Universitätsklinikum Leipzig
Medizin ist unsere Berufung.

M. Hodgkin Rezidivtherapie. Aktueller und kommender Einsatz der Checkpoint-inhibitoren

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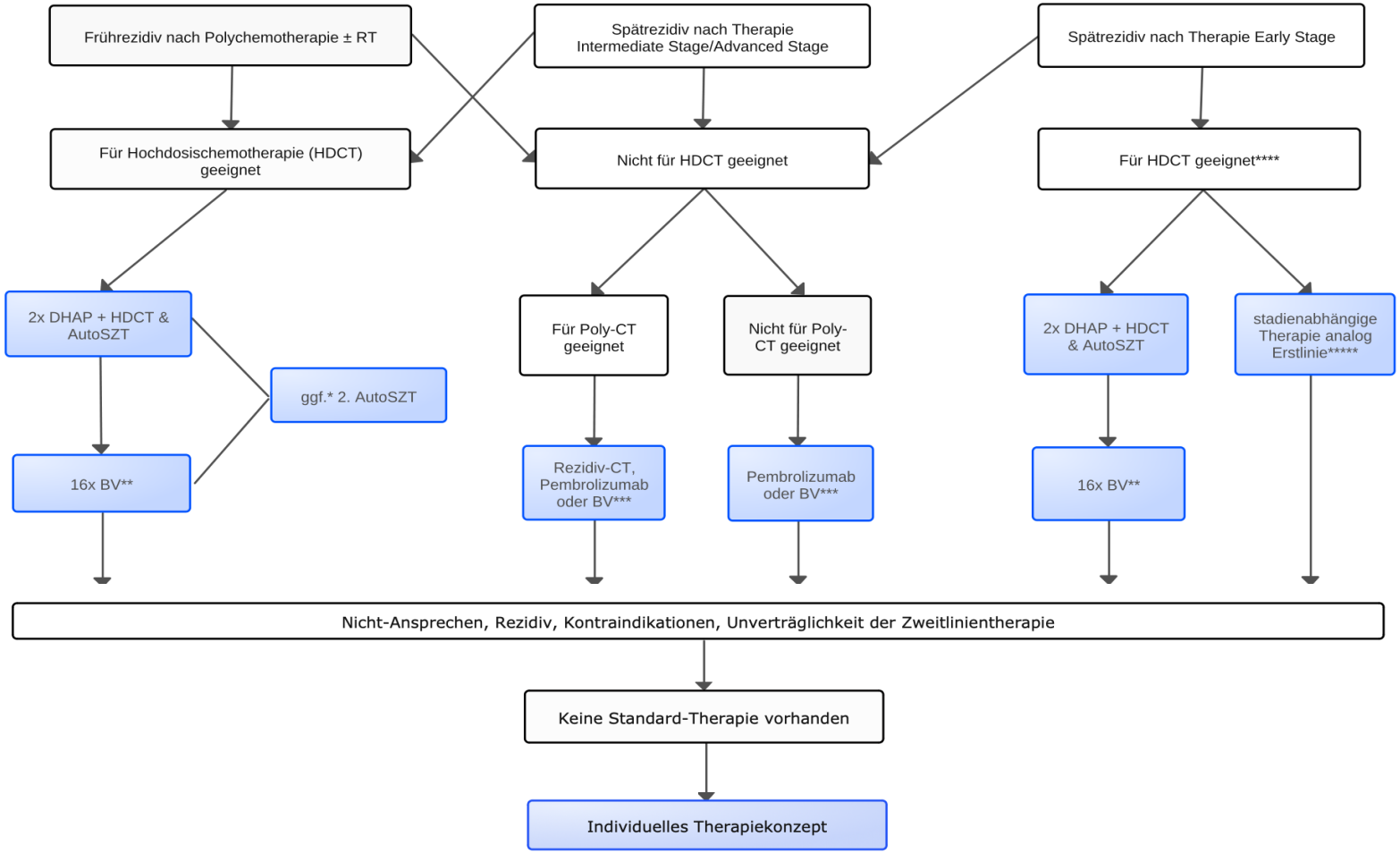
Rezidiv M Hodgkin

- 10-15% Patienten rezidivieren nach Erstlinientherapie
- Nur die Hälfte der Patienten durch eine Zweitlinienchemotherapie und autologe Transplantation geheilt[1]
- Erhaltungstherapie mit Brentuximab-Vedotin kann das Rezidivrisiko (Patienten mit Risikofaktoren) senken (PFS nach 5 Jahre 59% vs 41%)[2]
- Chemorefraktäre Erkrankung ist eine therapeutische Herausforderung

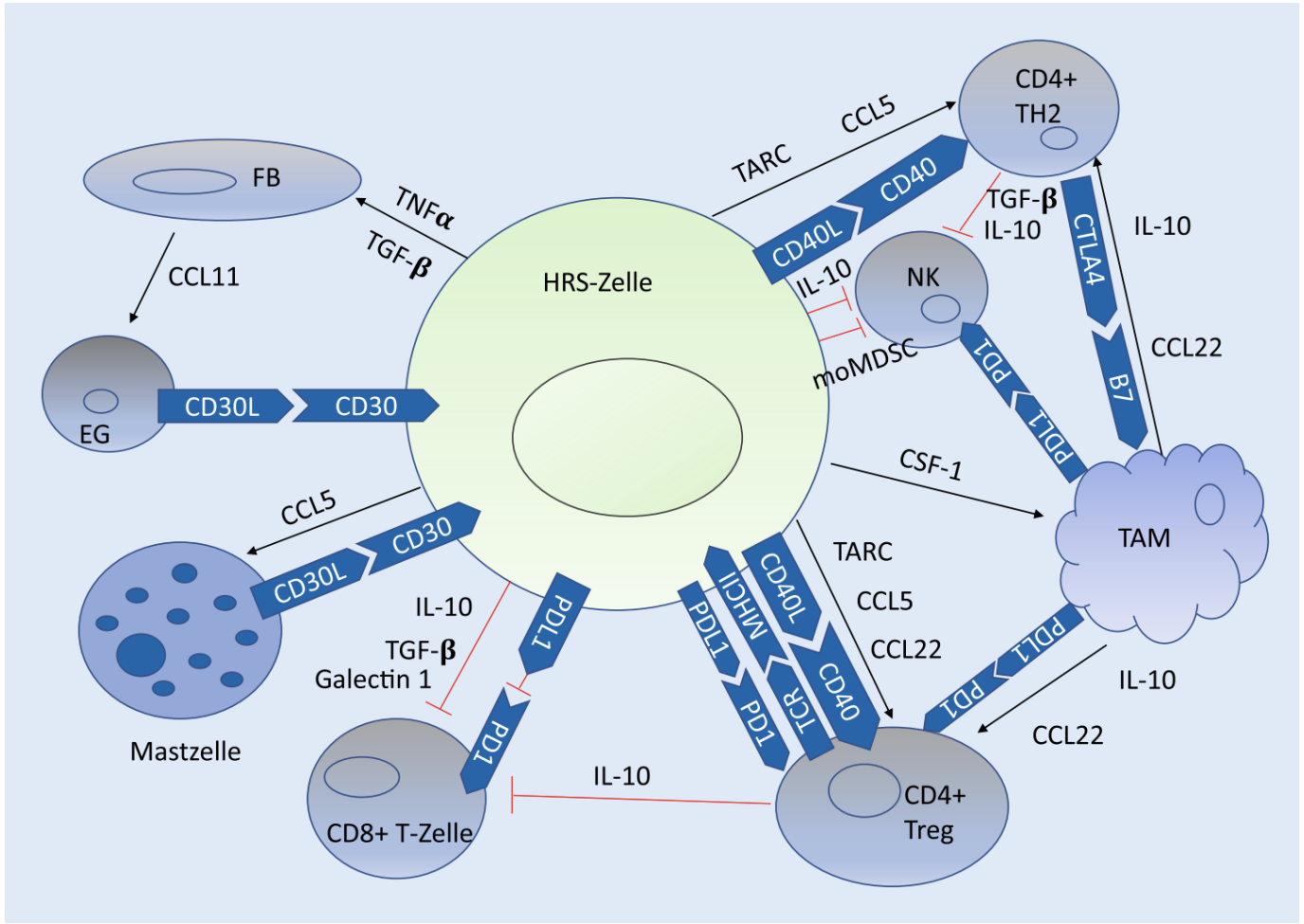
1 Sibon et al, Hematologica 2015
2 Moskowitz et al., Blood 2018

Rezidiv M. Hodgkin - Leitlinie



https://www.onkopedia.com/de/onkopedia/guidelines/hodgkin-lymphom/@@guideline/html/index.html

Hodgkin und Microenvironment



Microenvironment relevant für das Überleben der Reed-Sternberg Zelle (direkte oder indirekte Interaktion mit den Immunzellen)

Sasse et al., Die Innere Med, 2020

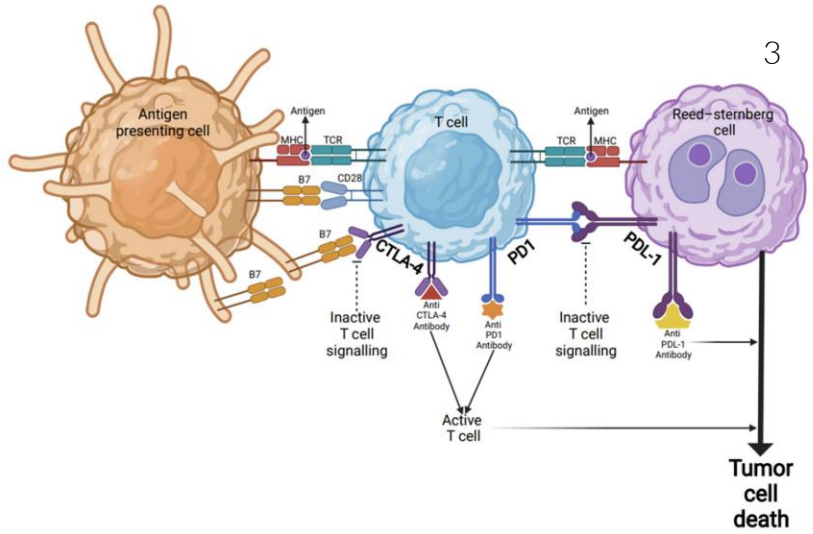
Hodgkin und T-Lymphozyt

- PD-L1 konstitutiv exprimiert auf der Reed-Sternberg Zellen
- Amplifikation der PDL1 Gene (9p24.1 Lokus) –Überexpression[1]

