Immune Checkpoints

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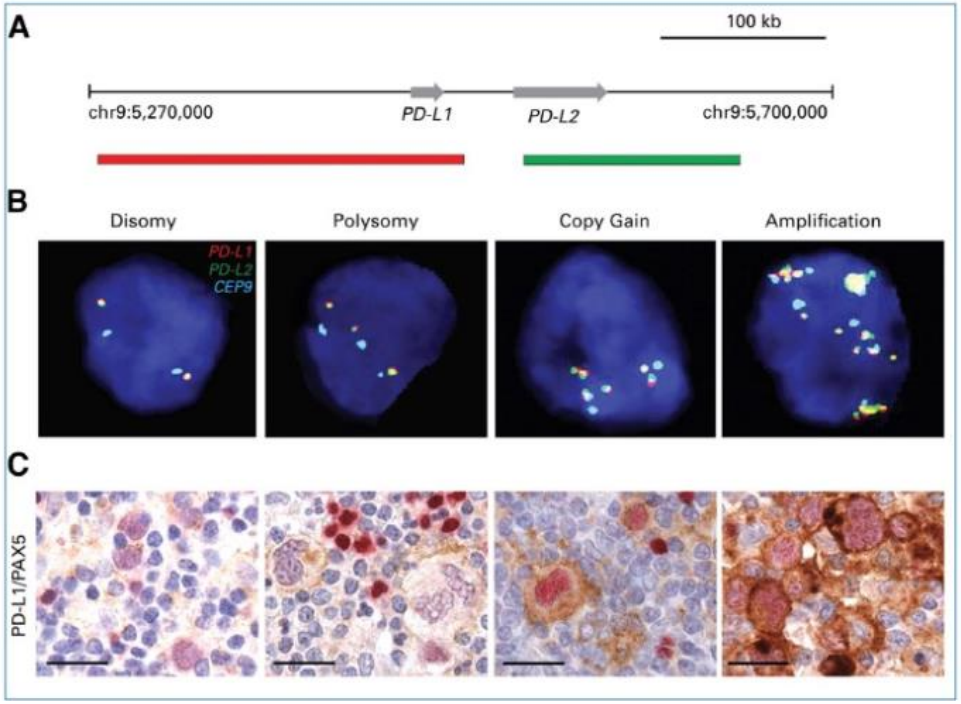
PD-1 and PD-L1/L2 Pathway

- PD-1 is an immune checkpoint receptor[1] . Binding of PD-1 by its ligands PD-L1 or PD-L2 leads to downregulation of T-cell function[1]. This mechanism is usurped by many tumors[1]
- Classical HL (cHL) is characterized pathologically by a failed immune response
- cHL frequently harbors alterations at 9p24.1 (including amplification), leading to overexpression of PD-L1 and PD-L2, on malignant Reed–Sternberg cells and on inflammatory cells in the tumor microenvironment → HL may have a genetically driven vulnerability to PD-1 blockade
- PD-1 blockade through mAb therapy (Nivolumab, Prembolizumab) can restore effective anti-tumor immunity[2,3]



9p24.1 encodes PD-L1, PD-L2

Vast majority of cases with copy gain or amplification

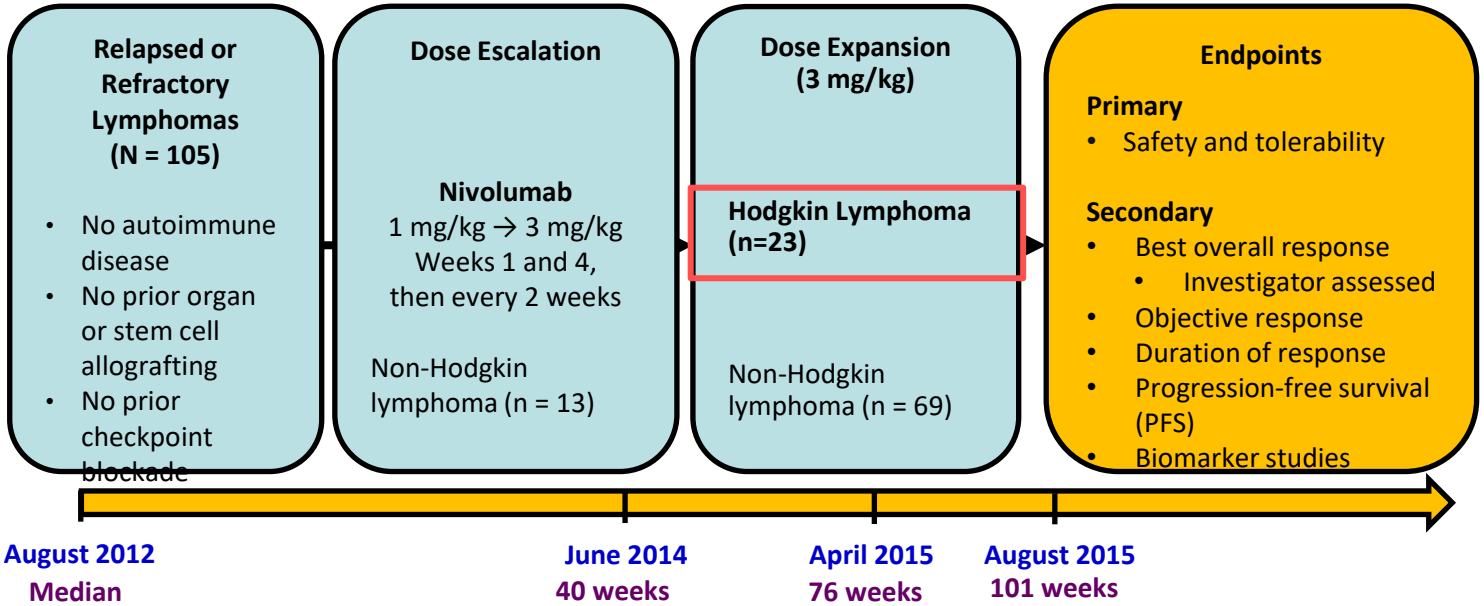
In chemotherapy treated patients, amplification associated with inferior PFS

