German Hodgkin Study Group
Deutsche Hodgkin Studiengruppe

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Treatment approaches in relapsed/refractory HL

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R/R Hodgkin Lymphoma

Key issues

- **Background**
- **Relapsed HL**
- **PD1**
- **Summary**

HDR2: European Study for
Relapsed Hodgkin Lymphoma*

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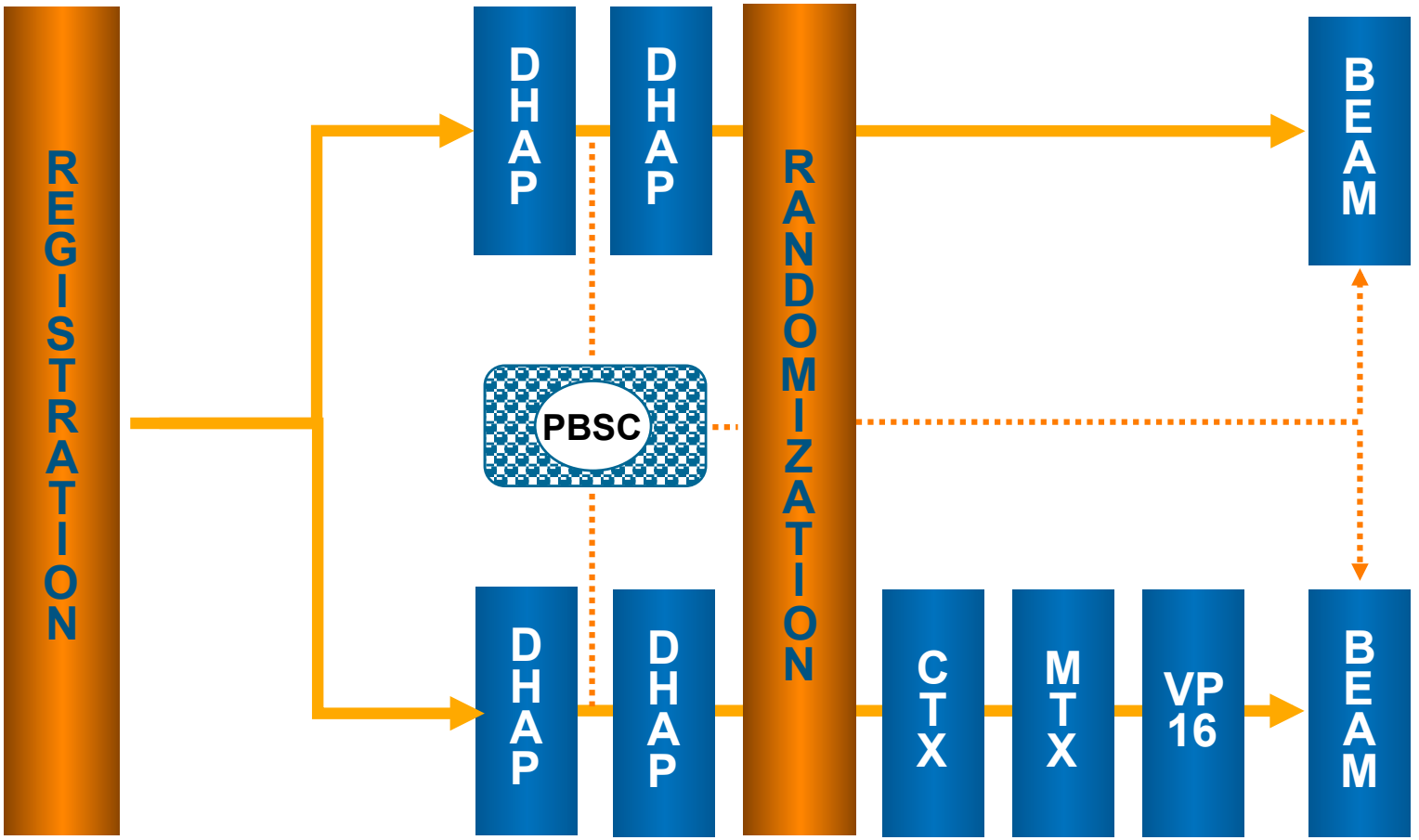

*GHSG, EORTC, EBMT, GELTAMO

Josting A, et al. J Clin Oncol. 2010;28(34):5074-5080

HDR2 Study for Relapsed HL

PFS by treatment arm (final analysis)

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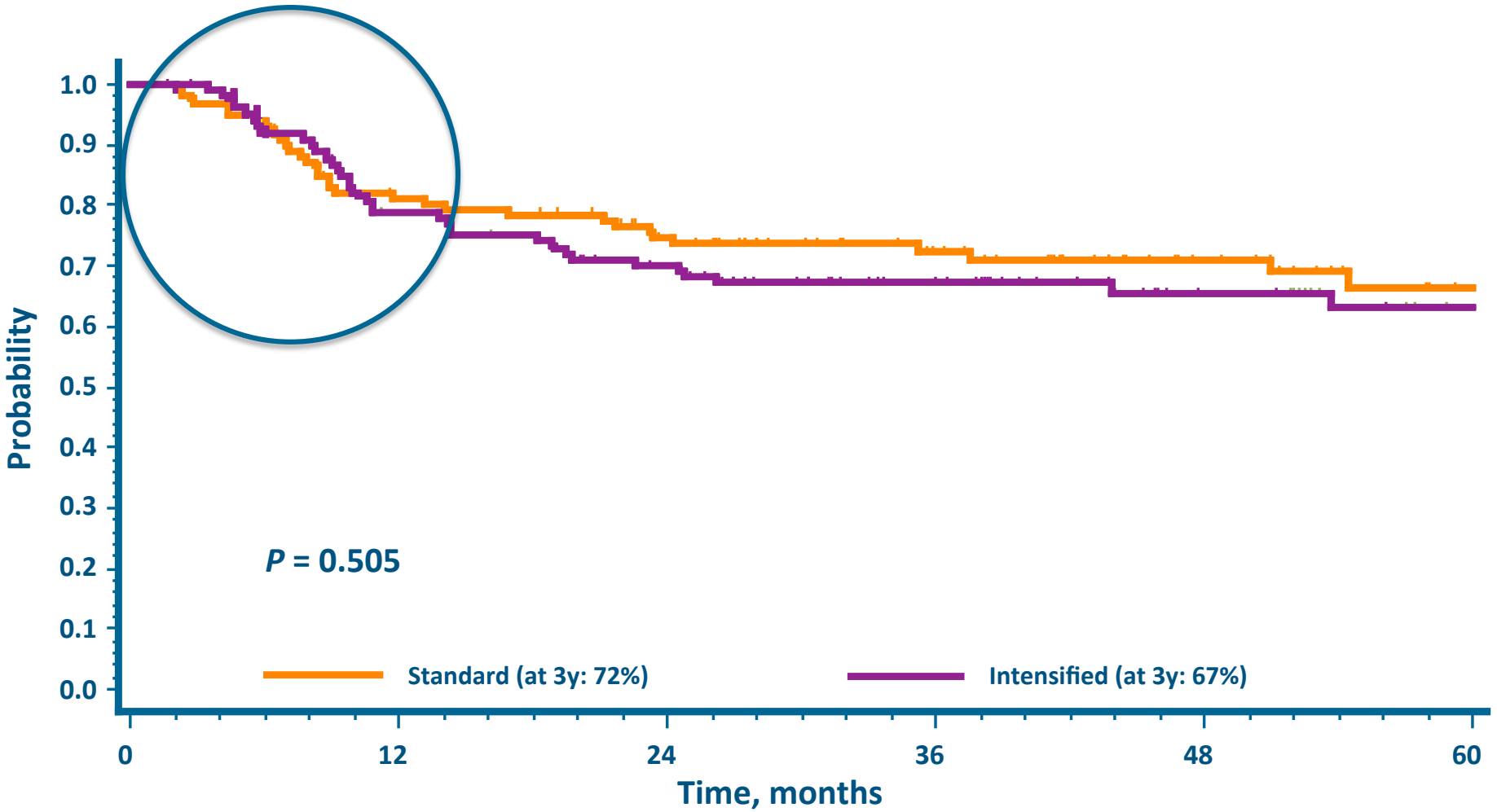