- PDL1 (PDL2) Interaktion (Tumorzelle) mit PD-1 Rezeptoren (T-Lymphozyten) -> reduzierte T-Zell Aktivierung und Proliferation[2]

- PDL1 überexprimiert auf den tumorassoziierten Makrophagen -> Unterregulation der NK- und CD4+ T-Zellen[3]

3



[1] Green et al., Blood, 2010
[2] Zou et al., Sci Transl Med 2016
[3] Vari et al, Blood, 2018

Check-Point Blockade

- Anti PD1 monoklonale Antikörper –>

Erholung der „Immunsurveilance“ -> Reduktion der Zahl der Tumorzellen[1]

- Zusätzlich:
  - Anstieg der CD4+ T-Lymphozyten,
  - dendritischer und
  - diferenzierter NK-Zellen (in peripherem Blut)

Korrelation mit klinischem Ansprechen[2,3]

[1]Merryman et al., Transplant Cell Ther, 2021
[2]Cader et al, Nat Med, 2020,
[3]Garcia-Marquez et al, Leukemia 2021

Nivolumab – CheckMate 039

- Phase I St
- Primärer
Sicherheit und
- Sekundärer Endpunkt: E
- 23 Patienten,
medianes Alter 35 (20-54),
meistens ≥4 Therapielinien

20/23 (87%) dokumentiertes Ansprechen

Table 2. Drug-Related Adverse Events in the 23 Patients.*

Event	Any Grade	Grade 3
	no. of patients (%)	
Any adverse event	18 (78)	5 (22)
Drug-related adverse events reported in ≥5% of patients		
Rash	5 (22)	0
Decreased platelet count	4 (17)	0
Fatigue	3 (13)	0
	3 (13)	0
	3 (13)	0
	3 (13)	0
	3 (13)	0
	2 (9)	0
	2 (9)	0
	(9)	1 (4)
		0
Stoma		
Drug-related ser		
Myelodysplastic syn		
Lymph-node pain		
Pancreatitis		

Ansell et al, NEJM, 2015

Nivolumab – CheckMate 205

- Phase II Studie
- Primärer Endpunkt: Ansprechen

- 243 Patienten mit Rezidiv nach ASCT – 3 Kohorten:
  - A – BV naive (N=63)
  - B – BV nach ASCT (N=80)
  - C – BV vor u/o nach ASCT (N=100)

Armand et al, JCO 2018
Ansell et al, Blood Advances, 2023

Nivolumab – Checkmate 205 (Demographie)

Characteristic	Cohort A (BV-naive) (n = 63)	Cohort B (BV after auto-HCT) (n = 80)	Cohort C (BV before and/or after auto-HCT) (n = 100)	Overall (N = 243)
Age, median (range), years	33 (18–65)	37 (18–72)	32 (19–69)	34 (18–72)
Female, n (%)	29 (46.0)	29 (36.3)	44 (44.0)	102 (42.0)
Stage at study entry, n (%)				
I	1 (1.6)	1 (1.3)	2 (2.0)	4 (1.6)
II	19 (30.2)	11 (13.8)	20 (20.0)	50 (20.6)
III	18 (28.6)	14 (17.5)	17 (17.0)	49 (20.2)
IV	24 (38.1)	54 (67.5)	61 (61.0)	139 (57.2)
Not reported	1 (1.6)	0	0	1 (0.4)
B symptoms at study entry, n (%)	10 (15.9)	18 (22.5)	25 (25.0)	53 (21.8)
Bulky disease at study entry, n (%)	10 (15.9)	17 (21.3)	22 (22.0)	49 (20.2)
Extralymphatic involvement, n (%)	24 (38.1)	36 (45.0)	45 (45.0)	105 (43.2)
Median prior lines of therapy (IQR)	2 (2–3)	4 (4–7)	4 (3–5)	4 (3–5)
Time from diagnosis to first dose of nivolumab, median (IQR), years	3.1 (2.0–7.5)	6.2 (3.3–8.3)	3.5 (2.3–6.4)	4.5 (2.4–7.6)

Armand et al, JCO 2018
Ansell et al, Blood Advances, 2023

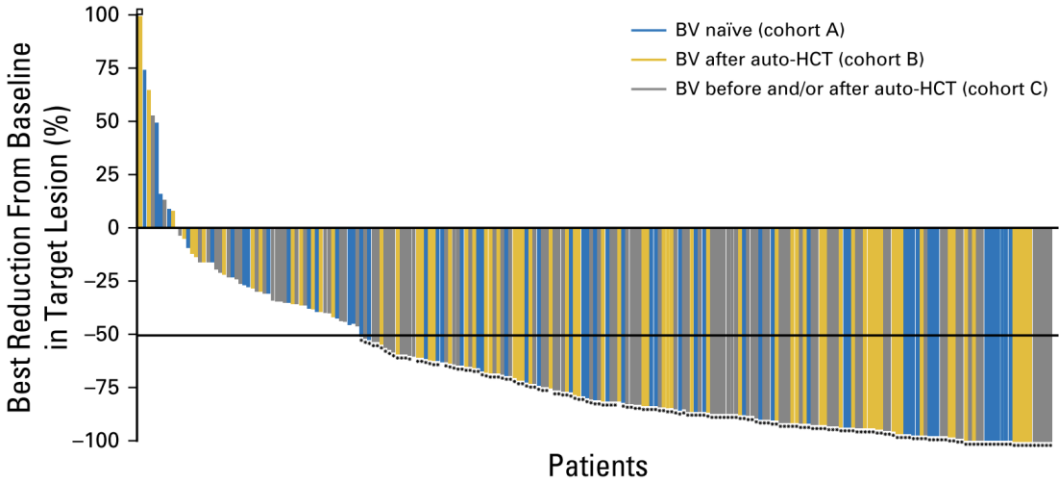
Nivolumab – Checkmate 205 (Sicherheit)

TRAEs (N = 243)	Any grade	Grade 3/4
Patients with TRAEs, n (%)	198 (81.5)	67 (27.6)
TRAEs occurring in ≥ 10% of patients, n (%)		
Fatigue	61 (25.1)	2 (0.8)
Diarrhea	39 (16.0)	2 (0.8)
Infusion-related reaction	34 (14.0)	1 (0.4)
Rash	29 (11.9)	2 (0.8)
Nausea	27 (11.1)	0
Pruritus	25 (10.3)	0
Immune-mediated AEs within 100 days of last dose		
Hypothyroidism/thyroiditis	35 (14.4)	0
Rash	29 (11.9)	4 (1.6)
Hepatitis	15 (6.2)	12 (4.9)
Pneumonitis	15 (6.2)	2 (0.8)
Hypersensitivity/infusion reactions	13 (5.3)	2 (0.8)
Diarrhea/colitis	6 (2.5)	5 (2.1)
Hyperthyroidism	6 (2.5)	0
Nephritis and renal dysfunction	3 (1.2)	1 (0.4)
Diabetes mellitus	2 (0.8)	1 (0.4)