Roemer et al J Clin Oncol 2016

1. Keir ME et al. Annu Rev Immunol. 2008; 2. Pardoll DM. Nat Rev Cancer. 2012;2; 3. Topalian et al. N Engl J Med. 2012.

Resultados Clínicos de los ensayos clínicos fase I y II

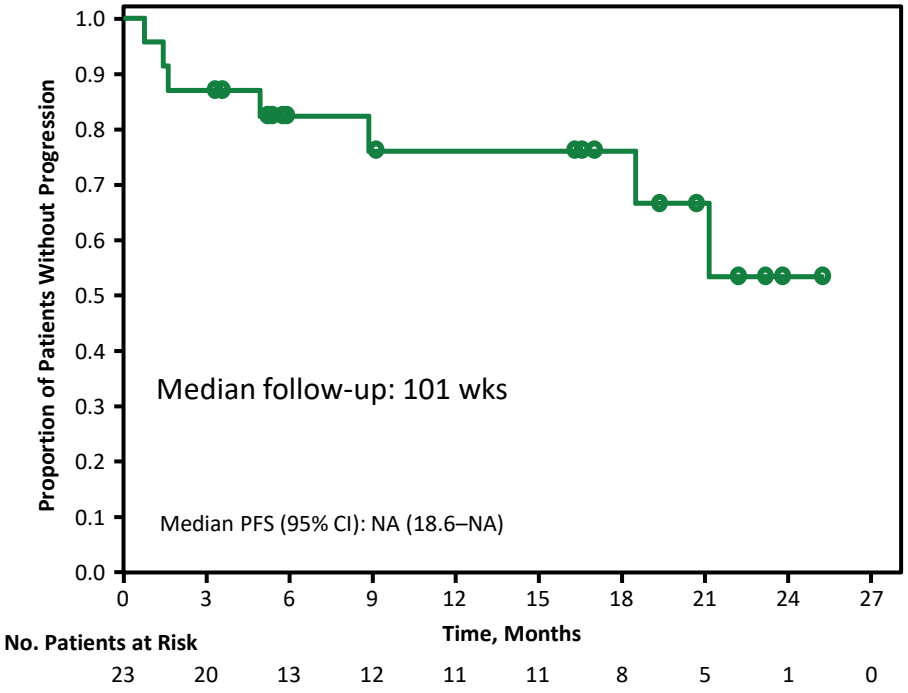
Fase 1 CHECKMATE 039 (CA209-039)

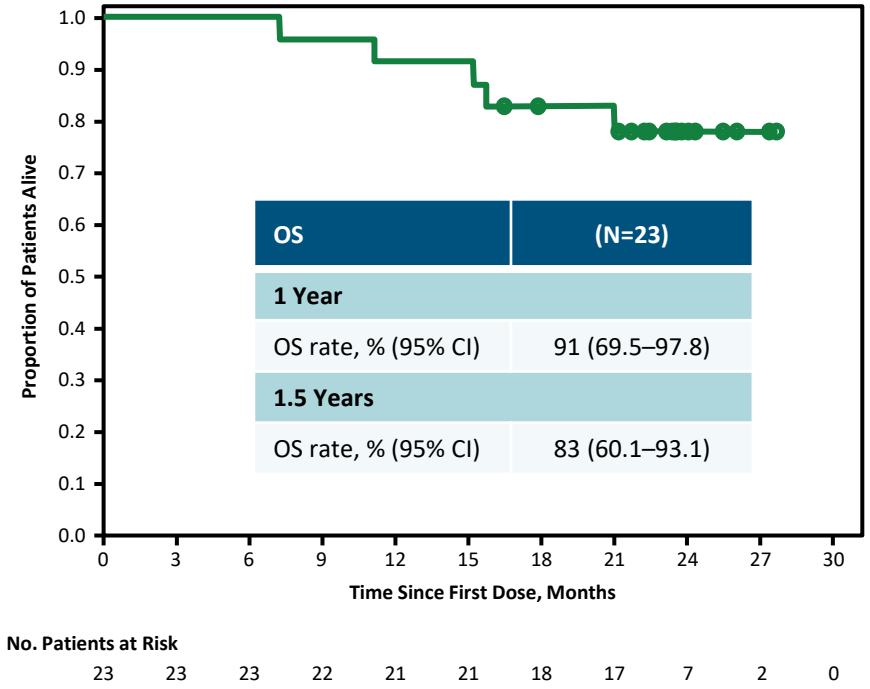


Best Objective Response	cHL (n = 23)	
	n (%)	95% CI
Objective response rate	20 (87)	66.4–97.2
CR	5 (22)	7.5–43.7
PR	15 (65)	42.7–83.6
SD	3 (13)	

