 S <sub>228</sub> P
PD-1	Novartis	Spartalizumab	Phase 3	IgG4 S <sub>228</sub> P
PD-1	BeiGene	Tislelizumab	Phase 3	IgG4mut, FcγR null
PD-1	Junshi	JS001	Approved	IgG4 S <sub>228</sub> P
PD-1	Hengrui	Camrelizumab	Phase 3	IgG4 S <sub>228</sub> P
PD-1	Innovent	Sintilimab	Approved	IgG4 S <sub>228</sub> P
PD-L1	Roche	Atezolizumab	Approved	IgG1mut, FcγR null
PD-L1	AstraZeneca	Durvalumab	Approved	IgG1mut, FcγR null
PD-L1	Merck KGaA/Pfizer	Avelumab	Approved	IgG1

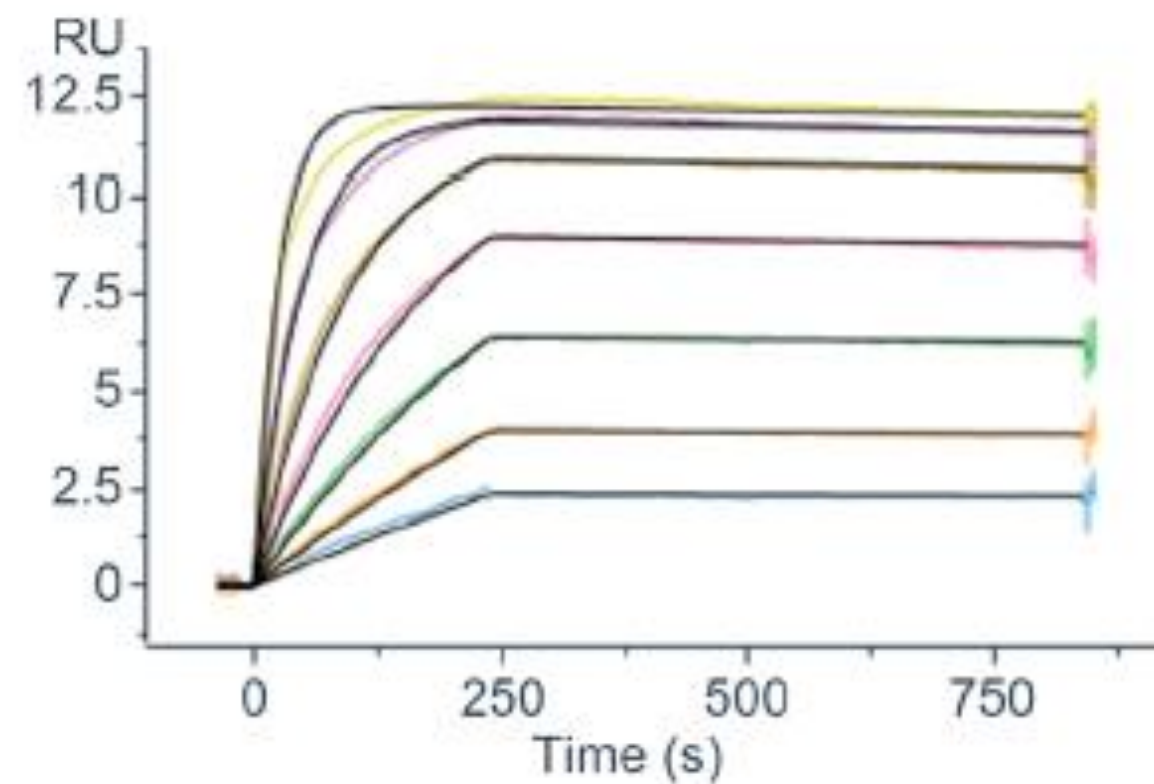


# Binding domains and kinetics are not the same

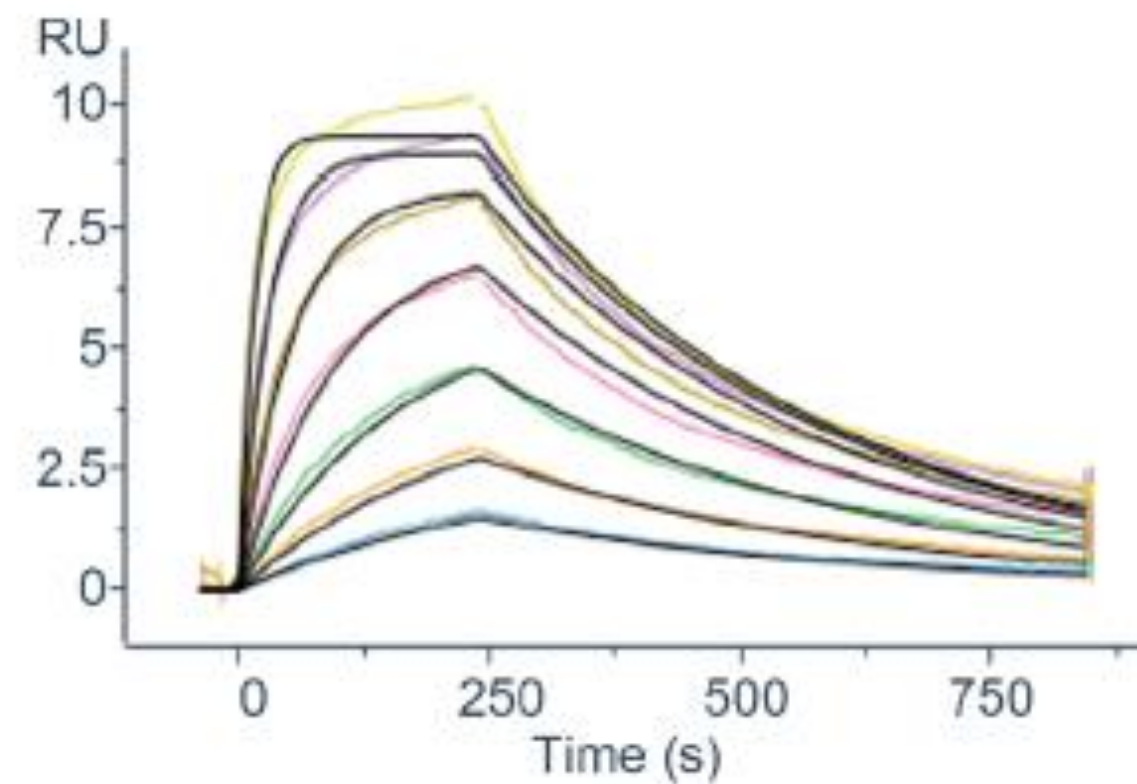


## Hong et al (2021) FEBS Open Bio

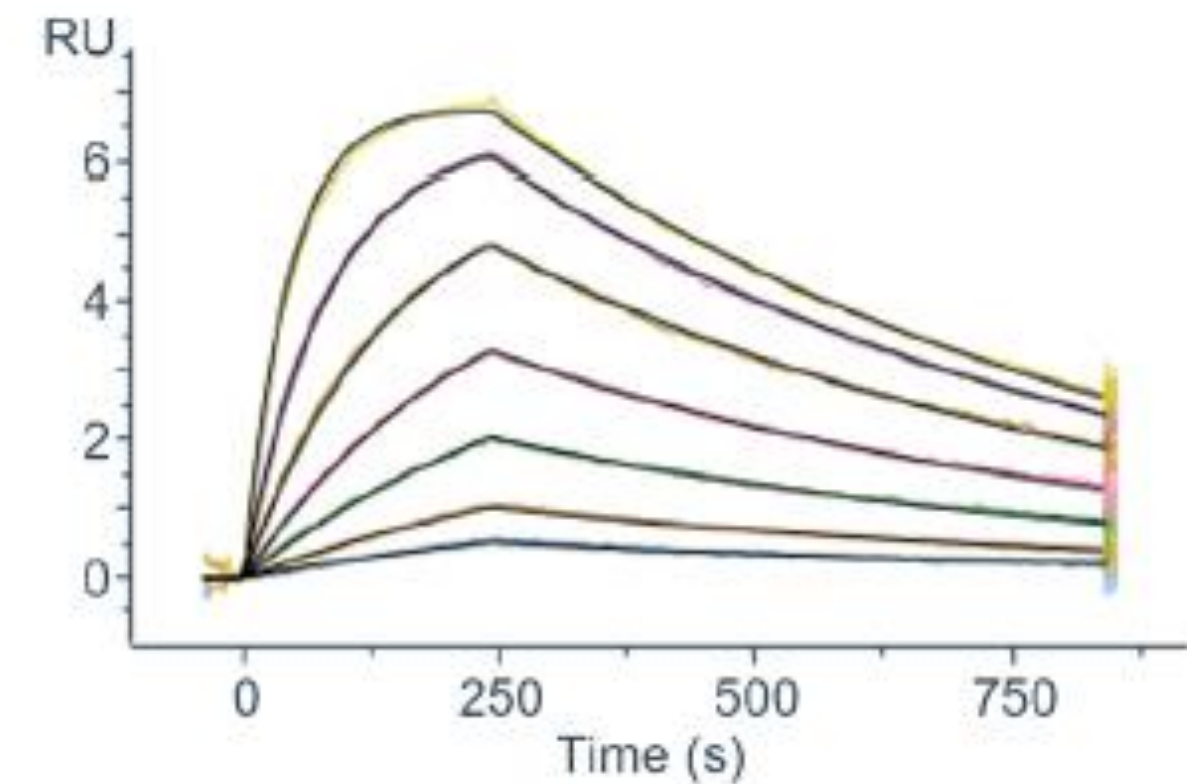
- Crystal structural studies of PD1-drug binding reveal some unique epitopes (note the CC' loop)
- Translates into different binding kinetics
- Tislelizumab has markedly prolonged dissociation rate



Tislelizumab

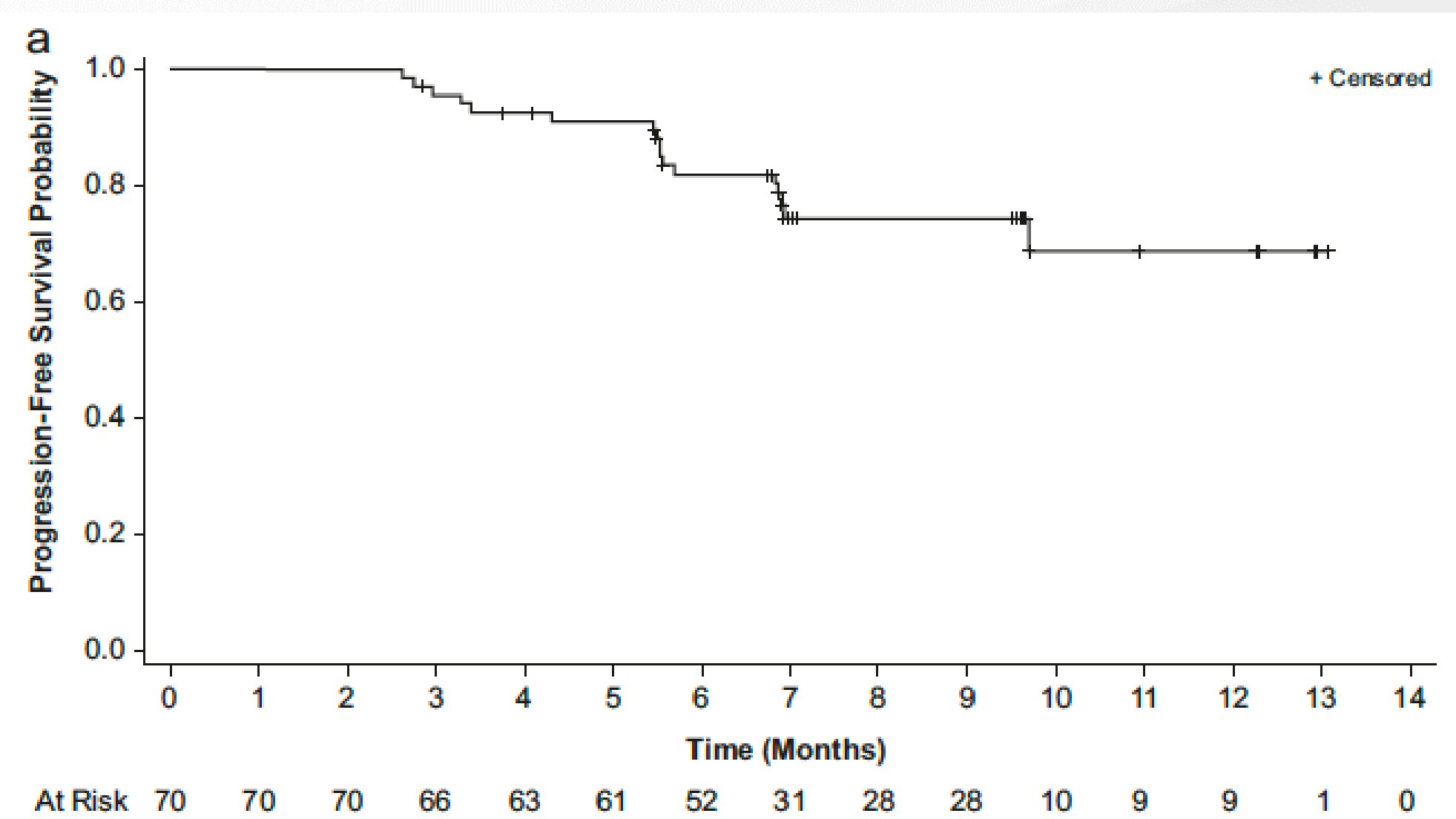
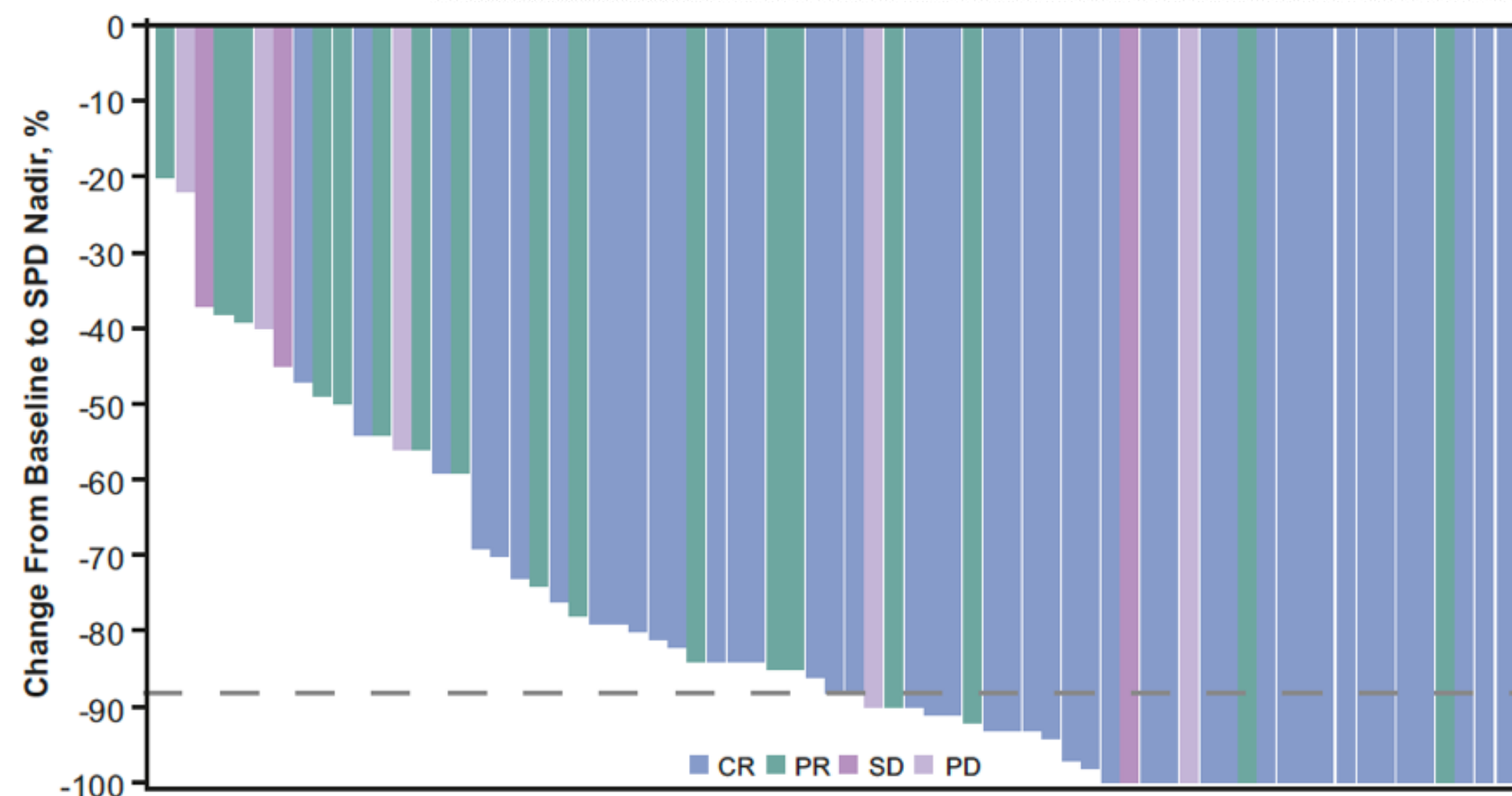