Armand et al, JCO 2018
Ansell et al, Blood Advances, 2023

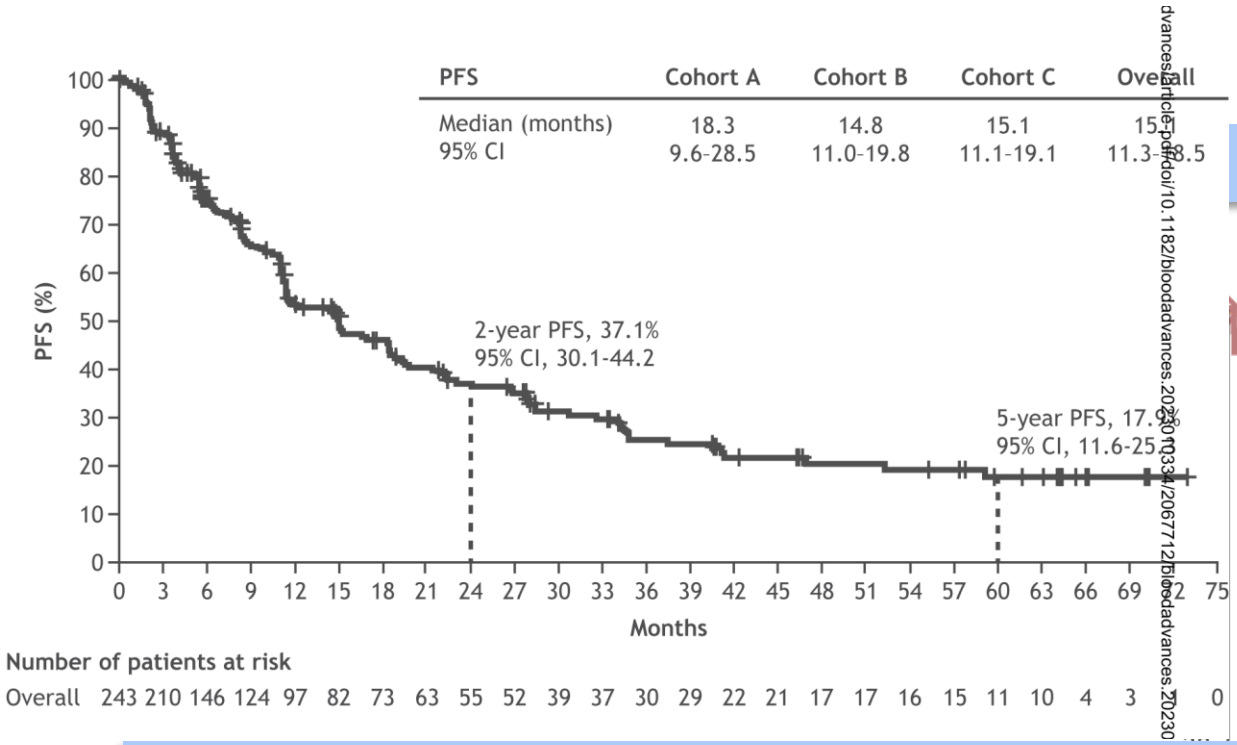
Nivolumab – Checkmate 205 - Ansprechen

Response	Cohort A (BV-naive) (n = 63)	Cohort B (BV after auto-HCT) (n = 80)	Cohort C (BV before and/or after auto-HCT) (n = 100)	Overall (N = 243)
ORR, % (95% CI)	65.1 (52.0–76.7)	71.3 (60.0–80.8)	75.0 (65.3–83.1)	71.2 (65.1–76.8)
BOR, n (%)				
CR	20 (31.7)	11 (13.8)	21 (21.0)	52 (21.4)
PR	21 (33.3)	46 (57.5)	54 (54.0)	121 (49.8)
SD	14 (22.2)	14 (17.5)	12 (12.0)	40 (16.5)
PD	8 (12.7)	7 (8.8)	11 (11.0)	26 (10.7)
Median time to response, months (range)	2.0 (1.5–4.6)	2.2 (1.6–11.1)	2.1 (0.8–17.9)	2.1 (0.8–17.9
IQR	1.9–2.3	1.9–3.0	1.9–3.8	1.9–3.6
Median time to CR, months (range)	3.9 (1.7–34.4)	4.4 (1.9–22.8)	4.2 (1.8–17.9)	4.0 (1.7–34.4
IQR	3.7–5.2	3.7–19.1	3.7–6.5	3.7–8.3
Median DOR, months (95% CI)	26.2 (15.2–NE)	16.6 (9.3–25.7)	18.2 (11.6–30.9)	18.2 (14.7–26.1)

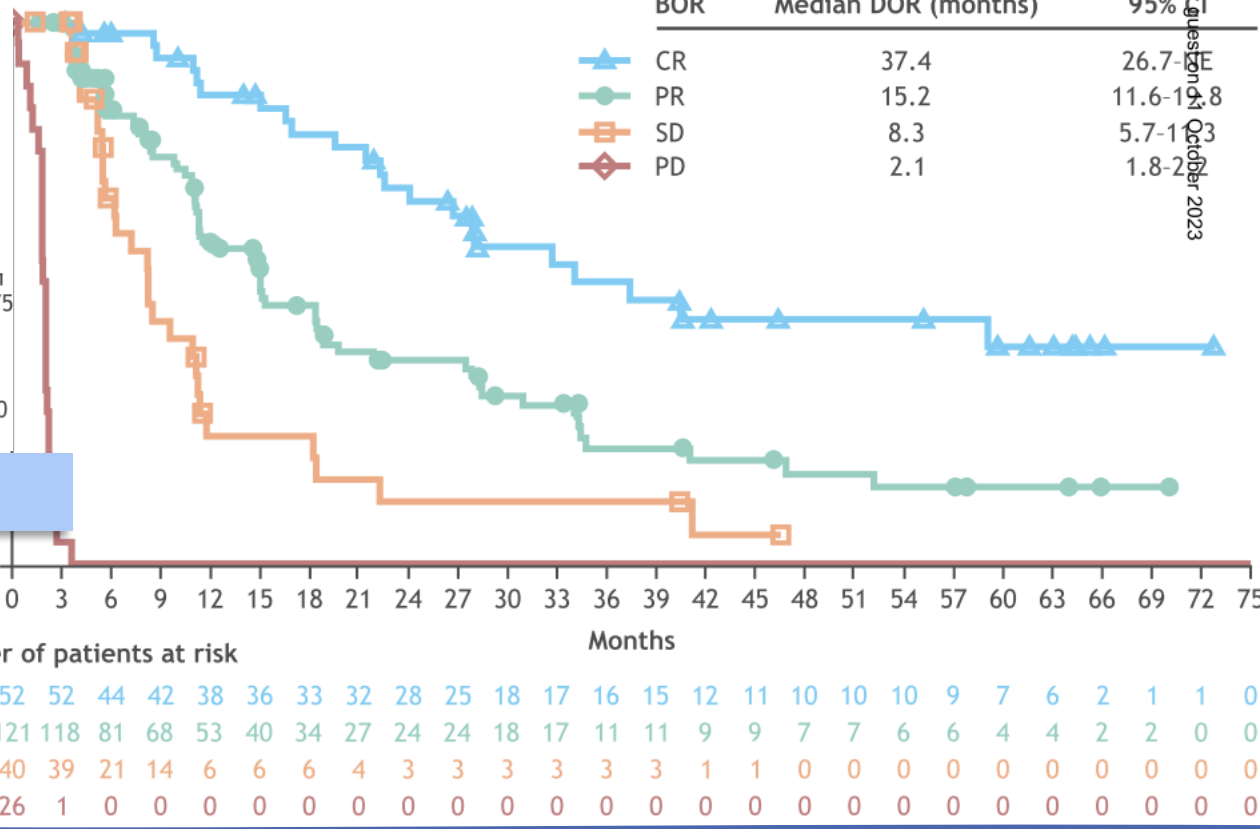


Armand et al, JCO 2018
Ansell et al, Blood Advances, 2023

Nivolumab – Checkmate 205 – 5 years follow-up



50% CR persistierte nach dem Absetzen der Anti-PD1 AK



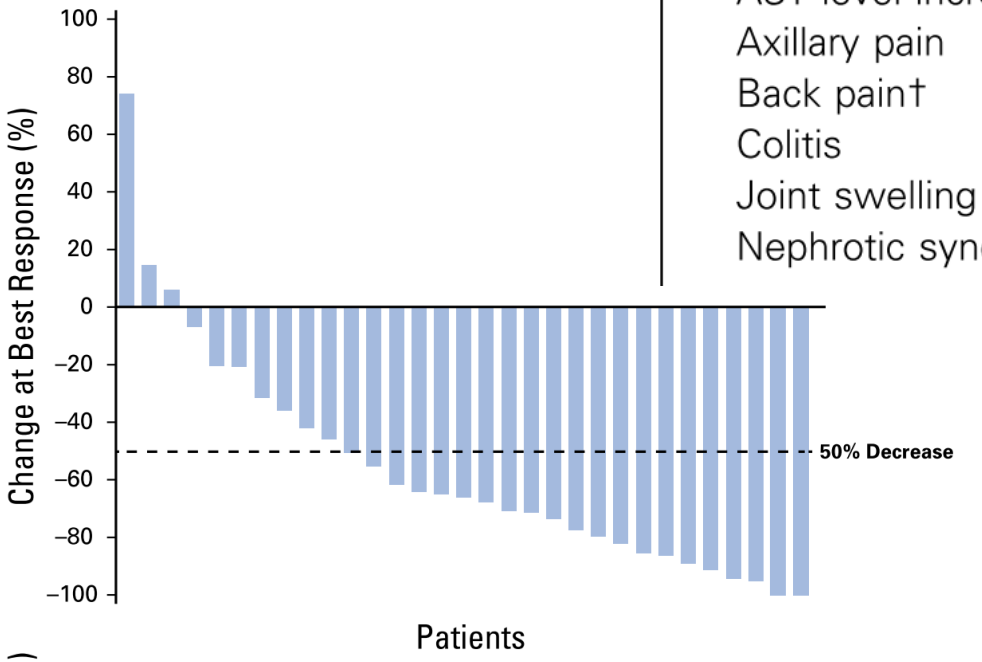
Gutes Ansprechen und akzeptable Nebenwirkungen.

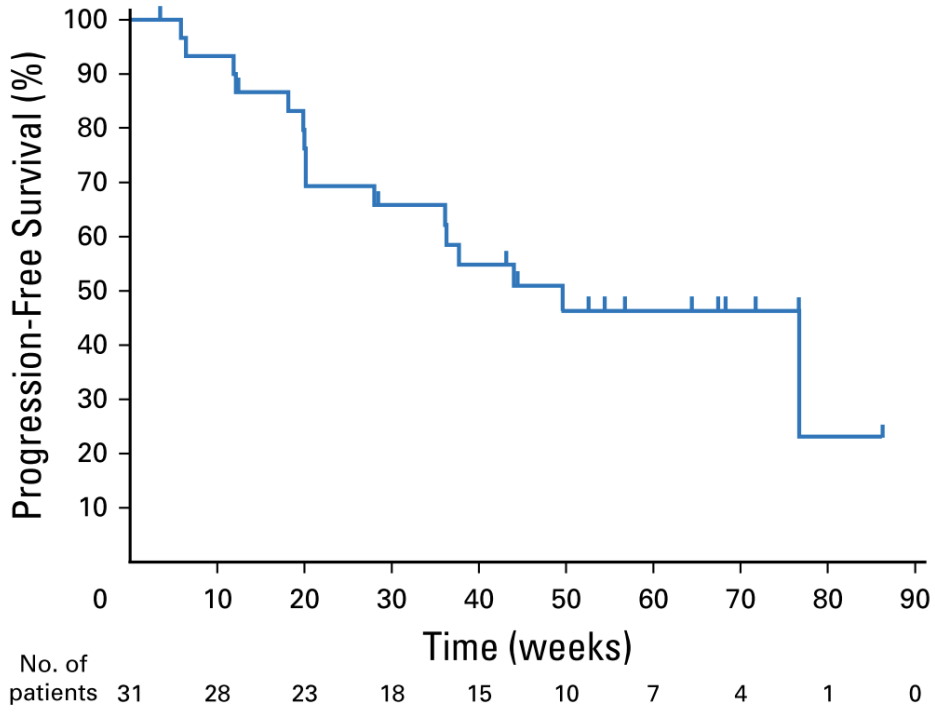
Ansell et al, Blood Advances, 2023

Pembrolizumab – Keynote-013

- Phase IB Studie
- Endpunkte: Sicherheit und anti-tumor Aktivität
- N=31, med. Alter 32 (20-67), Progress unter oder nach BV

Treatment-related AEs of grade ≥ 3
- ALT level increased*
- AST level increased*
- Axillary pain
- Back pain†
- Colitis
- Joint swelling
- Nephrotic syndrome†