Ansell et al. NEJM 2015

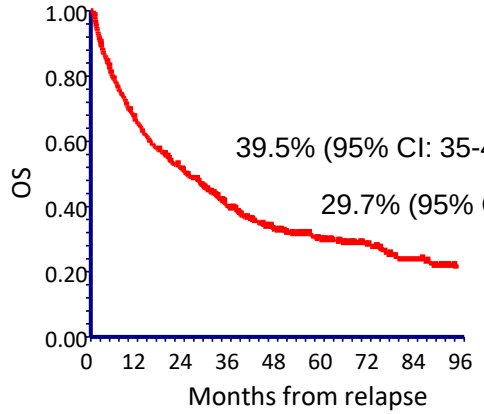
CHECKMATE 039 Outcomes



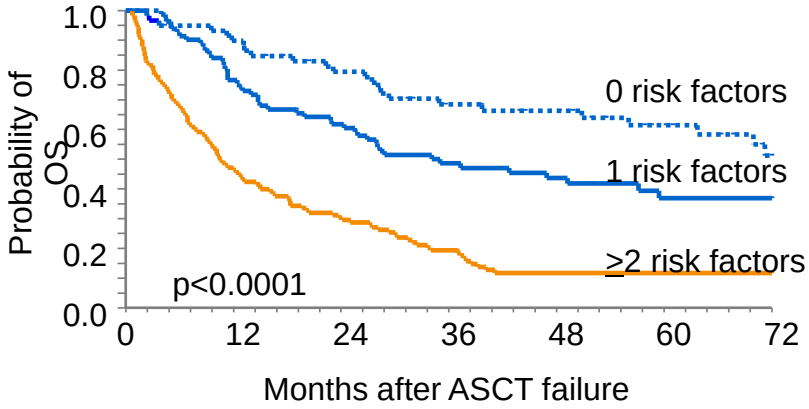


Ansell et al. NEJM 2015

OS from relapse after an ASCT. The experience of the LWP EBMT/GITMO



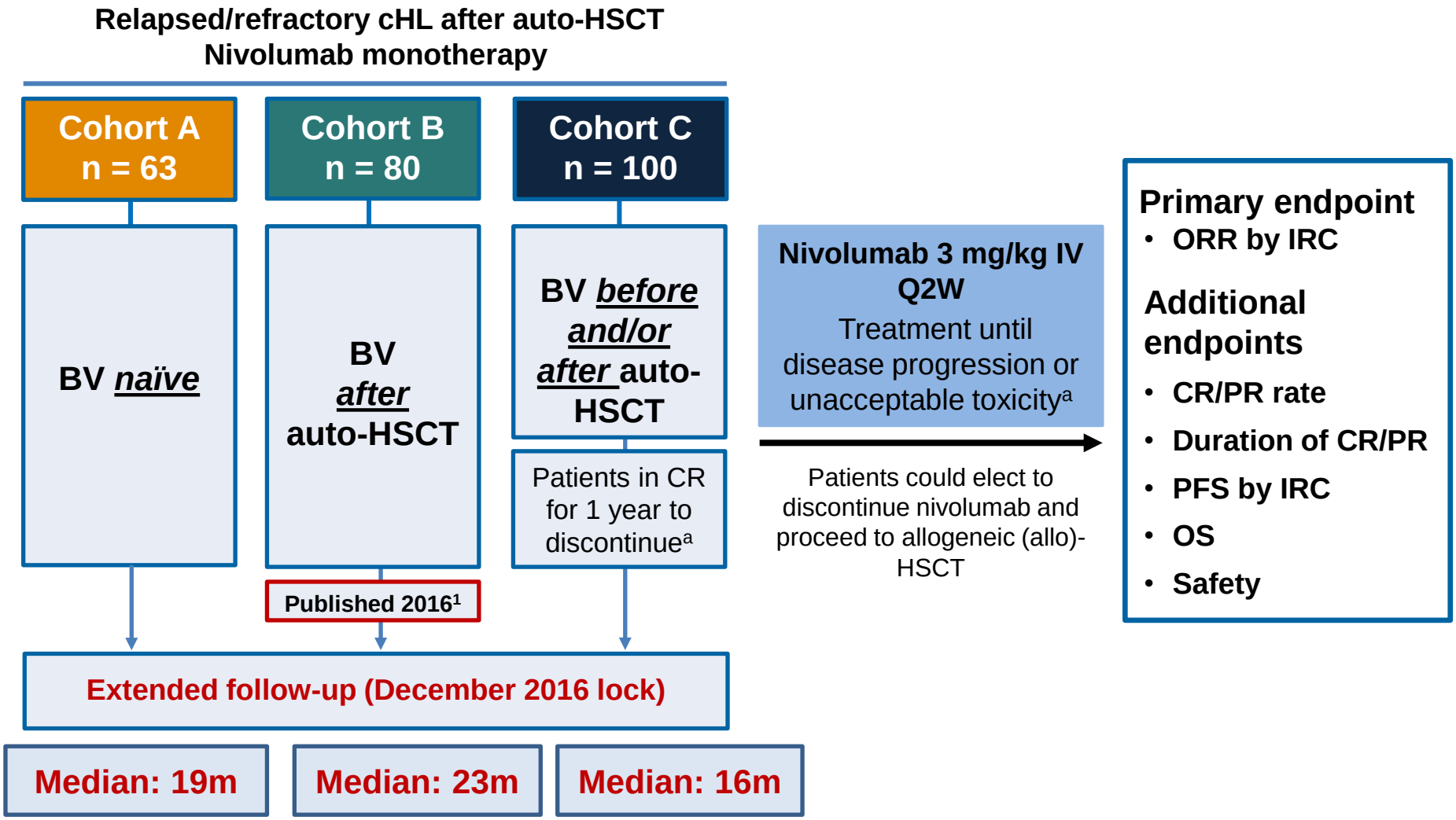
Median follow-up of survivors 50 months (75% of cases > 34 months)



- Stage at relapse
- B symptoms at relapse
- Bulky disease at relapse
- Extranodal involvement at relapse
- Poor performance status at relapse
- Early relapse (<6 months) after one ASCT

Martínez et al. Ann Oncol, 2013

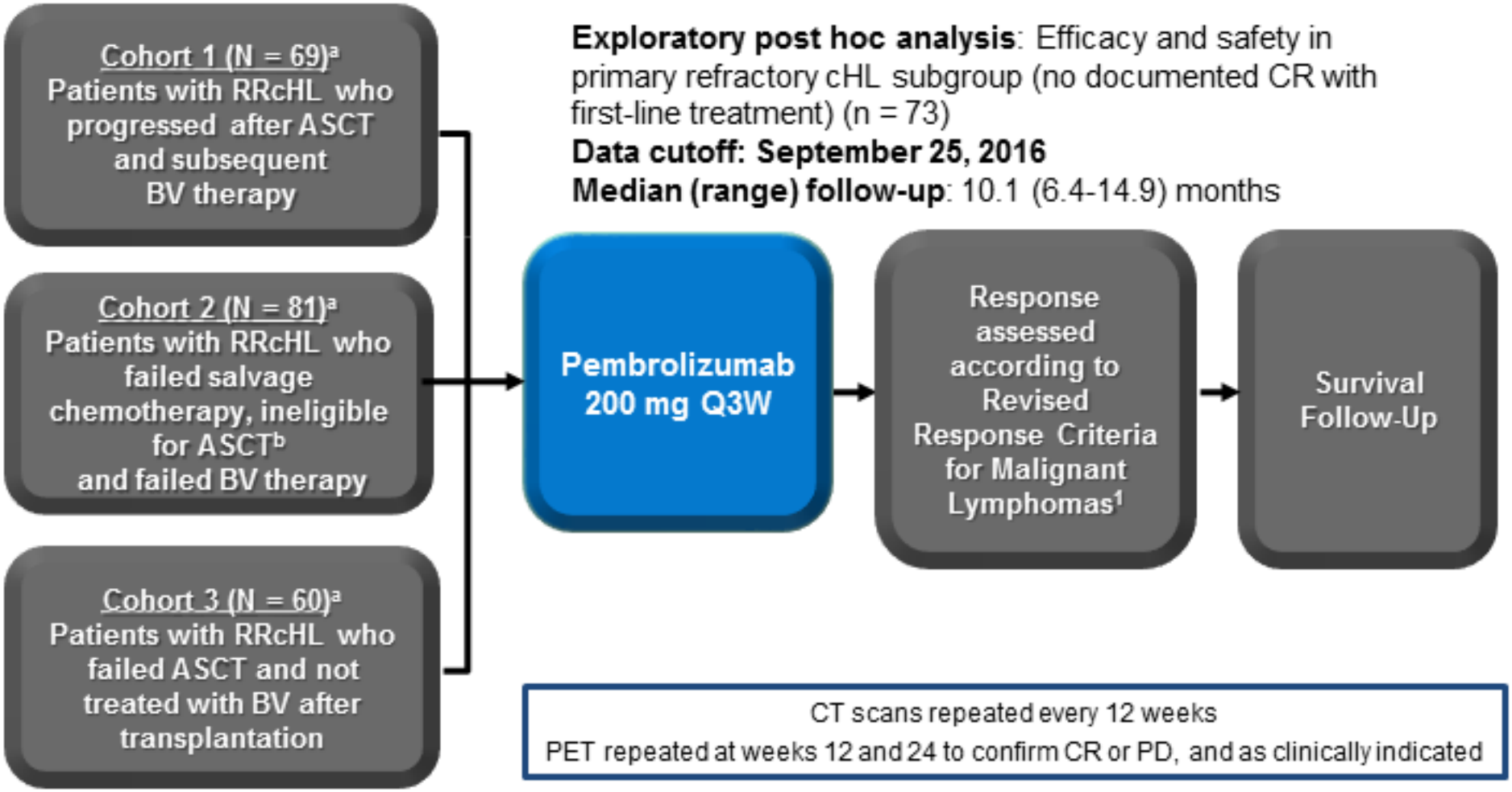
Phase 2 CheckMate 205 Study Design



[a]Could restart treatment if relapse within 2 years. BV = brentuximab vedotin; 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

Armand P, JCO 2018

KEYNOTE-087: Study Design



[a]Patients in all cohorts had to have ECOG PS 0-1.
[b]Unable to achieve a CR or PR to salvage chemotherapy.

