Indolent Lymphomas and Hodgkin Lymphoma: Achieving Curability

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Dicloure$

- Consulting & advisory roles: Roche-Genentech, Celgene, Pharmacyclics, Astra-Zeneca, Abbvie, Seattle Genetics, Epizyme, TG Therapeutics, Bayer, Astellas, Morphosys
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- Speaker's Bureau – none
- Employee - none

* All research funding to institution

Presentation includes off label use of nivolumab, lenalidomide and discussion of numerous non-approved investigational agents.

History of Chemotherapy: Alkylating Agents

WWI/WWII – chemical warfare
- Skin ulcerations
- Blindness
- Lung Damage
- Nausea, vomiting
- Mutagenic
- Carcinogenic

- Accidental exposure led to low lymphs
- May have similar effect on cancer cells
- 1940's – first i.v. tx of lymphoma with mustard – impressive, brief responses

Alkylating Agents in Lymphoma/CLL

NHL
R-CHOP
R-CVP
B-R
ICE
BEAM

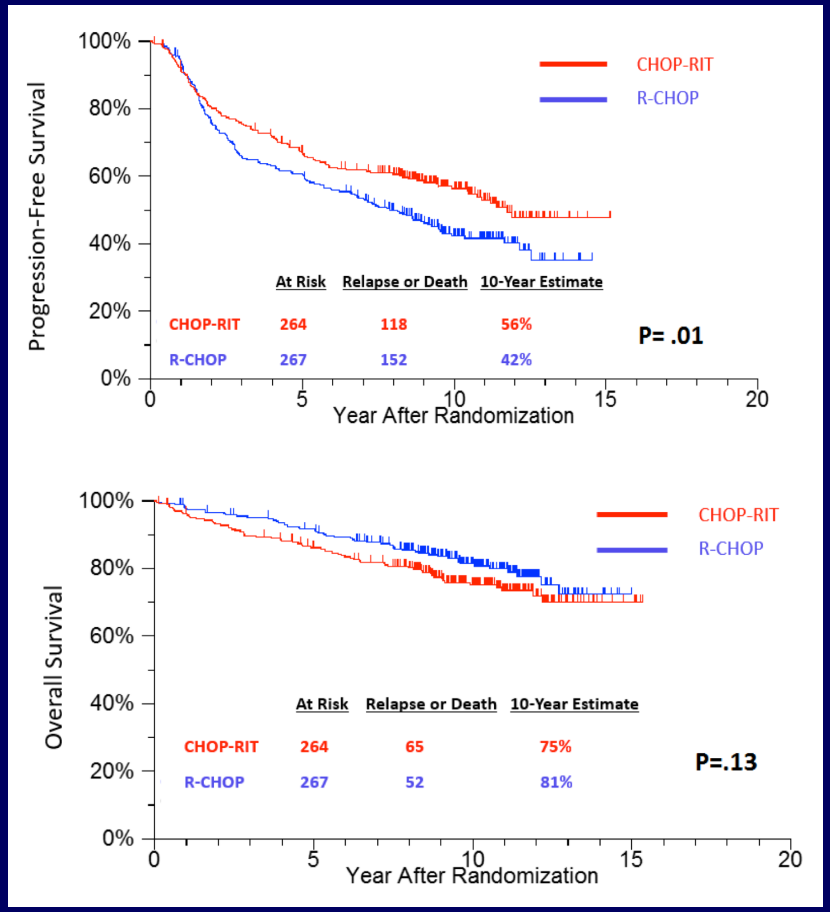
Hodgkin's
MOPP
ABVD
BEACOPP

CLL
FCR
BR

Various
Chlorambucil
Busulphan

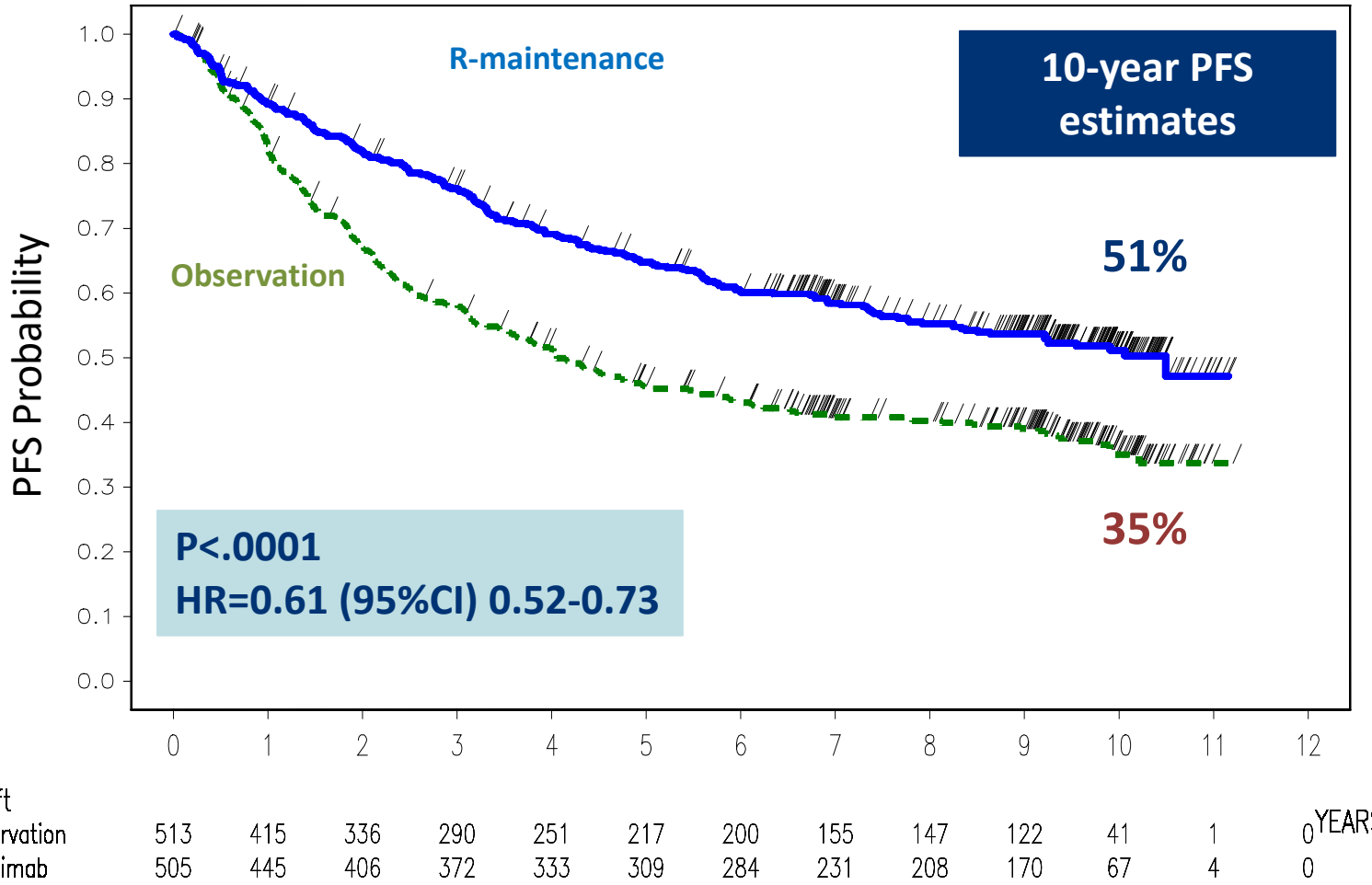
Progression-Free and Survival Curves for S0016

Med f/u 10.3 y

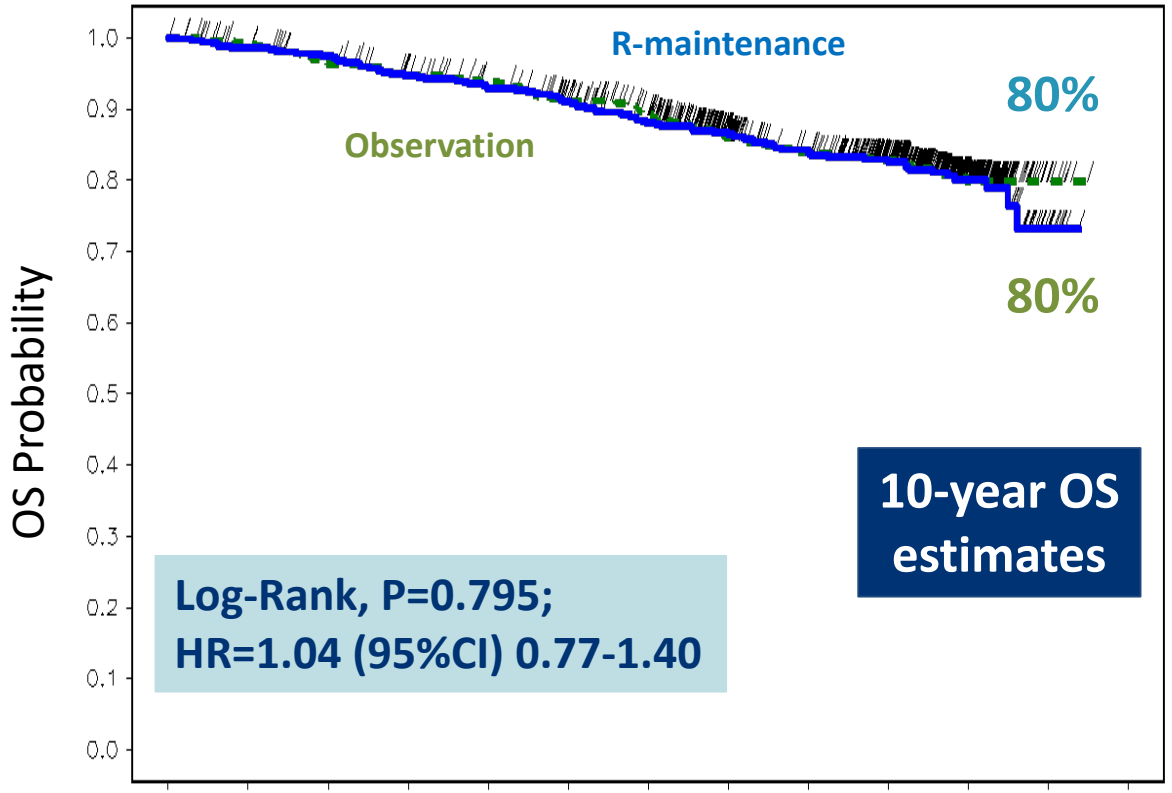


Shadman et al JCO 36:697, 2018

PRIMA : Progression Free Survival at 10 years (from randomization)



PRIMA : Overall Survival at 10 years (from randomization)

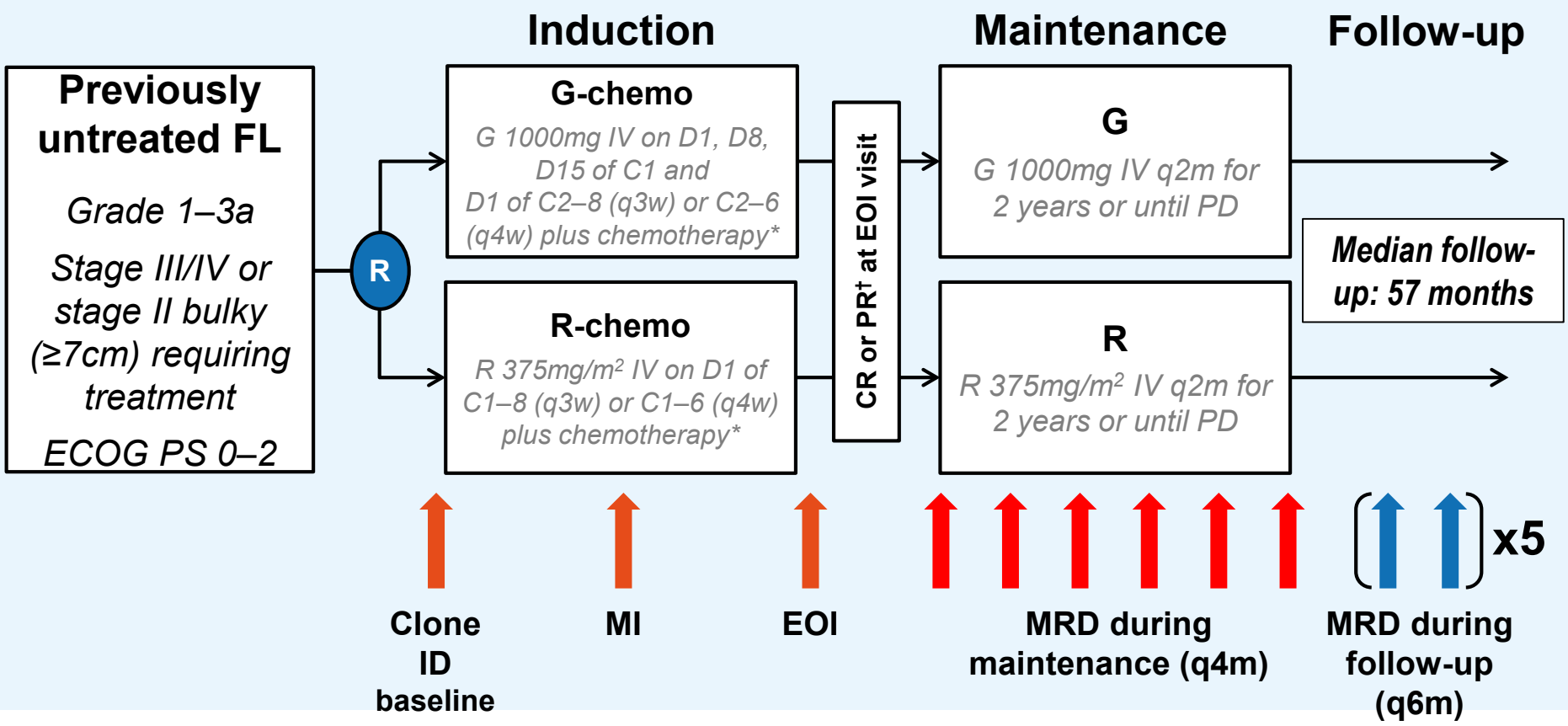


Final safety results

Safety Parameter	Observation N = 508	Rituximab Maintenance N = 501
Adverse events (includes Grade 3–5 toxicities, Grade 2–5 infections, and serious AEs)	194 (38%)	285 (57%)
Grade 3/4 adverse events	**86 (17%)**	**122 (24%) ***
Serious adverse events	**68 (13%)**	**106 (21%)**
Total deaths	83 (16%)	84 (17%)
Grade 5 AEs	3 (<1%)	8 (2%)