Pembrolizumab



Nivolumab

# Tislelizumab clinical data



## Song et al (2020) Leukemia

- 70 pts, median age 33y, median prior lines 3, mostly BV naïve, 52% refractory, 82% not suitable ASCT
- Median FU 9.8mo; 24% discontinued Rx
- ORR: 87%; CRR: 63% (52% CRR in primary refractory)
- Infusion reactions 36% (1 G3); 4 pts discontinued due to irAE (3 pneumonitis; 1 renal injury)

# Trial results compared

PD1 inhibitor	Phase	Population	ORR / CRR	PFS	Reference
Nivolumab	2	Relapse post ASCT BV naïve or BV exposed	69% / 16%	Med 14.7m	Armand (2018) JCO
Pembrolizumab	2	Relapse post ASCT with cohort prior; BV naïve or exposed	72% / 28%	Med 13.7m	Chen (2019) Blood
Avelumab	1	Relapse post ASCT or ASCT ineligible or post-alloSCT	41.9% / 19.4%	Not reported	Herrera (2021) Blood Advances
Sintilimab	2	Relapse post ASCT or ineligible	80.4% / 34%	6mo PFS 77%	Shi (2019) Lancet Haematol
Camralizumab	2	Relapse post ACST or ineligible	78% / 37%	6mo PFS 81%	Song (2019) Clin Cancer Res
Tislelizumab	2	Relapse post ASCT or ineligible	82% / 63%	6mo PFS 84%	Song (2020) Leukemia

**Significant trial heterogeneity**

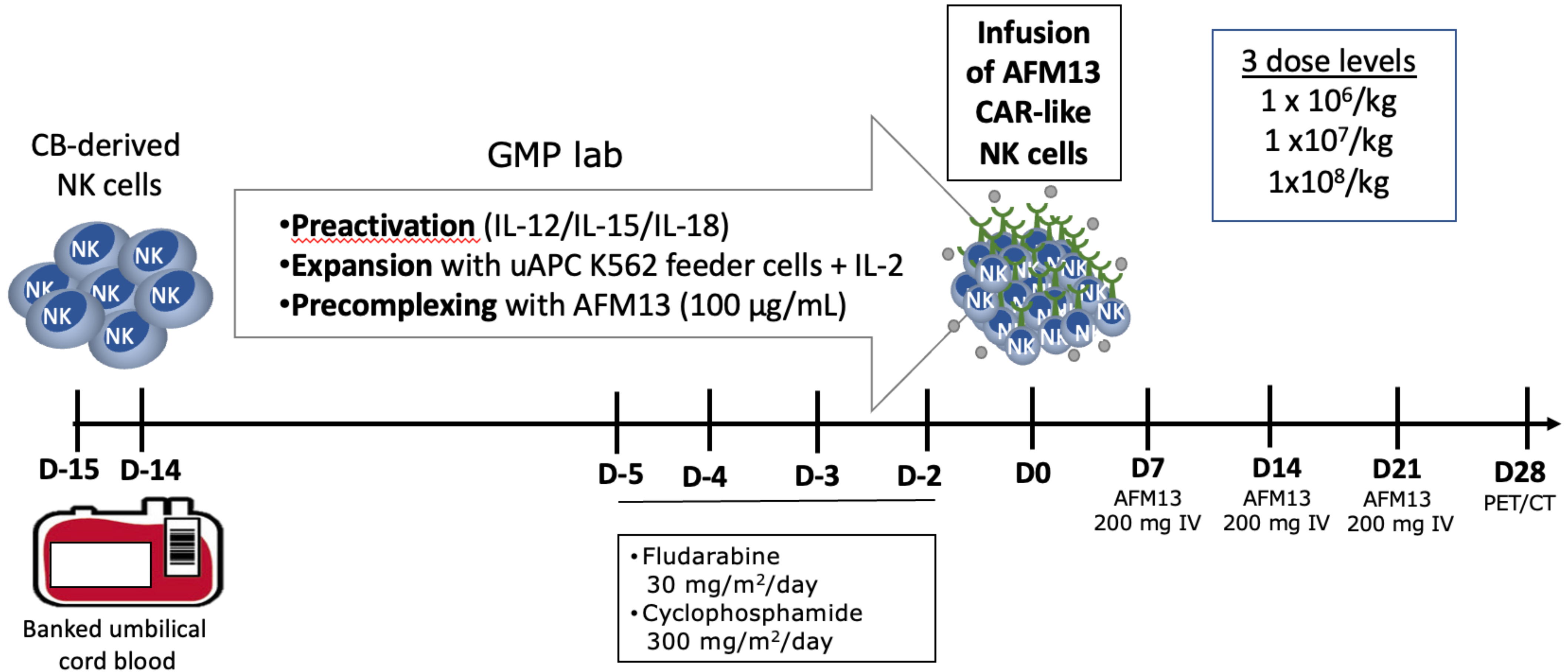
# Innate Cell Engager AFM13 Combined with Preactivated and Expanded Cord Blood-Derived NK Cells for Patients with Double Refractory CD30+ Lymphoma

Yago Nieto, Pinaki Banerjee, Indreshpal Kaur, Lori Griffin, Christina Ganesh, Melissa Barnett, Roland Bassett, Lucila Kerbauy, Rafet Basar, Mecit Kaplan, Sanjida Islam, Daniel Esqueda, Jeremy Ramdial, Samer Srour, Chitra Hosing, Neeraj Saini, Amin Alousi, Muzaffar Qazilbash, Uday Popat, Sairah Ahmed, Karenza Alexis,\* Michael Emig,\* Andreas Harstrick,\* Elizabeth J Shpall, Katayoun Rezvani

The University of Texas MD Anderson Cancer Center  
Department of Stem Cell Transplantation and Cellular Therapy, and Affimed\*



# AFM13-complexed CB-Derived NK cells for Refractory/Relapsed CD30+ Lymphoma (NCT04074746) Treatment Schema



# Patient Population

<b>Baseline characteristics</b>	<b>N=42</b>
Age, median (range)	43 (20–75)
Gender (male/female)	27 / 15
Diagnosis (Hodgkin / NHL)	37 / 5
No. prior lines therapy, median (range)	7 (1–14)
Prior brentuximab vedotin	42
Prior anti-PD-1	39
Prior SCT (autologous / allogeneic / both)	25 (15 / 4 / 6)
Prior CD30.CAR-T	4
No. prior relapses/progressive disease, median (range)	5 (1–14)
Response to immediately prior therapy	41 PD, 1 SD

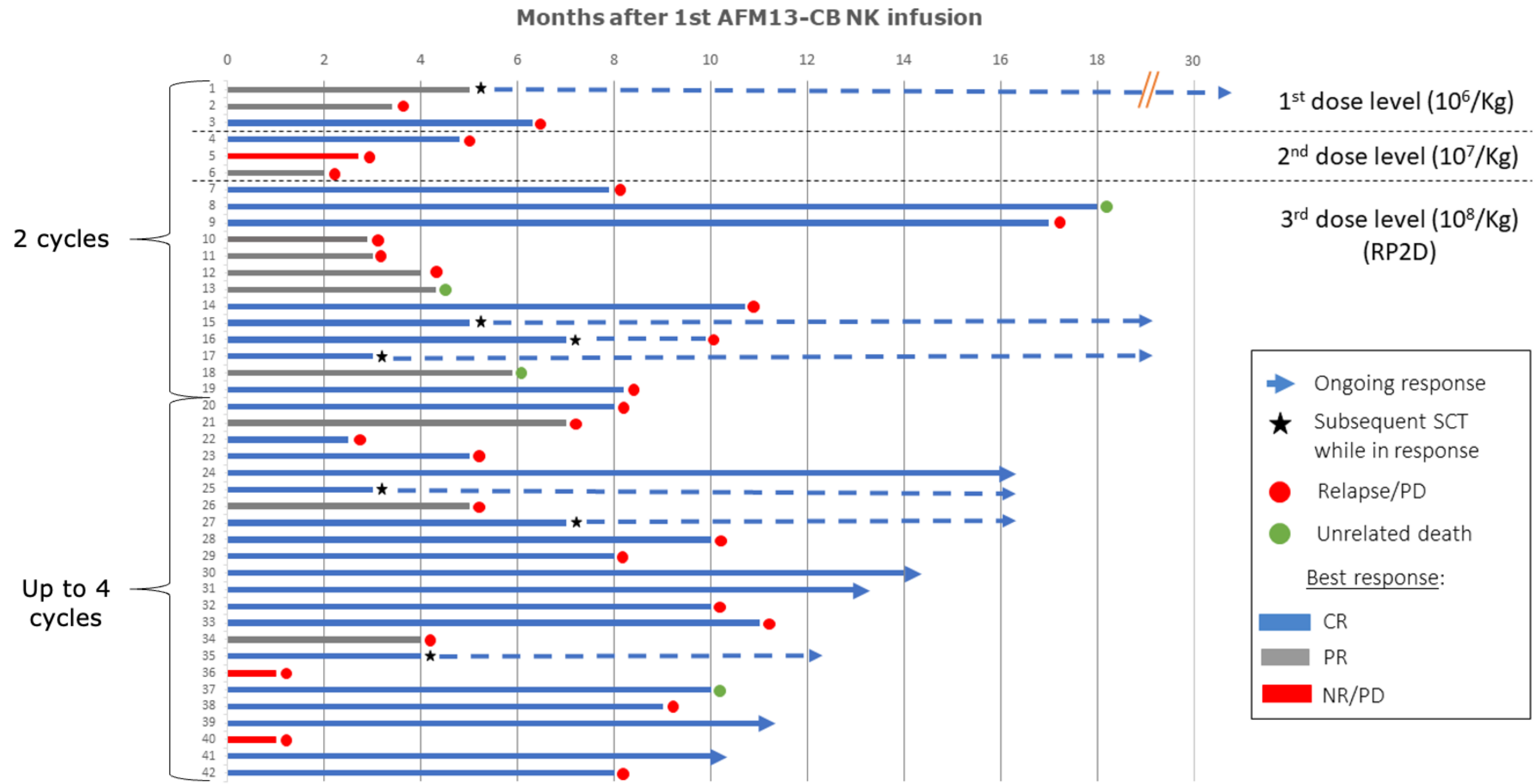
# Safety

1. No cases of cytokine release syndrome (CRS), neurotoxicity (ICANS) or GVHD
2. Infusion-related reactions were infrequent:
  - 27 (1 G3, 21 G2) in 349 infusions of AFM13 alone (7.7%)
  - 1 G2 in 117 infusions of AFM13-NK cells (0.8%)
3. Moderate myelotoxicity of lymphodepleting FluCy:
  - Neutropenia:
    - 42% pts G4, 31% G3 after cycles 1 & 2
    - 58% pts G4, 16% G3 after cycles 3 & 4
    - 1 case of neutropenic fever (1%)
  - Thrombocytopenia:
    - 16% pts G4, 8% G3 after cycles 1 & 2
    - 41% pts G4, 12% G3 after cycles 3 & 4
    - No cases of bleeding
4. No difference in toxicities between dose levels
  - No DLT was encountered
  - Dose level 3 ( $10^8$  NK/Kg) was established as the RP2D