HL, Hodgkin lymphoma; PFS, progression free survival

Josting A et al, J Clin Oncol. 2010:28:5074-80

Survival in Hodgkin Lymphoma

Relapse After Autologous HSCT

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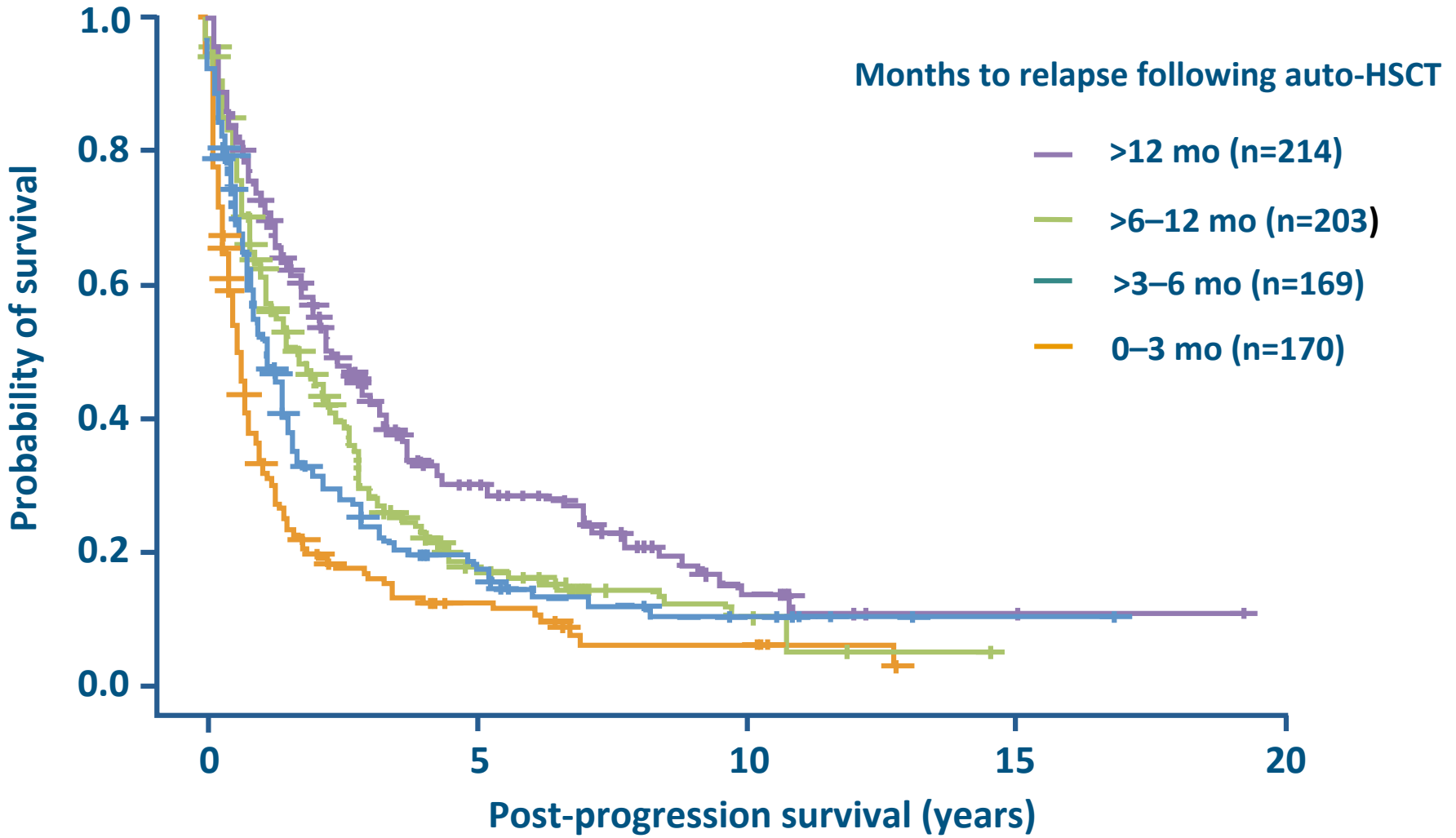
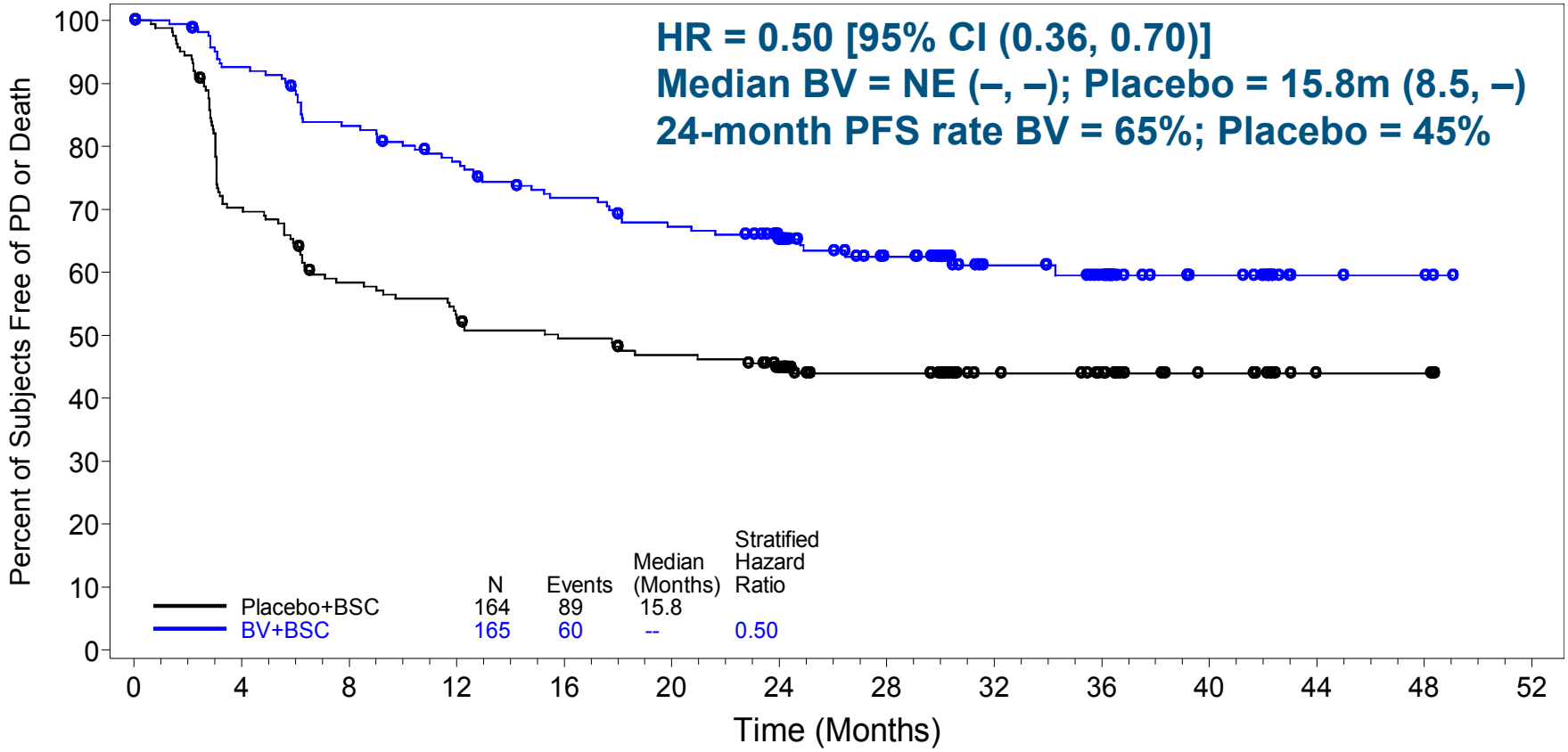


auto-HSCT = autologous hematopoietic stem cell transplant

Arai S et al. Leukemia & Lymphoma 2013;54:2531–2533.

AETHERA
PFS per Investigator



N at Risk (Events)														
Pla+BSC	164 (0)	113 (48)	92 (67)	83 (76)	77 (81)	71 (85)	61 (88)	45 (89)	28 (89)	23 (89)	13 (89)	3 (89)	3 (89)	0 (89)
BV+BSC	165 (0)	149 (12)	133 (27)	122 (36)	111 (45)	103 (52)	90 (55)	62 (58)	40 (59)	33 (60)	16 (60)	4 (60)	3 (60)	0 (60)

PFS, progression free survival; HR, hazard ratio; BV, brentuximab vedotin; NE, non evaluable; BSC, best supportive care; Pla, placebo

Moskowitz et al, Lancet 2015;385:1853-62

RIC-Allo Trial in Relapsed or Refractory HL (Relapse Rate)