1. Cheson BD et al. *J Clin Oncol*. 2007;25:579-586.

Chen R. JCO 2017

Demographics

	CHECKMATE-205[a]	KEYNOTE-087[b]
Age, years	34 (18–72)	31 (18–73)
Male, %	58	50.8
ECOG PS, % 0 1	 54 46	 56 44
Disease stage at study entry, % IV	57	-
Previous lines of therapy Prior radiotherapy, %	**4 (2–15)** 68	**4 (1–12)** 36
Time from diagnosis to first dose of anti-pd1, years	**4.5 (1.0–30.6)**	**6.2 (1.3–25.1)**
Time from auto-HSCT to first dose of anti-pd1	2.0 (0.2–19.0) years	5 (0.5–102.5) months

Data are median (range) unless otherwise stated. ECOG PS = Eastern Cooperative Oncology Group performance status

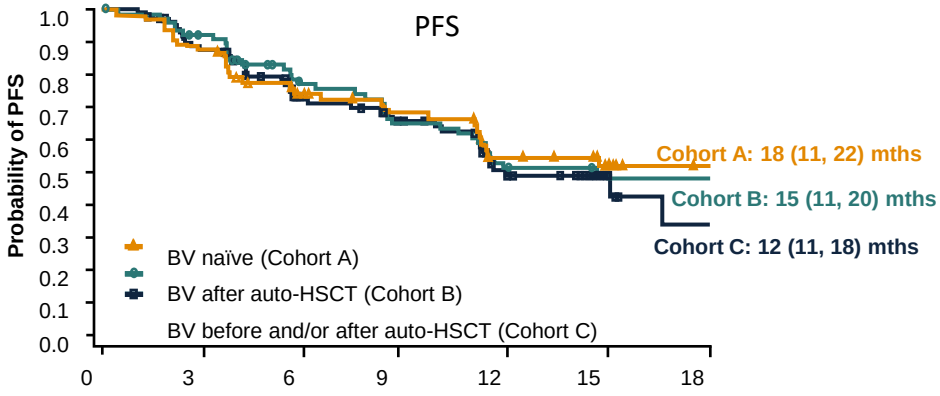
a.- Armand P, JCO 2018; b.- Chen R. JCO 2017

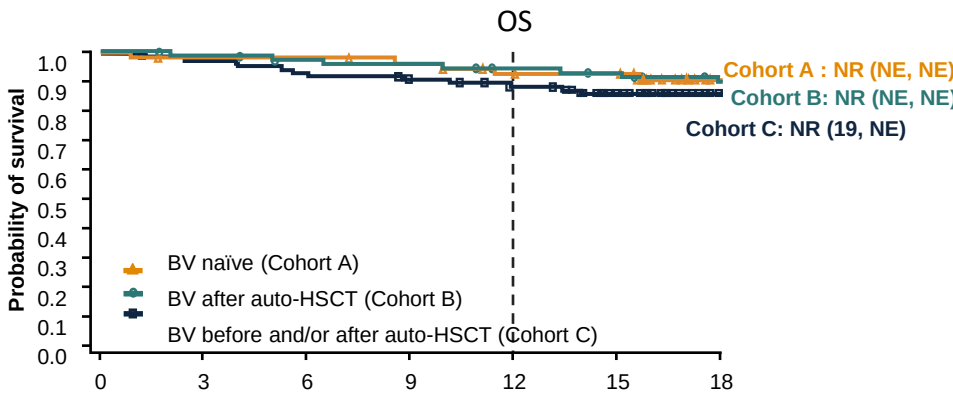
Response

	CHECKMATE-205[a]				KEYNOTE-087[b]			
	Cohort A	Cohort B	Cohort C	All	Cohort 1	Cohort 2	Cohort 3	All
Objective response per IRC, % (95% CI)	**65 (52, 77)**	**68 (56, 78)**	**73 (63, 81)**	**69 (63, 75)**	**79 (49, 95)**	**70 (51, 84)**	**92 (75, 99)**	**71,9 (65,78)**
Complete remission	29	13	12	16	21	27	19	27
Partial remission	37	55	61	53	57	42	73	44
Stable disease	24	21	15	19	14	6	0	11
Progressive disease	11	8	10	9	0	18	8	15
Unable to determine	0	4	2	2	7	6	0	2

a.- Armand P, JCO 2018; b.- Chen R. JCO 2017

Outcome CHECKMATE-205





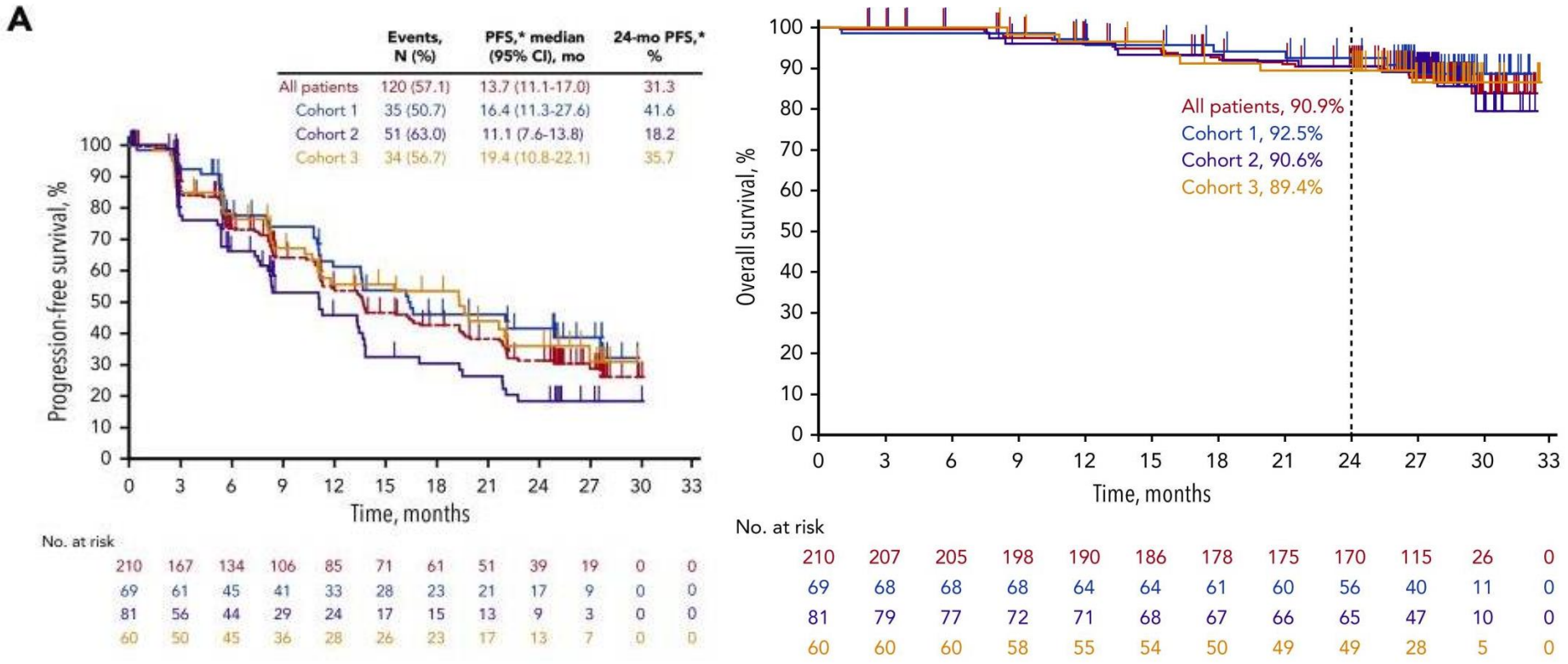
- Median (95% CI) PFS for overall patients (N = 243) was 15 (11, 19) months