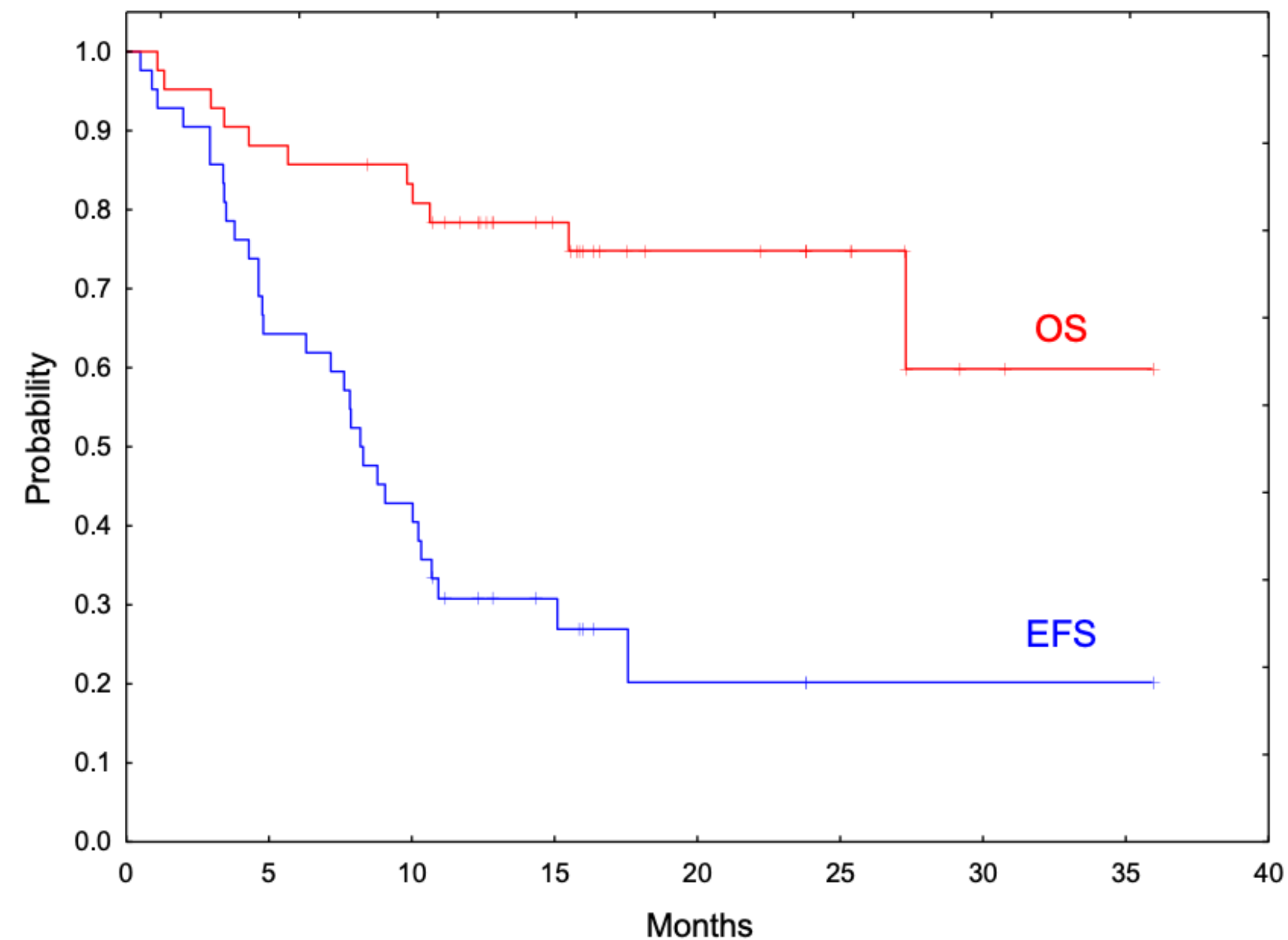




# Duration of responses

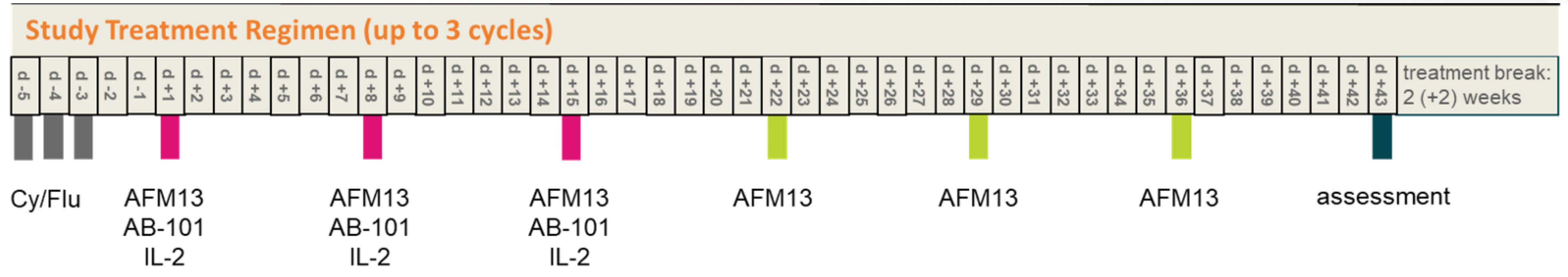


# Outcomes at median f/u of 16 (8-36) months



	Patients treated at RP2D			
	Overall (N=36)		Hodgkin (N=32)	
	2 cycles (N=13)	4 cycles (N=23)	2 <u>cycles</u> (N=12)	4 <u>cycles</u> (N=20)
<b>Median EFS</b>	6 <u>months</u>	12 <u>months</u>	6 <u>months</u>	12 <u>months</u>
At 6 months	62%	70%	67%	68%
At 12 months	31%	29%	33%	27%
<b>Median OS</b>	NR	NR	NR	NR
At 6 months	85%	87%	92%	85%
At 12 months	85%	85%	92%	82%

# New study with AFM13/NK cells - treatment schedule

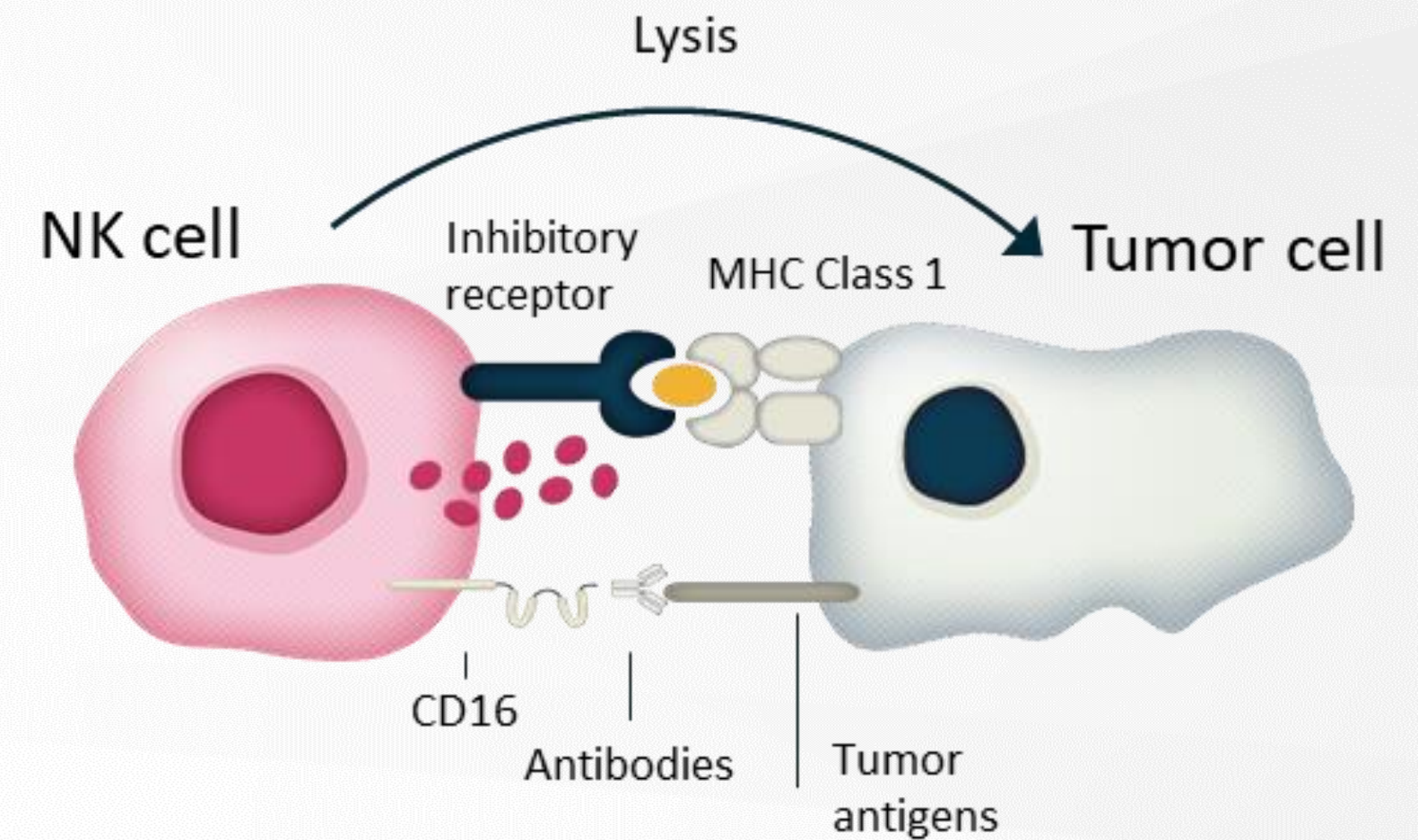


- **AFM13:** AFM13 will be administered intravenously at a fixed dose of 200 mg or 300 mg
- **AB-101:** AB-101 will be administered (within 30 minutes and no more than 90 minutes after thawing) approximately one hour following completion of AFM13 administration.
- **IL-2:** IL-2 will be administered at a dose of  $6 \times 10^6$  IU/dose subcutaneously at least 1 hour and no more than 4 hours following each AB-101 dose

# AB-101: A Potent, Safe, Highly Scalable NK Cell To Enhance mAb Therapy

- AB-101 is a non-genetically modified allogeneic off-the-shelf NK cell therapy with selected characteristics:
  - CD16 polymorphism for enhanced combination with ADCC mAbs
  - KIR B-Haplotype for enhanced innate activity in allogeneic setting
- To date, the therapeutic potential of multi-dose NK cell/mAb combinations has not been fully assessed due to limited scale of cell production

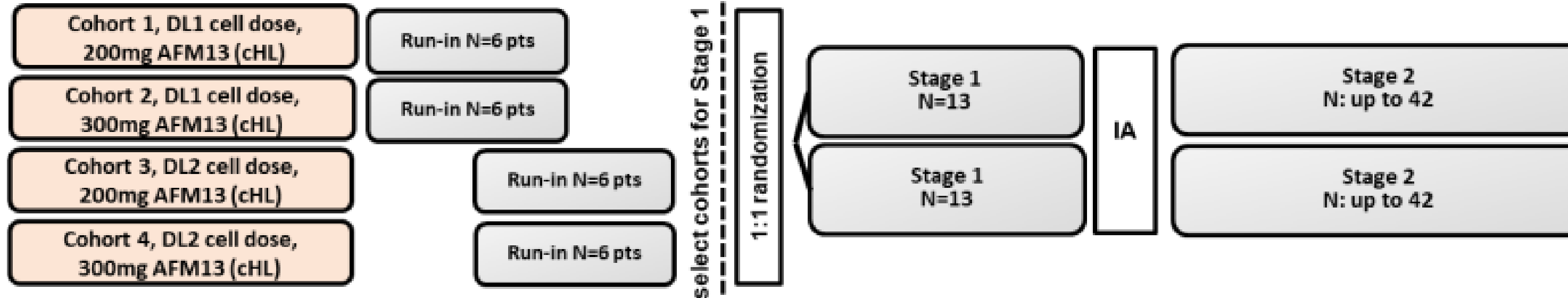
ADCC:



- AB-101 has low regulatory risk and a scale of production supporting large data-rich studies to assess:
  - The therapeutic potential of NK cells with multiple standard of care monoclonal antibodies including ADCC and CPI mechanisms
  - The optimal lymphodepletion, cell dose/schedule and cytokine support
  - Exploratory biomarkers to define patient populations that would most benefit from allogeneic NK therapy

# Study Design

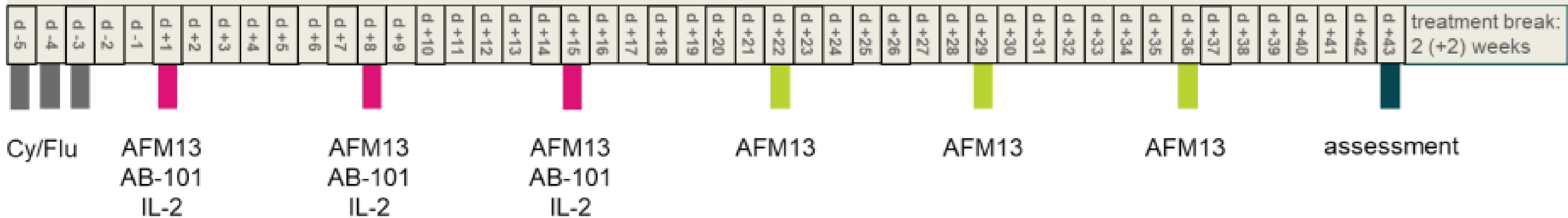
## Phase 2 trial (Simon Two-Stage Design)