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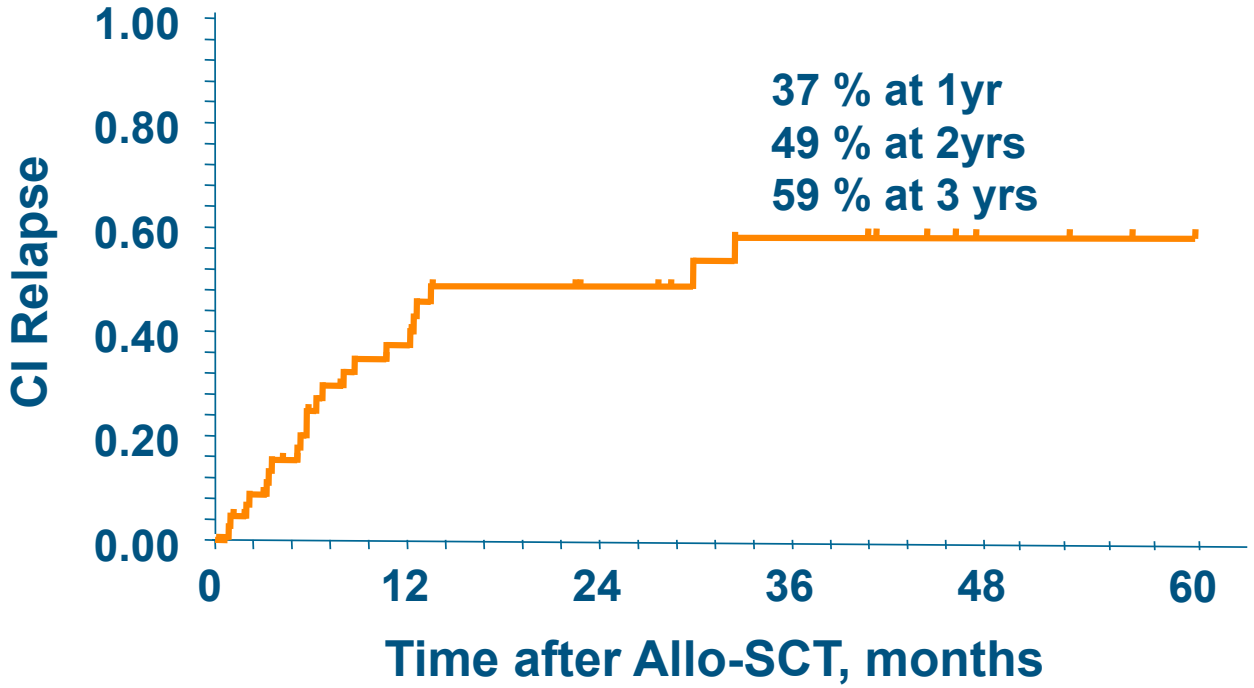
≥3 lines of tx, RR 1.7 (1.2 – 2.5), *P* = .03
Refractory disease, RR 2.1 (1.5 – 2.9), *P* = .01



Median time to relapse: 6m (3-35)

RIC-allo - reduced-intensity conditioning allogenic stem cell transplantation; HL – Hodgkin lymphoma; tx – therapy; allo-SCT- allogeneic stem cell transplantation

Sureda A, et al. Blood. 2009;114: A 658

Antibodies and other drugs used
in Hodgkin Lymphoma

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- **Lenalidomide (IMID)**
- **Everolimus, Temsirolimus (mTor-inhibitor)**
- **Rituximab, Ofatumumab (anti-CD20)**
- **Panobinostat, Vorinostat (H-DAC Inhibitors)**
- **TKI´s, JAK2i, PARPi**
- **Brentuximab Vedotin (anti-CD30 ADC)**
- **PD-1 inhibitors**

R/R Hodgkin Lymphoma

Key issues

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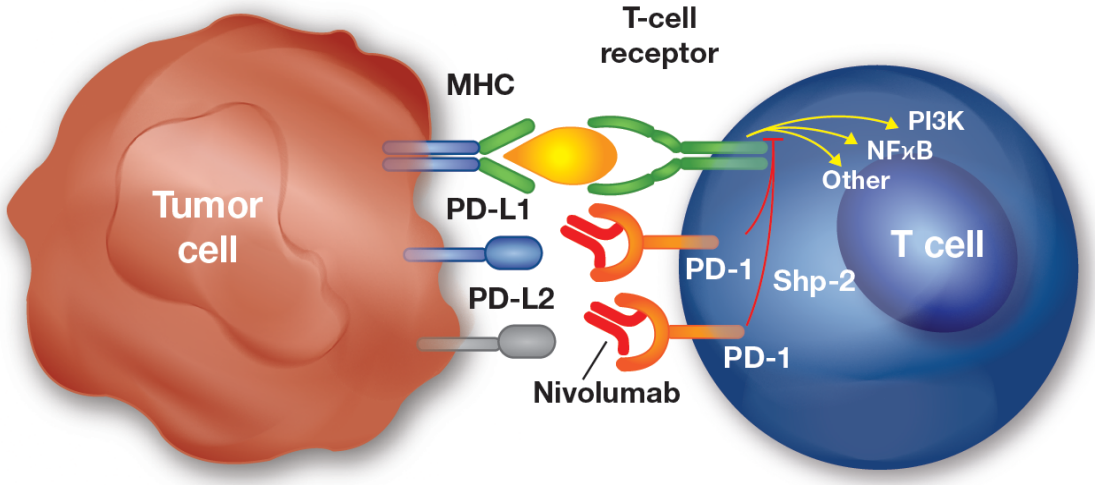
PD1 Inhibition in Classical HL
Mechanism of action

- **Patients with cHL show high frequency of 9p24.1 alterations and overexpression of PD-L1 and PD-L2[1]**
- **Nivolumab is a fully human immunoglobulin G4 monoclonal antibody targeting the programmed death-1 (PD-1) receptor immune checkpoint pathway**



Nivolumab blocks signaling through the PD-1 receptor

cHL = classical Hodgkin lymphoma; MHC = major histocompatibility complex; NFκB = nuclear factor kappa B; PD-L1/2 = programmed death ligand 1/2; PI3K = phosphoinositide-3–kinase; Shp-2 = Src homology region 2-containing protein tyrosine phosphatase

1. Roemer MGM et al, J Clin Oncol 2016;34:2690–7

Nivolumab in Lymphoma Patients

Duration of Response Phase 1b*

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Lymphoma	n	ORR (%)	F´-up (w)	Response (w)
Multiple Myeloma	27	4	46	12+
DLBCL	11	36	23	6-77+
Follicular NHL	10	40	91	27-82+
CTCL/MF	13	15	43	24-50+
PTCL	5	40	31	11-79+
HL	23	87	86	2-91+

*74 weeks median follow-up

PD-L1 and PD-L2 Expression in cHL

with 9p24.1 Amplification

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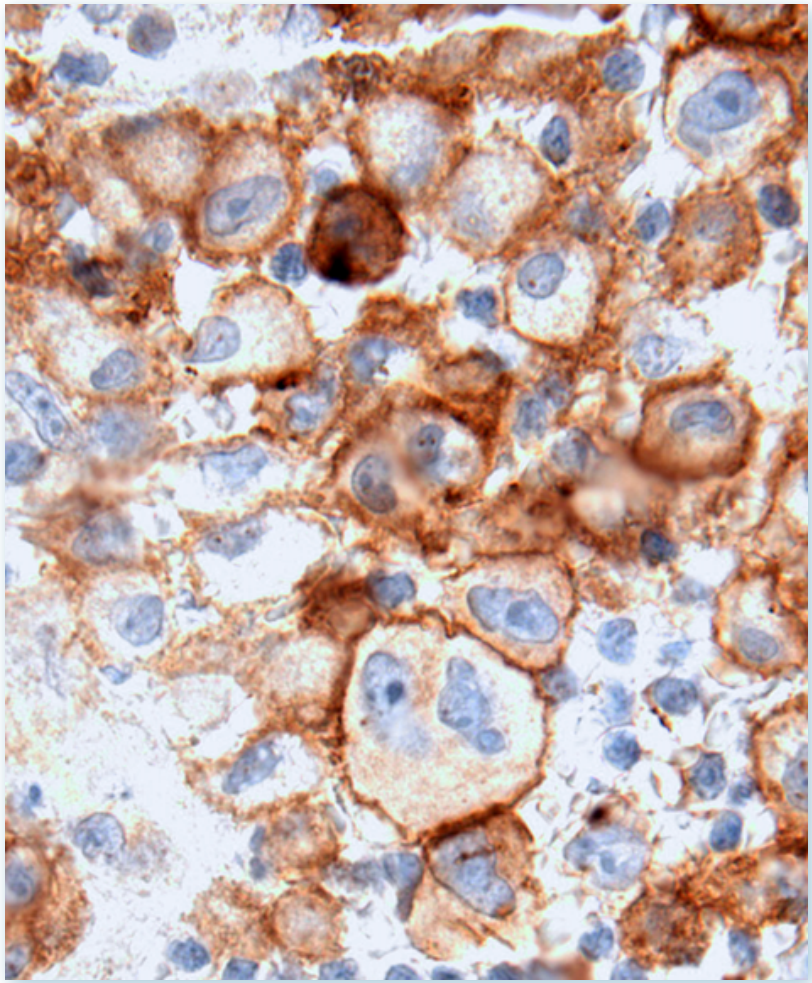
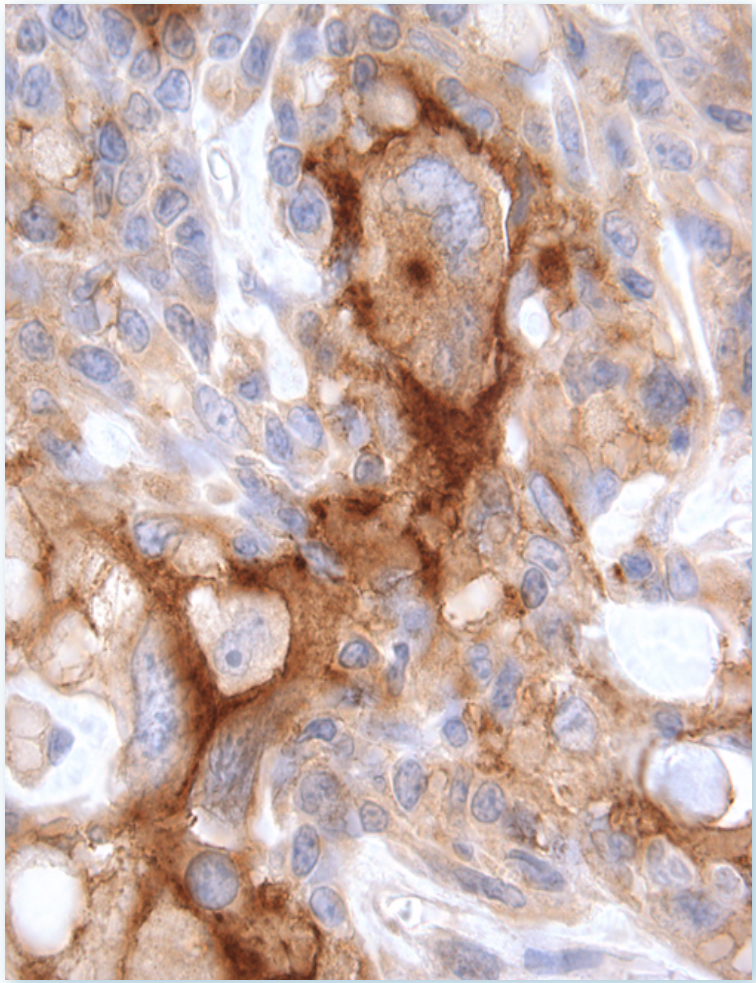
PD-L1