DOR (per IRC) by cohort	Cohort A n = 41/63	Cohort B n = 54/80	Cohort C n = 73/100	Overall n = 168/243
Median DOR in all responders, months	**20 (13, 20)**	**16 (8, 20)**	**15 (9, 17)**	**17 (13, 20)**
Median DOR in CR patients, months	**20 (NE, NE)**	**20 (4, NE)**	**15 (8, NE)**	**20 (16, NE)**
Median DOR in PR patients, months	**17 (9, NE)**	**11 (7, 18)**	**13 (9, 17)**	**13 (9, 17)**

All values are medians (95% CI). n = responders/patients. NE = not evaluable

Armand P, JCO 2018

Outcome KEYNOTE-087

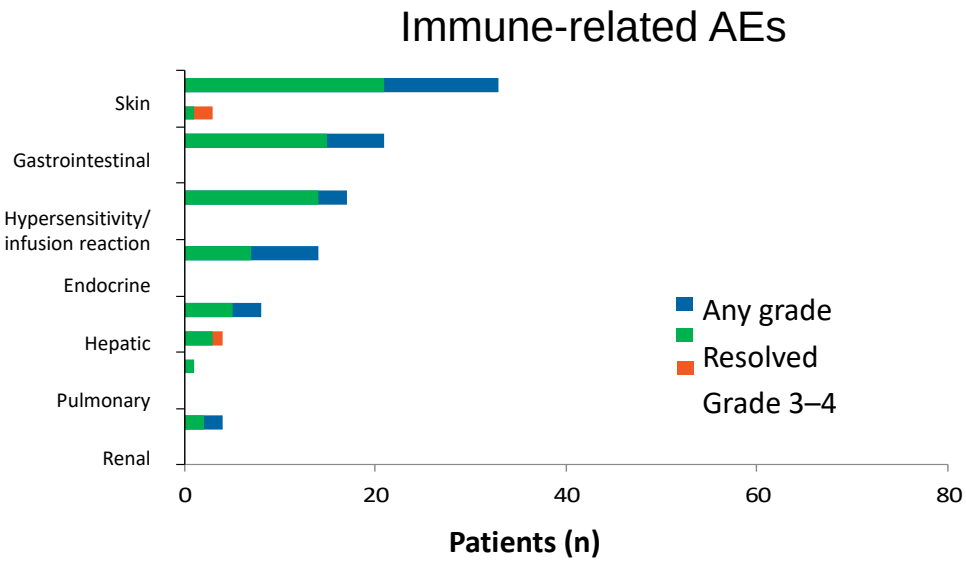


Median follow-up 27.6 months

Chen et al. Blood 2019

Treatment Related Adverse Events. Checkmate-205 Cohort B

Total patients with an event (%)	Any grade	Grade 3–4
Any AE	79 (99)	32 (40)
Treatment-related AE	72 (90)	20 (25)
Treatment-related AE leading to discontinuation:	3 (4)	2 (3)
Autoimmune hepatitis	1	1
Increased ALT and AST	1	1
Multi-organ failure*	1	0
Treatment-related serious AE	5 (6)	0
Treatment-related death	0	0

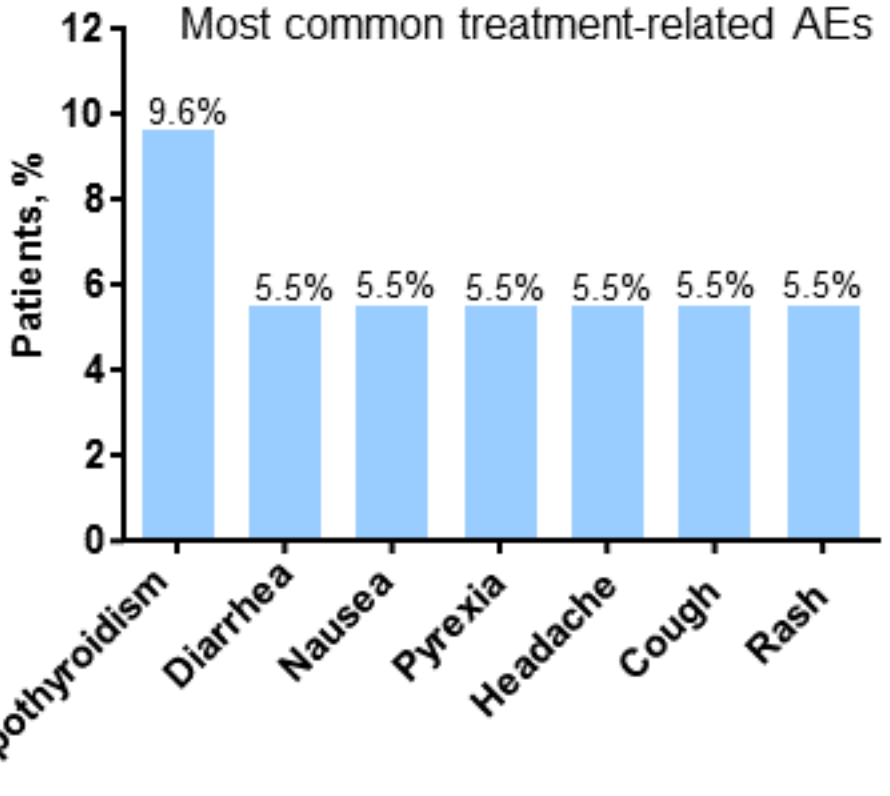


- Serious AEs (SAEs) included pyrexia, tumor progression, arrhythmia, infusion reaction, septic meningitis, and pneumonia (≤4% each)
- *One patient experienced a grade 5 SAE of multi-organ failure due to Epstein Barr virus–positive T-cell lymphoma
- Drug-related pneumonitis reported in 2 patients (grade 2 and grade 3) between first dose and 35 days after last dose
- Majority of events were manageable, with resolution occurring when immune-modulating medications were administered

Armand P, JCO 2018

Treatment Related Adverse Events. Keynote 087

Treatment-related AE	n (%)
Any grade	46 (63.0)
Grade 3/4	6 (8.2)
Grade 5	0
Led to discontinuation	3 (4.1)



- Treatment-related AEs were similar between the primary refractory subgroup and total population
- Treatment-related AEs leading to discontinuation: myocarditis, cytokine release syndrome, infusion-related reaction, and pneumonitis
- Death unrelated to treatment: 1 (during safety follow-up, graft vs host disease)