## Exploratory part in CD30+ PTCL



## Study Treatment Regimen (up to 3 cycles)



# Study periods

## Screening (≤28 days)

- Cohort 1-5: Medical history, ECOG, physical exam, ECG.
- Cohort 5 only: Baseline Biopsy (w/i 90 days)

## Treatment

- 1 cycle = 6 weeks (43 days)
- 2-week rest intervals between cycles (+2-weeks for AE recovery)
- Up to 3 cycles

## Safety Follow-up (≤30 days)

- ≤ 30±5 days of last IMP administration OR
- before start of any new anti-cancer treatment

## Long-term Follow-up (≤18 months)

- Progression or survival?
- Visit every 3 months

## Screening Visit

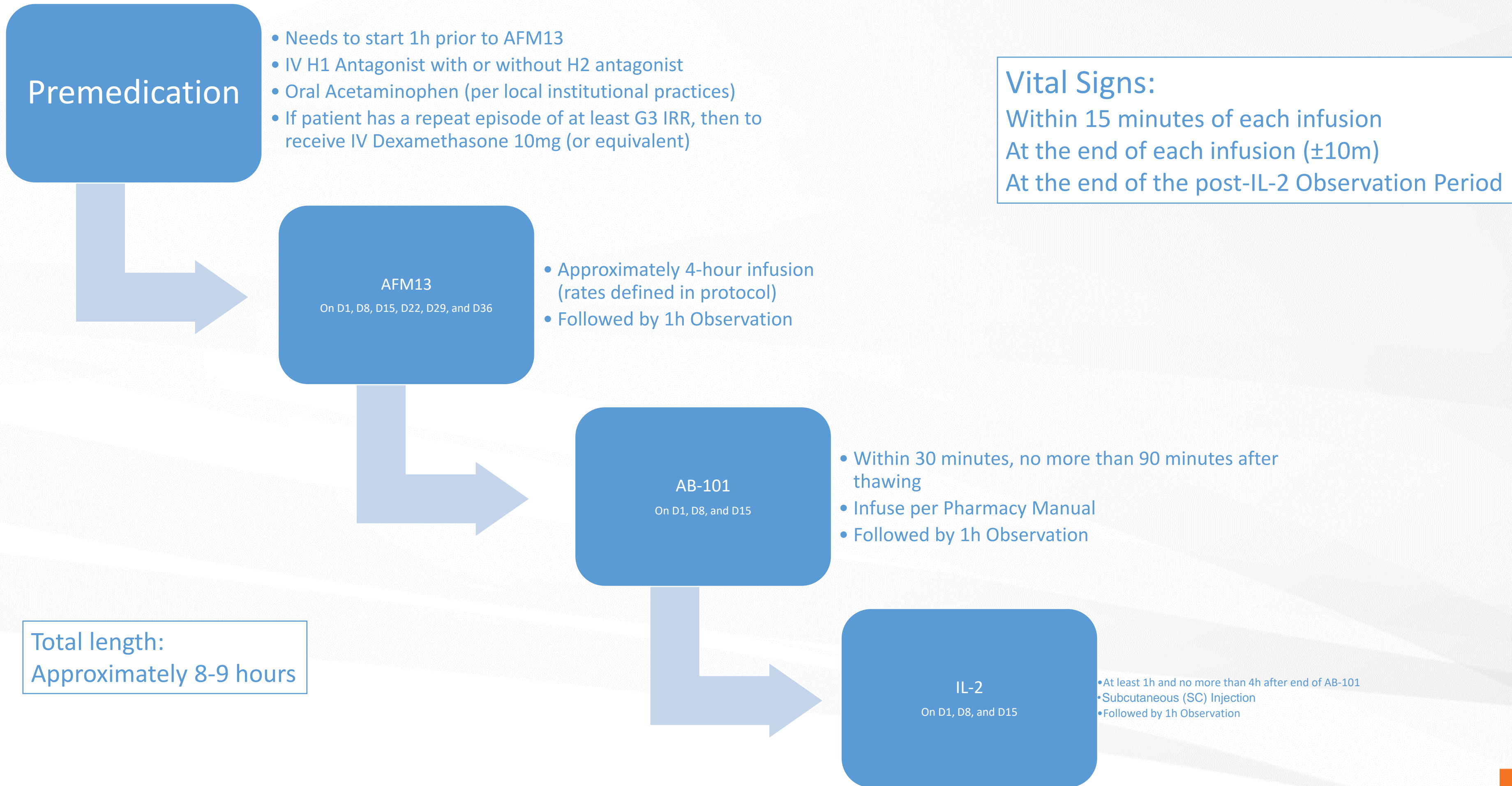
- Assign unique subject-ID to each subject (re-screened subjects: New subject-ID)
- Confirm eligibility
- Submit subject eligibility packet to the Medical Monitor (review / approval)

## EOT

≤14days of last IMP administration



# AFM13 and AB-101 Infusion Day Flow Chart

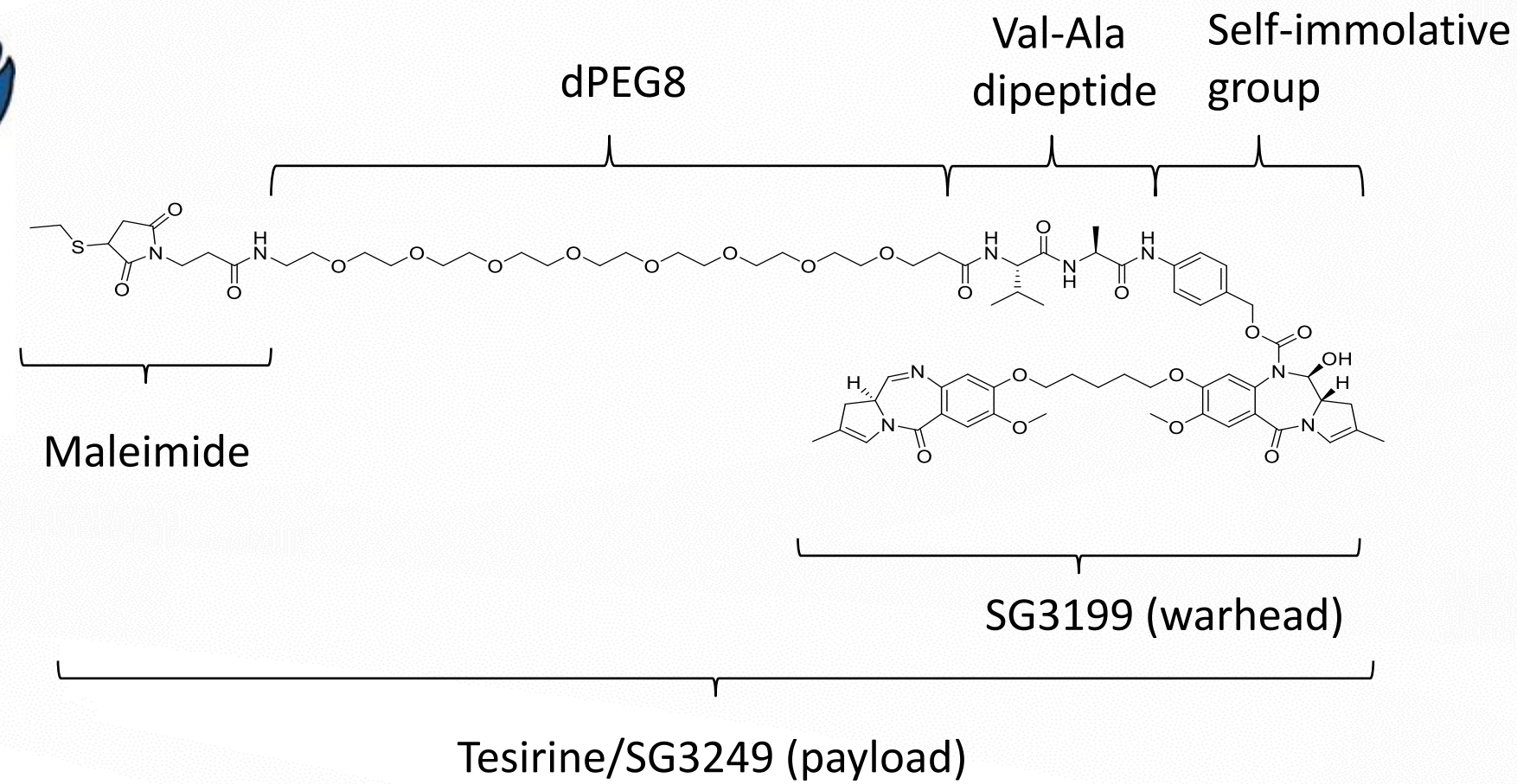
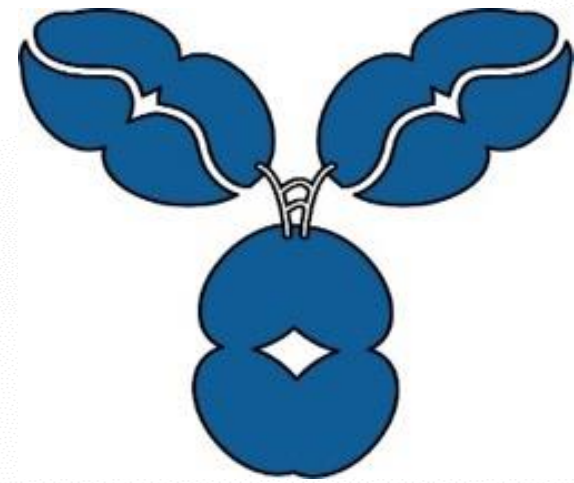


# Antibody : Drug conjugates

Is new better?