Armand et al, JCO, 2016

Pembrolizumab - Keynote 087

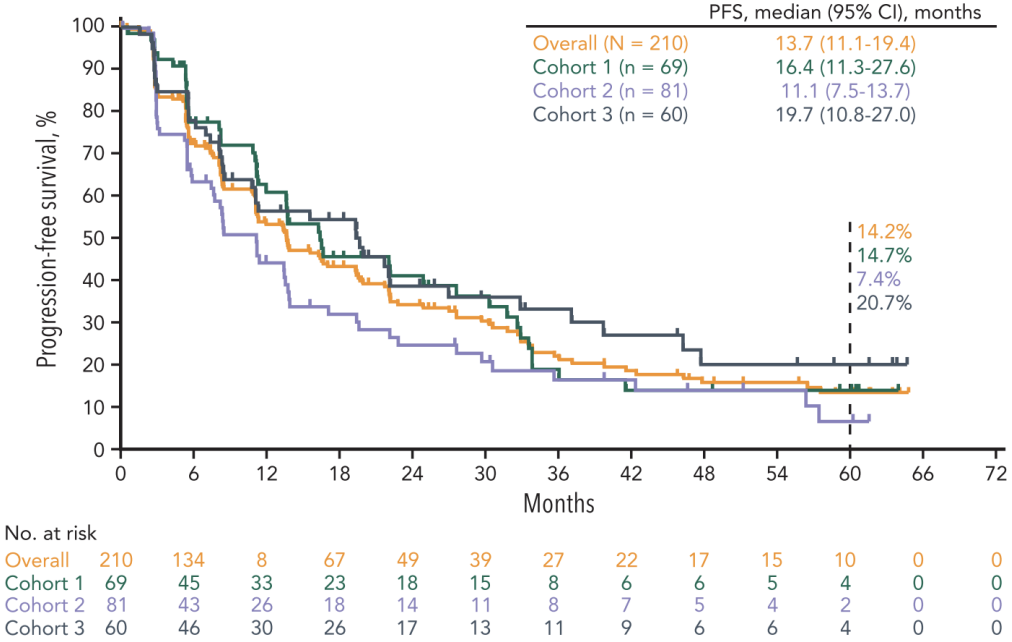
- Phase II Studie, Primärer Endpunkt ORR
- N=210 Patienten mit Rezidiv :
  - cohort 1 nach ASCT und BV, N=69,
  - cohort 2 salvage Chemotherapie und BV ohne ASCT, N=81
  - cohort 3 ASCT ohne BV, N=60

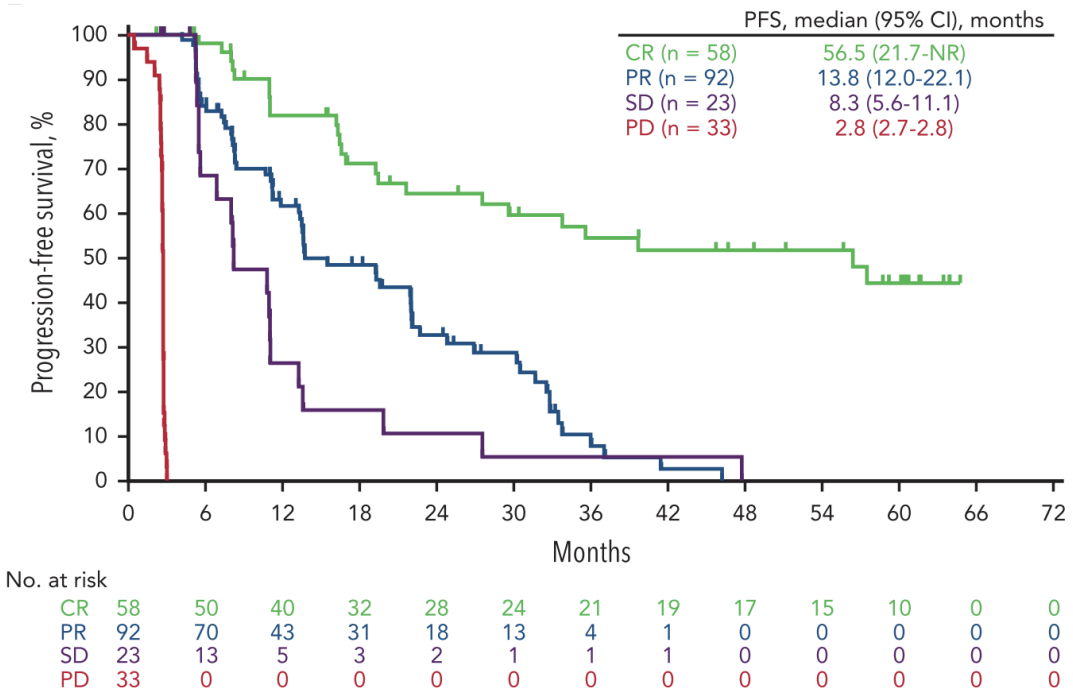
- Pembrolizumab mono für 24 Monate

- Nach Erreichen einer CR, falls PD nach Absetzen– Reexposition möglich

Chen et al., JCO, 2017,
Armand et al, Blood, 2023

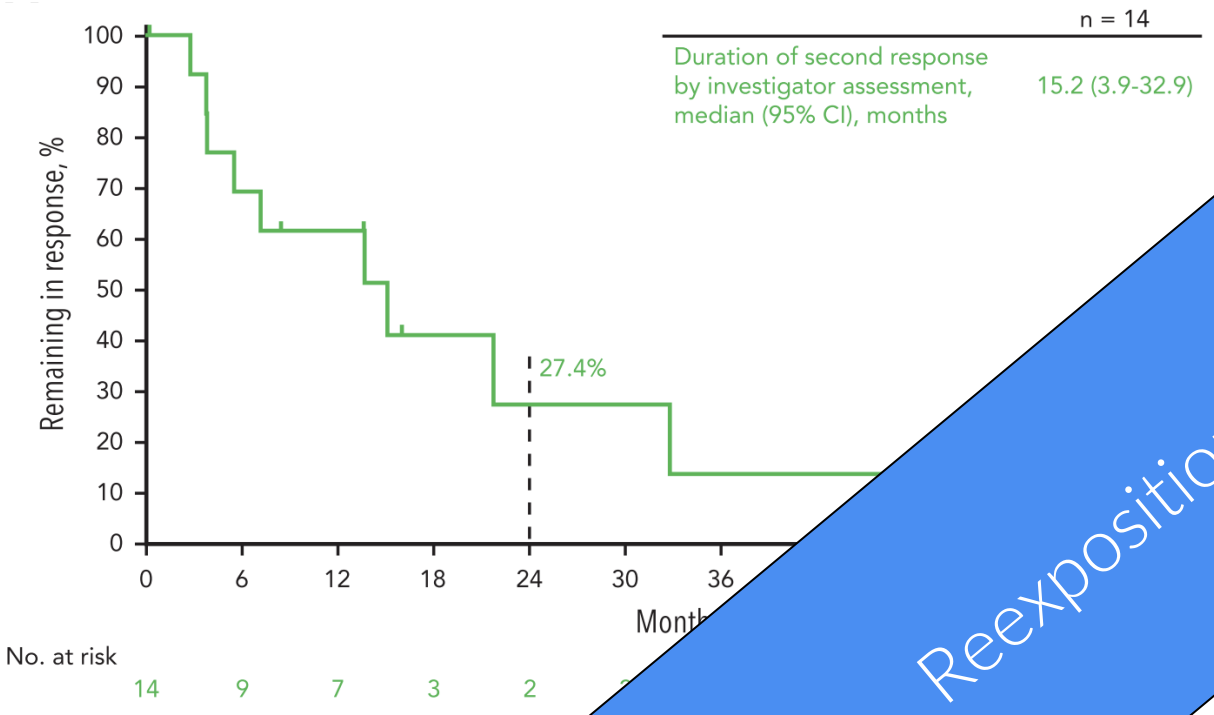
Pembrolizumab - Keynote 087 - PFS





Chen et al., JCO, 2017,
Armand et al, Blood, 2023

Pembrolizumab - Keynote 087 - Reexposition



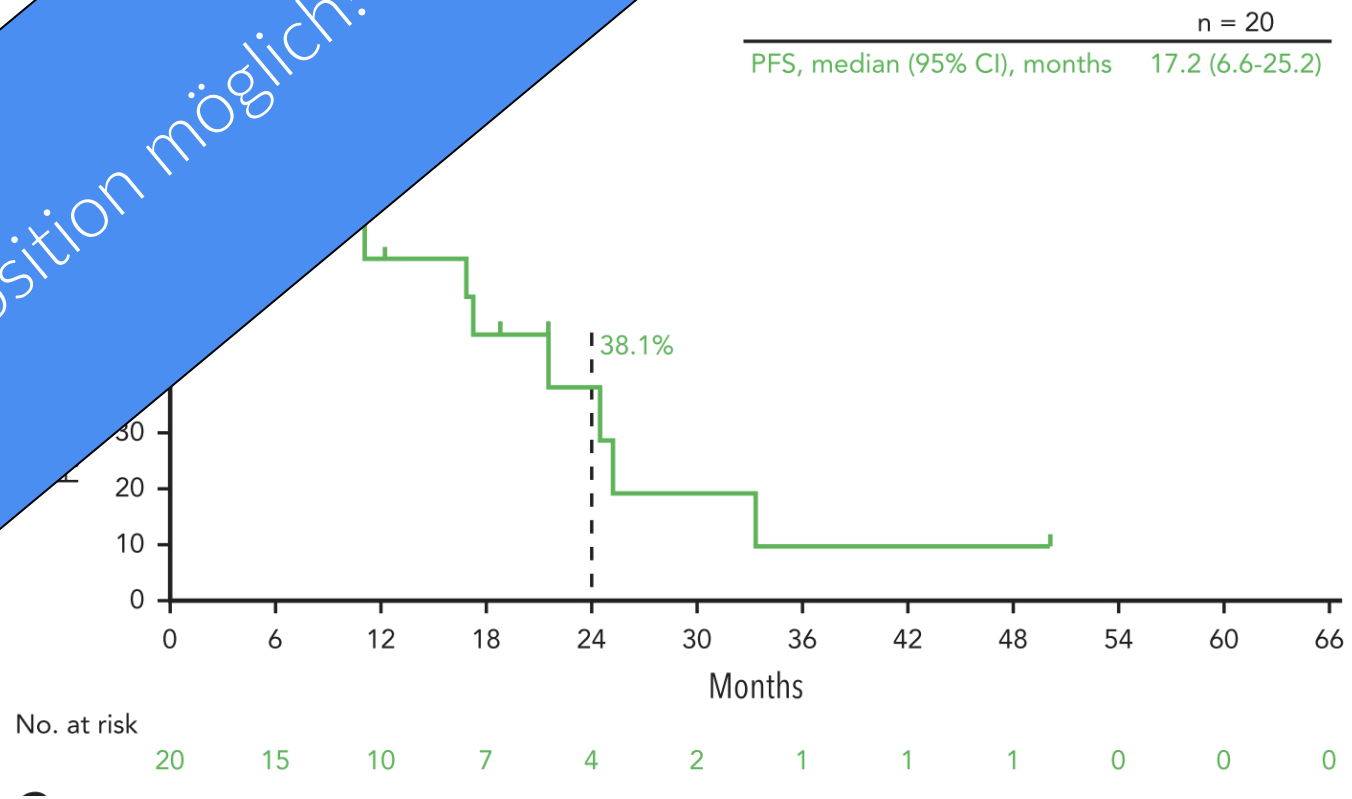
n = 14

Duration of second response by investigator assessment, median (95% CI), months 15.2 (3.9-32.9)