* Difference essentially represented by neutropenia and infections

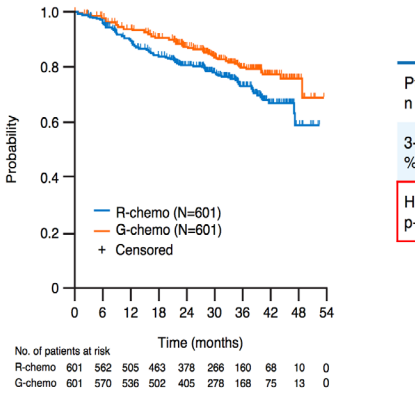
GALLIUM Study with MRD assessment



*CHOP, CVP, or bendamustine: choice was by site (FL); †Patients with SD at EOI were followed up for PD for up to 2 years.
C, cycle; CR, complete response; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CVP, cyclophosphamide, vincristine, prednisone; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; PD, disease progression; PR, partial response; q4m, every 4 months; q3w, every 3 weeks; SD, stable disease

GALLIUM Study: PFS and OS

INV-assessed PFS (FL; primary endpoint)



	R-chemo, n=601	G-chemo, n=601
Pts with event, n (%)	144 (24.0)	101 (16.8)
3-yr PFS, % (95% CI)	73.3 (68.8, 77.2)	80.0 (75.9, 83.6)
HR (95% CI), p-value*	0.66 (0.51, 0.85), p=0.0012	

Median follow-up: 34.5 months

*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

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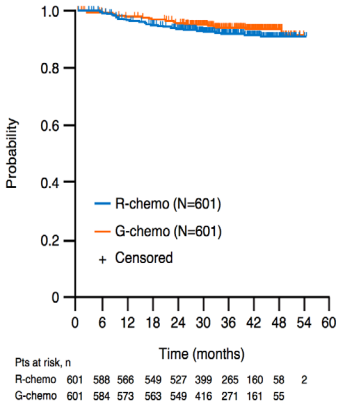
OS (FL)



	R-chemo, n=601	G-chemo, n=601
Pts with event, n (%)	46 (7.7)	35 (5.8)
3-yr OS, % (95% CI)	92.1 (89.5, 94.1)	94.0 (91.6, 95.7)
HR (95% CI), p-value*	0.75 (0.49, 1.17), p=0.21	

Median follow-up: 34.5 months

*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

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Marcus et al, NEJM 377:1331, 2017

GALLIUM Safety Data

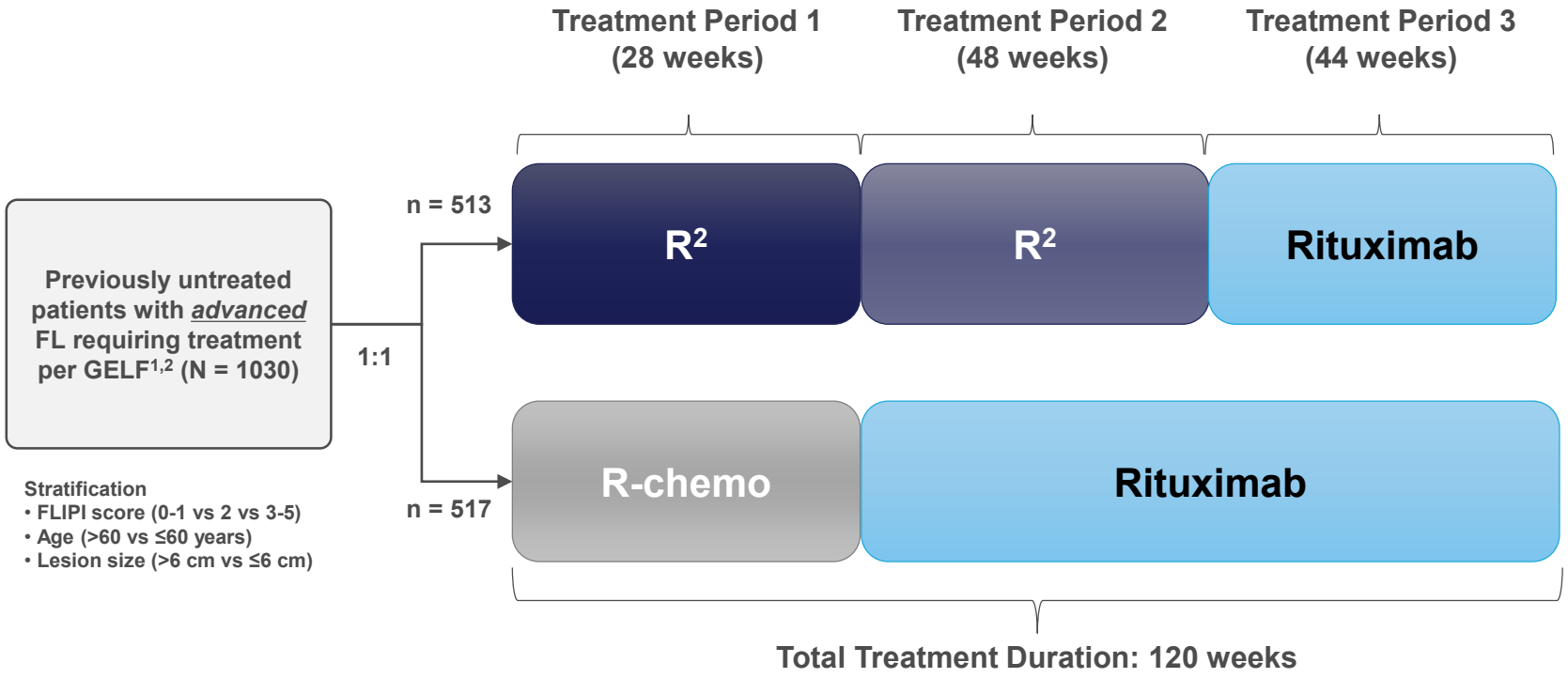
Safety summary (FL)

% (n)	R-chemo (n=597)	G-chemo (n=595)
Any AE	98.3% (587)	99.5% (592)
Grade ≥3 AEs (≥5% in either arm)	67.8% (405)	74.6% (444)
Neutropenia	37.9% (226)	43.9% (261)
Leucopenia	8.4% (50)	8.6% (51)
Febrile neutropenia	4.9% (29)	6.9% (41)
IRRs*	3.7% (22)	6.7% (40)
Thrombocytopenia	2.7% (16)	6.1% (36)
Grade ≥3 AEs of special interest by category (selected)		
Infections†	15.6% (93)	20.0% (119)
IRRs‡	6.7% (40)	12.4% (74)
Second neoplasms§	2.7% (16)	4.7% (28)
SAEs	39.9% (238)	46.1% (274)
AEs causing treatment discontinuation	14.2% (85)	16.3% (97)
Grade 5 (fatal) AEs	3.4% (20)	4.0% (24)**
Median (range) change from baseline in IgG levels at end of induction, g/l¶	-1.46 (-16.4–9.1)††	-1.50 (-22.3–6.5)‡‡

*As MedDRA preferred term; †All events in MedDRA System Organ Class 'Infections and Infestations'; ‡Any AE occurring during or within 24h of infusion of G or R and considered drug-related; §Standardized MedDRA query for malignant or unspecified tumors starting 6 mo after treatment start; ¶Ig levels were measured during screening, at EOI and end of maintenance and during follow-up; **Includes patient who died after clinical cut-off date from AE starting before cut-off date; ††n=472; ‡‡n=462

Marcus et al, NEJM 377:1331, 2017

RELEVANCE: STUDY DESIGN



Co-primary endpoints per 1999 IWG criteria*

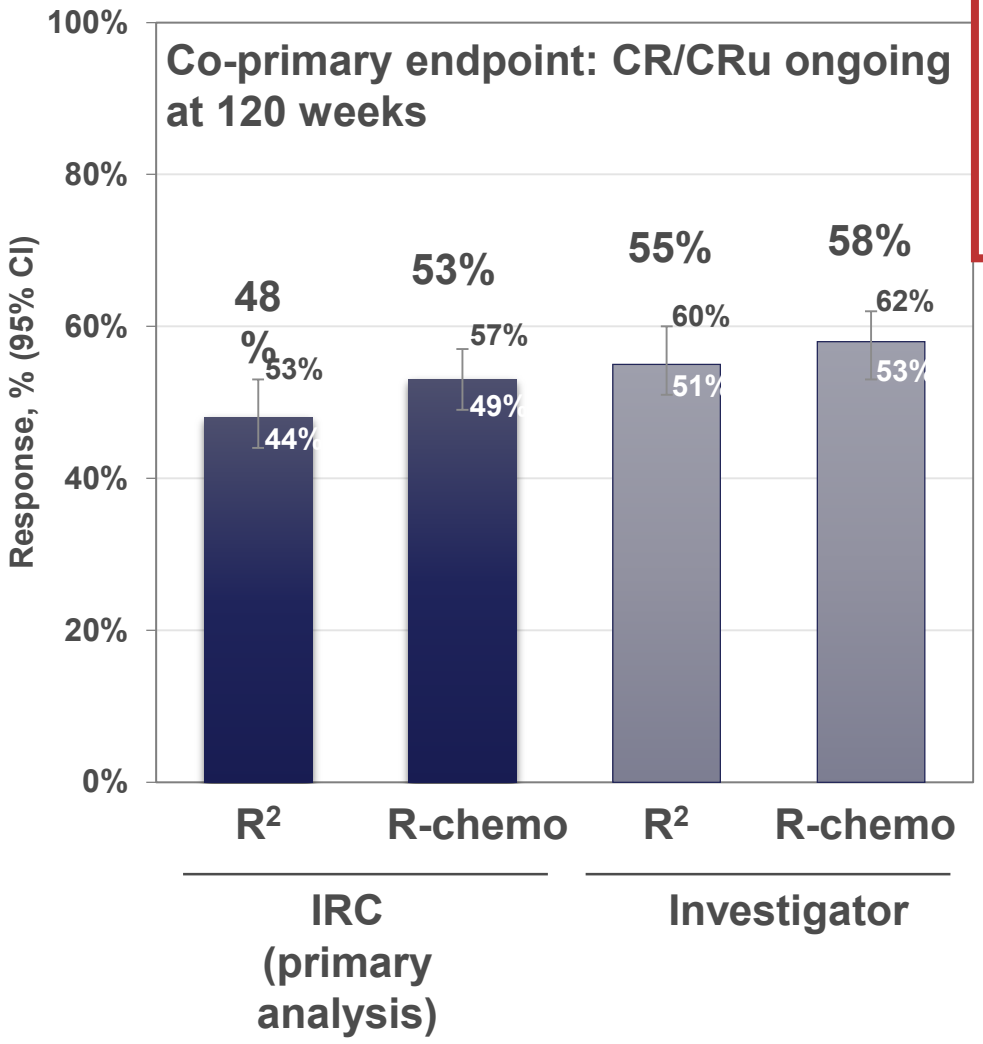
- CR/CRu at 120 weeks
- PFS (first interim analysis at ~50% of targeted events)

Dosing schedule

- **R²:** Lenalidomide 20 mg/d, d2-22/28 until CR/CRu at 6, 9, or 12 cycles, then 10 mg/d (total 18 cycles) and rituximab 375 mg/m²/wk c1 and d1 c2-6; continued in responders q8wk for 12 cycles
- **R-chemo:** 3 options (R-CHOP, R-B, R-CVP) plus 2 years rituximab maintenance
  - Included 72% R-CHOP, 23% R-B, and 5% R-CVP

NCT01476787; NCT01650701; EUDRA 2011-002792-42. *Per central (IRC) review by 1999 IWG with CT.
1. Salles et al. *Lancet.* 2011;377:42-51. 2. Brice et al. *J Clin Oncol.* 1997;15:1110-1117.