# Camidanlumab tesirine

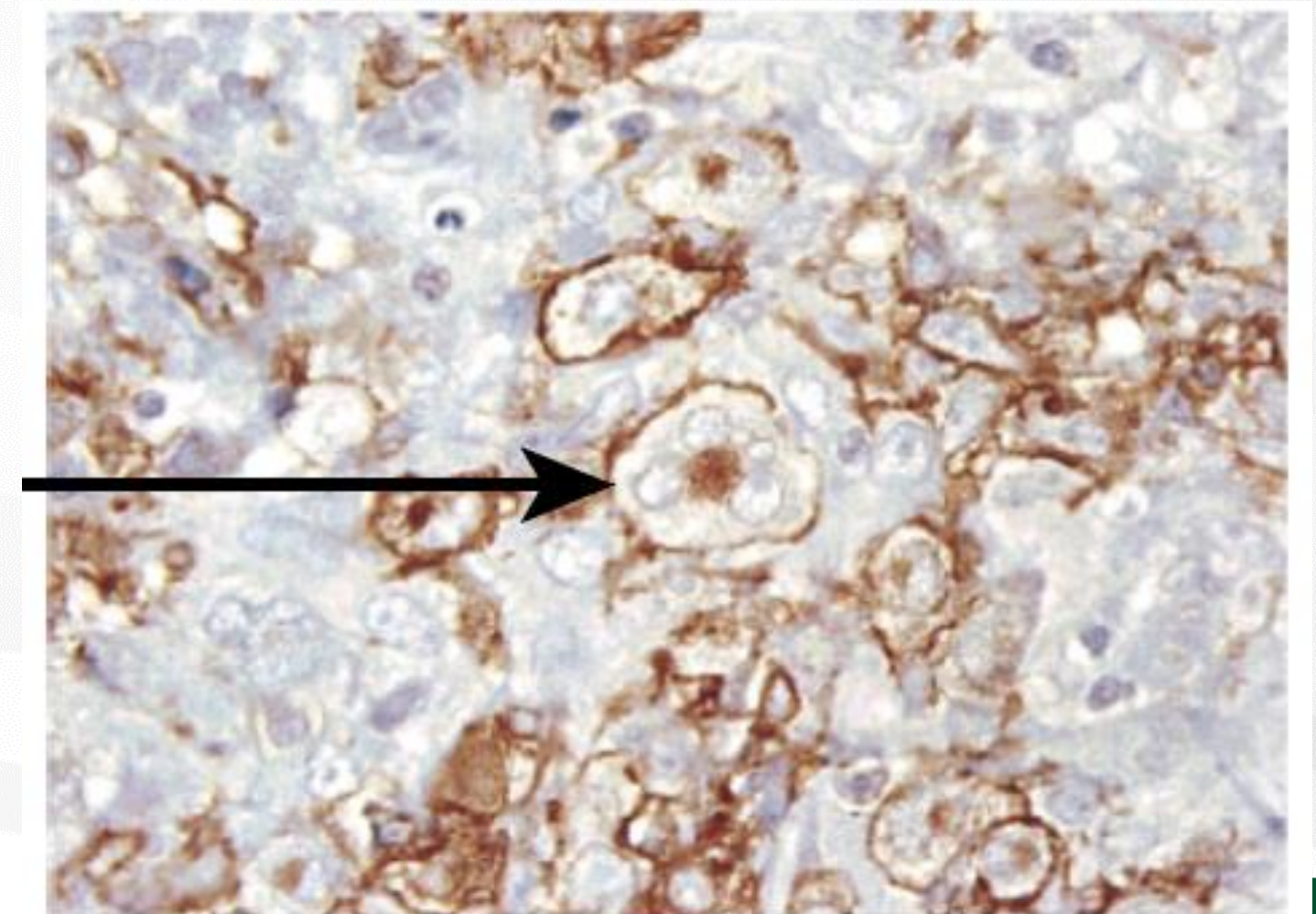


## Immunological rationale

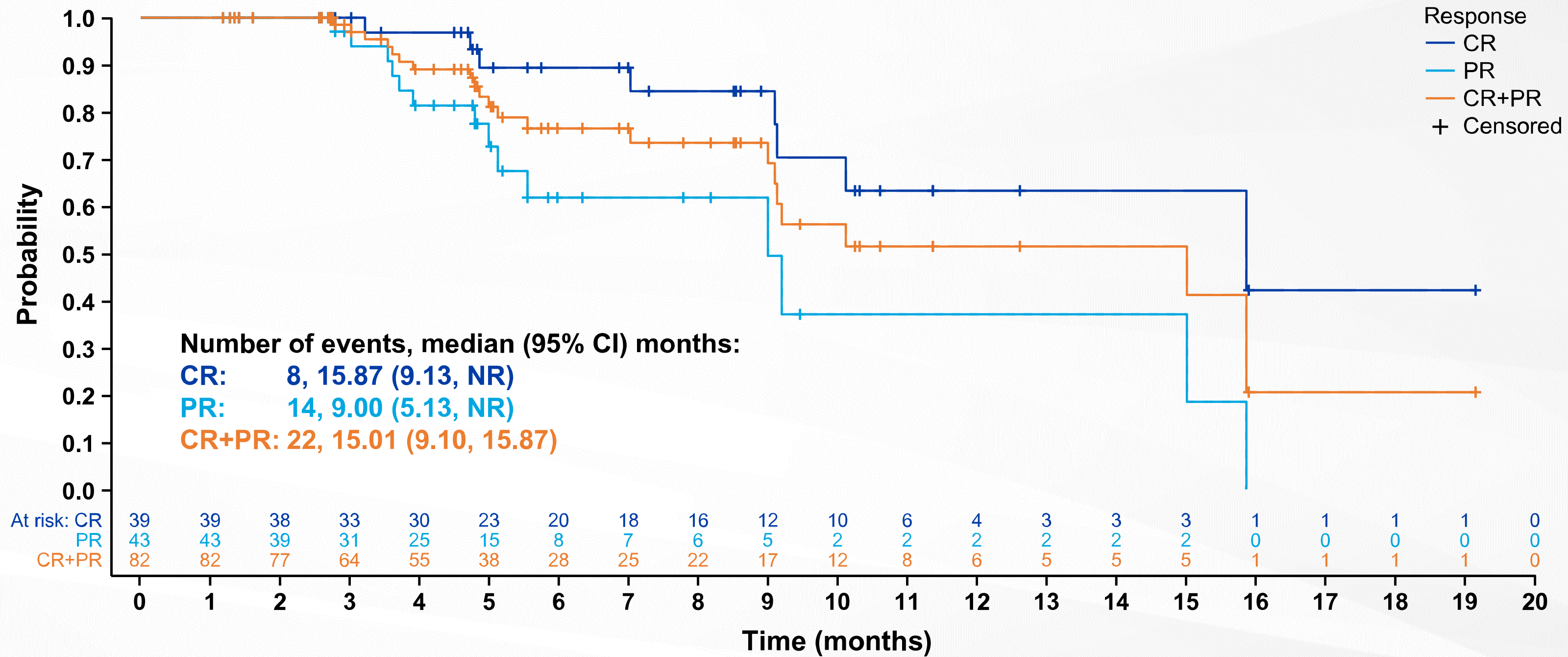
- Targeting of CD25+ Tregs may increase the Teff:Treg  $\rightarrow$  immunological tumor eradication
- Anti-CD25 therapies synergize with PD-1 blockade to eradicate established tumors

## Mode of action

1. Cami binds to the CD25 antigen on the tumor cell surface
2. ADC internalization, linker cleavage and PBD release
3. Cytotoxic DNA cross-link formation
4. Stalled DNA replication fork causing cell death cell death



# Progression-free Survival by BOR



Median (range) follow-up: 10.7 (1.2-25.2+) months

# Safety – Patients with Guillain–Barré Syndrome (GBS)/polyradiculopathy

- Baseline characteristics:
  - Median age: 35y (23-68)
  - 3/8 patients had prior SCT
  - Median days since last checkpoint inhibitor: 187 (50-377)
- Median number of Cami cycles (range): 3.5 (2-7)
  - 4/8 cases presented after 2 cycles; 3/8 had onset after 30 days post last-dose

Summary of Patients with GBS/polyradiculopathy

Patient	AE by preferred term	Max grade	Duration (days)	IVIG/PLEX / Steroids	Outcome at last assessment
1	GBS	4	523	Y/Y/Y	Ongoing at grade 1
2	GBS	4	43	Y/Y/N	Recovered
3	GBS	3	50	Y/Y/Y	Not recovered; patient died of sepsis
4	GBS	3	287	Y/N/Y	Ongoing at grade 1
5	GBS	3	111	Y/Y/Y	Ongoing at grade 1 <sup>a</sup>
6	GBS	2	119	Y/N/N	Recovered
7	Polyneuropathy <sup>b</sup> , Meningitis, Facial paralysis, SIADH	4	72	Y/N/Y	Recovered
8	Radiculopathy	2	165	Y/Y/Y	Recovered

Data cut off: November 1, 2021

<sup>a</sup> Also received rituximab with clinical improvement. <sup>b</sup> Verbatim: polyradiculoneuritis.

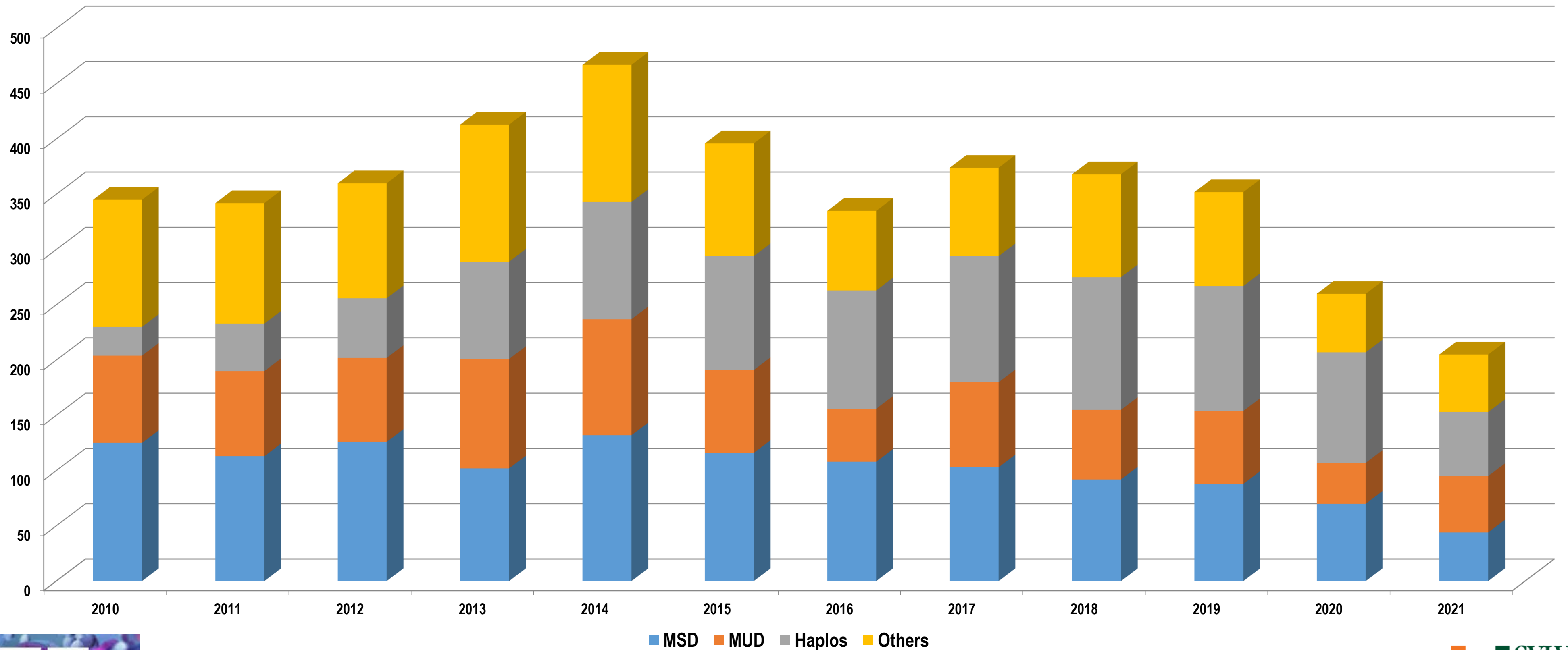
IVIG, intravenous immunoglobulin; PLEX, plasma exchange; SCT, stem cell transplant; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