Reexposition möglich!

n = 20

PFS, median (95% CI), months 17.2 (6.6-25.2)



Chen et al., JCO, 2017,
Armand et al, Blood, 2023

Pembrolizumab – Keynote 204

- Phase 3 randomisierte Studie
- N=304 Patienten, Rezidiv nach ASCT oder ungeeignet für ASCT
- Primärer Endpunkt: PFS

Characteristic, n (%)	Pembrolizumab n=151	BV n=153
Median age, years (IQR range)	36 (28-53)	35 (28-50)
≥65 years	27 (18)	22 (14)
Male	84 (56)	90 (59)
ECOG PS		
0	86 (57)	100 (65)
1	64 (42)	53 (35)
2[a]	1 (1)	0
Geographical region		
North America	27 (18)	30 (20)
Europe	49 (32)	46 (30)
Japan	9 (6)	7 (5)
Other	66 (44)	70 (46)
Prior auto-SCT	56 (37)	56 (37)
Disease status after frontline therapy		
Primary refractory	61 (40)	62 (41)
Relapsed <12 months	42 (28)	42 (27)
Relapsed ≥12 months	48 (32)	49 (32)
Median number of previous lines of therapies (IQR)	2 (2-3)	3 (2-3)
1	27 (18)	28 (18)
≥2	124 (82)	125 (82)
Prior BV	5 (3)	10 (7)
Prior radiation	58 (38)	61 (40)
Bulky disease	35 (23)	25 (16)
Baseline B-symptoms*	43 (28)	36 (24)
Baseline bone marrow involvement	12 (8)	5 (3)

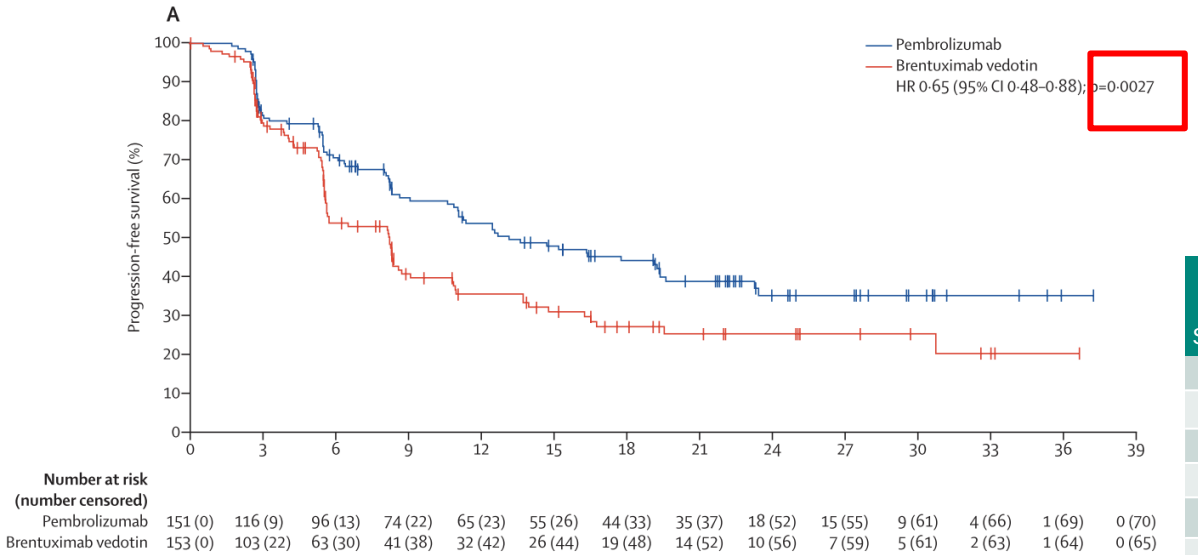
Kuruvilla J, et al. *Lancet Oncol.* 2021

Pembrolizumab – Keynote 204 Response rates

Response	Pembrolizumab n=151	Brentuximab vedotin n=153
Proportion of patients with objective response, n (%)	99 (65.6)	83 (54.2)
95% CI	57.4-73.1	46.0-62.3
Estimated difference (95% CI)	11.3 (0.2-22.1)	
P-value	0.023	
Best overall response, n (%)		
Complete response	37 (25)	37 (24)
Partial response	62 (41)	46 (30)
Stable disease	21 (14)	36 (24)
Progressive disease	26 (17)	28 (18)
Not evaluable	1 (1)	1 (1)
No assessment	4 (3)	5 (3)
Median time to response, months (IQR)	2.8 (2.7-3.0)	2.8 (2.7-2.9)
Median duration of response, months (95% CI)	20.7 (12.4-NR)	13.8 (5.8-NR)

Kuruvilla J, et al. *Lancet Oncol.* 2021

Pembrolizumab – Keynote 204 – Ansprechen



Subgroup	Pembrolizumab group n/N	Pembrolizumab group Median PFS (95% CI)	Brentuximab vedotin group n/N	Brentuximab vedotin group Median PFS (95% CI)	Hazard Ratio (95% CI)
Overall	81/151	13.2 (10.9-19.4)	88/153	8.3 (5.7-8.8)	0.65 (0.48-0.88)
Prior autologous stem-cell transplant					
Yes	30/56	14.7 (8.3–NR)	27/56	10.8 (5.8–19.6)	0.72 (0.42-1.23)
No	51/95	12.5 (8.3–19.4)	61/97	5.7 (5.5–8.3)	0.61 (0.42-0.89)
Disease status after frontline therapy					
Primary refractory	34/61	12.5 (8.2–23.4)	38/62	5.5 (3.1–8.2)	0.52 (0.33-0.83)
Relapsed <12 mo	22/42	16.4 (8.3–NR)	24/42	11.0 (8.2–16.6)	0.82 (0.45-1.48)
Relapsed ≥12 mo	25/48	13.6 (7.0–NR)	26/49	8.3 (5.6–14.0)	0.72 (0.41-1.25)
Sex					
Female	38/67	15.2 (11.1–19.6)	43/63	5.7 (5.6–8.8)	0.49 (0.31-0.78)
Male	43/84	11.4 (8.2–NR)	45/90	8.4 (5.8–14.0)	0.75 (0.49-1.14)
Age					
<65 yr	60/124	19.3 (11.3–NR)	72/131	8.3 (5.7–11.0)	0.59 (0.42-0.84)
≥65 yr	21/27	8.2 (3.0–11.4)	16/22	5.5 (3.9–8.3)	0.64 (0.32-1.30)
Age					
<65 yr	60/124	19.3 (11.3–NR)	72/131	8.3 (5.7–11.0)	0.59 (0.42-0.84)
≥65 to <75 yr	16/18	8.0 (2.8–11.4)	10/16	5.7 (3.9–8.4)	0.79 (0.31-1.98)
≥75 to <85 yr	5/9	8.3 (2.8–NR)	6/6	3.5 (0.9–14.8)	0.25 (0.05-1.30)

Kuruvilla J, et al. *Lancet Oncol.* 2021

Pembrolizumab – Keynote 204 – Immun-bedingte AEs

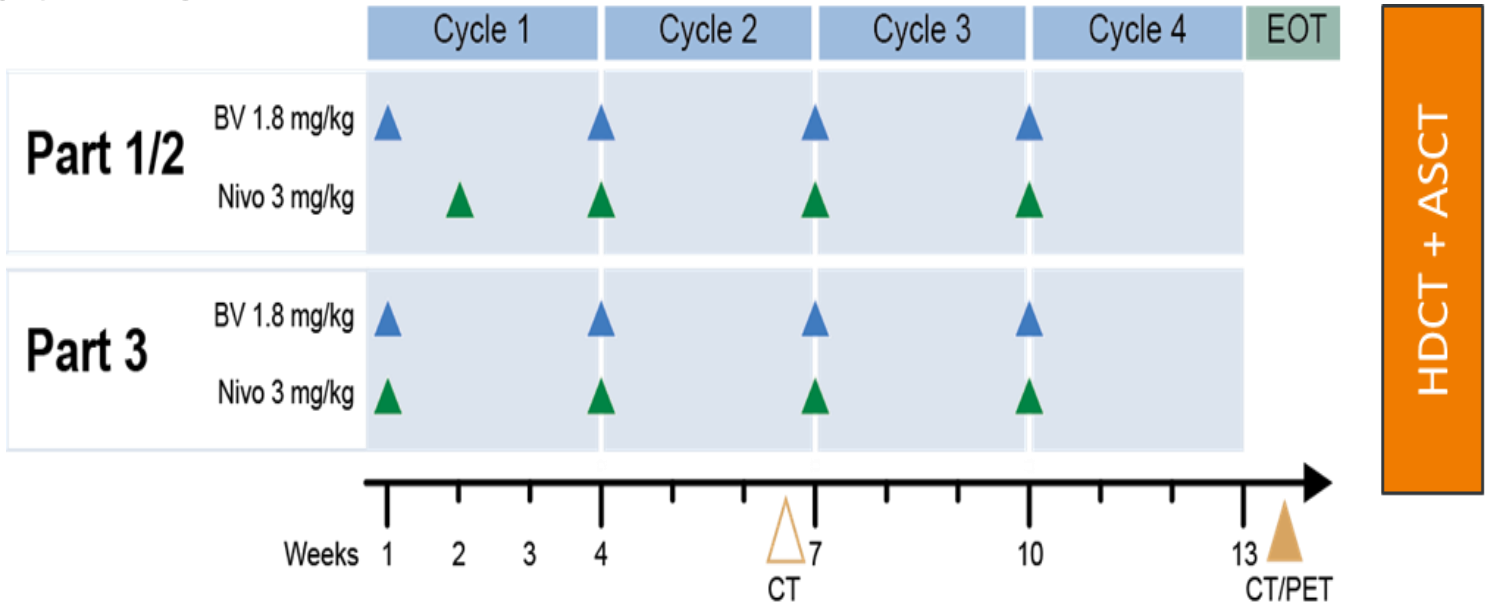
Event, n (%)	Pembrolizumab N = 148	Brentuximab Vedotin N = 152
Any immune-mediated AE	49 (33.1)	11 (7.2)
Hypothyroidism	28 (18.9)	4 (2.6)
Pneumonitis	16 (10.8)	
Hyperthyroidism	8 (5.4)	
Severe skin reactions	3 (2.0)	
Myocarditis	2 (1.4)	
Pancreatitis		
Thyroiditis		
Uveitis		
Adrenal insufficiency		
Colitis		
Encephalitis		0
Hepatitis		0
Myositis		0
Nephritis		1 (0.7)