Chen R. JCO 2017

Immune checkpoint inhibitors approved in relapsed/refractory HL

Pembrolizumab
ORR 67-78%
CR 26-32%
2017: approved after 3 prior therapies

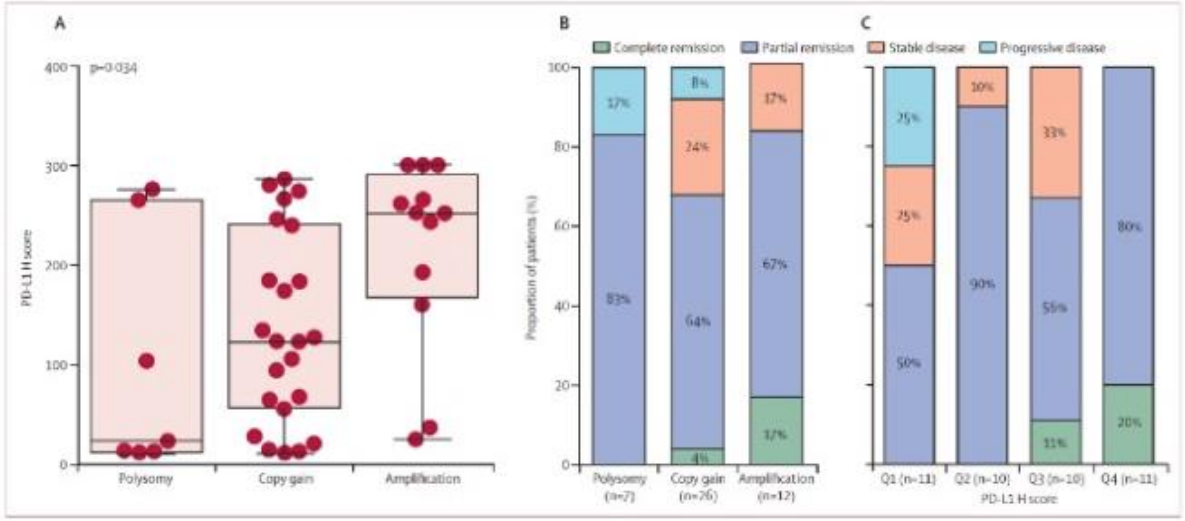
Chen et al. Blood 2019

Nivolumab
ORR 65-73%
CR 12-29%
2016: approved after ASCT and BV

Armand et al JCO 2018

Grade 3-4 immune mediated AEs rare.

4-6% of patients discontinued therapy for toxicity.



Younes et al. Lancet Onc 2016

PD-1 blockade pre-alloSCT

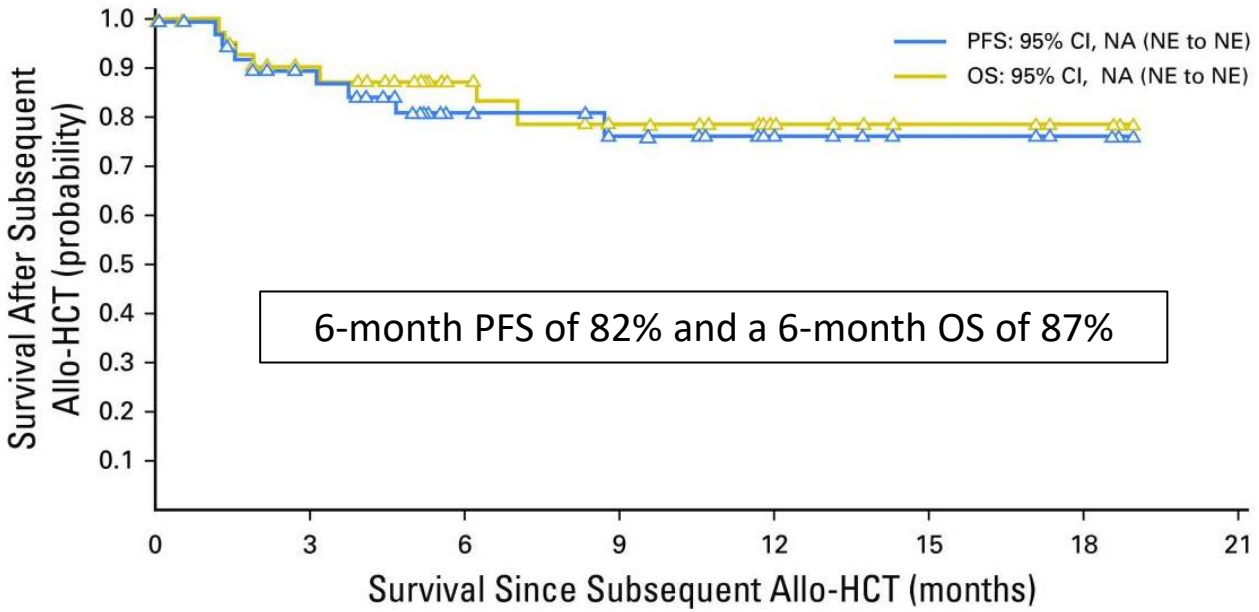
	n= 49
Median time from CBT to allo	1.5 months (0.4–14)
ORR n(%)	69%
Immune related AE	NR
aGVHD Gr 2-4	29,9%
aGVHD Gr 3-4	20%
cGVHD	15,3% at 6 months
TRM (%)	13% at 6 months
CIR	7% at 6 months

Adverse event, n (%)	Patients (n = 49)	Remarks
Hepatic veno-occlusive disease	1 (2)	– Case met modified Seattle criteria and resolved – Patient eventually died due to multiorgan GVHD
Hyperacute GVHD[a]	3 (6)	All G3
Chronic GVHD	8 (16)	7/8 limited stage, 1/8 reported as mild
Steroid-responsive febrile syndrome[b]	6 (12)	Resolution reported for 3 patients
Encephalitis	2 (4)	– Both G3 – One case resolved with corticosteroids and one with antiviral treatment

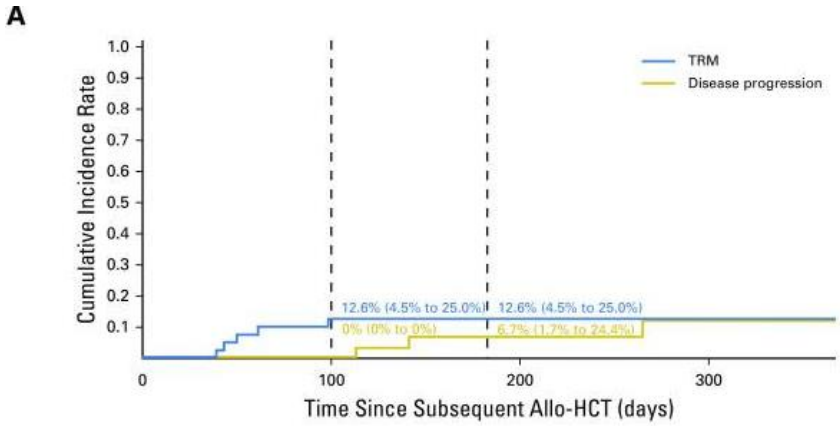
[a]Within 14 days of transplantation; [b]Fever without infection, which may have been accompanied by skin, joint or liver symptoms