# CAR T-cell therapy

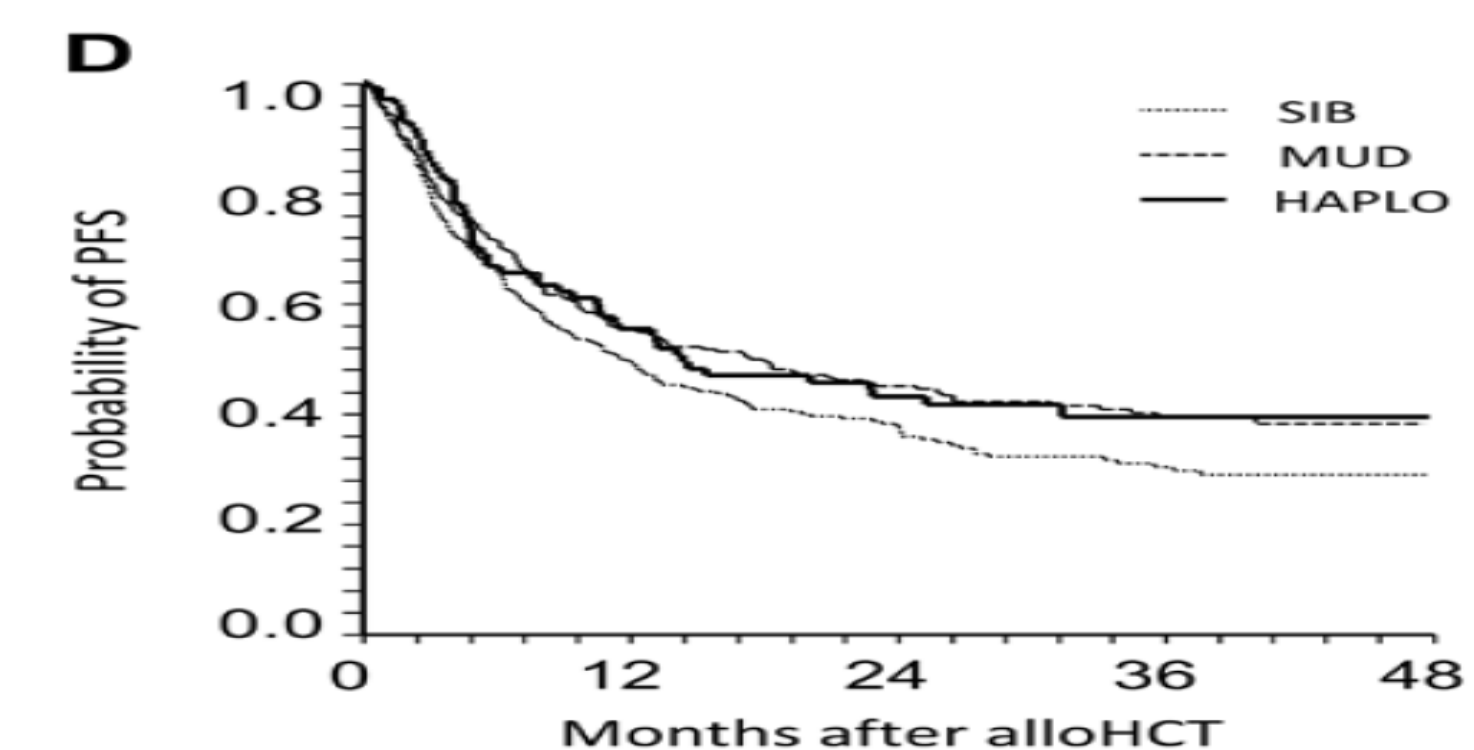
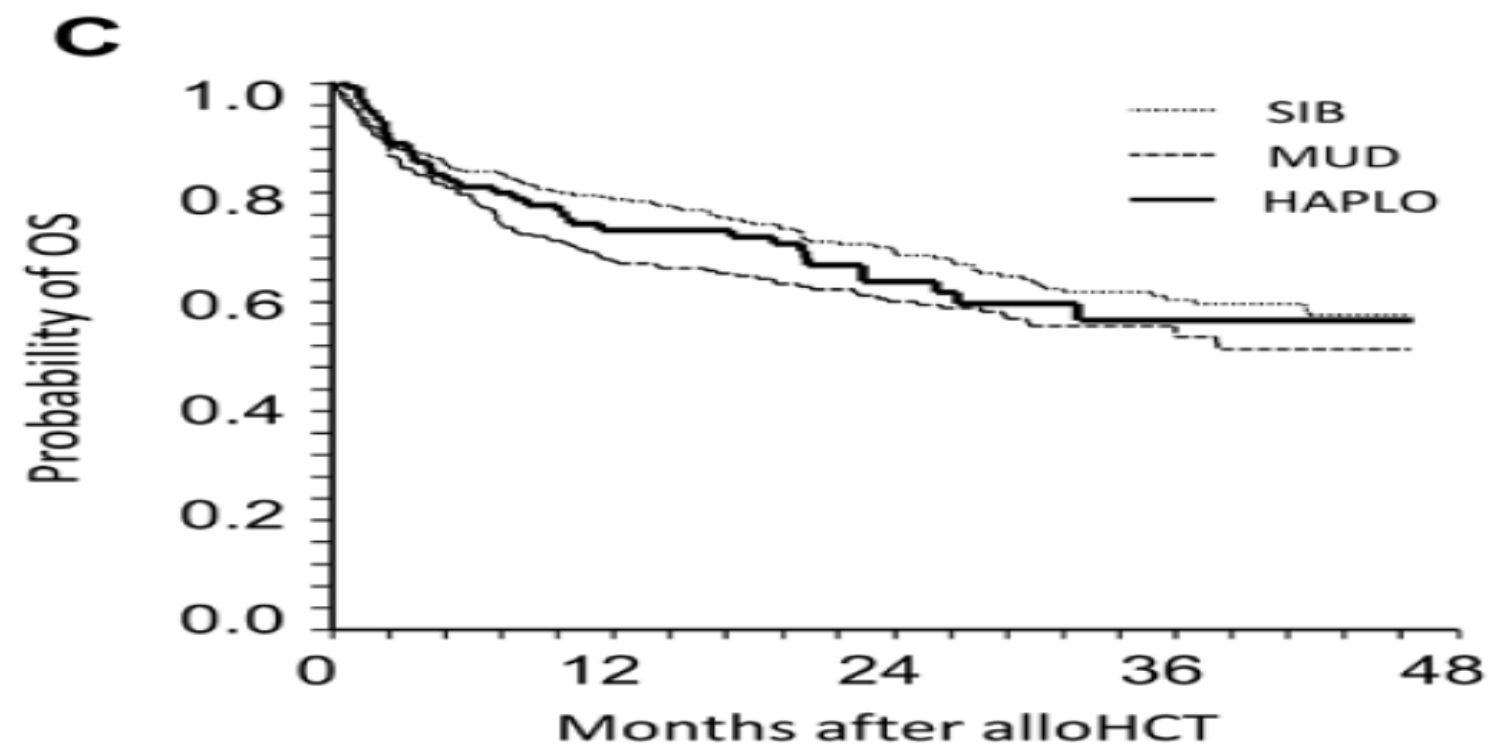
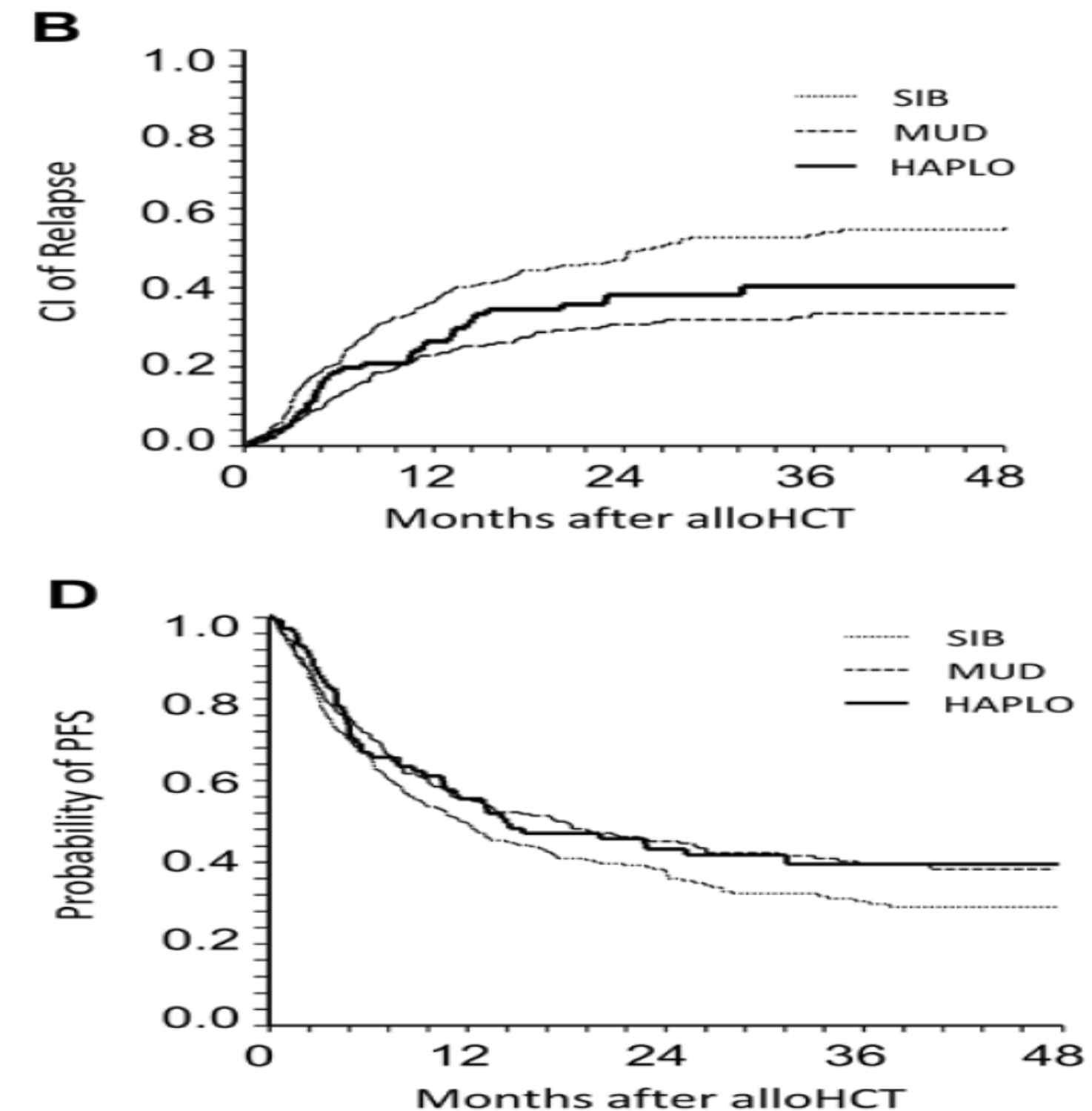
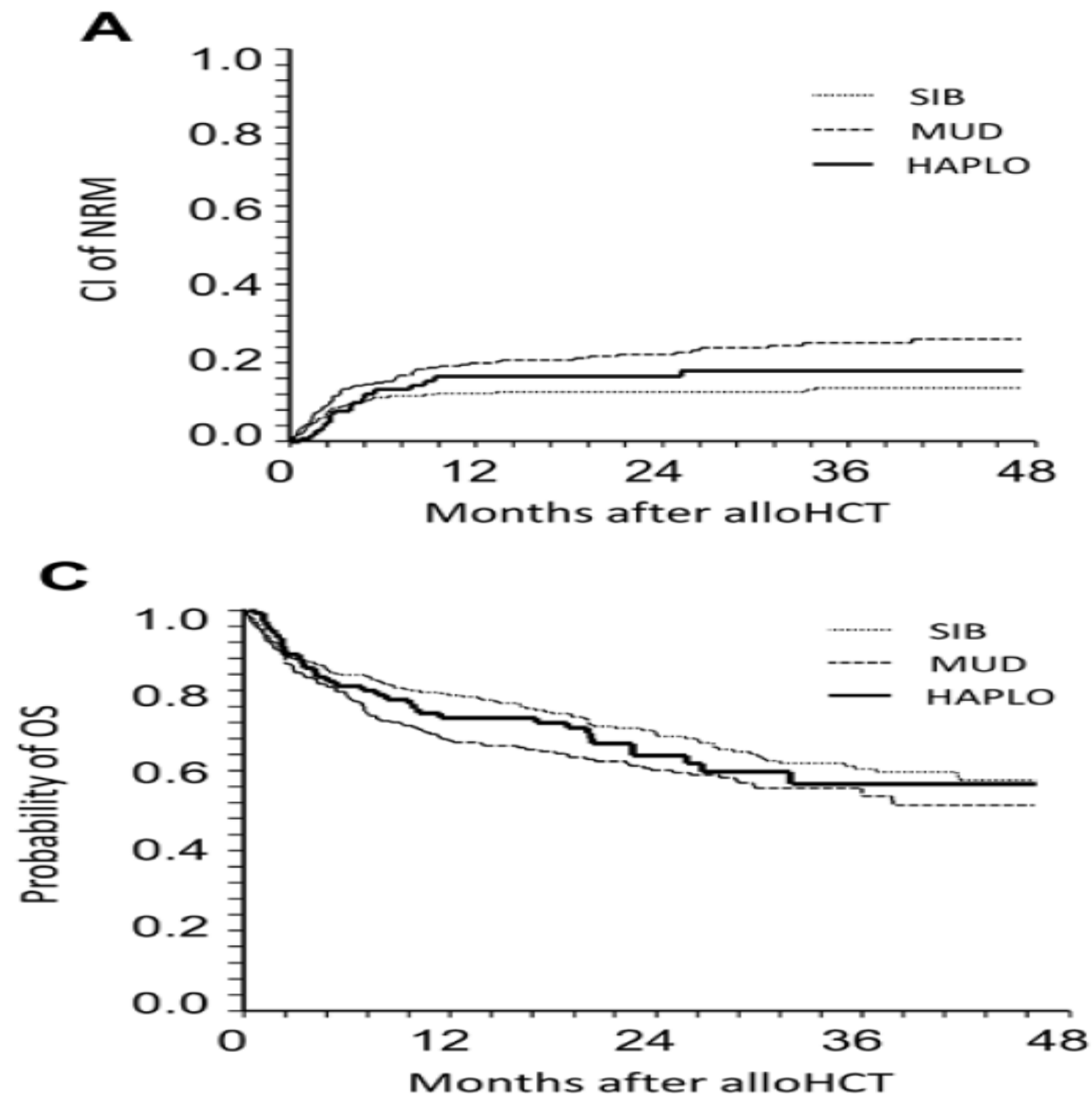
Are we seeing progress?

Not Really.....

# HCT in cHL. The EBMT Experience



# Haplo-HCT with Cy-Post Compare Favourably with MSD and MUDs



# Allotransplants after CPIs

N = 209

87 Haplo/PtCy

25 non-Haplo/PtCy

91 non-Haplo/non-PtCy

6 PtCy + ATG

Median age: 31.5 yrs

Male patients - 60%

HCT-CI

0-2 - 129

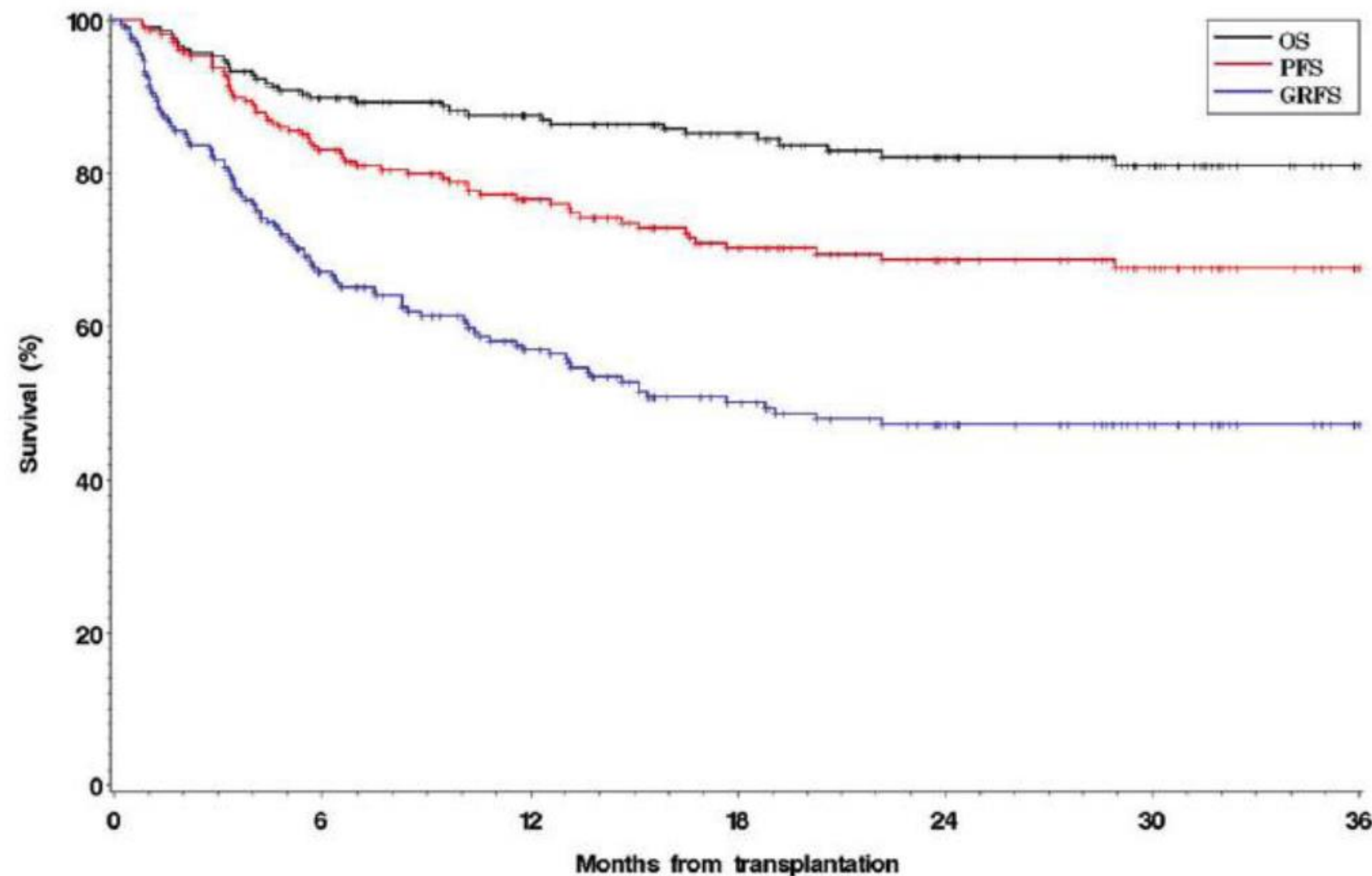
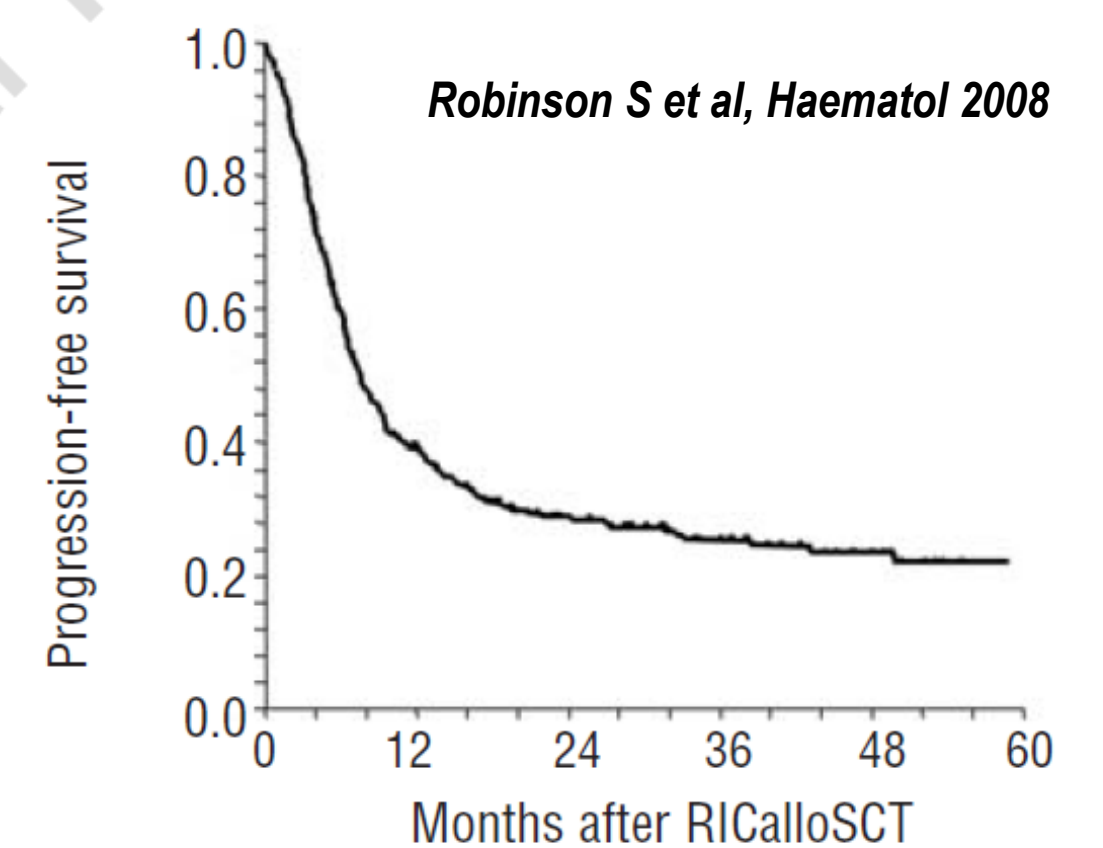
≥ 3 - 66