Gr. 3-5 AE bei 11 (7%) Patienten mit Pembro und 3 (2%) Patienten mit BV.
16 Pat. mit Pneumonitis

Kuruvilla J, et al. *Lancet Oncol.* 2021

BV und Nivolumab

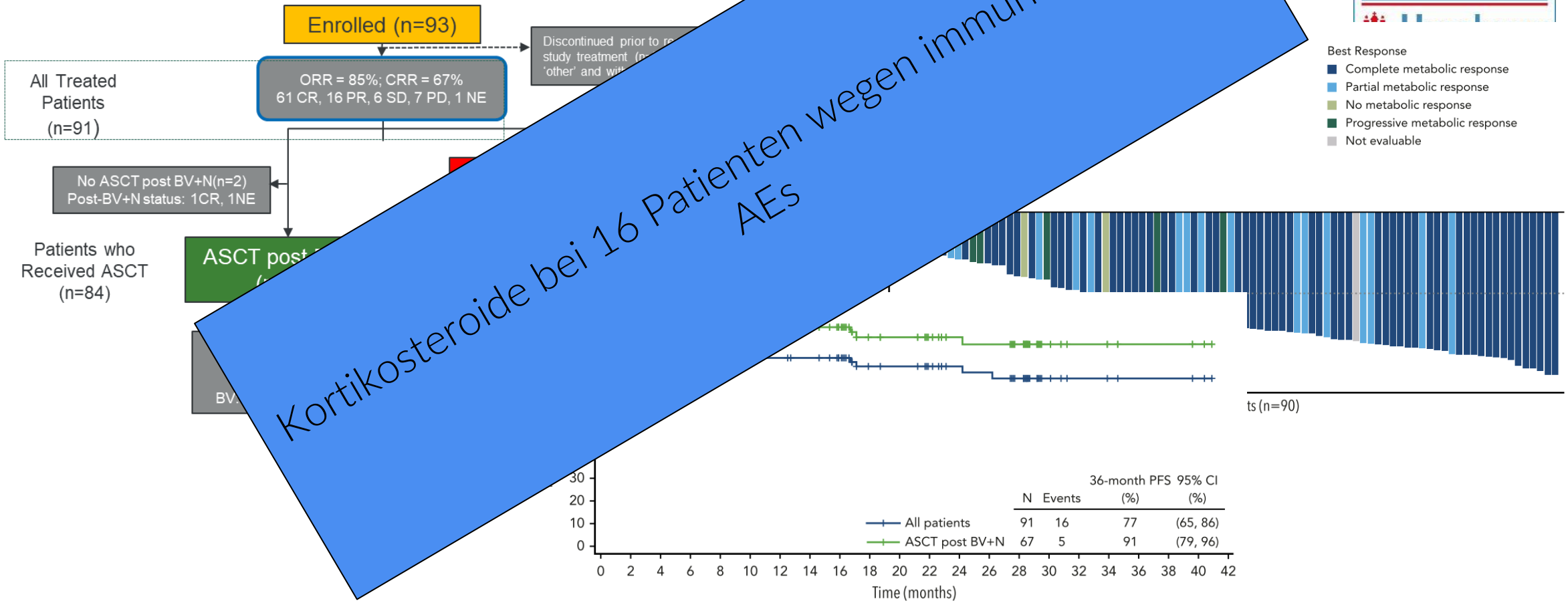
- Phase I-II Studie
- N=91 Patienten mit r/r HL, Primäre Ziele: Sicherheit und Anti-Tumor Aktivität
- Möglichkeit einer ASCT nach EOT



Advani et al, Blood, 2021

BV und Nivolumab

Kortikosteroide bei 16 Patienten wegen immun-bedingter AEs

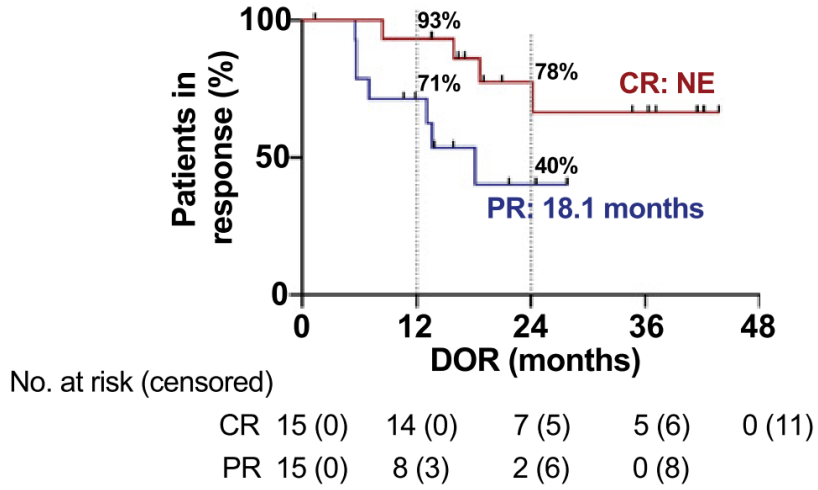


Advani et al, Blood, 2021

PD1-Blockade und HMA

- Kombination: Camrelizumab+Decitabine
- 51 Patienten mit r/r HL nach mindestens 2 Therapielinien

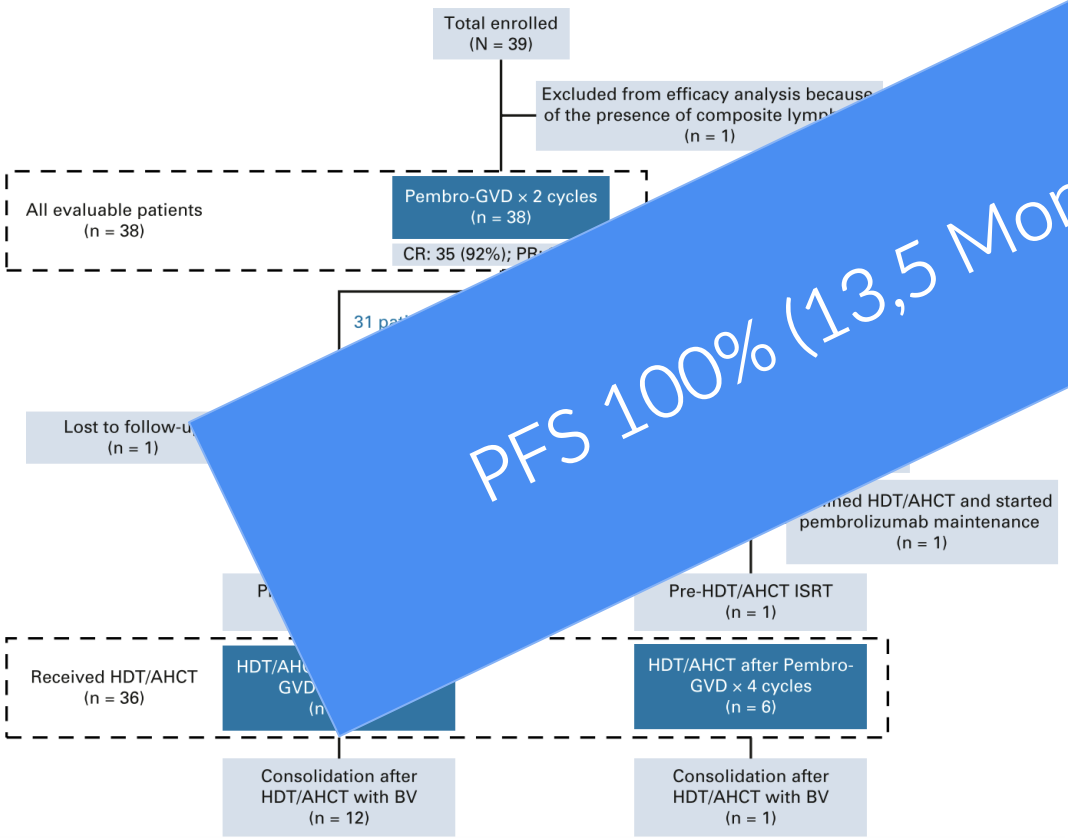
Adverse event	Any grade	Grade 3–4
Any adverse event	48 (94)	26 (51)
Reactive capillary endothelial proliferation	39 (76)	0
Leukocytopenia	30 (59)	17 (33)
Increased triglyceride	12 (24)	0
Pyrexia	11 (22)	1 (2)
Pain in the lesion	7 (14)	0
Increased uric acid	6 (12)	0
Increased transaminase	5 (10)	0
Hypothyroidism	4 (8)	0
Fatigue	4 (8)	0
Myalgia	4 (8)	0
Nausea	4 (8)	0
Thrombocytopenia	3 (6)	1 (2)
Thrombocytosis	3 (6)	0
Rash	3 (6)	0
Pneumonitis	3 (6)	0