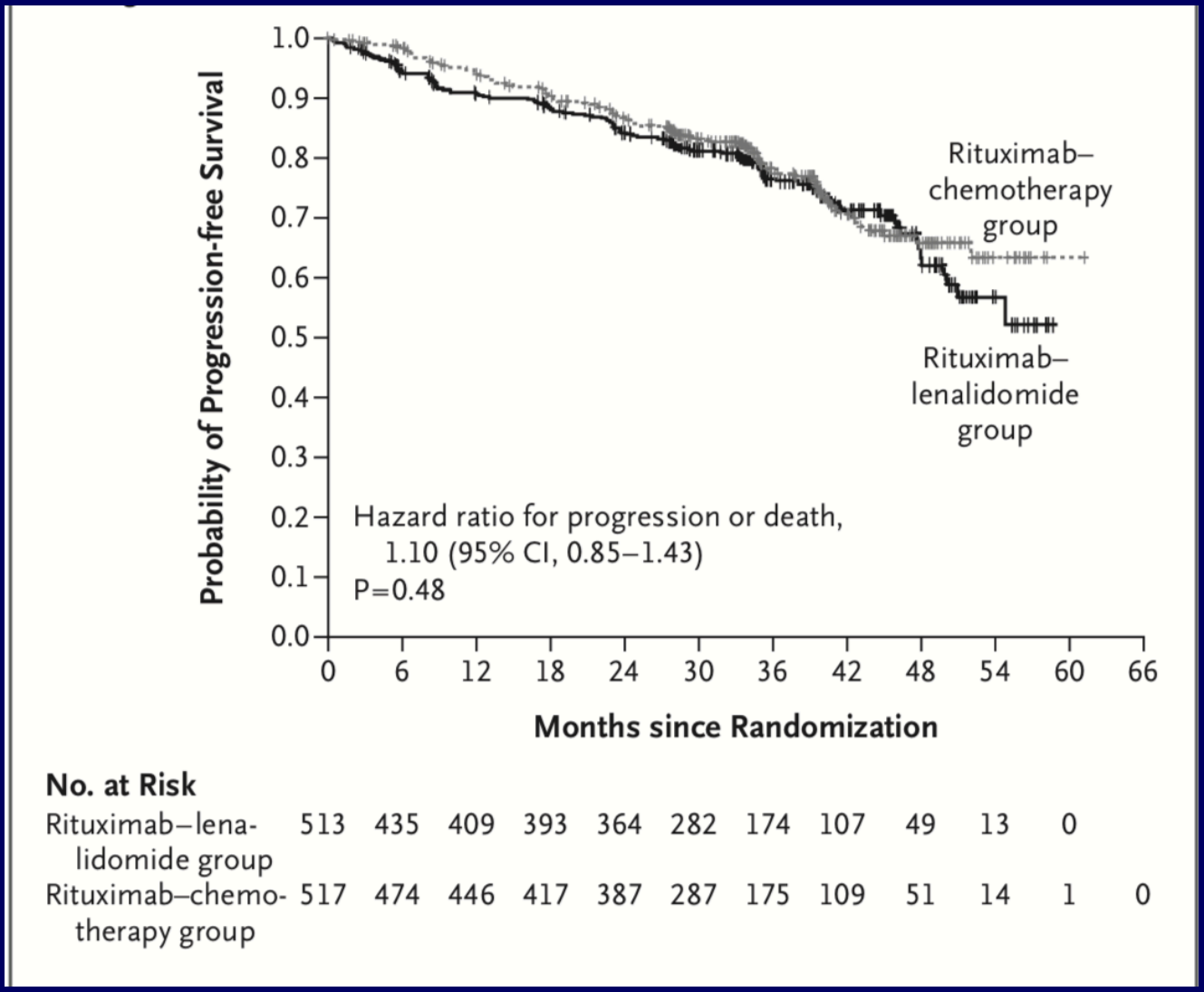
RELEVANCE: RESPONSE (ITT)



- Best overall response (CR+CRu+PR)
  - 84% R^2 vs 89% R-chemo (IRC)
  - 86% R^2 vs 92% R-chemo (investigator)
- SPD reduction of ≥ 50% at 12 weeks was 81% for R^2 and 90% for R-chemo
- ORR ongoing at 120 weeks
  - 61% R^2 vs 65% R-chemo (IRC)
  - 65% R^2 vs 68% R-chemo (investigator)
- Probability of maintaining response (CR/CRu/PR) for ≥ 3 years for R^2 vs R-chemo, respectively
  - 77% vs 74% (IRC)

Data cut-off 31May2017. SPD, sum of the products of the diameters.

RELEVANCE - PFS

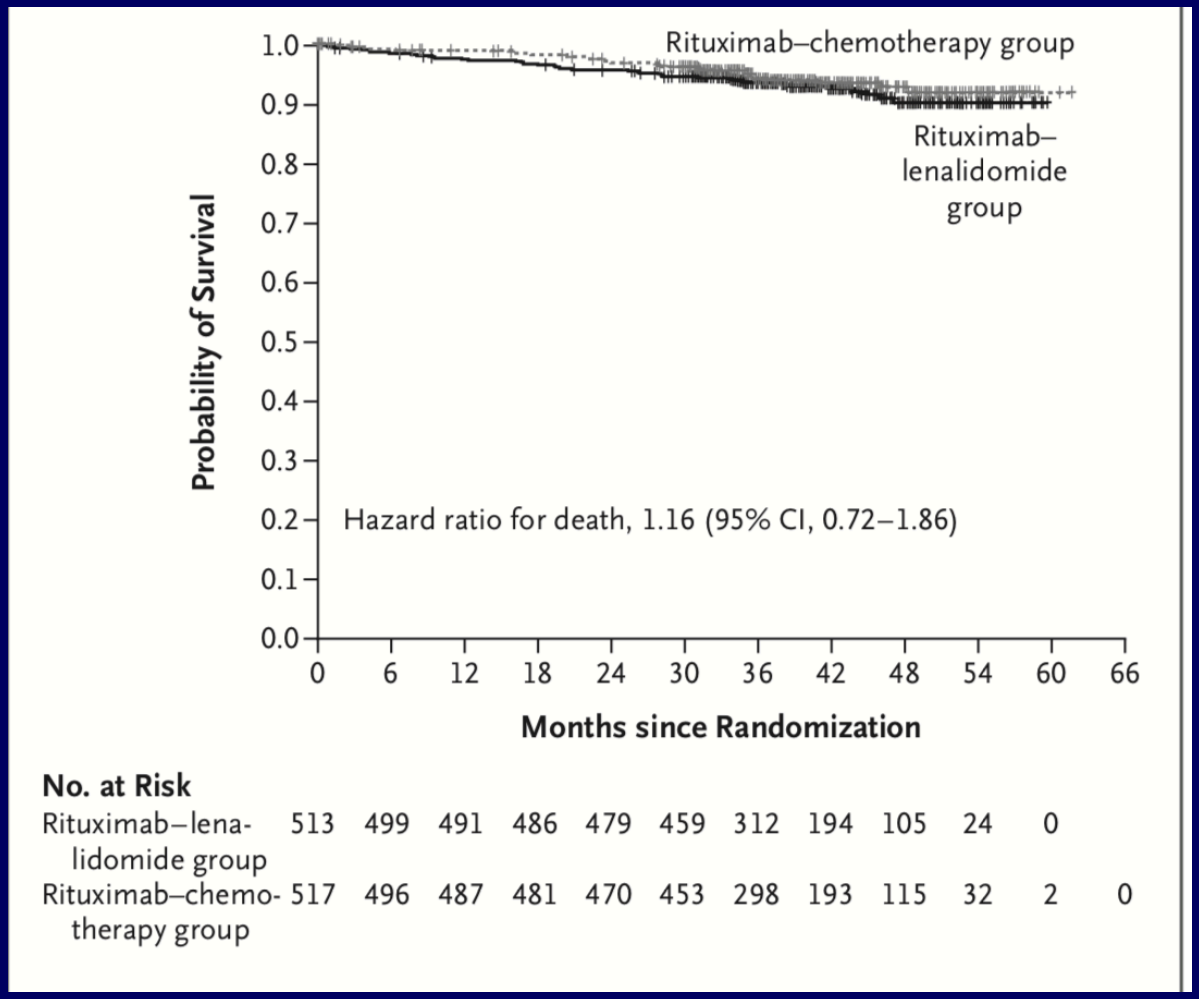


No. at Risk

Rituximab–lenalidomide group	513	435	409	393	364	282	174	107	49	13	0	
Rituximab–chemotherapy group	517	474	446	417	387	287	175	109	51	14	1	0

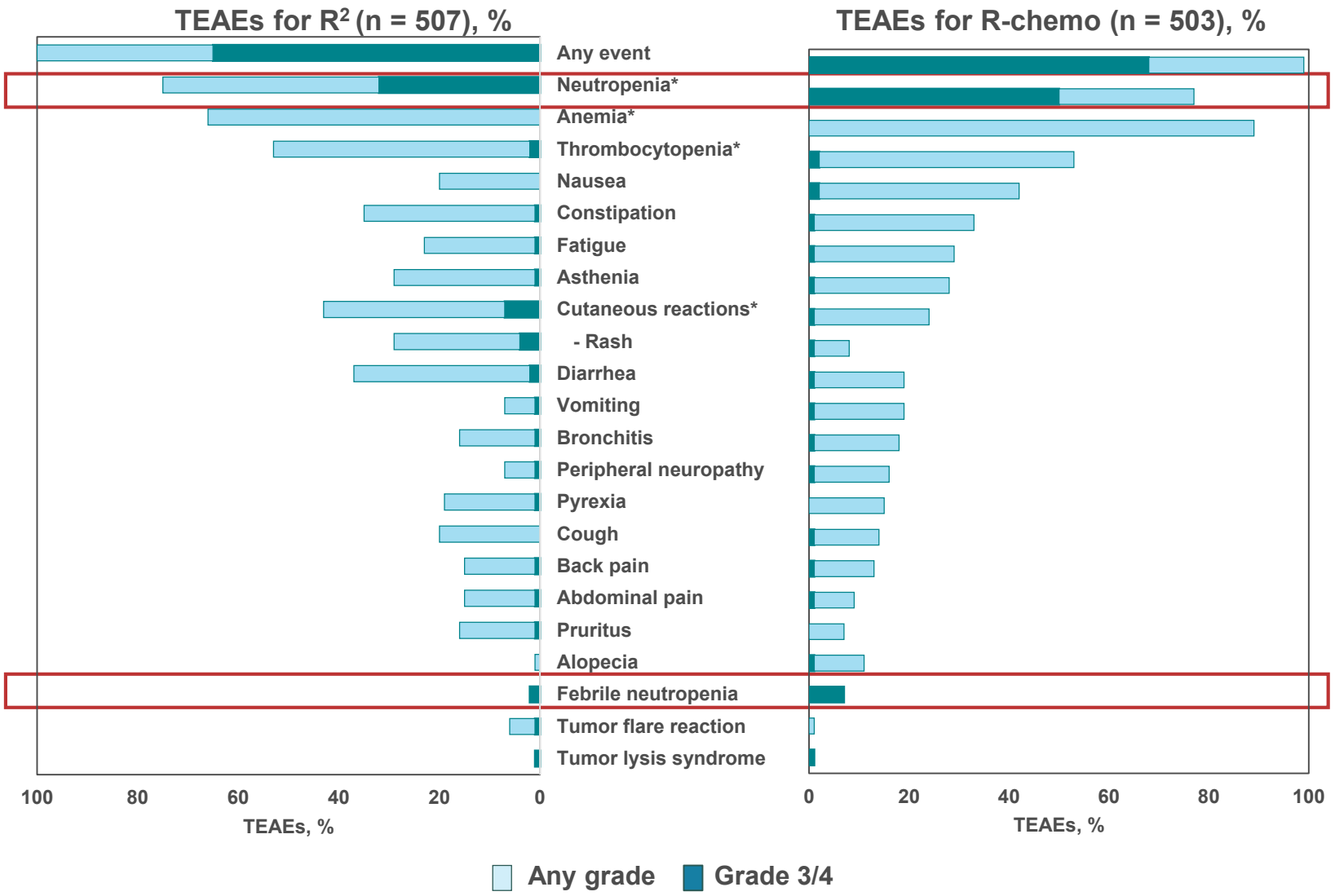
Morschhauser et al, NEJM 379:934, 2018

RELEVANCE-OS



Morschhauser et al, NEJM 379:934, 2018

RELEVANCE: TREATMENT-EMERGENT ADVERSE EVENTS



Data cut-off 31May2017. Includes any-grade TEAEs (≥15%) and select AEs of interest as assessed per NCI CTCAE v4.03.
*Hematologic AEs were based on laboratory tests; all anemia events were grade 1. *Cutaneous reactions included preferred terms from skin and subcutaneous tissue disorders (including rash), gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, and reproductive system and breast disorders.

FL Response Rates for Approved and Emerging Single-Agent PI3K Inhibitors*

	Copanlisib[1–3]	Idelalisib[4,5]	Duvelisib[6–8]	Buparlisib[9,a]	Umbralisib (TGR1202)[10–13]
Current indication(s)	3rd-line FL	3rd-line FL; 3rd-line SLL; 2nd-line CLL	N/A	N/A	N/A
Future indication(s)	2nd-line NHL	2nd-line CLL	2nd-line CLL; 3rd-line FL; 2nd-line PTCL	2nd-line FL, MCL, DLBCL	CLL; ≥2nd-line NHL
MoA	PI3Ki (α,δ)	PI3Ki (δ)	PI3Ki (δ,γ)	Pan-PI3Ki	PI3Ki (δ), cMyc
Administration	IV	Oral	Oral	Oral	Oral
Dosing schedule	60 mg Day 1, 8, 15 (28-day cycle)	150 mg, twice daily	25 mg, twice daily	Once daily	Once daily
Study population	≥3rd line[b] (FL, n=104)	≥3rd line[b] (FL, n=72)	≥3rd line[b] (FL, n=83)	≥2nd line (FL, n=5)	≥2nd line (FL, n=12)
ORR (FL)	59%	54%	41%	25%	53%
PFS (FL)	11.2 months	11 months	8.3 months	NR	16
CR (FL)	14%	8%	1.2%	NR	12

*. Cheson et al Clin Leuk Lymph Myeloma, e-pub, on line, 2019

Warnings and Grade ≥3 AEs for Approved and Emerging PI3K Inhibitors for Indolent NHL*