Chen et al, Clin Cancer Res. 2013; 19:3462

PD-L2



Courtesy of S. Rodig

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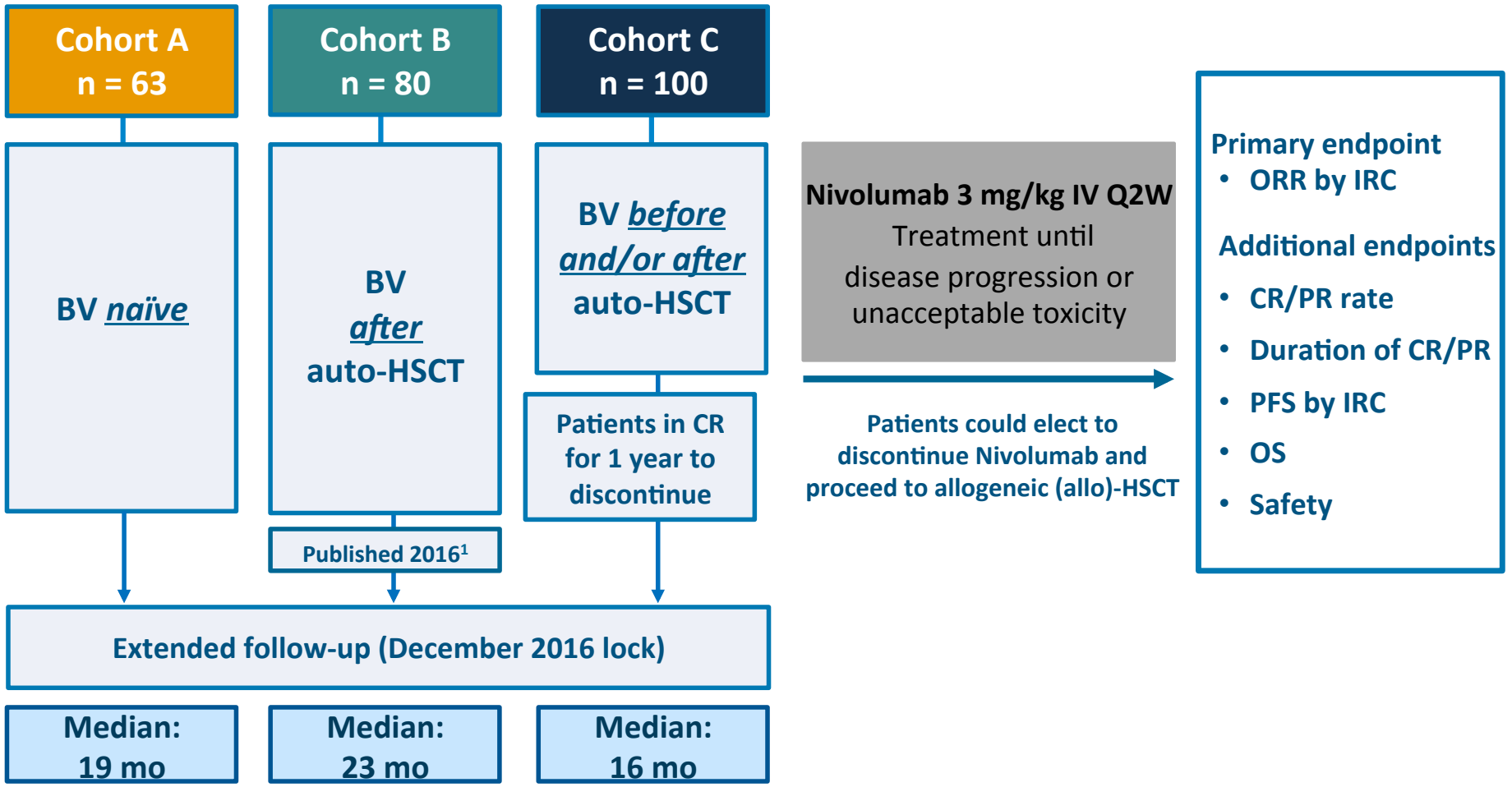
Study Design



CR = complete response; DOR = duration of response; IRC = Independent Radiology Review Committee; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; Q2W = every 2 weeks.

1. Younes A et al, Lancet Oncol 2016;17:1283–94

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Demographics

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	BV naïve[a] (Cohort A) n = 63	BV after auto-HSCT (Cohort B) n = 80	BV before and/or after HSCT (Cohort C) n = 100	Overall N = 243
Age, years	33 (18–65)	37 (18–72)	32 (19–69)	34 (18–72)
Male, %	54	64	56	58
ECOG PS (%) 0 1	62 38	53 48	50 50	54 46
Disease stage at study entry, % IV	38	68	61	57
Previous lines of therapy Prior radiotherapy, %	2 (2–8) 59	4 (3–15) 74	4 (2–9) 69	4 (2–15) 68
Time from diagnosis to first dose of nivolumab, years	3.1 (1.0–30.6)	6.2 (1.3–25.1)	3.5 (1.0–24.9)	4.5 (1.0–30.6)
Time from auto-HSCT to first dose of nivolumab, years	1.0 (0.3–18.2)	3.4 (0.2–19.0)	1.7 (0.2–17.0)	2.0 (0.2–19.0)

[a]All pts received auto-HSCT. Data are median (range) unless otherwise stated. ECOG PS = Eastern Cooperative Oncology Group performance status