Wang et al, Clin Canc Res, 2021

PD1 Blockade und Chemotherapie (Pembrolizumab + GVD)

- Phase 2 Studie
- N=39 Patienten mit r/r HL (nach mind



PFS 100% (13,5 Monate Beobachtungszeit)

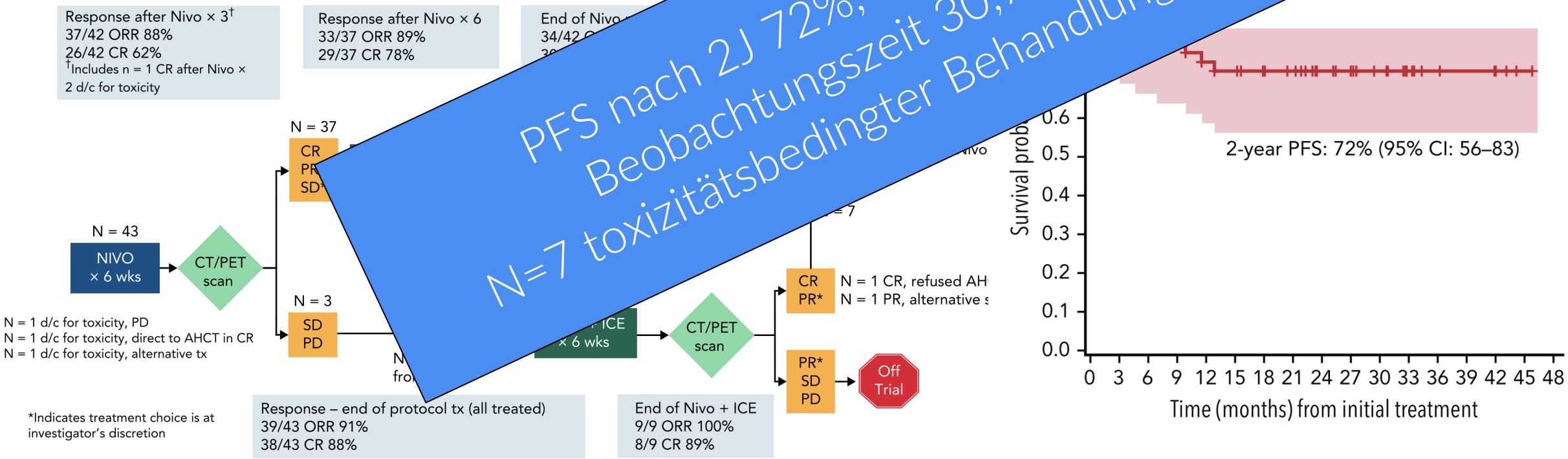
AEs Gr. 3:
Hautausschlag (n = 1)
erhöhte AST/ALT (n = 4),
Mucositis (n = 2)
Neutropenie (n = 4)
Hyperthyroidismus (n = 1)

Moskowitz et al, JCO 2021

PD1 Blockade und Chemotherapie (Nivolumab + ICE)

- Phase II randomisierte Studie
- primär refraktäre HD oder Rezidiv nach 1. Therapielinie

PFS nach 2J 72%, OS 95% (mediane Beobachtungszeit 30,7 Monate)
N=7 toxizitätsbedingter Behandlungsabbruch

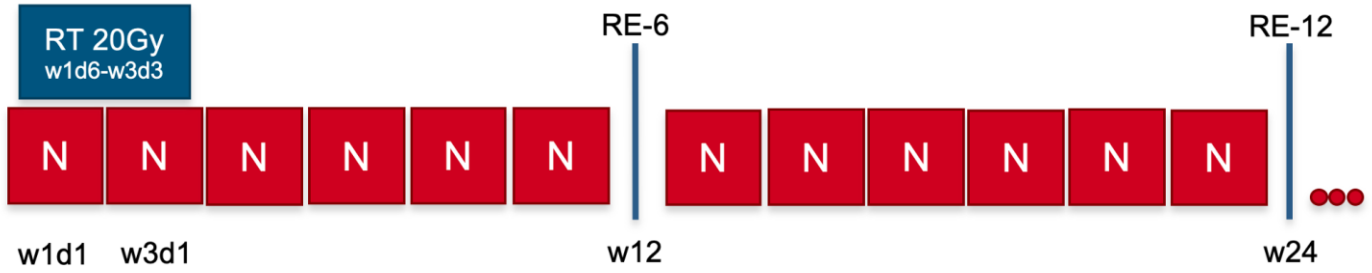


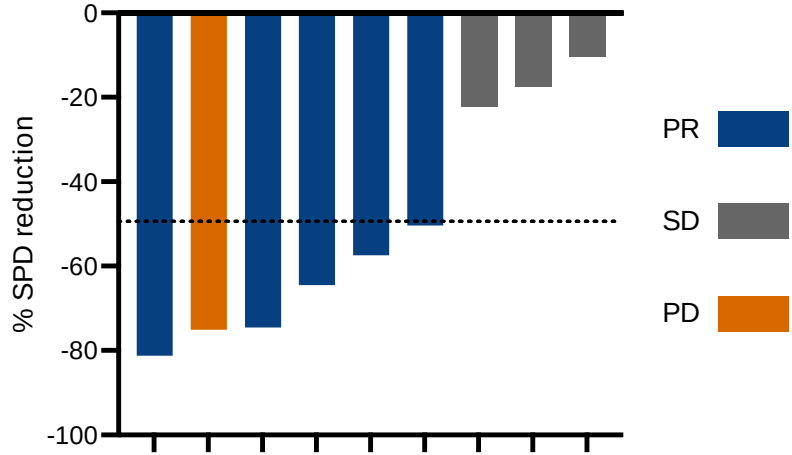
Mei et al, Blood 2022

PD1 Blockade und Radiotherapie

- AERN Studie - abskopaler Effekt der Strahlentherapie mit PD1 (außerhalb des Strahlenfeldes)
- Fraktioniert 20 Gy auf „single“ Läsion
- Nivolumab bis 1,5 Jahre, PD oder relevante Toxizität

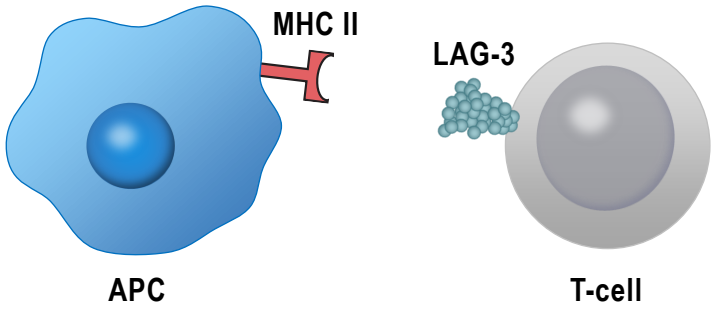
relapsed/refractory Hodgkin lymphoma
- PD on anti-PD1
- SD >6 months on anti-PD1

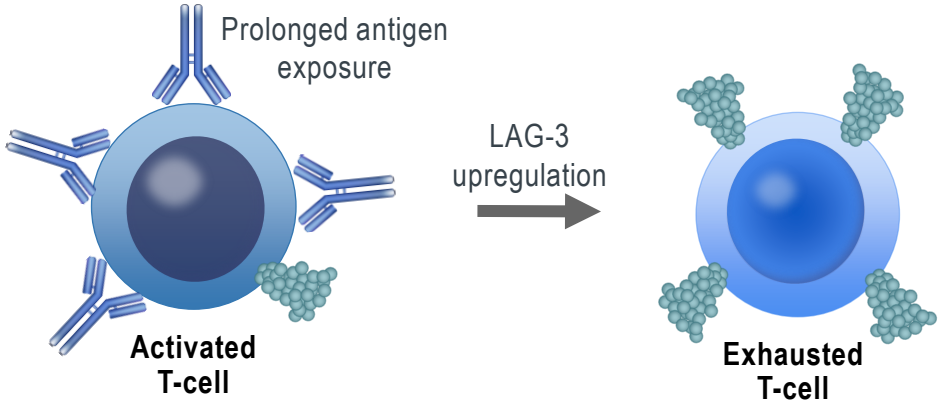




Bröckelmann et al., EHA 2022

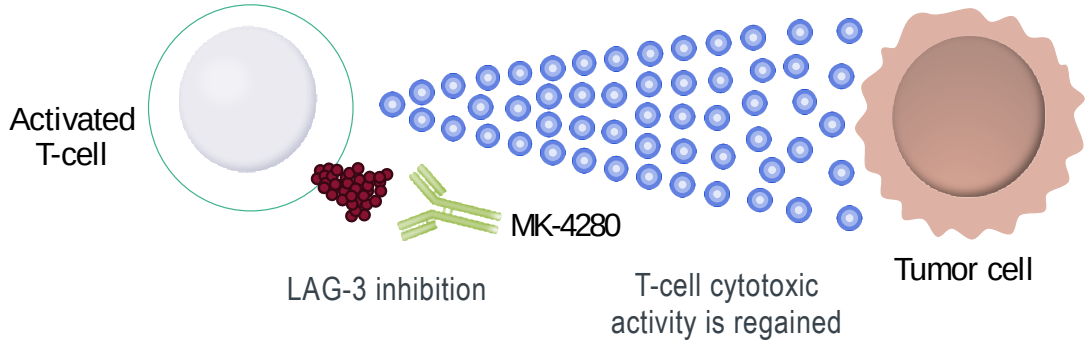
PD1 Blockade und andere immunologische Targets - LAG3