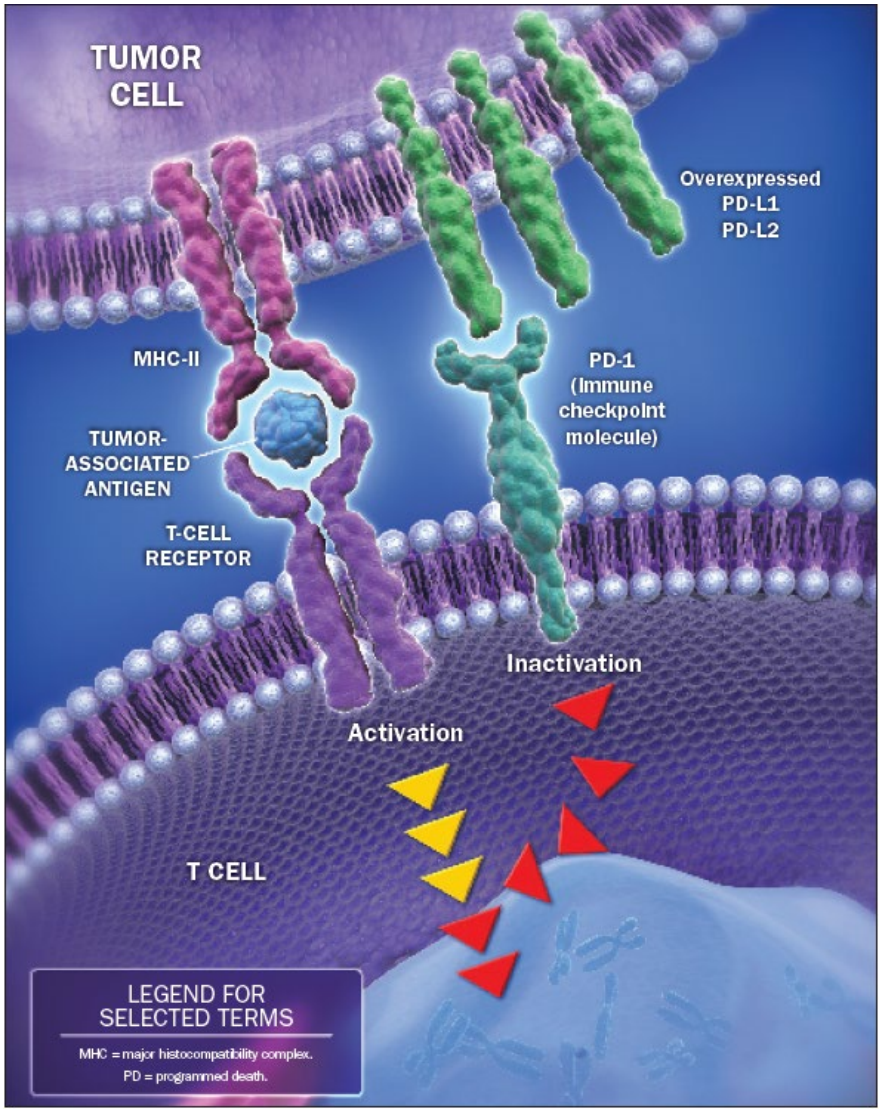
	Copanlisib[1,2]	Idelalisib[3]	Duvelisib[5]	Buparlisib[6,a]	Umbralisib (TGR1202)[4]
Black box warning	None	Fatal and/or serious toxicities: • Hepatotoxicity (11–18%) • Severe diarrhea or colitis (14–19%) • Pneumonitis (4%) • Infections (21–36%) • Intestinal perforation	N/A	N/A	N/A
Grade ≥3 AEs (in FL patients unless otherwise noted)[b]					
Hyperglycemia	41% (infusion-related)	N/A	N/A	52%	N/A
Hypertension	26% (infusion-related)	N/A	N/A	<10%	N/A
Pneumonitis	1%	16%[d]	2%	N/A	<1.5%[a]
Lung infection	16%		9%[e]	N/A	5%[e]
Diarrhea	5%	14%	15%	65%	3%
Colitis	1%[c]		5%	<10%	<1.5%[a]
ALT increased	1.4%	18%	6%	>10%	3%
AST increased	1.4%	12%	N/A	>10%	3%

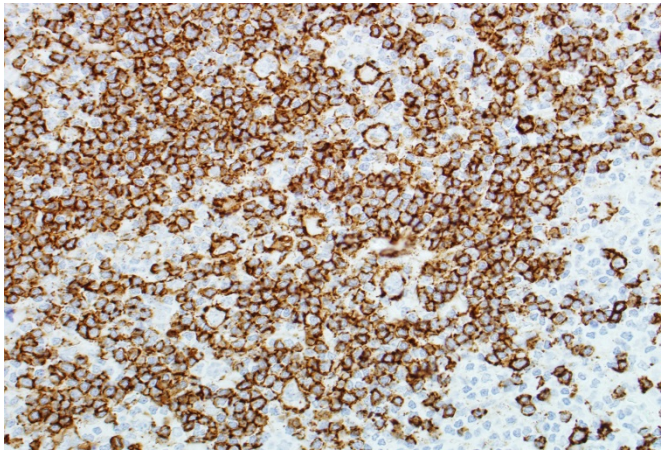
Cheson et al Clin Leuk Lymph Myeloma, e-pub on line, 2019

Response Rates to Ibrutinib

- CLL/SLL – 91%
- WM – 90%
- MCL – 67%
- MZL – 48%
- *FL – 20.9%*

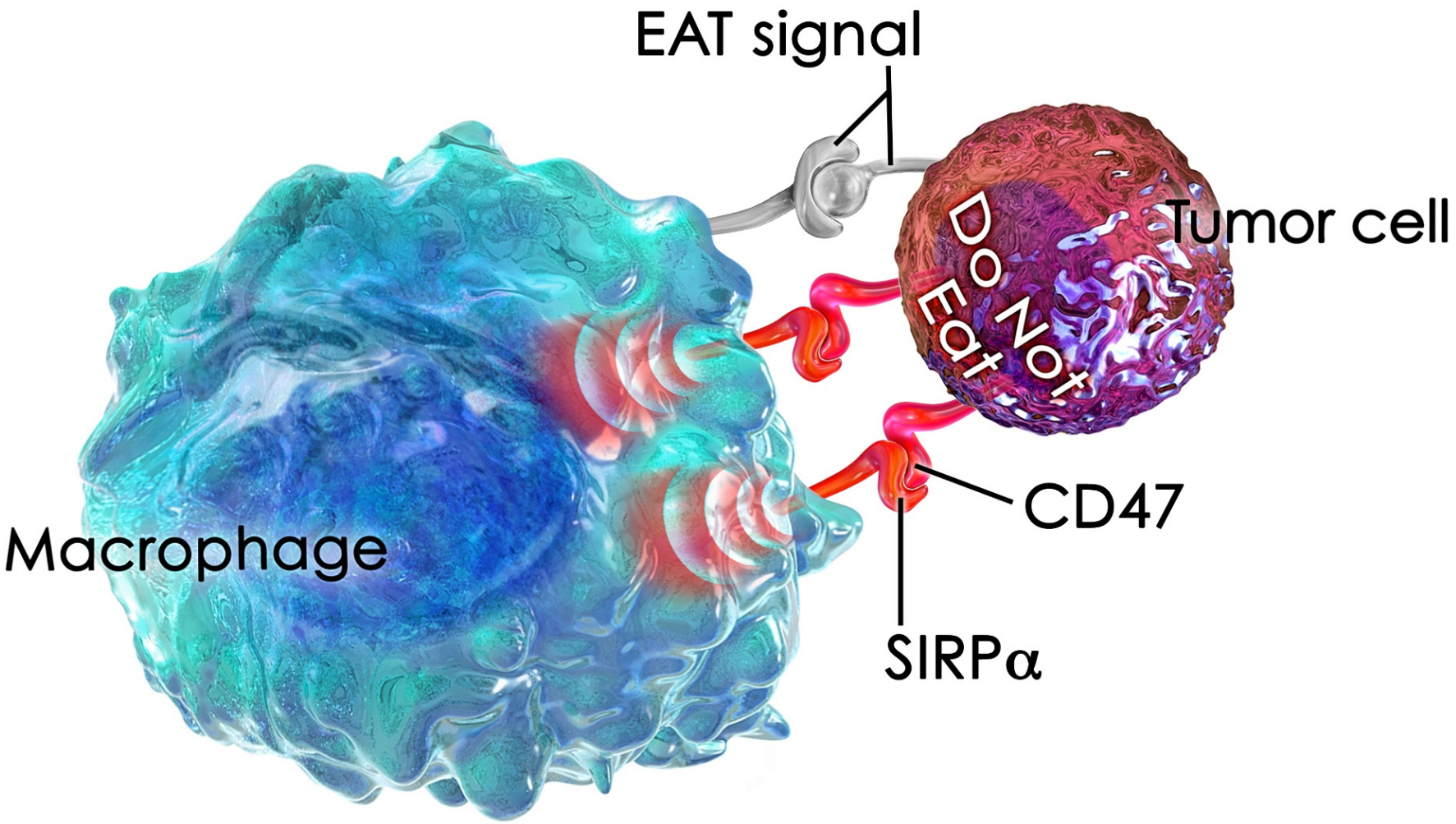
PD-1 Pathway and Immune Surveillance



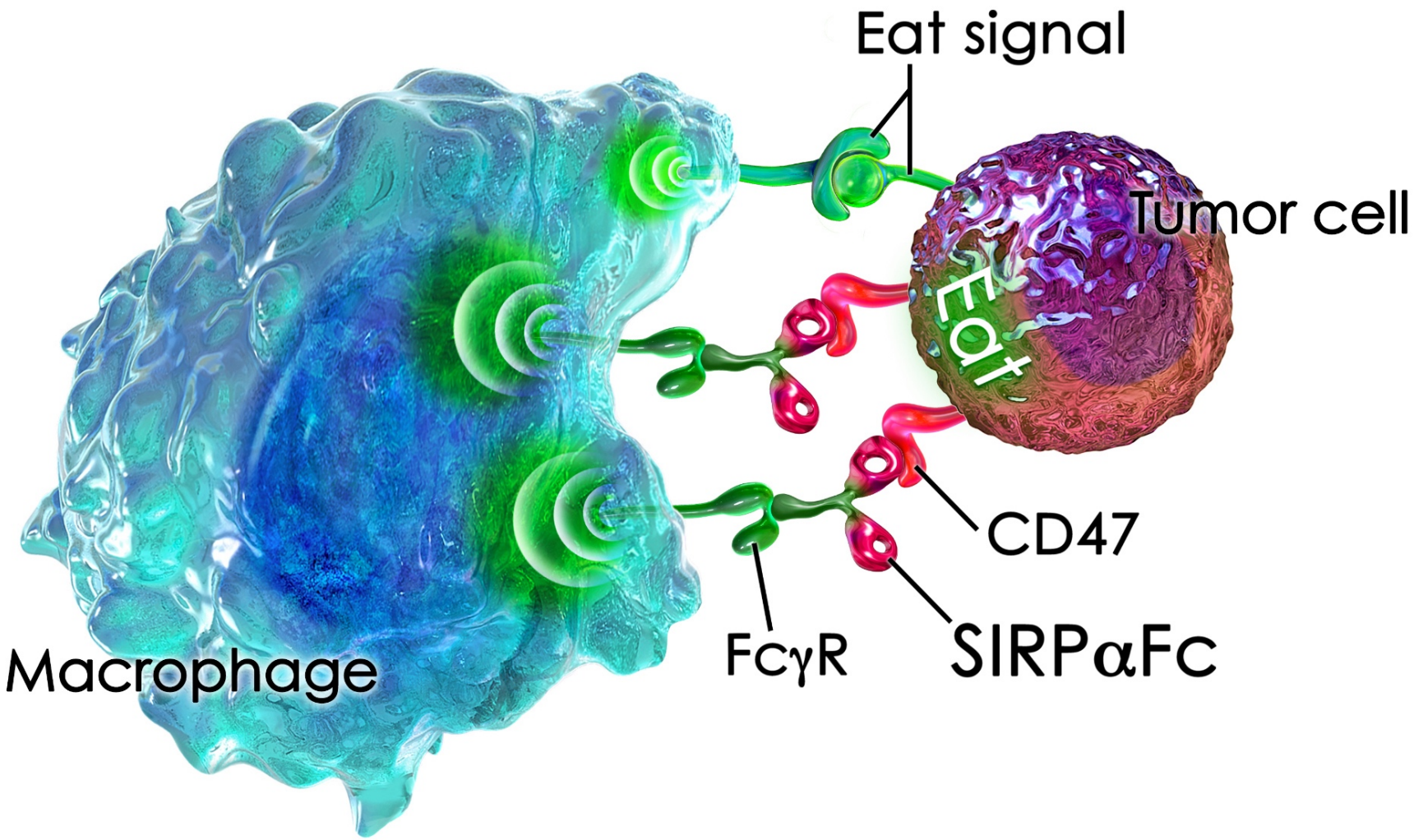


- PD-1 is expressed on the surface of activated T cells
- Its ligands, PD-L1 and PD-L2, are overexpressed in certain tumor cells
- Binding of PD-1 to its ligands inhibits T-cell activation, allowing tumors to evade the immune response