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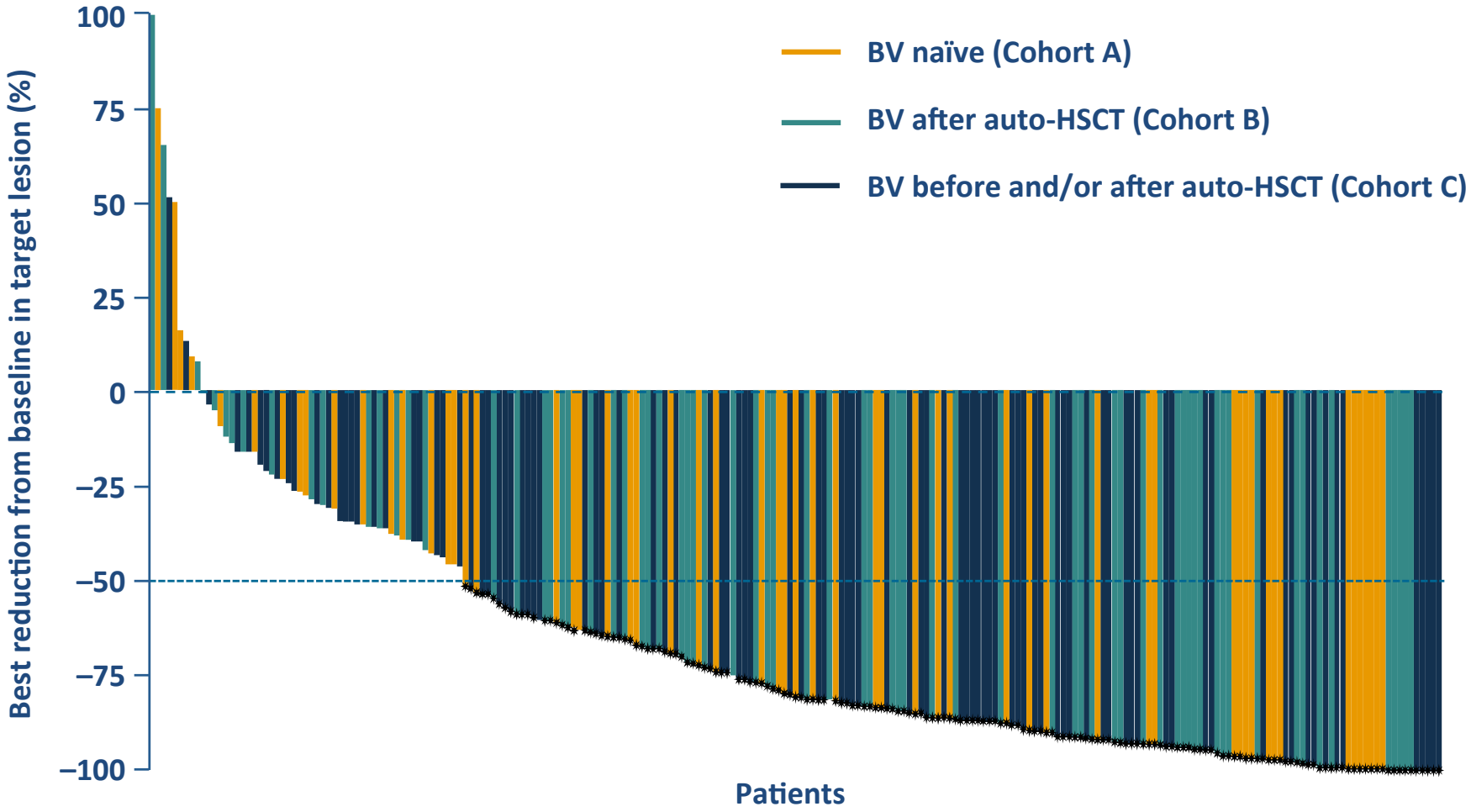
Change in Target Lesion per IRC



Asterisks (*) denote responders

Engert et al, EHA 2017

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Best Overall Response

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	BV naïve (Cohort A) n = 63	BV after auto-HSCT (Cohort B) n = 80	BV before and/or after auto-HSCT (Cohort C) n = 100	Overall n = 243
Objective resp.[a] % (95% CI)	65 (52, 77)	68 (56, 78)	73 (63, 81)	69 (63, 75)
Best overall response, %				
Complete remission[b]	29	13	12	16
Partial remission	37	55	61	53
Stable disease	24	21	15	19
Progressive disease	11	8	10	9
Unable to determine	0	4	2	2

Per investigator assessment, 33% pts achieved CR and 39% PR

[a]Defined according to 2007 International Working Group criteria. Responses were assessed by IRC; [b]All CRs

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Safety Outcomes after Extended Follow-up

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Patients with drug-related AEs (≥10%), serious AEs (≥1%), or AEs leading to discontinuation (≥1%)	Overall population n = 243	
Drug-related AEs, %	**Any grade**	**Grade 3–4**
Fatigue	23	1
Diarrhea	15	1
Infusion-related reaction	14	<1
Rash	12	1
Drug-related serious AEs, %		
Infusion-related reaction	2	<1
Pneumonitis	1	0
Drug-related AEs leading to discontinuation, %		
Pneumonitis	2	0
Autoimmune hepatitis	1	1

Engert et al, EHA 2017

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PFS by Best Overall Response

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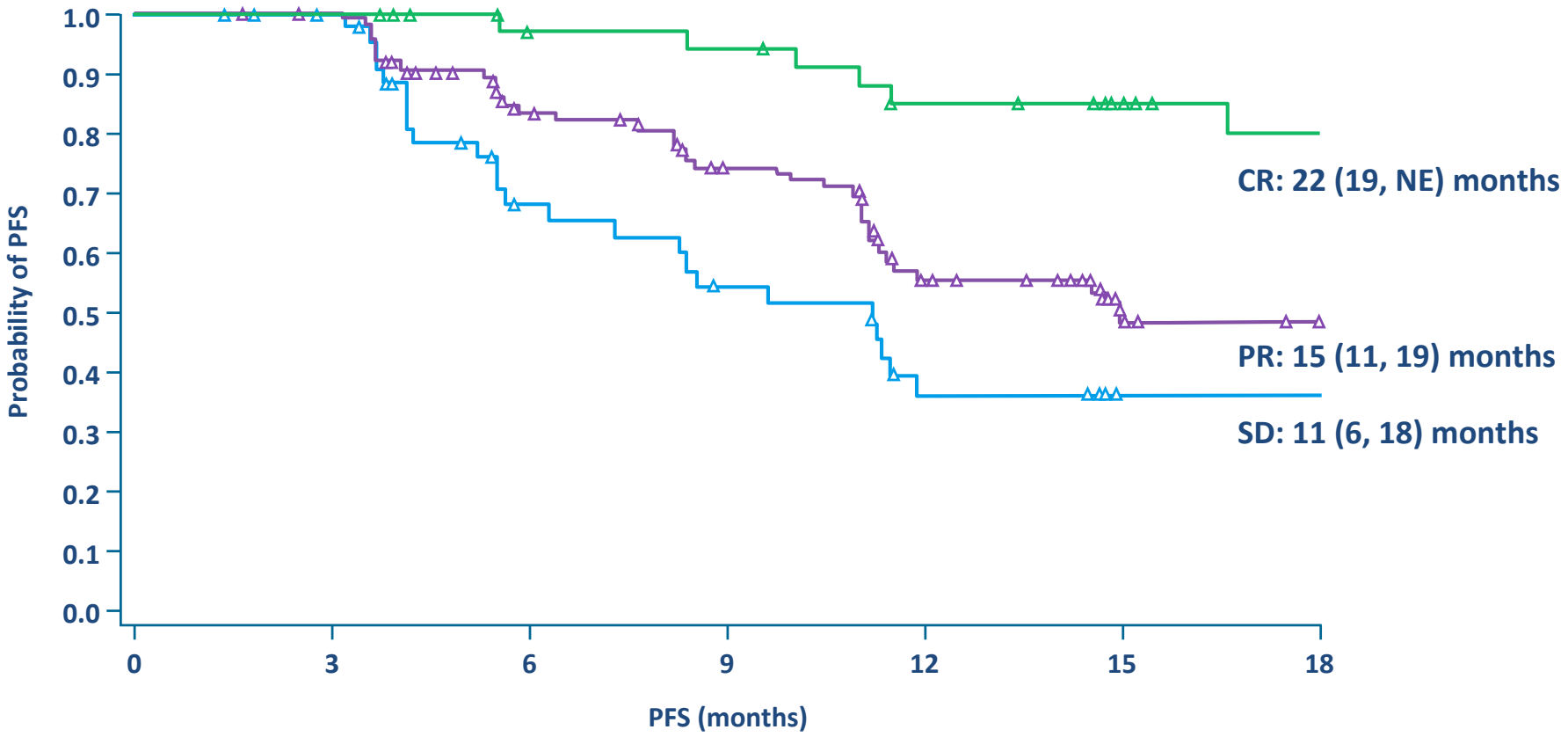

Number of patients at risk							
CR	40	40	33	32	27	20	16
PR	128	126	89	71	46	25	21
SD	47	44	25	19	11	8	8