Median number of tx: 4 (2-11)

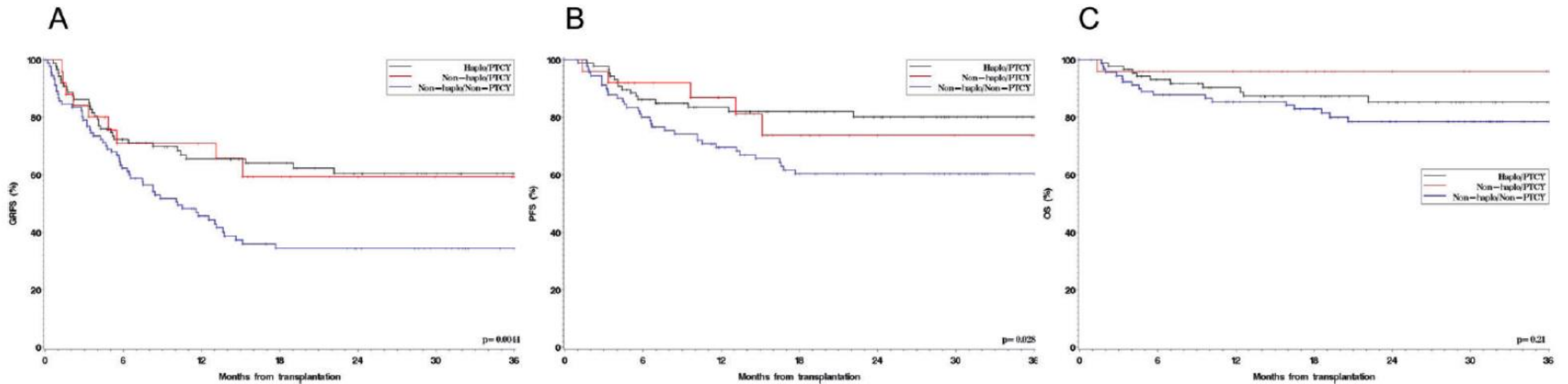
Best response to CPIs CR - 39%

Median time from last dose CPIs  
to Allo-HCT, 81 days

CR before allo-HCT - 58%



# Allotransplants after CPIs



**Fig. 2 Survival outcomes based on donor type and GVHD prophylaxis regimen. A GRFS, B PFS, C OS based on donor type and GVHD prophylaxis regimen. (Note: the six patients who received PTCy + ATG are not included in this figure).**



# Allotransplant after CPIs

Table 2 Multivariable analysis for PFS, OS, and GRFS.

Variable	PFS		OS		GRFS	
	HR	<i>p</i>	HR	<i>p</i>	HR	<i>p</i>
<b>Age</b>						
≤50 ( <i>n</i> = 187)						
>50 ( <i>n</i> = 22)	3.1	<b>0.001</b>	3.0	<b>0.012</b>	2.7	<b>0.0002</b>
<b>Remission status at alloHCT</b>						
Non-CR ( <i>n</i> = 88)						
CR ( <i>n</i> = 121)	0.5	<b>0.012</b>	0.6	0.12	0.7	0.14
<b>Doses of PD-1 mAb</b>						
1-9 (or unknown) ( <i>n</i> = 102)						
10+ ( <i>n</i> = 107)	0.8	0.49	0.6	0.14	0.7	<b>0.039</b>
<b>Haplo/PTCY</b>						
No/No ( <i>n</i> = 91)						
Yes/yes ( <i>n</i> = 87)	0.4	<b>0.005</b>	0.6	0.29	0.4	<b>0.0002</b>
No/yes ( <i>n</i> = 25)	0.3	<b>0.022</b>	0.1	<b>0.023</b>	0.4	<b>0.009</b>
<b>ATG</b>						
No ( <i>n</i> = 163)						
Yes ( <i>n</i> = 46)	0.5	0.09	0.7	0.40	0.5	<b>0.027</b>
Interaction ATG + PCY	17.4	<b>&lt;0.0001</b>	27.5	<b>&lt;0.0001</b>	6.5	<b>0.001</b>
<b>Best overall response to PD-1 blockade</b>						
CR/PR/SD ( <i>n</i> = 186)						
PD ( <i>n</i> = 22)	2.2	<b>0.044</b>	1.3	0.68	2.0	<b>0.024</b>

Statistically significant *p* < 0.05 values are in bold.

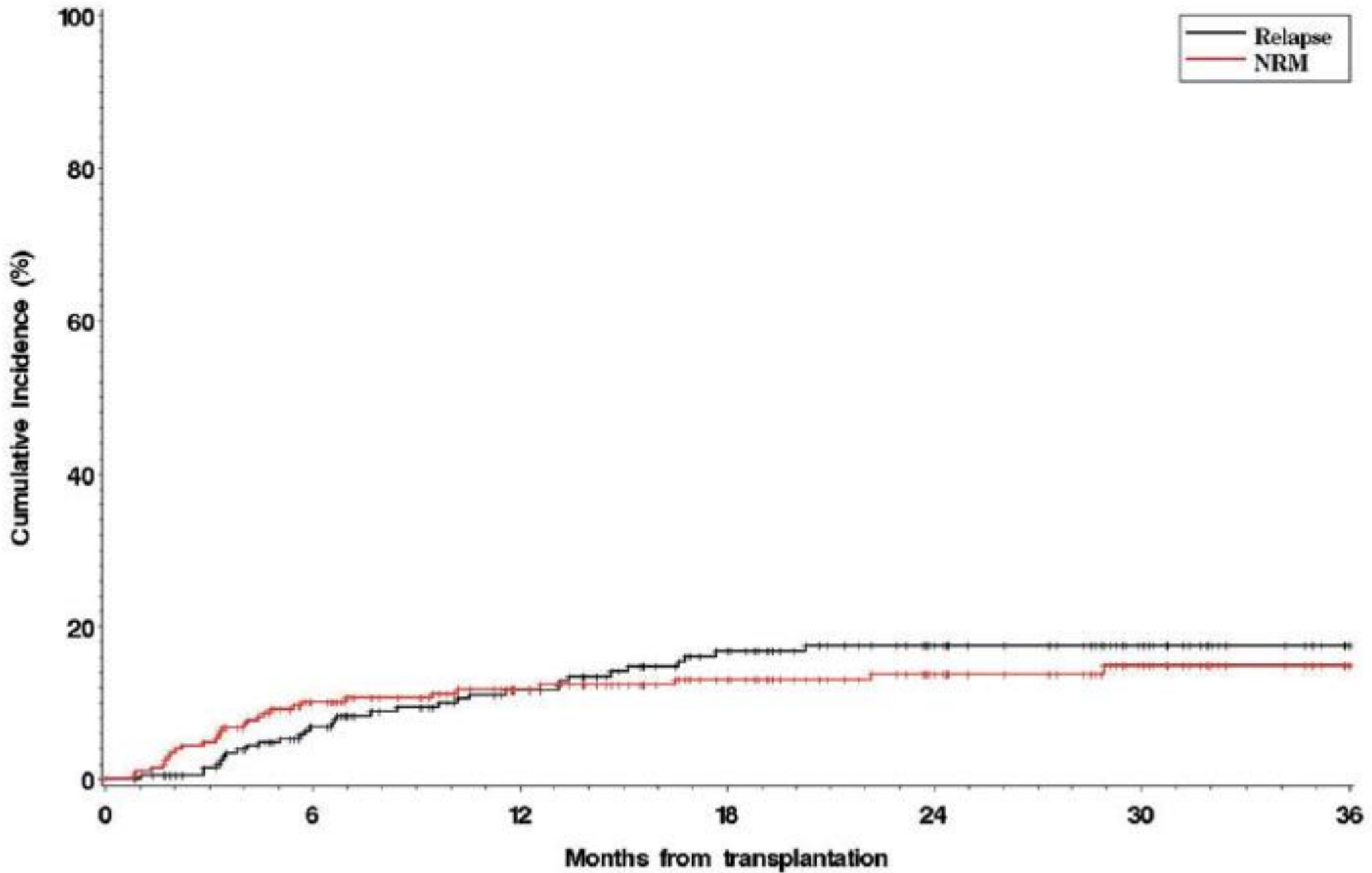
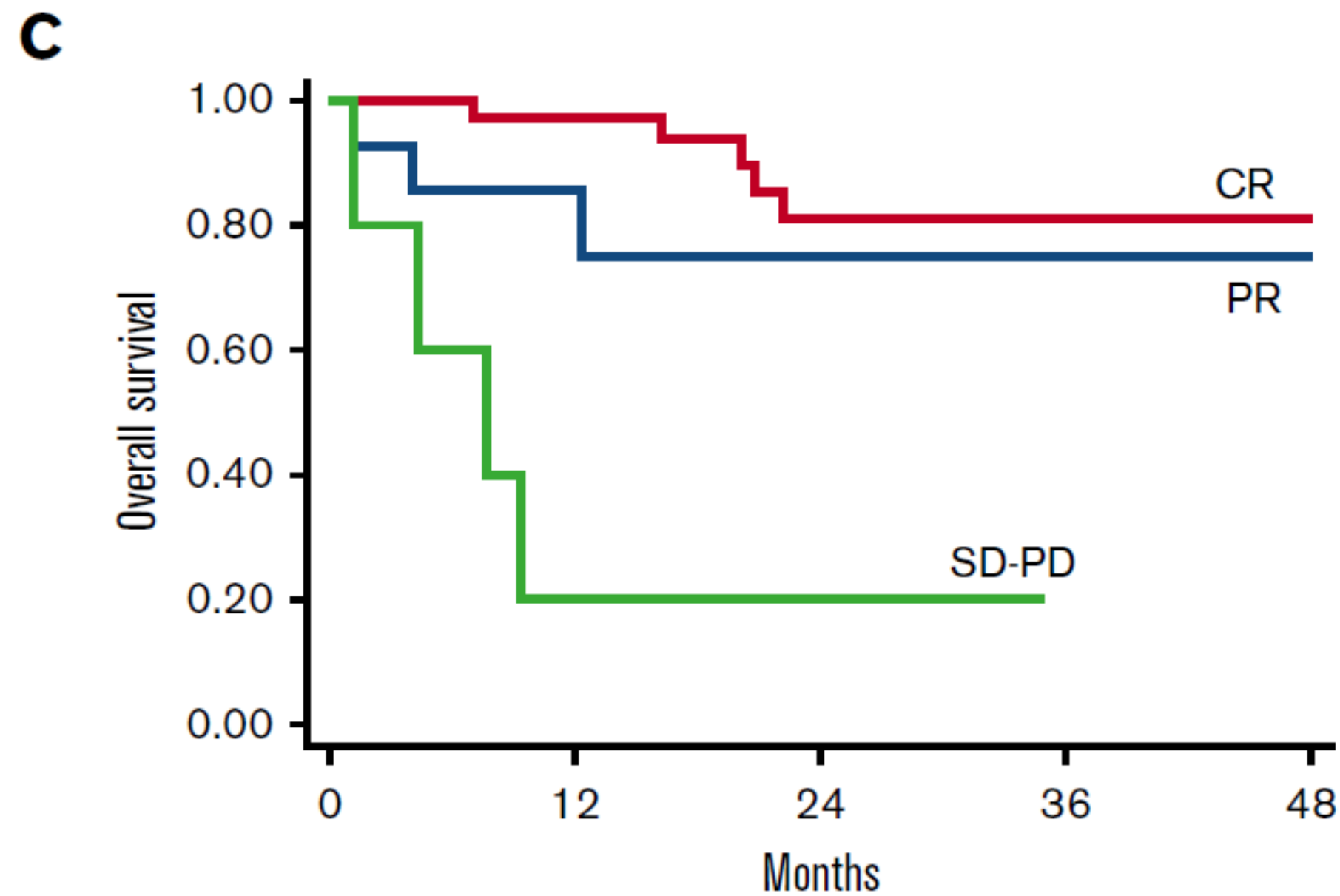