CD47 Inhibition of Phagocytosis



SIRPαFc Blockade of the CD47 Signal



Macrophage Phagocytosis

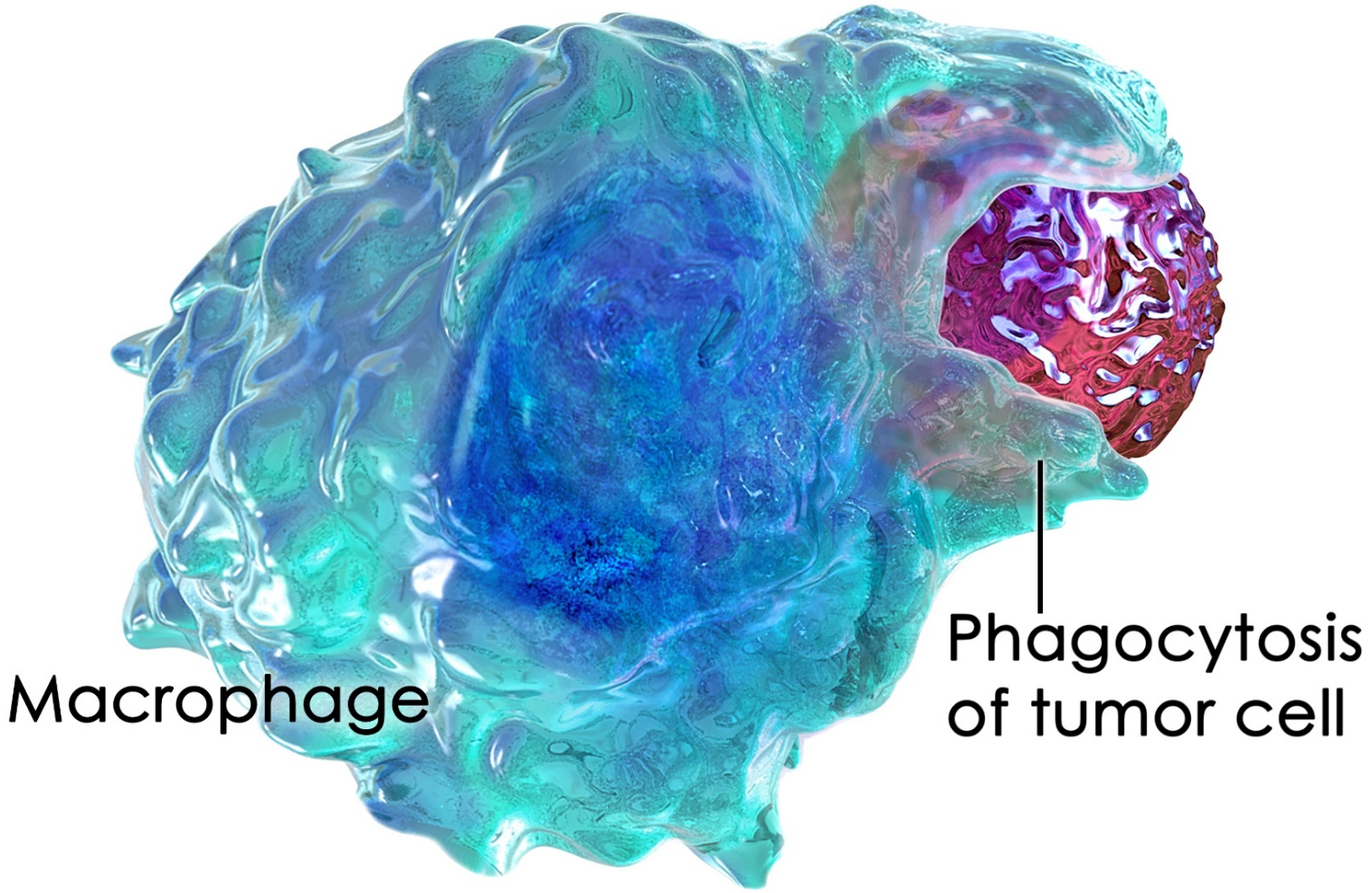


Table 2. Clinical Responses to Combination Therapy with 5F9 and Rituximab.*

Response	All Patients (N=22)	Patients with DLBCL (N=15)	Patients with Follicular Lymphoma (N=7)
Objective response	11 (50)	6 (40)	5 (71)
Complete response	8 (36)	5 (33)	3 (43)
Partial response	3 (14)	1 (7)	2 (29)
Stable disease	3 (14)	3 (20)	0
Progressive disease	8 (36)	6 (40)	2 (29)
Disease control	14 (64)	9 (60)	5 (71)

Advani et al NEJM 379:1711, 2018

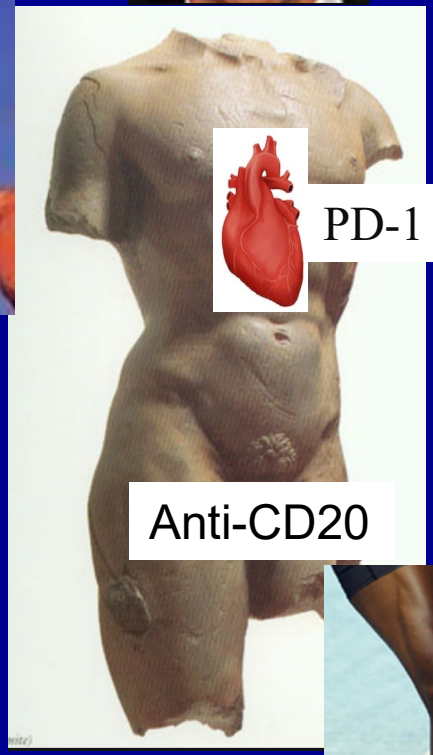
New Targeted Agents for NHL

Agent	Target
Obinutuzumab/Ublituximab	CD20
Polatuzumab vedotin Blinatumomab	CD79b CD3/CD19
MOR-208	CD19
Ibrutinib, Acalabrutinib	Btk
Idelalisib, Copanlisib, Umbralisib	PI3-K
Venetoclax (ABT-199) Tazemetostat	Bcl-2 EZH2
Selinexor	Nuclear transport
Lenalidomide	Multiple
Nivolumab/Pembrolizumab	PD-1
Atezolizumab	PDL-1
Anti-CD47	CD47

BTK

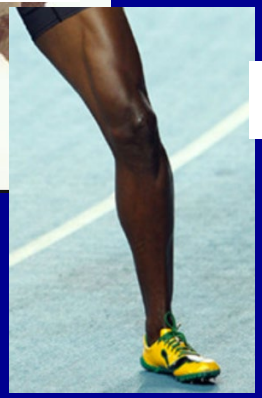
TBD

PI3K



PD-1

Anti-CD20



Bcl-2

Bruce D. Cheson, M.D.

The Frankenstein Principle

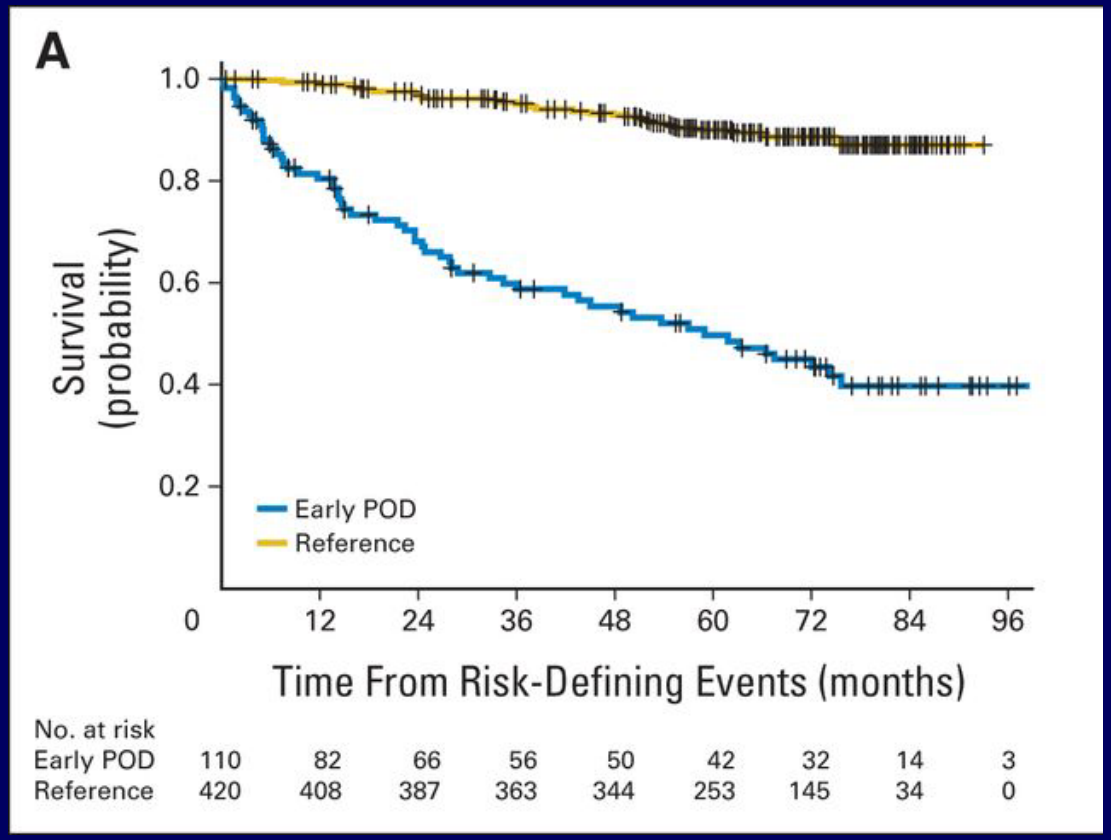
Duration of Recent Studies

Study	Start Year	Accrual Duration	Follow-up	First Publication
PRIMA	2004	24 mos	36 mos	2011
SOO16	2004	90 mos	4.9 yrs	2013
FOLLO5	2006	46 mos	12 mos	2013
GALLIUM	2011	3 years	34.5 mos	2018

Surrogates to Predictors

- Maintain CR at 30 months (FLASH)
- Event within 2 years
- Event within 1 year
- PET following induction
- MRD
- M7-FLIPI
- GEP
- TMTV

OS from a risk-defining event after diagnosis in FL patients who received R-CHOP chemotherapy in the National LymphoCare Study group

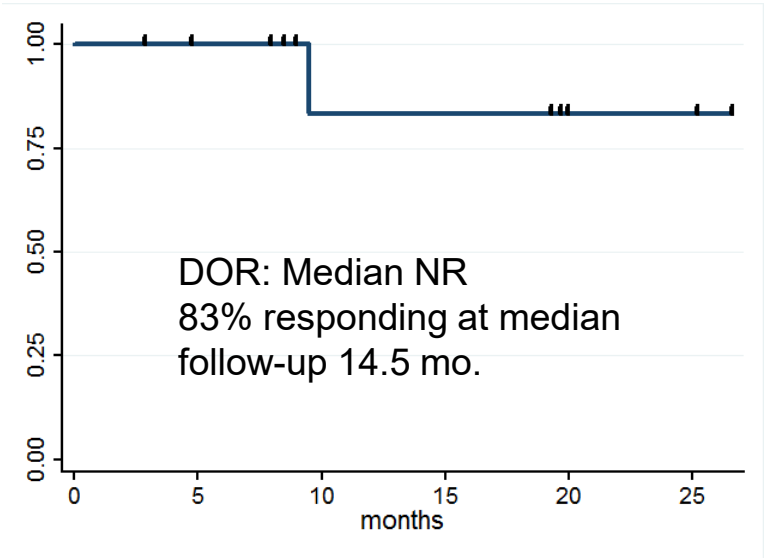


Carla Casulo et al. JCO 2015;33:2516-2522

CAR T-cell Efficacy in Follicular Lymphoma (CTL019)

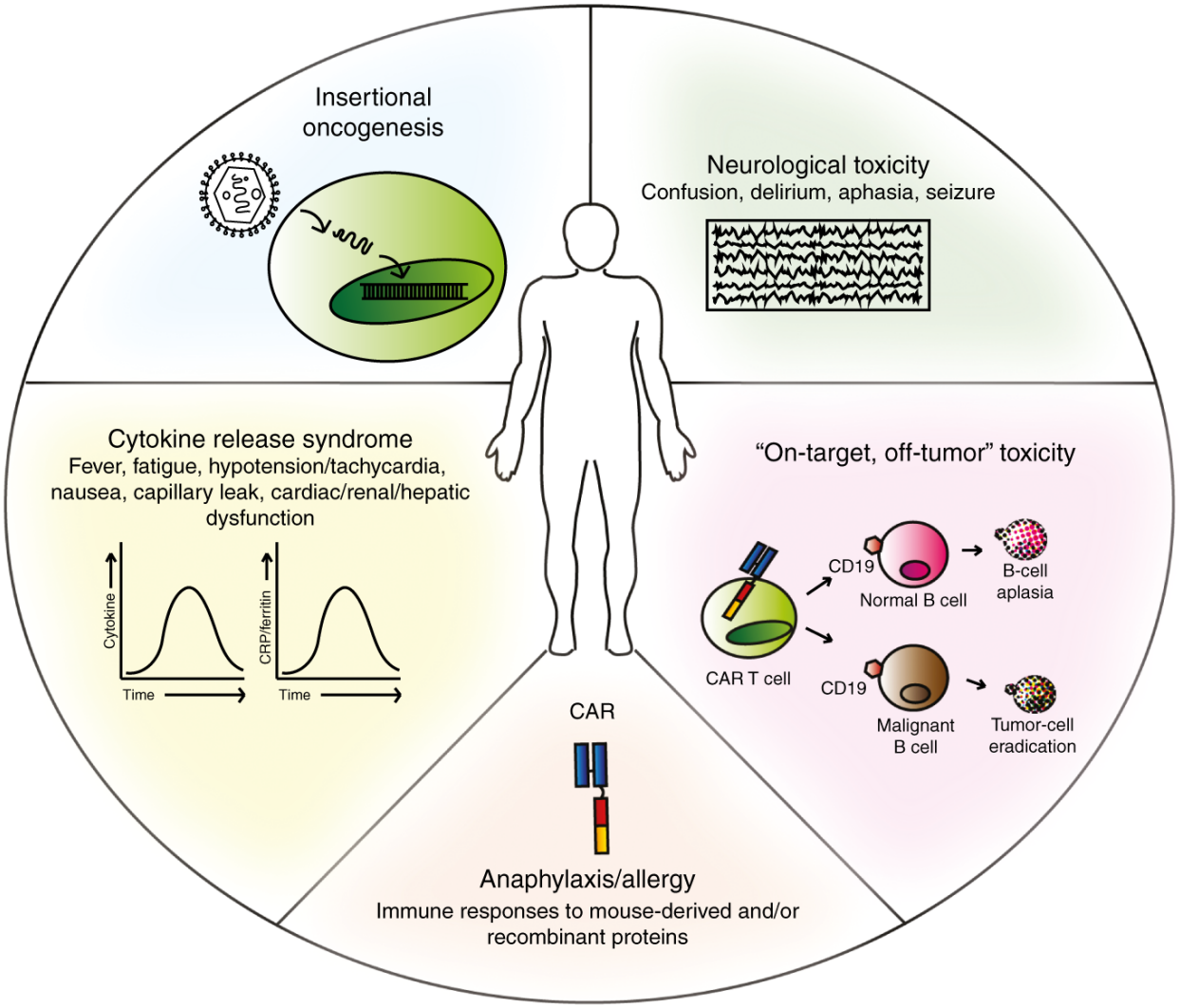
Response at 3 mo. (N = 14)	Best Response (N = 14)
ORR: 79%	ORR: 79%
CR: 7 (50%)	CR: 10 (71%)
PR: 4	PR: 1
PD: 4	PD: 3

Duration of Response (n = 11; CR + PR)



Chong EA, et al. *Blood*. 2016;128: abstract 1100.