Median (95% CI) PFS for overall patients (N = 243) was 15 (11, 19) months

Engert et al, EHA 2017

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Overall Survival

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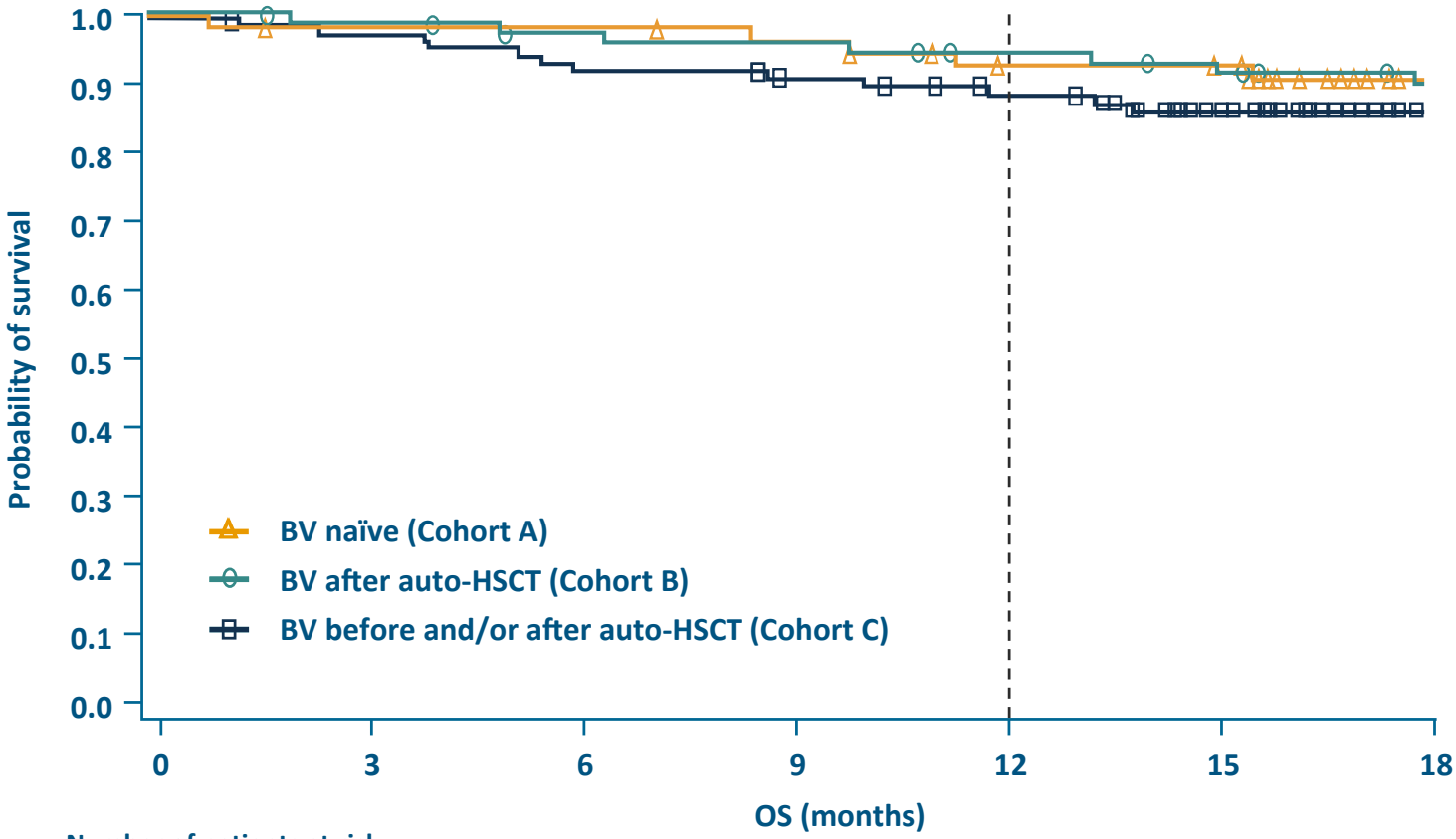


Cohort A : NR (NE, NE)

Cohort B: NR (NE, NE)

Cohort C: NR (19, NE)

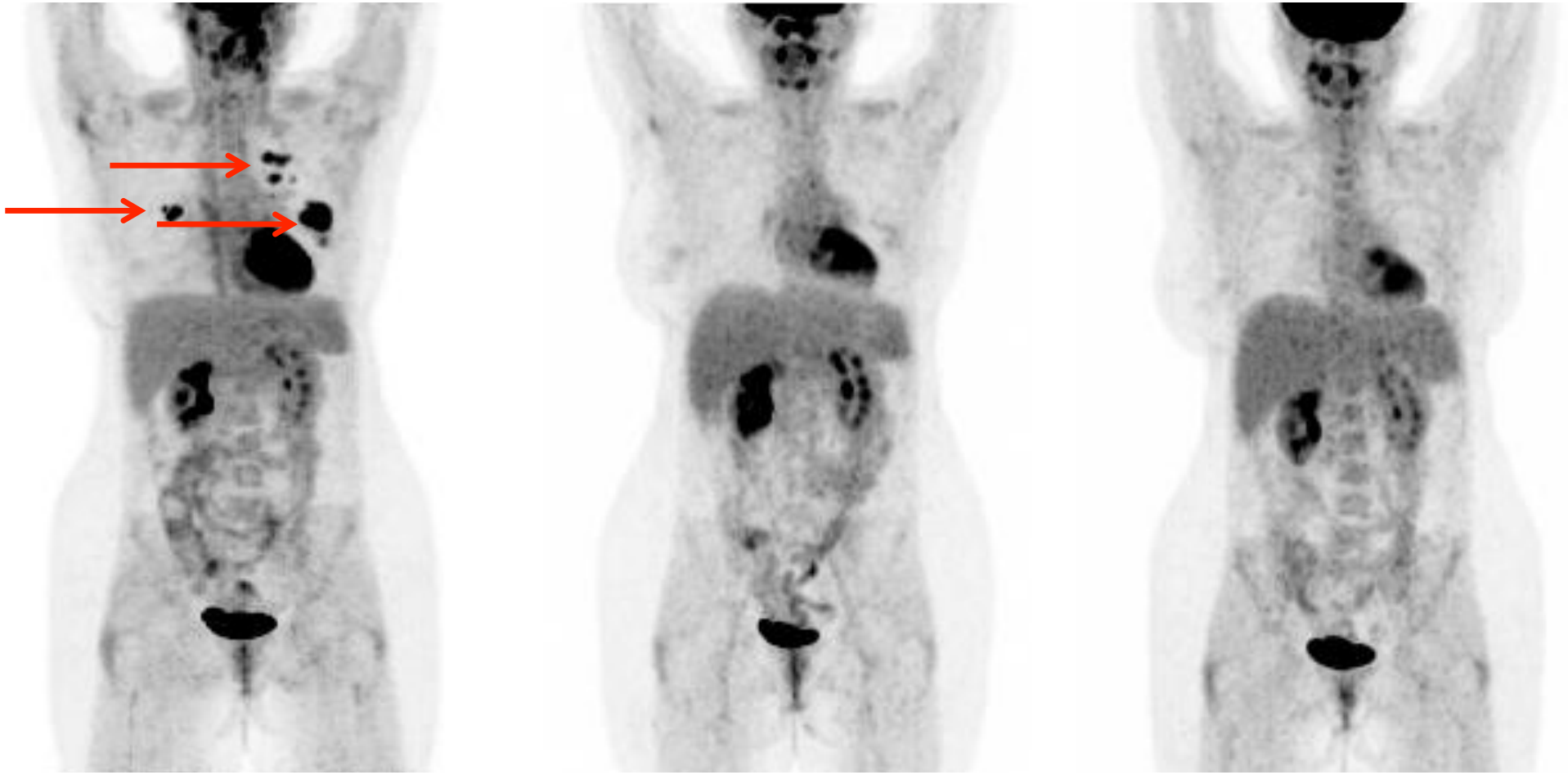
Number of patients at risk

Cohort A	63	61	61	59	55	54	36
Cohort B	80	78	75	74	71	68	63
Cohort C	100	97	93	90	83	65	17

All values are medians (95% CI). NR = not reached

Patient M.M.; 39 years

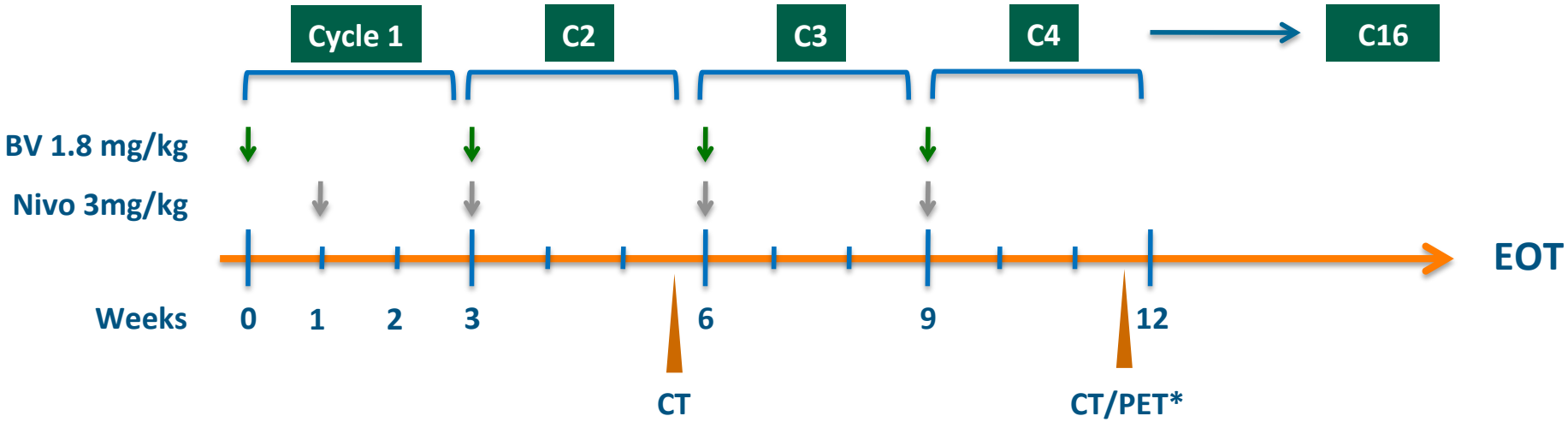
Diagnosed 2011 (5 prior therapies)