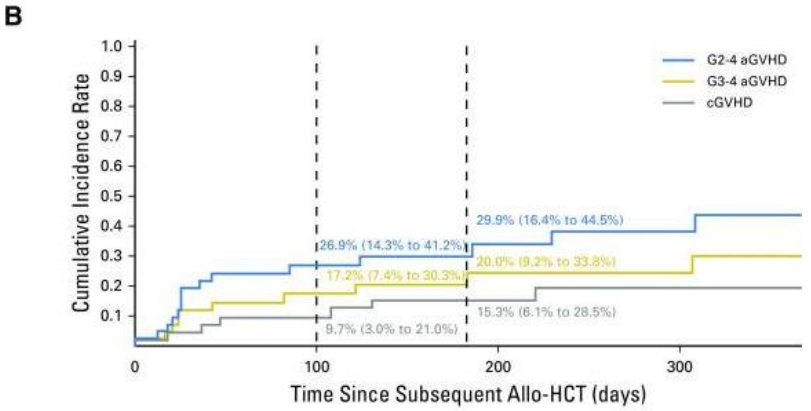
Armand P, JCO 2018

PD-1 blockade pre-alloSCT. Outcomes



6-month PFS of 82% and a 6-month OS of 87%

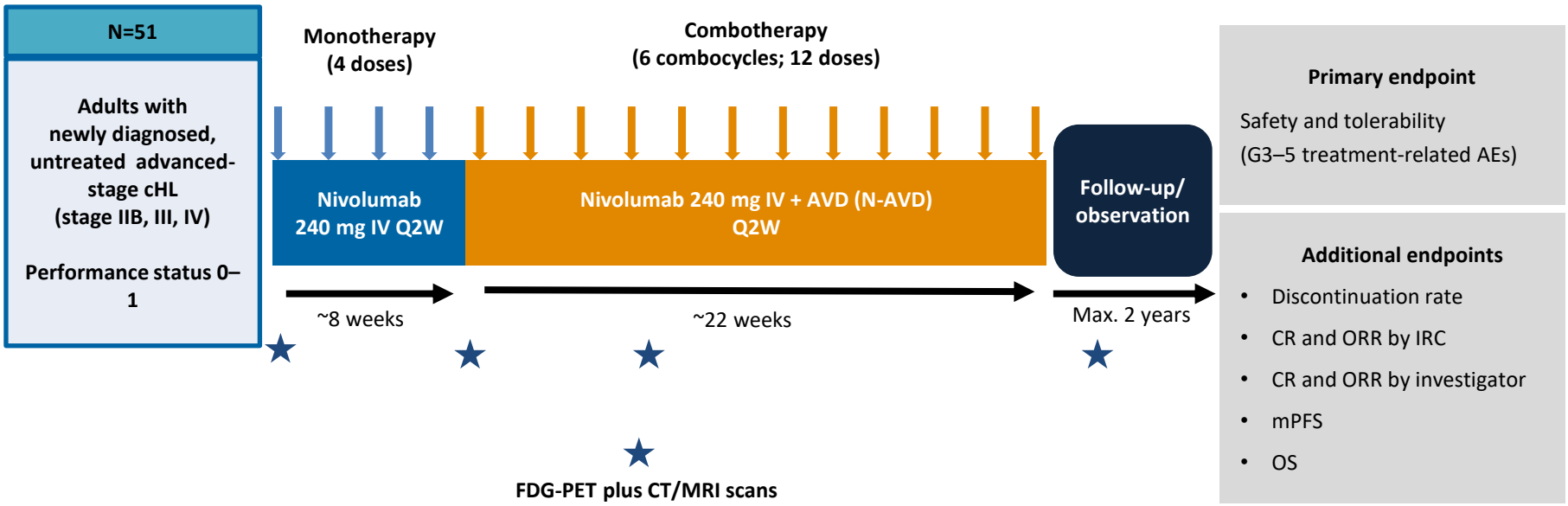


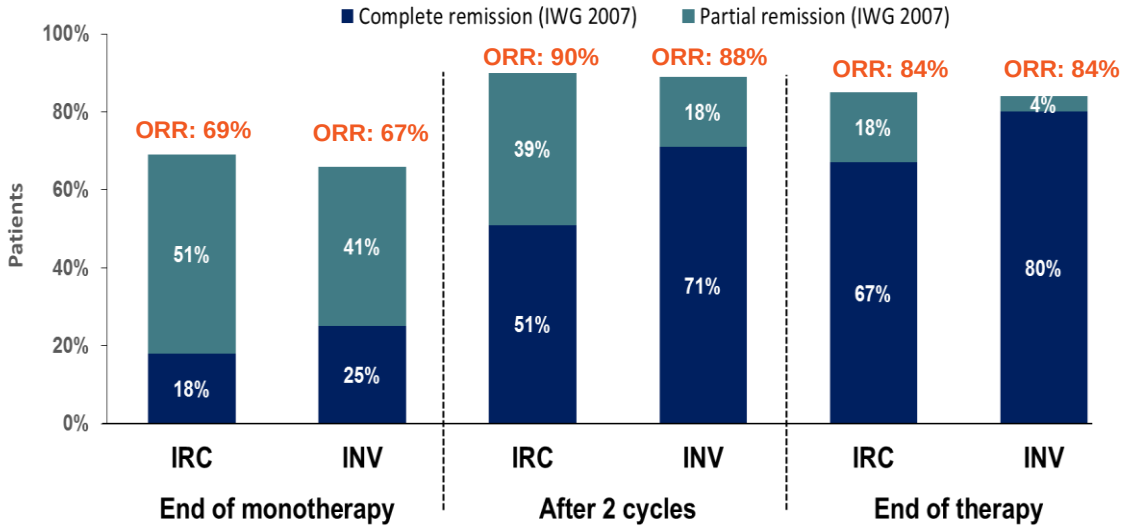


Armand P. JCO 2018

Combinations with immune checkpoint inhibitors

Phase 2 CheckMate 205 Newly Diagnosed advance stage cHL





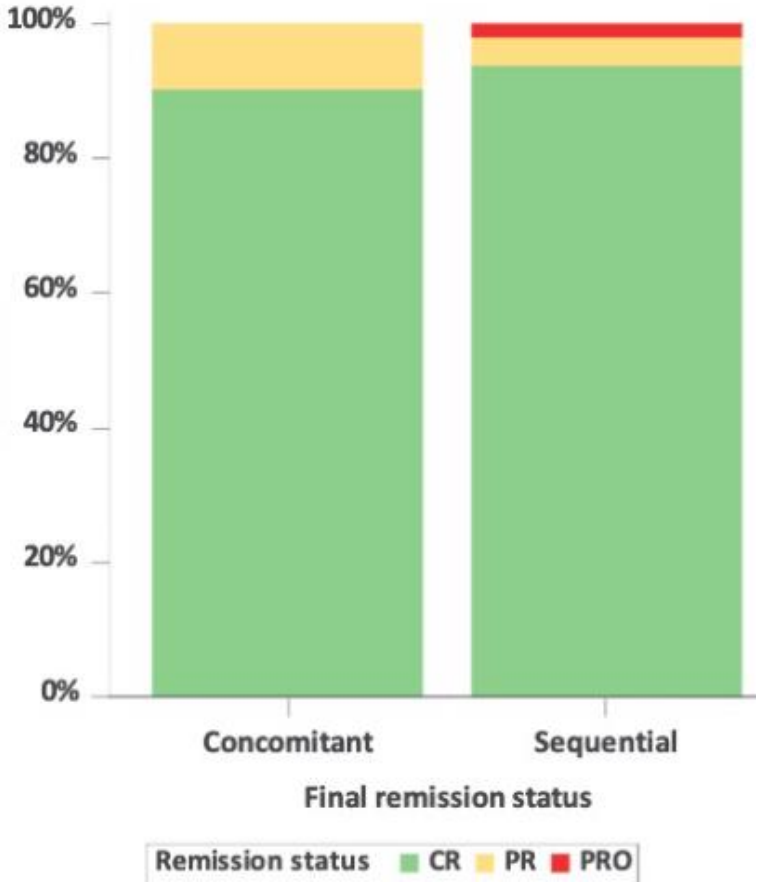
- At end of therapy, ORR per investigator for the ITT population was 84%, with 80% of patients achieving CR
- Five patients were non-evaluable at end of therapy[a]

R Ramchandren, JCO 2019

NIVAHL- Nivo-AVD in Early-stage Unfavorable cHL

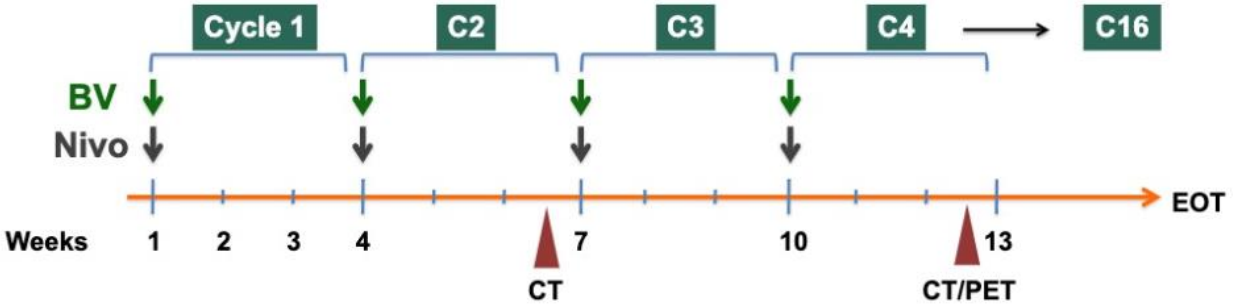
	Concomitant (N=51*)			Sequential (N=50*)		
Status	N	%	95% CI	N	%	95% CI
CR	46	**90%**	78.6% - 96.7%	47	**94%**	83.5% - 98.7%
PR	5	**10%**		2	**4%**	
NC	-			-		
PD	-			1	**2%**	
ORR	51	**100%**		49	**98%**	

* Efficacy analysis set: major protocol deviations (<4 doses nivolumab or <6 doses AVD) excluded unless due to PD