Toxicities of chimeric antigen receptor (CAR) T-cell therapy

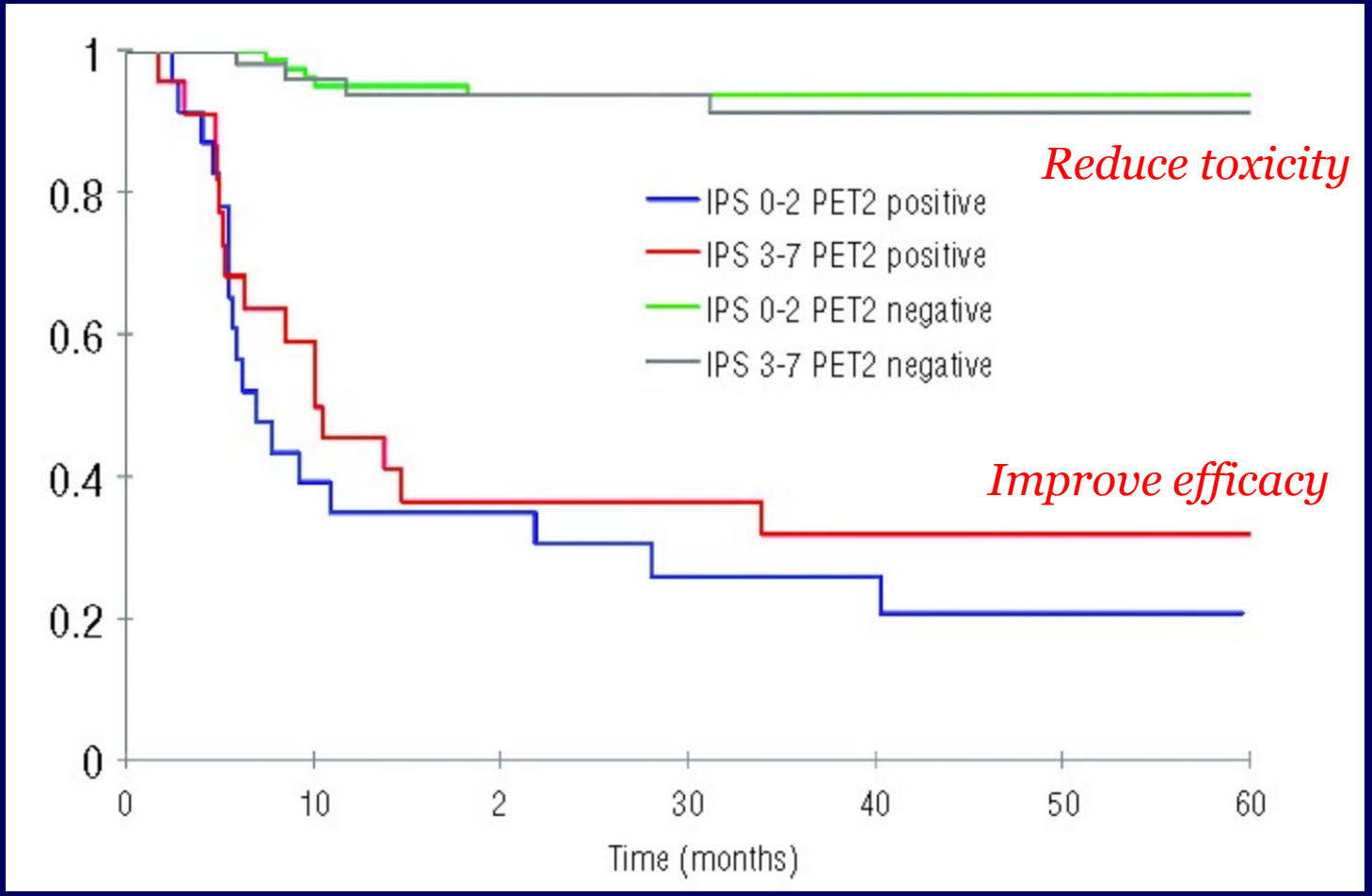


Bonifant et al. Molecular Therapy — Oncolytics 3: 16011 (2016)

CONCLUSIONS

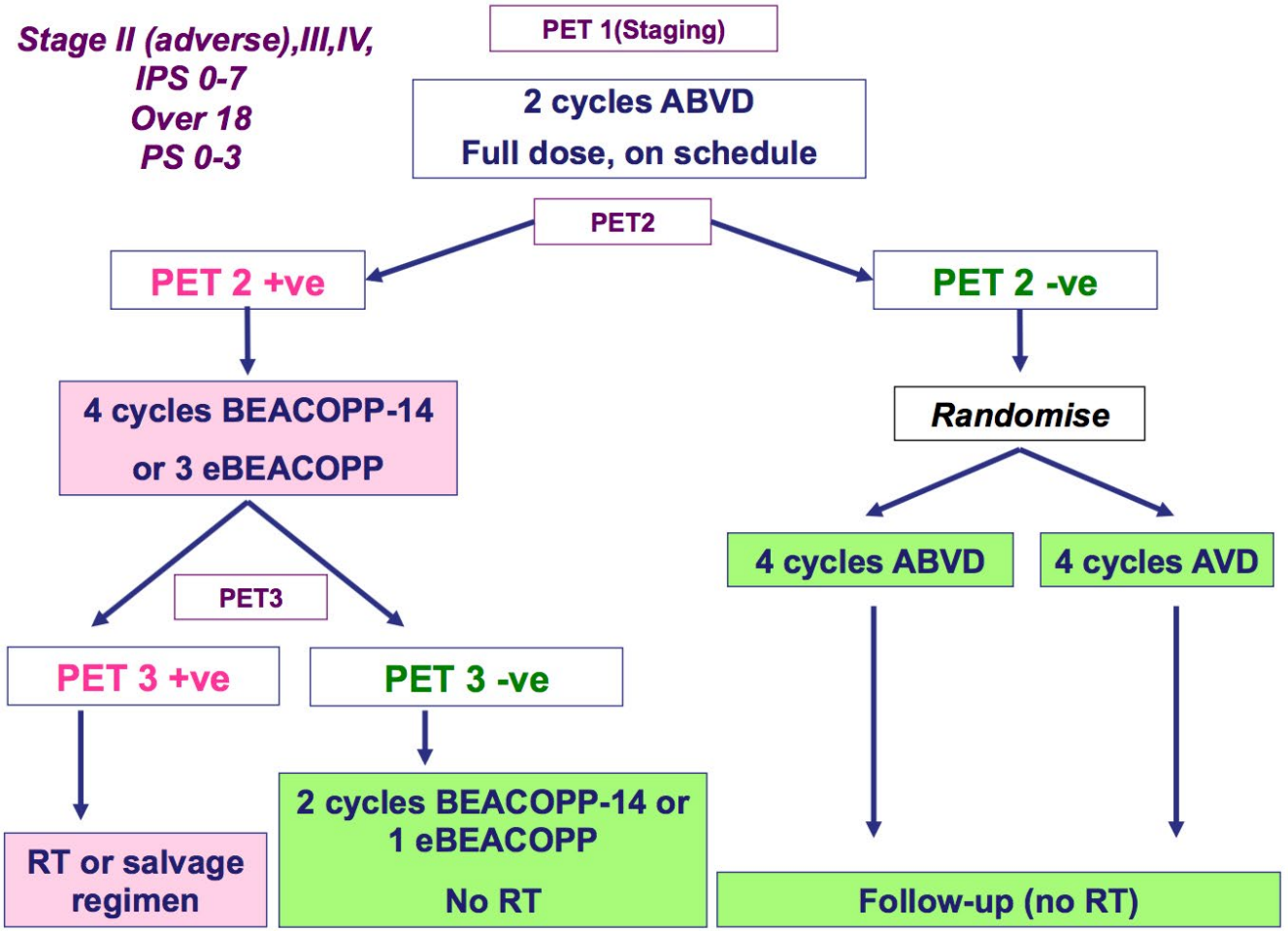
- Significant unmet needs in FL and other iNHL
- Chemo-free *does not* have to be ***more*** effective than chemo to replace it
- Single non-chemo agents are not sufficient
- Need to carefully develop rational combinations
- Precision medicine with NGS/biomarkers for response/resistance/toxicity
- Chemo will be relegated to historical interest
- Focus on front-line, not cleaning up failures
- Chemo-free will eventually lead to ***cure***

Interim PET in HL Using the Deauville 5-PS



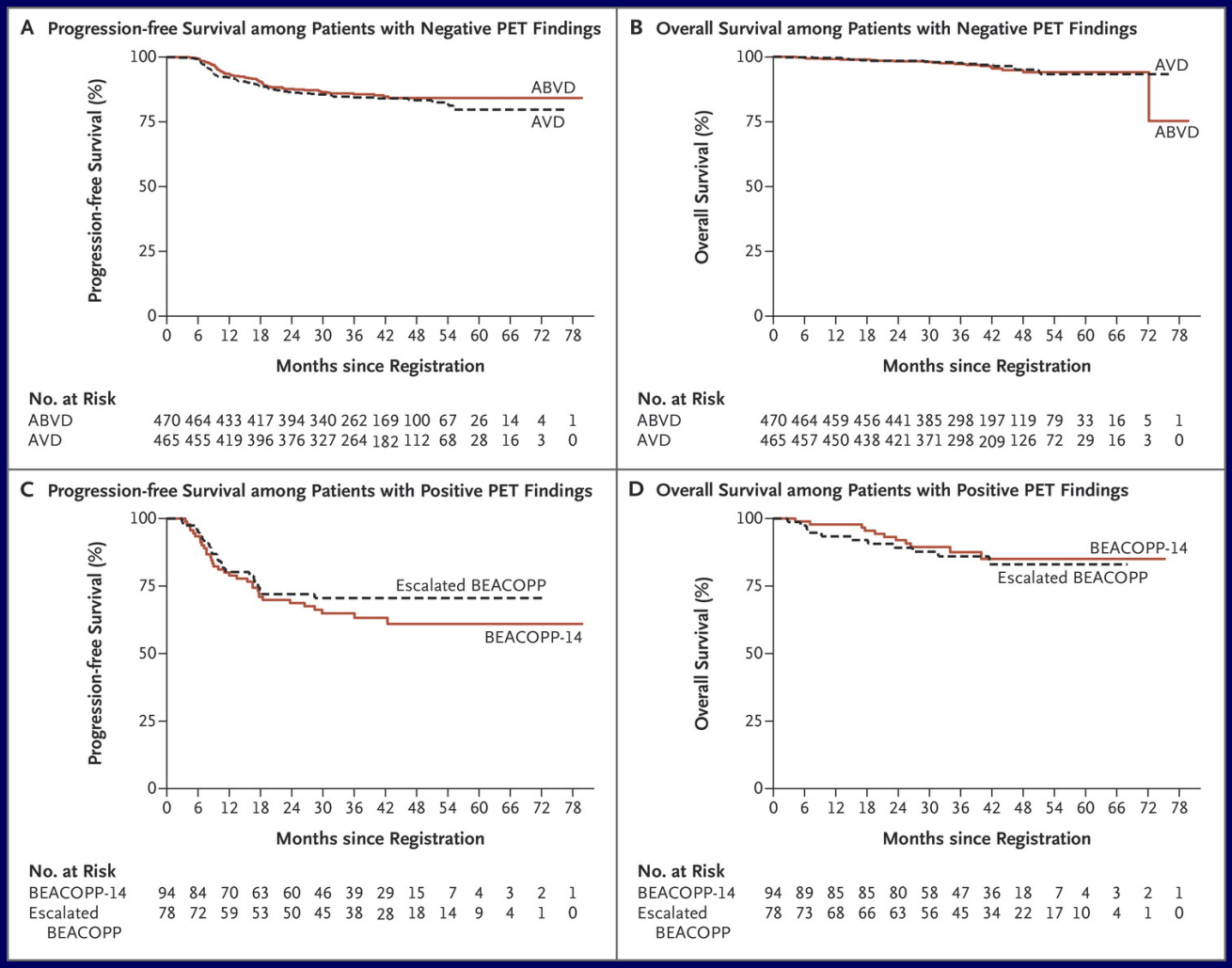
Gallamini, et al, Haematologica 99:1107, 2014

RATHL: Schema



Johnson et al, NEJM 374:2419, 2016

Progression-free and Overall Survival.



Johnson P et al. N Engl J Med 2016;374:2419-2429.