October 2014 | February 2015 | May 2015

Phase 1/2 Study

BV and Nivolumab in Pts with r&r cHL



- Up to 16 total cycles of combination therapy
- Standard dosing of both drugs
- Staggered dosing for cycle 1 only
- Pts could go on to HDCT & ABMT
- Risk of pneumonitis

Alex F Herrera et al, ASH 2016 A1105

Immunomodifiers in Lymphoma
Selection

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Antibody	Target	Company
Nivolumab	PD1	BMS
Pembrolizumab	PD1	MSD
REGN2810	PD1	Regeneron
Durvalumab	PD-L1	Celgene
Avelumab	PD-L1	Pfizer
Ipilimumab	CTLA-4	BMS

PD1 Inhibition, klinische Studien

Hohe Effektivität beim Hodgkin Lymphom

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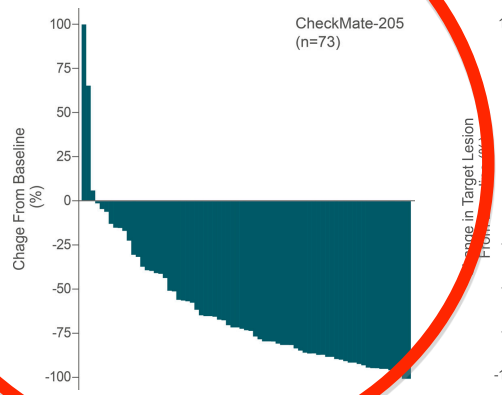
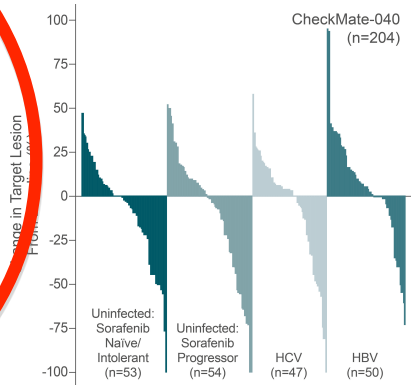
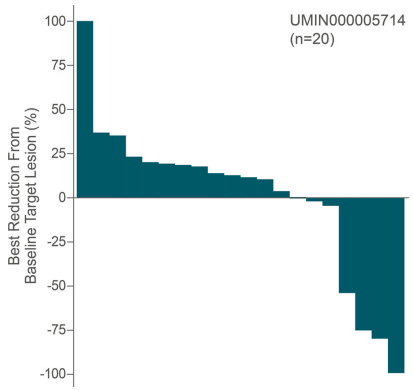
Hodgkin Lymphoma[1]



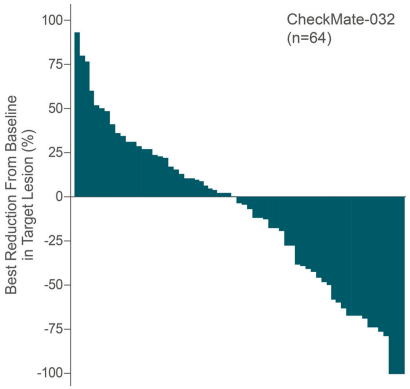
Hepatocellular Carcinoma[2]



Ovarian Cancer[3]

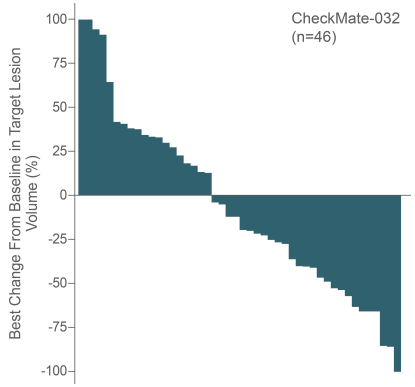


Urothelial Cancer[4]



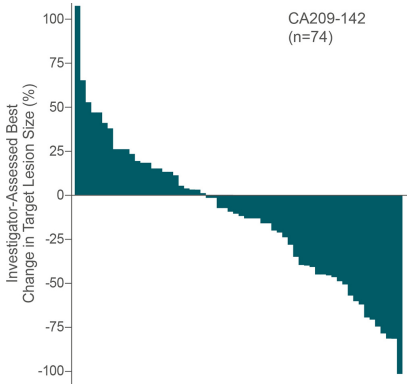
Small Cell Lung Cancer[5]

(Nivolumab 1 mg/kg BW + Ipilimumab 3 mg/kg BW)

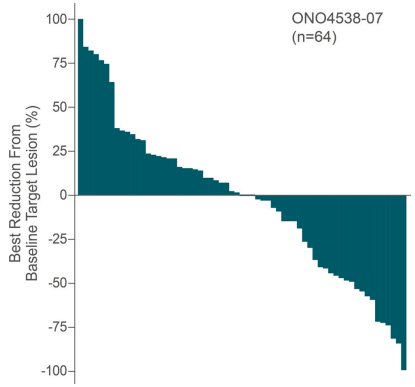


Colorectal Cancer – MSI-H[6]

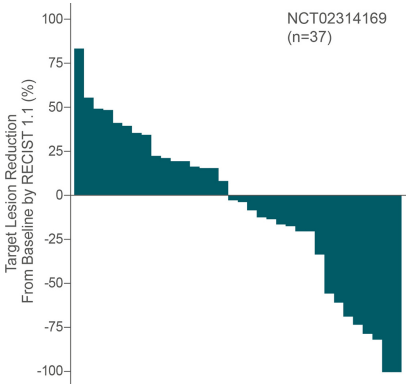
(Nivolumab 3 mg/kg BW)



Esophageal Cancer[7]



Anal Cancer[8]



1.Younes ASCO 2016, A7535. 2. Sangro ASCO 2016, A4078. 3. Hamanishi JCO 2015. 4.Sharma ASCO 2016, A4501. 5.Antonia ASCO 2016, A100. 6.Overman ASCO-GI 2017. 7.Van Morris ASCO 2016 A503

R/R Hodgkin Lymphoma

Key issues

- **Background**
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- **Summary**

R/R Hodgkin Lymphoma
Summary

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- **HL has become one of the best curable cancers; long-term side effects of chemo- and radiotherapy**
- **PD1 inhibitors in cHL demonstrated durable responses irrespective of prior BV treatment or refractoriness to prior therapies**
- **CR rate of 29% in BV-naïve pts; acceptable safety profile**
- **Nivolumab offers long-term treatment option for a broad spectrum of patients with cHL progressing after auto-HSCT**
- **Ongoing trials evaluate Nivolumab in other settings, including frontline**
- **Future trials including BV and anti-PD1 Moabs will increasingly replace chemo- and radiotherapy in HL**


GÜRZENICH, COLOGNE
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PD1 Inhibition

Outcomes After Allo-HSCT (n=44)