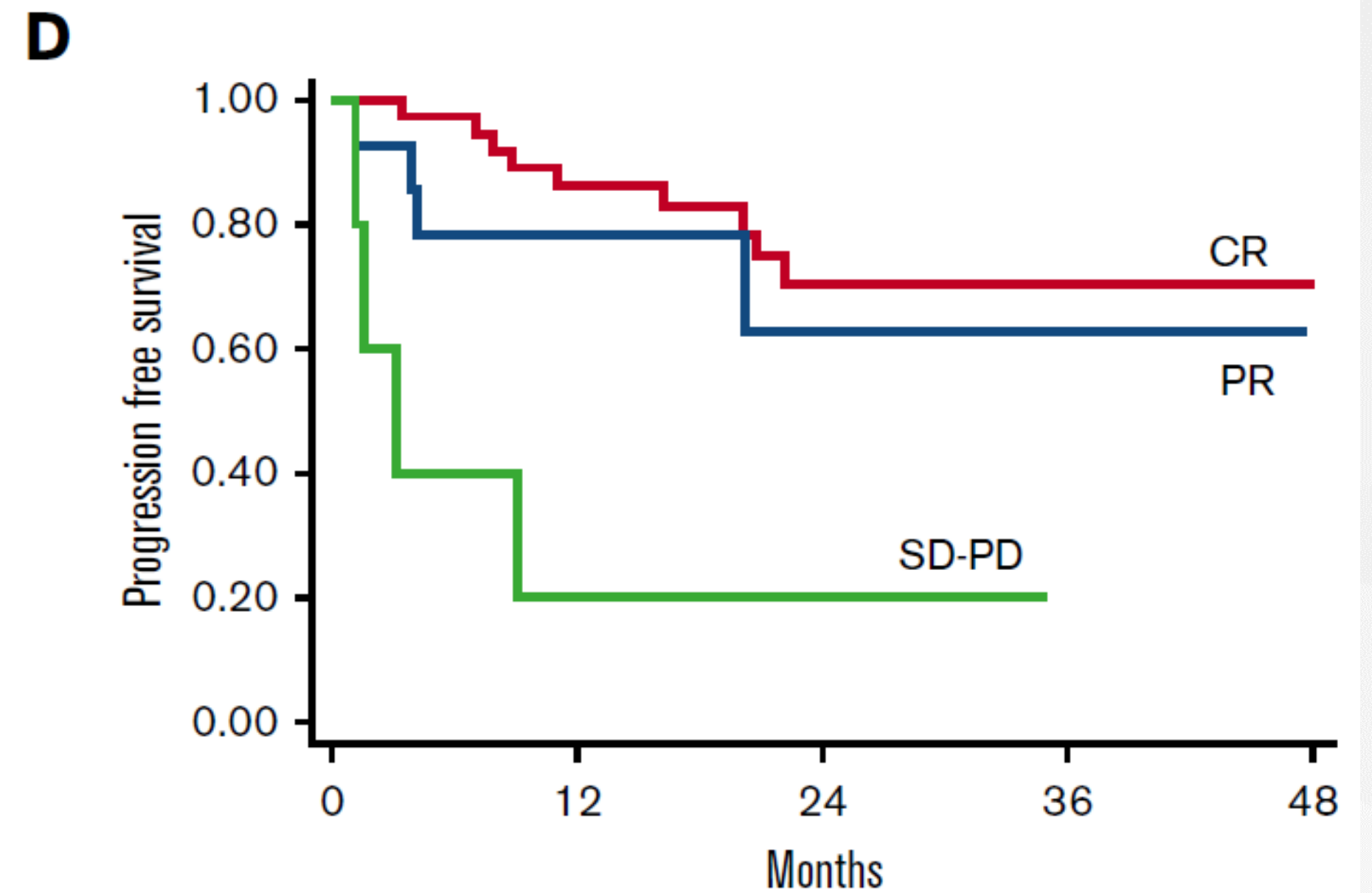
Fig. 3 CIR and NRM among all patients.

# Check Point Inhibition (Yes/No) Before Allotransplant in HL



Number at risk

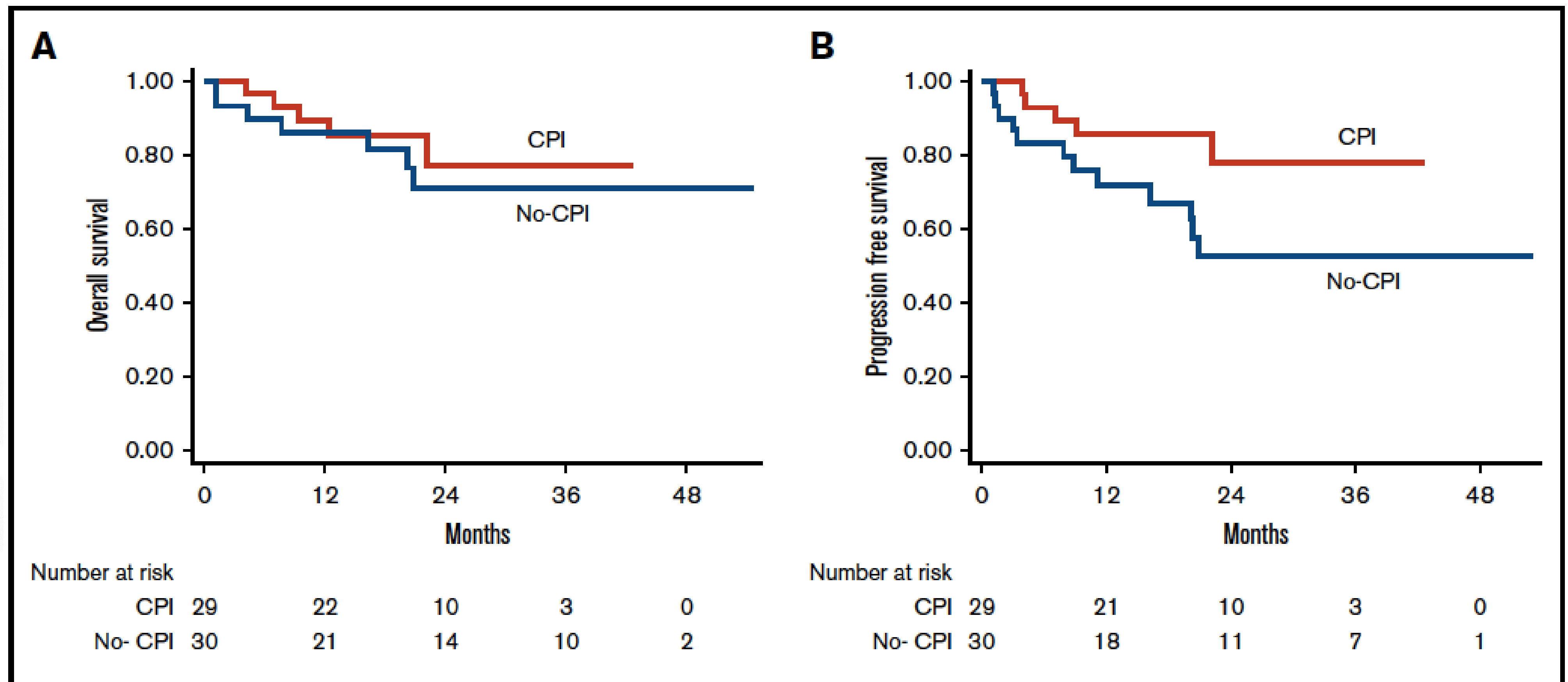
Months	0	12	24	36	48
CR	40	33	18	9	1
PR	14	9	5	4	1
SD-PD	5	1	1	0	0



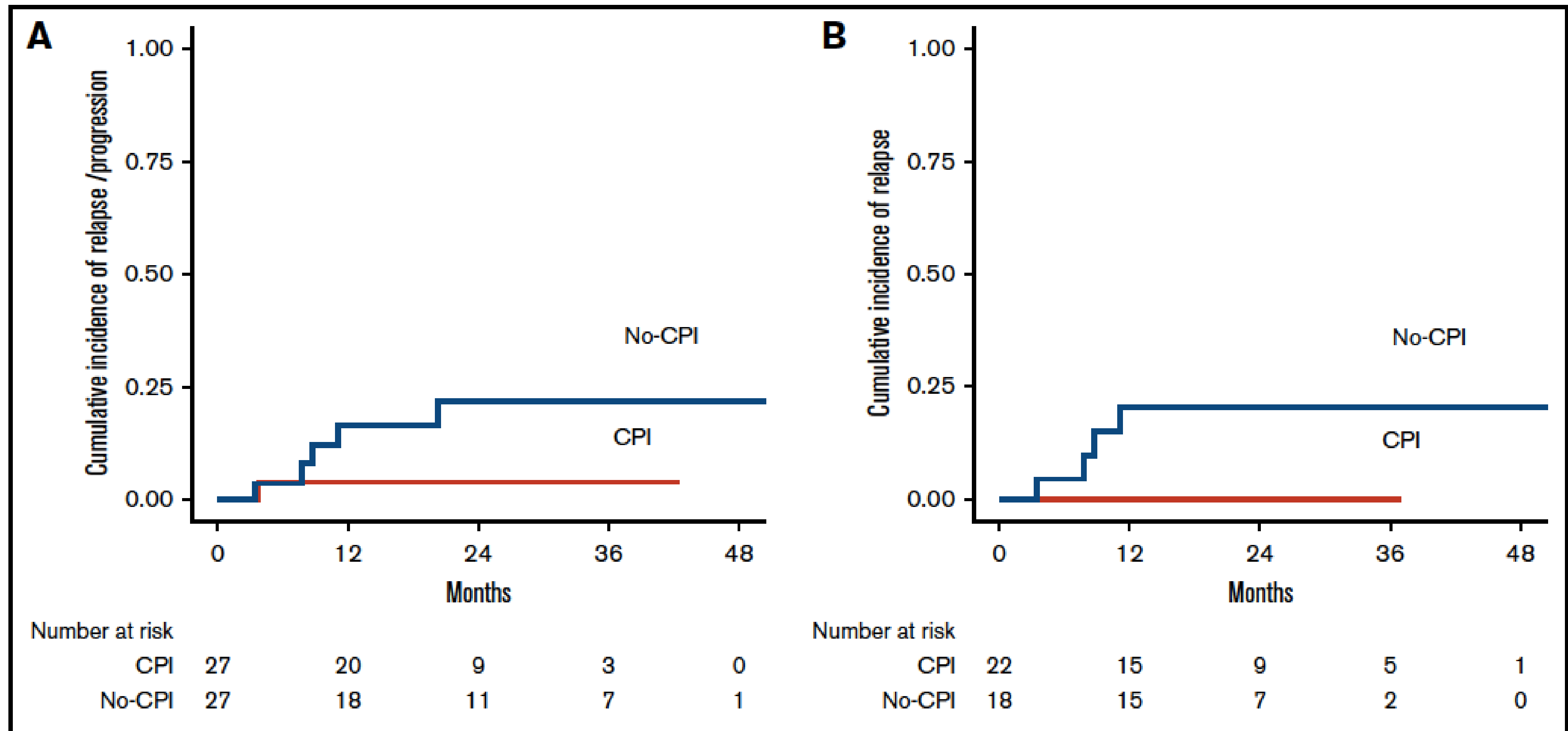
Number at risk

Months	0	12	24	36	48
CR	40	30	16	7	1
PR	14	8	4	3	0
SD-PD	5	1	1	0	0

# Check Point Inhibition (Yes/No) Before Allotransplant in HL



# Check Point Inhibition (Yes/No) Before Allotransplant in HL



# Conclusions

- **YES**, allo-HCT still has a role in the treatment of patients with RR HL
  - Numbers have gone down and position within the treatment pathway modified because of the introduction of new drugs
  - Only curative strategy for patients with HL relapsing after auto-HCT
- Combination of CPIs and allo-HCT is highly effective and safe
- Need to better understand when and how allo-HCT should be performed in those patients candidates for the procedure

# I want to thank the HL patients for participating in these research studies over the past 32 years

Lymphoma faculty at MSKCC where I spent 25 years of my life especially Joachim Yahalom who was the co-PI of all the pre-BV studies and Alison Moskowitz the co-PI of all the studies before I left in mid 2018 and now I am her co-PI!

Lastly, the lymphoma faculty at the University of Miami

# Lymphoma Service-Sylvester Comprehensive Cancer Center, University of Miami Health System

- Izidore Lossos
- Juan Alderuccio
- Alvaro Alencar
- Georgio Pongas
- Michelle Stanchina
- Juan Ramos
- Joe Rosenblatt
- Jonathan Schatz
- Craig Moskowitz



Griffen Cancer Research Building



Royal County Down Northern Ireland

We see 1000 lymphoma consults each year

Gemma, Dylan and Ethan