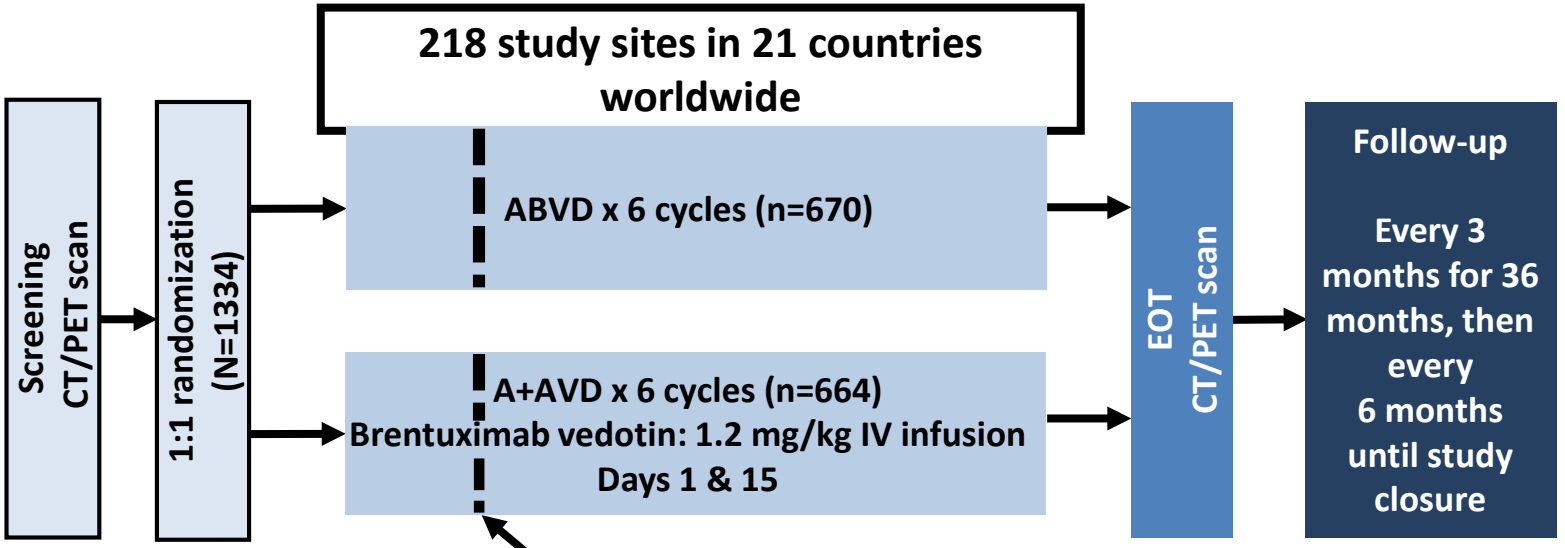
Toxicity of therapy: ABVD vs AVD

% of patients experiencing grade 3-4 events

	ABVD cycles 1-2	ABVD cycles 3-6	AVD cycles 3-6	P-value
Neutropenia	57.3	58.4	57.5	0.78
Thrombocytopenia	1.3	1.3	3.2	0.045
Neutropenic fever	2.1	4.7	2.2	0.032
Infection	6.3	14.5	10.1	0.040
Thrombo-embolism	1.4	4.9	2.6	0.061
Respiratory AEs	0.7	3.6	0.6	0.002
Any non-haematological toxicity	16	31	21	<0.001

Johnson et al NEJM 374:2419, 2016

ECHELON-1: Open-label, global, randomized, phase 3 study of A+AVD versus ABVD in patients with newly diagnosed advanced cHL

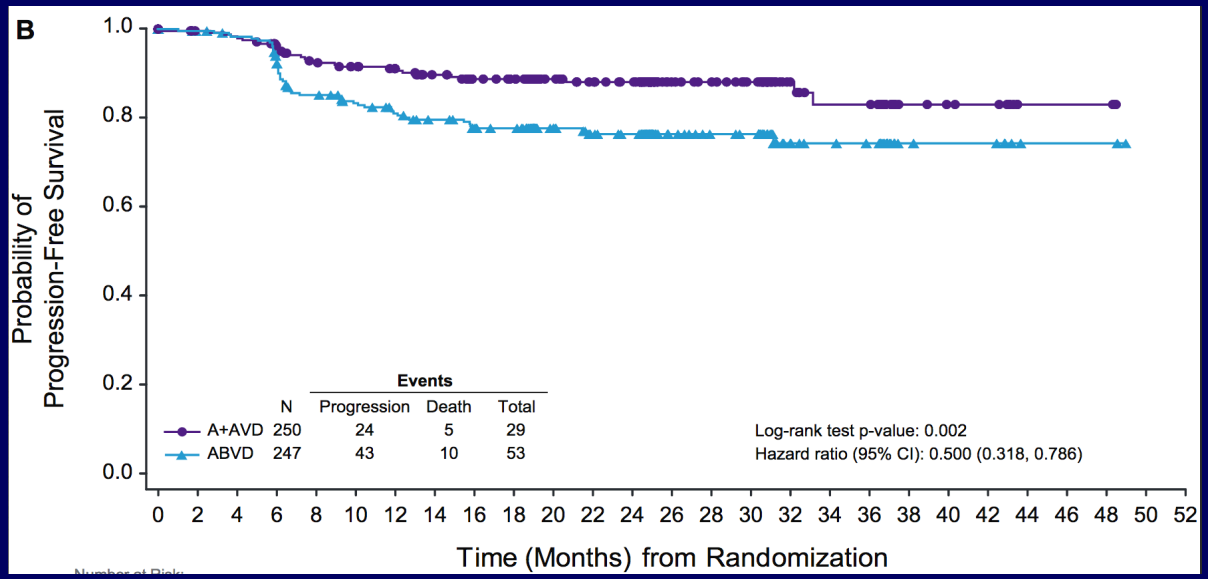


- **Inclusion criteria**
  - cHL stage — III or IV
  - ECOG PS — 0, 1 or 2
  - Age — ≥18 years
  - Measurable disease
  - Adequate liver and renal function

cHL, classic Hodgkin lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end-of-treatment; PFS, progression-free survival

Connors et al, NEJM 378:331, 2018

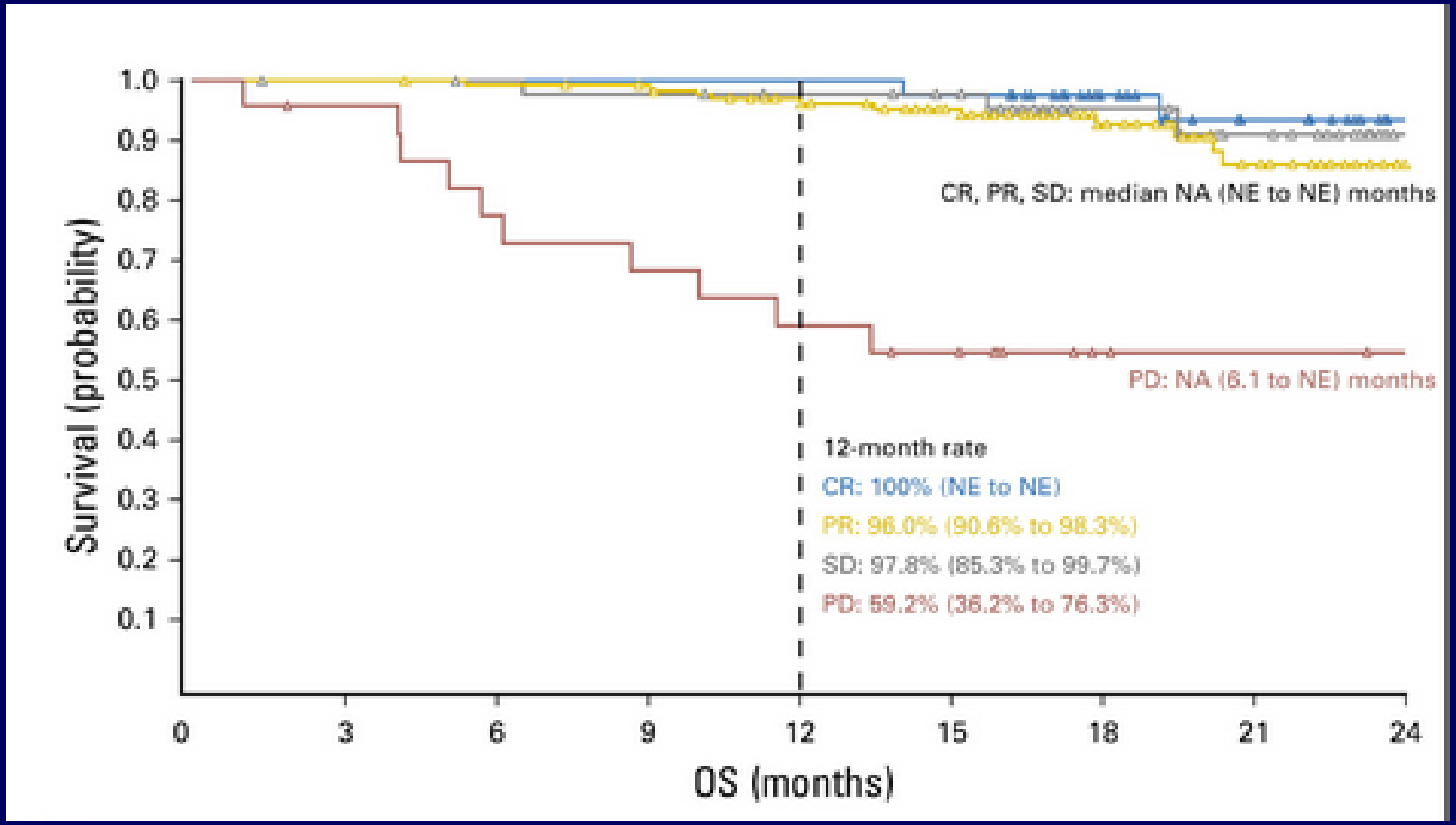
ECHELON-1 in US



Adverse event category, n (%)	A+AVD (N=249)	ABVD (N=240)
Neutropenia[a]		
Incidence of neutropenia (any grade)	154 (62)	130 (54)
Grade 3 or higher neutropenia	146 (59)	109 (45)
Incidence of febrile neutropenia[b]	51 (20)	22 (9)
Peripheral neuropathy[c]		
Incidence of peripheral neuropathy (any grade)	198 (80)	134 (56)
Grade 1 peripheral neuropathy	102 (41)	104 (43)
Grade 2 peripheral neuropathy	53 (21)	28 (12)
Grade 3 peripheral neuropathy	43 (17)	2 (<1)
Pulmonary toxicity[d]		
Incidence of pulmonary toxicity (any grade)	7 (3)	25 (10)
Grade 3 or higher pulmonary toxicity	4 (2)	14 (6)

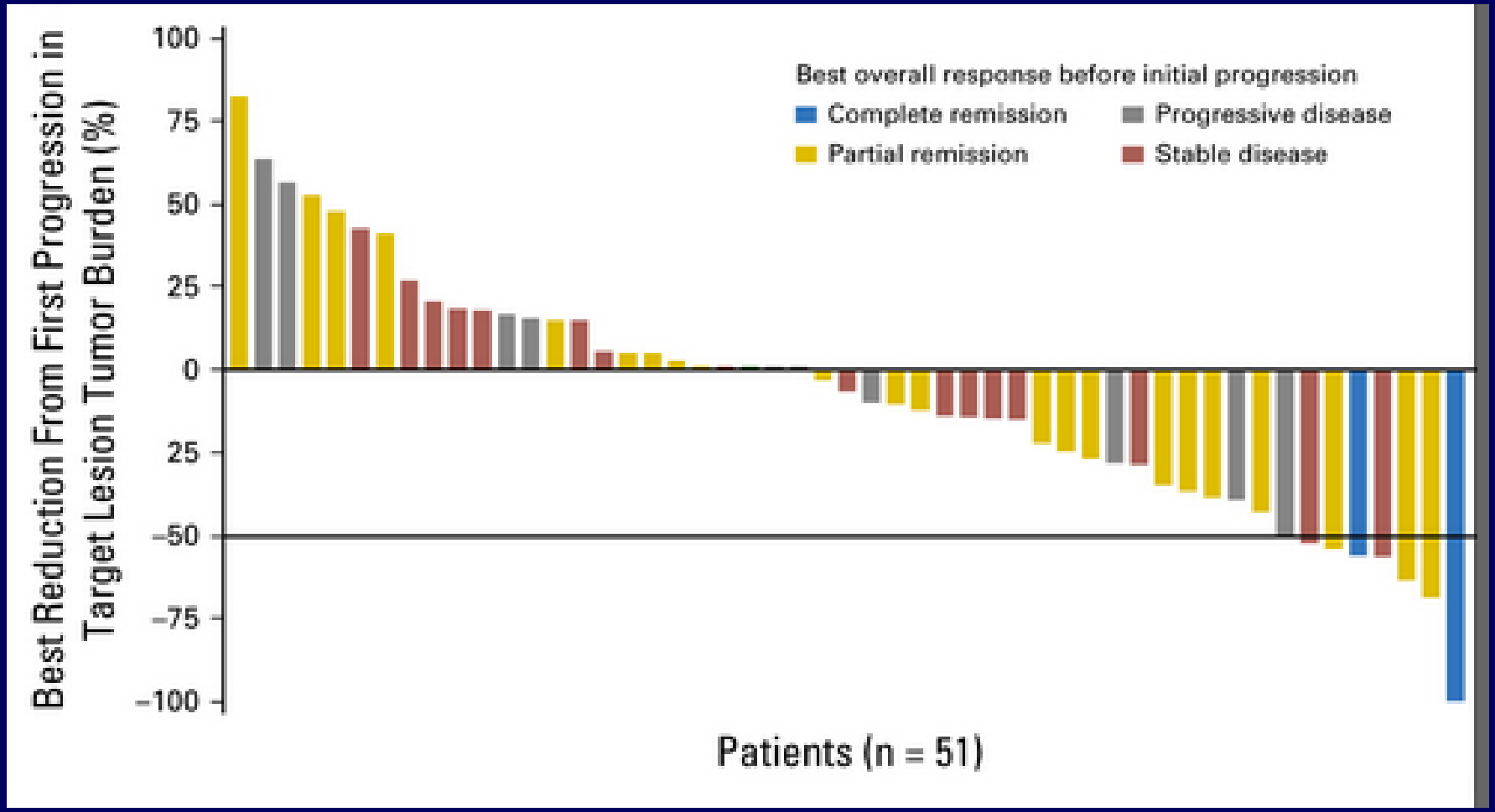
Ramchandren et al Clin Cancer Res e-pub, 2019