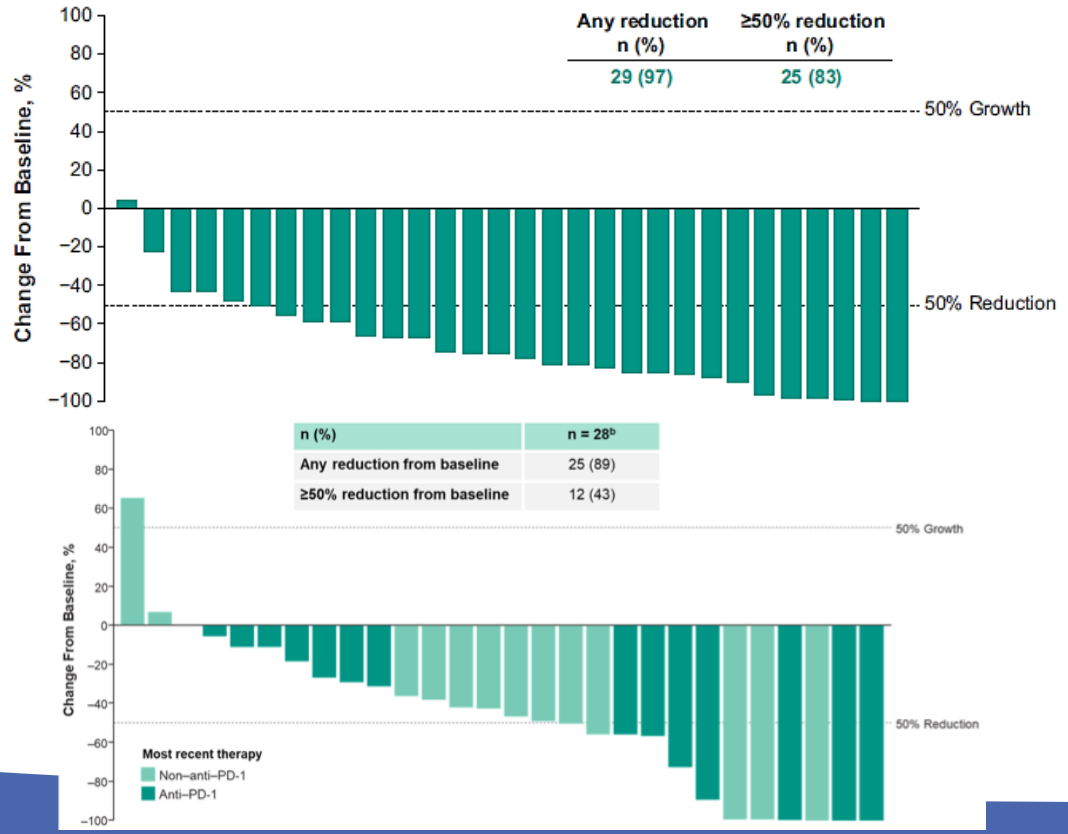
Favezelimab (MK-4280) Blocks the Interaction Between MHC Class II Receptors and LAG-3

Favezelimab (MK-4280) Could Inhibit LAG-3 Upregulation Restoring T-cell Effector Functions Targeting Tumor Cells



Pembro + LAG-3 Inhibitor (MK4280 Studie)

- Phase I/II Studie, 64 Patienten, davon 30 PD1 naive, 34 mit PD1 Preexposition
- Kombination von Pembrolizumab + Favezelimab (Anti-LAG-3)



Timmermann et al, EHA 2023

	N = 30
Objective response rate,[2b] n (% [95% CI])	24 (80 [61-92])
BOR, n (%)	
CR, n (%)	10 (33)
PR, n (%)	14 (47)
SD, n (%)	3 (10)
PD, n (%)	3 (10)

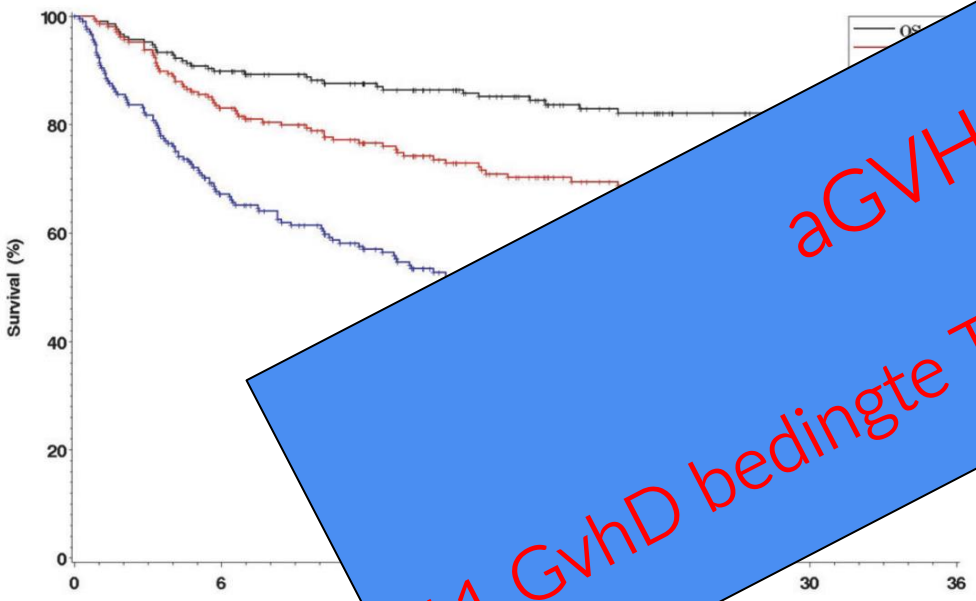
Johnson et al, EHA 2023

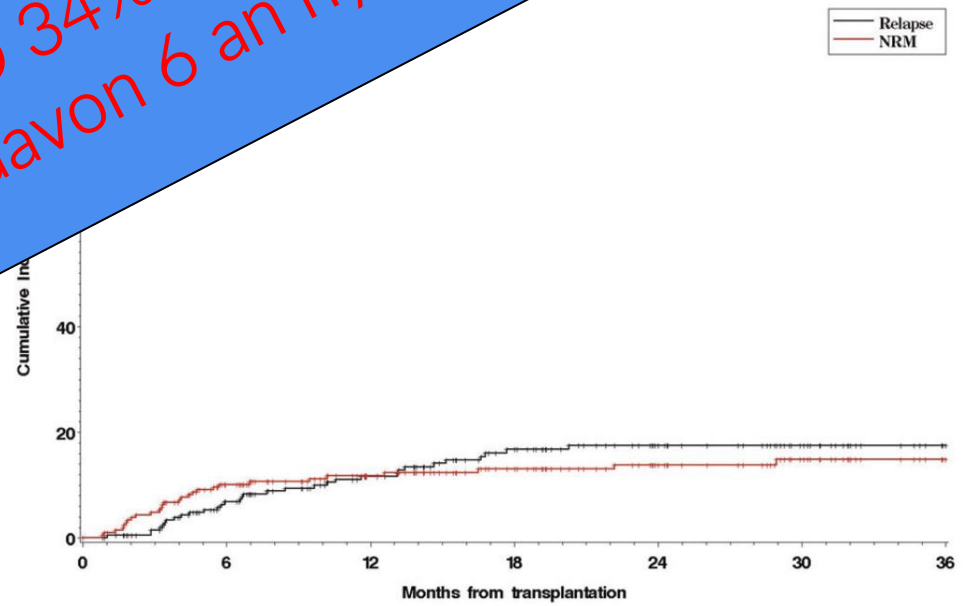
	Total N = 34	Most recent therapy Anti-PD-1 N=17	Most recent therapy Non-Anti-PD-1 N=17
Objective response rate, n (% [95% CI])	10 (29 [15-48])	6 (35 [14-62])	4 (24 [7-50])
BOR, n (%)			
CR, n (%)	3 (9)	1 (6)	2 (12)
PR, n (%)	7 (21)	5 (29)	2 (12)
SD, n (%)	12 (35)	8 (47)	4 (24)
PD, n (%)	7 (21)	2 (12)	5 (29)
Not available[a], n (%)	5 (15)	1 (6)	4 (24)

Check-Point Inhibition and allo HSCT

- retrospektive EBMT-Analyse von 209 Patie

aGVHD 54%, Gr. 3-4 15%
chrGvHD 34%
11 GvhD bedingte Todesfälle (davon 6 an hyperakuten GvHD)





Merryman et al., Leukemia 2021

Schlussfolgerung – Anti PD1 Behandlung

- langanhaltende Remissionen bei einem Teil der Patienten nach multiplen Rezidiven
- Therapiestop bei CR >1 Jahr ist möglich. Reexposition effektiv
- Konsolidierende hoch-dosis Therapie bei Respondern auf PD1-Blockade effektiv
- effektiv in 1. Rezidiv - > Vermeidung der hoch-dosis Therapie zukünftig?

- Allogene Transplantation nach Anti-PD1 Behandlung möglich (hohe Rate der GvHD)

Vielen Dank!!!!

GHSG Studienzentrale

Studienteam der UKL:
- Karolin Hubert
- Lymphomteam

- Prof. Dr. M. Herling
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Phase II und III Studien

Study	Phase	Key Inclusion	Agent	*n*	ORR (CR)	PFS (Median Follow Up)	OS	mDOR (Median Follow Up)
Multiple R/R Disease: anti-PD-1 mAb monotherapy								
Younes 2016 [18] Armand 2018 [19] Ansell 2021 [20]	II	Post ASCT +/− BV	Nivo	243	71% (21%)	37% (24 m) 18% (60 m)	87% (24 m) 71% (60 m)	18 m (58 m)
Chen 2017 [21] Chen 2019 [22] Armand 2021 [23]	II	Post ASCT +/− BV or R/R to first line salvage therapy	Pembro	210	71% (28%)	44% (60 m)	71% (60 m)	7 m (60 m)
Zinzani 2020 [24]	II	Primary Refractory Disease subgroup	Pembro	71	82% (35%)	32% (24 m)	94% (24 m)	17 m (28 m)
Kuruvilla 2021 [25]	III	Post or ineligible for ASCT	Pembro vs. BV	304	N/A	54% vs. 36 (12 m)	N/A	N/A
Song 2020 [26] Song 2022 [27]	II	Post or ineligible for ASCT	Tislelizumab	70	87% (67%)	41% (36 m)	85% (36 m)	32 m (10 m)
Nie 2019 [28] Liu 2021 [29]	II	Post 2+ prior LOT	Camrelizumab	19	90% (32%)	67% (24 m)	63% (24 m)	NR
Song 2019 [30]	II	Post ASCT	Camrelizumab	75	76.0% (28%)	81% (6 m) 67% (12 m)	NR	NR