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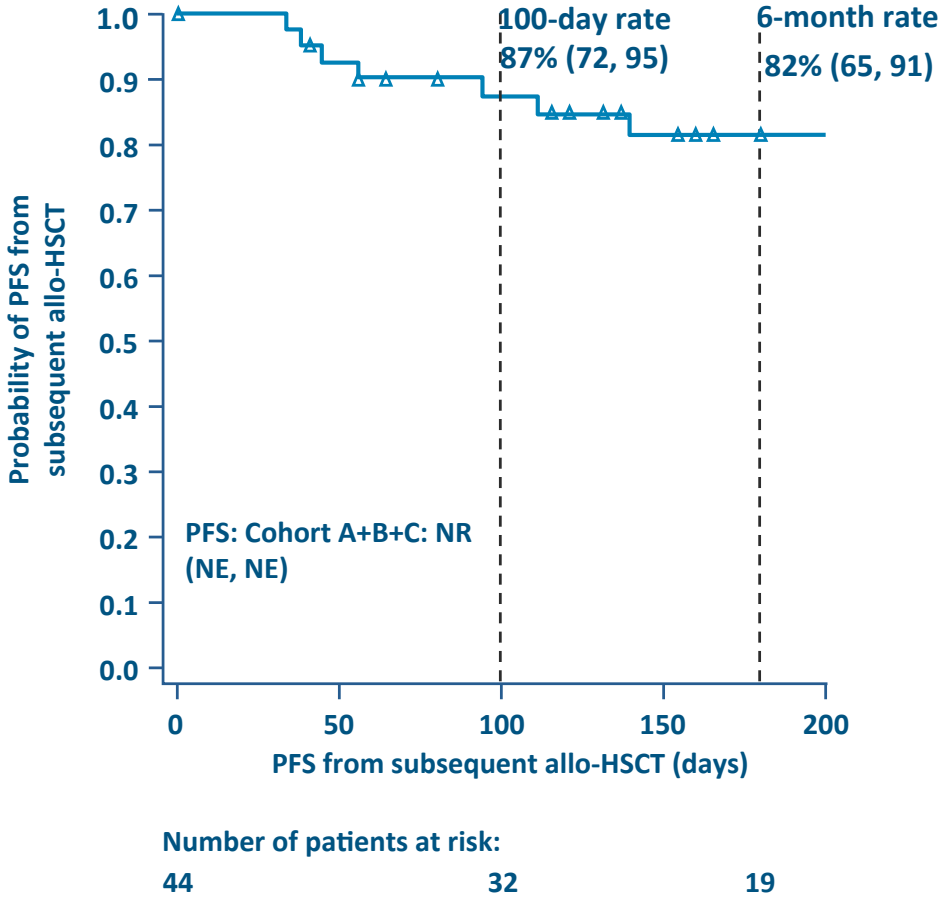
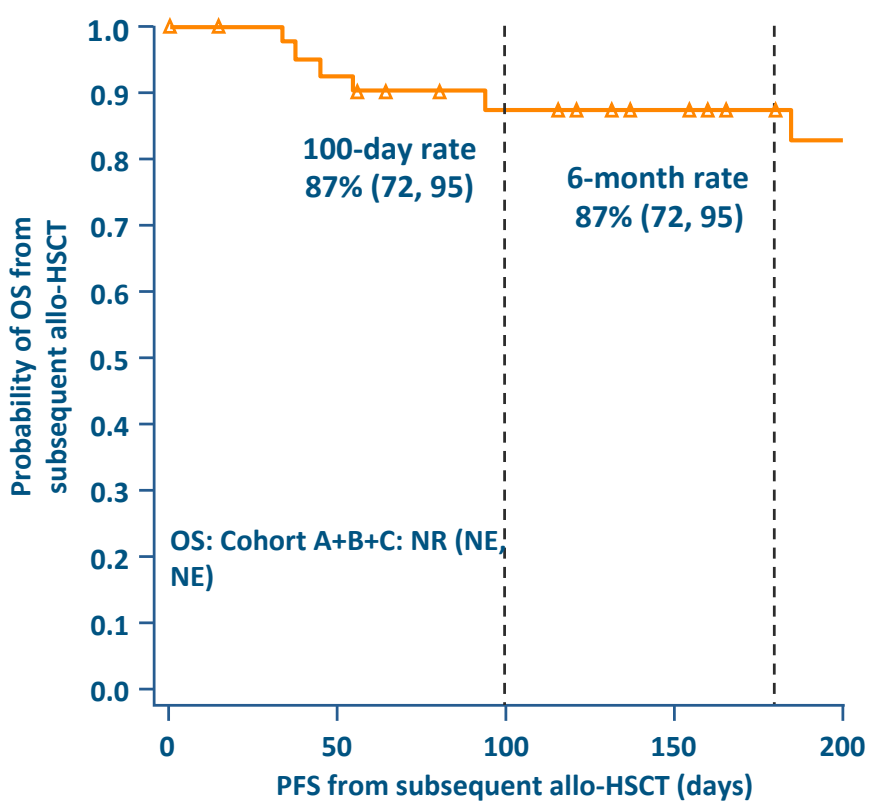
Progression-free survival



Number of patients at risk:

44	32	19

Overall survival



Number of patients at risk:

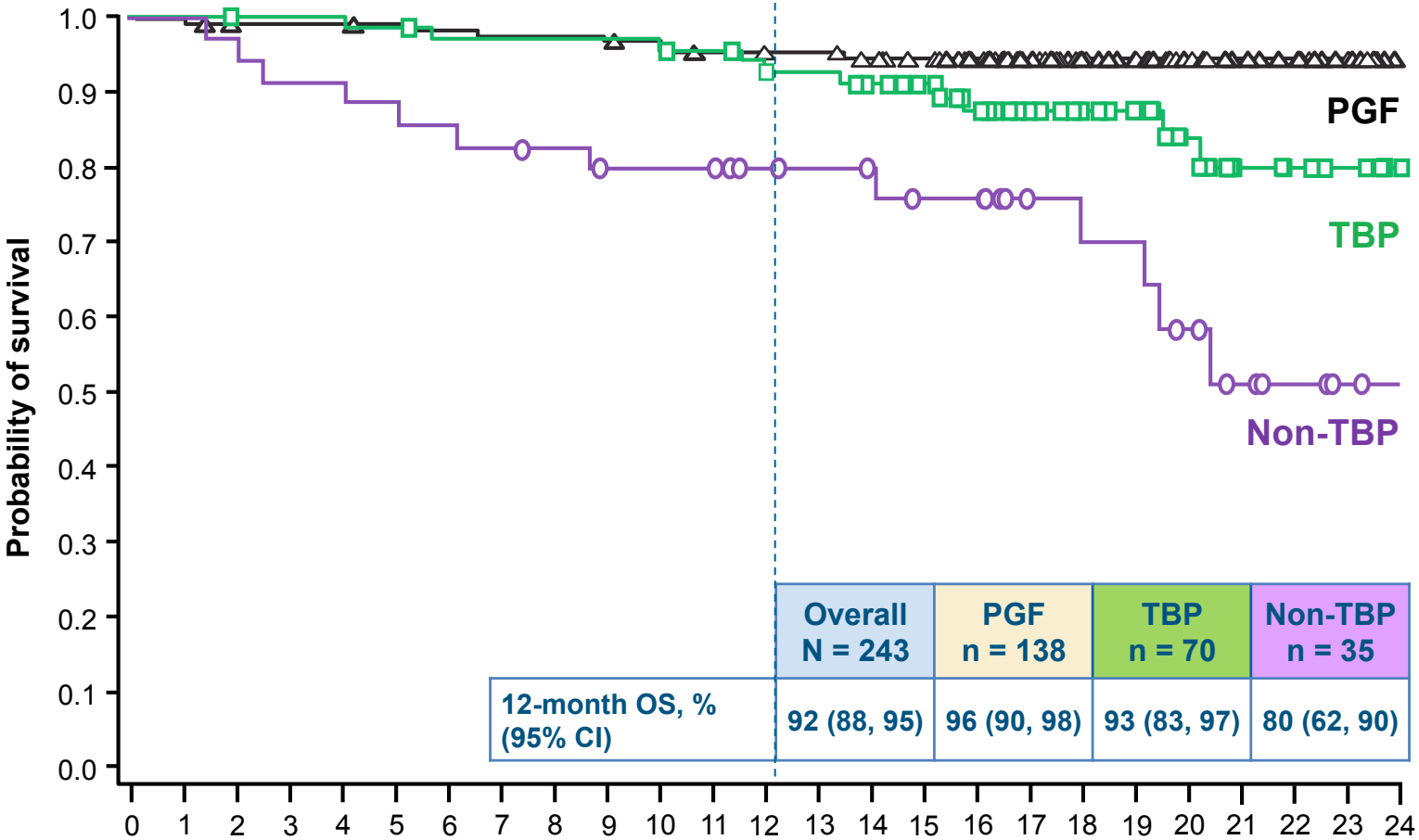
44	32	21

Values are % (95% CI) or median (95% CI)

Morschhauser ISHL10, 2016

Nivolumab beyond Progression

Outcomes in R/R cHL - Survival



	Overall N = 243	PGF n = 138	TBP n = 70	Non-TBP n = 35
12-month OS, % (95% CI)	92 (88, 95)	96 (90, 98)	93 (83, 97)	80 (62, 90)

Number of patients at risk

PGF	138	135	135	133	132	129	126	123	105	74	54	45	15
TBP	70	69	69	66	66	66	60	57	44	30	21	14	7
Non-TBP	35	34	32	30	28	26	23	21	19	12	9	4	1

PGF, progression-free patients

Cohen et al; ASH 2017: A650