Long Term-FU of Nivo in R/R HL



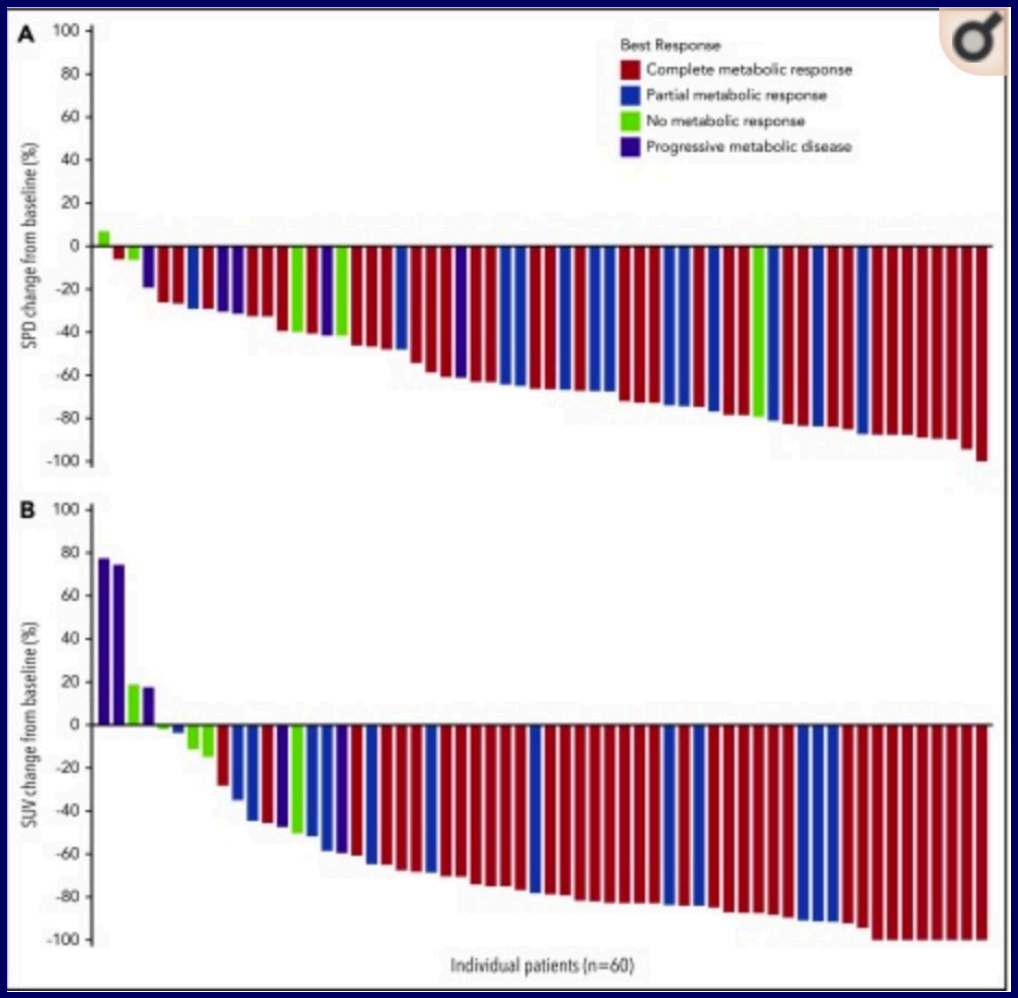
Armand et al JCO 36:1428, 2018

Continuation of Nivo Post PD



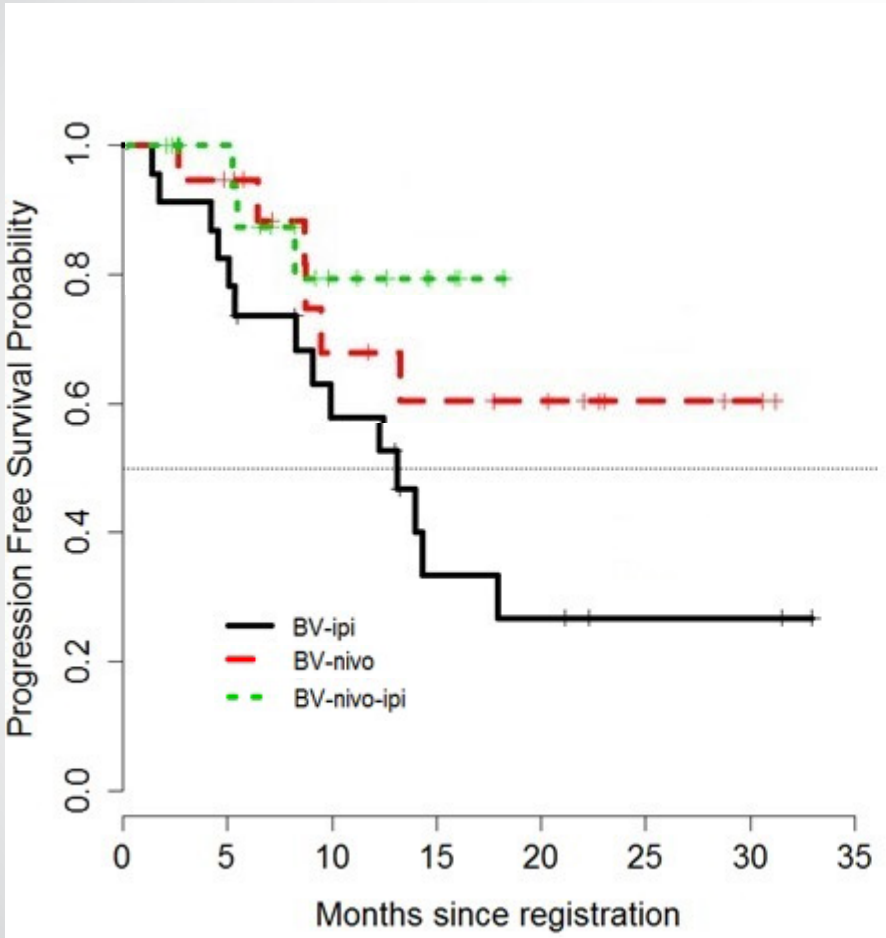
Armand et al JCO 38:1428, 2018

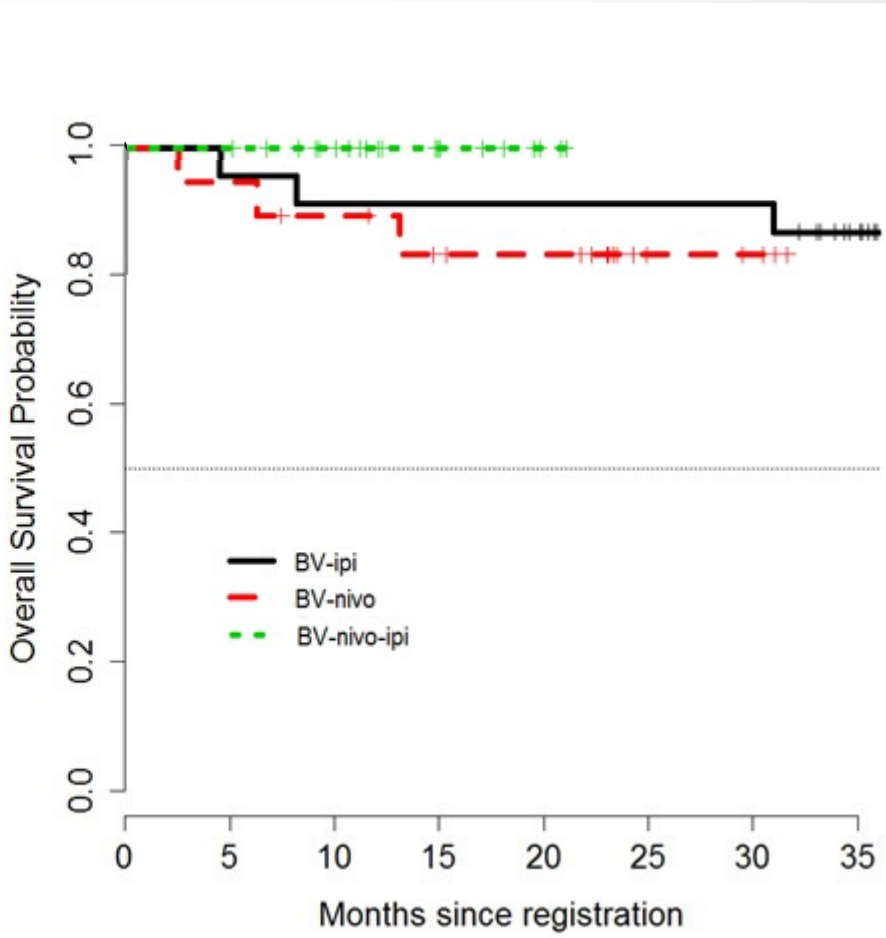
BV-Nivo in R/R/ HL (n=62)



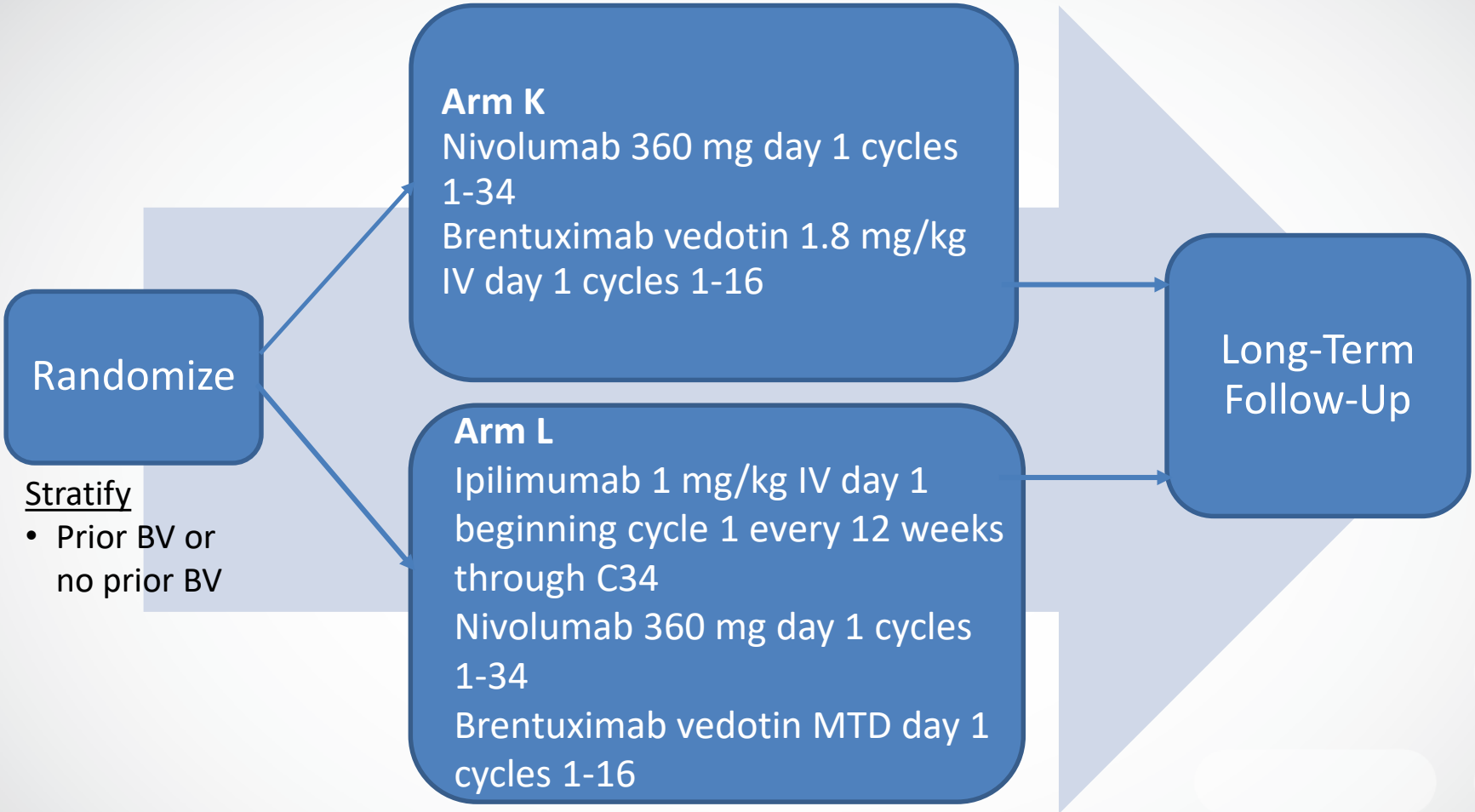
Herrera et al Blood 131:1183, 2018

PFS and OS By Treatment Arm/Combination





E4412 Phase 2 Currently Accruing



Phase II Accrual Goal=120 patients
Cycle=21 days

Conclusions

- BV and CPIs have revolutionized the treatment of patiens with HL
- Optimal use remains unclear
  - Line of treatment
  - Pre/post transplant – auto/allo
  - Combination vs sequence
- Will clearly prolong survival of patients with HL
- Next generation approach is needed to increase rate of cure