PJ Bröckelmann, ASH 2019

Phase 2 Nivo-BV Frontline HL >60 years



- Key eligibility criteria:
  - ECOG ≤2; CrCl ≥30 ml/min; DLCO >50%; measurable disease of ≥1.5 cm
  - No autoimmune disease; ineligible for or declined conventional combination chemotherapy
- Standard dosing of BV (1.8 mg/kg) and Nivo (3 mg/kg) every 3 weeks
- Primary Endpoint: ORR
- Secondary/Additional Endpoints: Safety, CRR, DOR, OS, PFS
  - Response assessments per Lugano 2014 and LYRIC

Patients who received ≥1 dose of BV or Nivo	N=21 n (%)
Median age (range)	72.0 years (60-88)
Male (%)	15 (71)
ECOG = 0/1, n (%)	4/16 (19/76)[a]
Histologic subtype of HL, n (%)	
Nodular Sclerosis	7 (33)
Mixed Cellularity	2 (10)
Lymphocyte-rich cHL	3 (14)
cHL not otherwise specified	8 (38)
Other	1 (5)
Disease stage III-IV, n (%)	16 (76)
Bulky disease, n (%)	10 (48)
Extra-nodal involvement, n (%)	8 (38)
B symptoms, n (%)	9 (43)

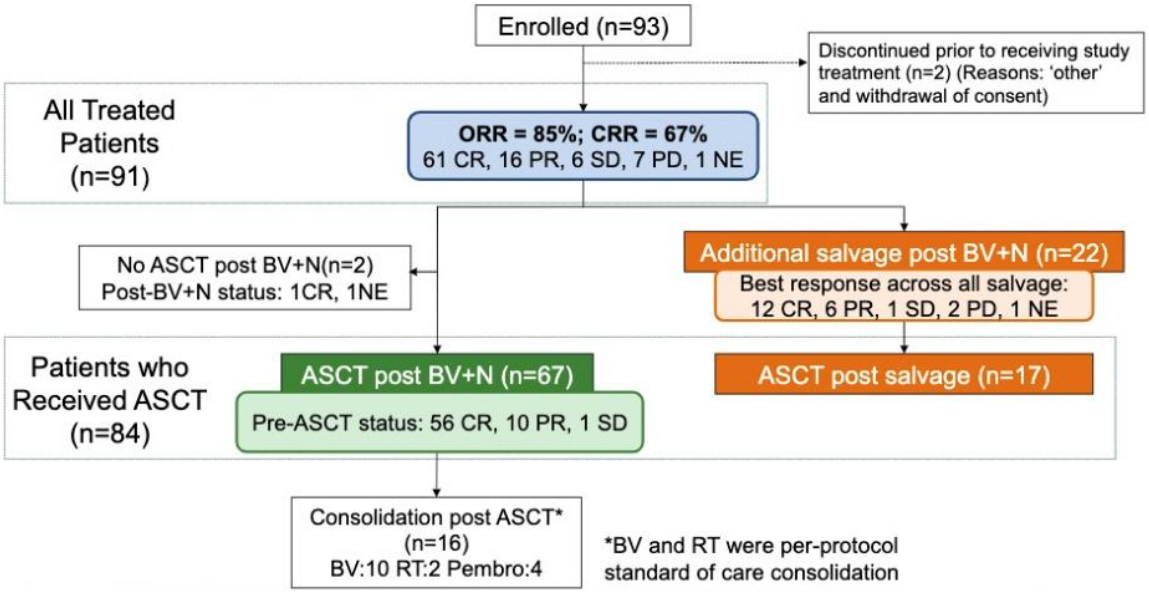
a ECOG performance missing in 1 patient

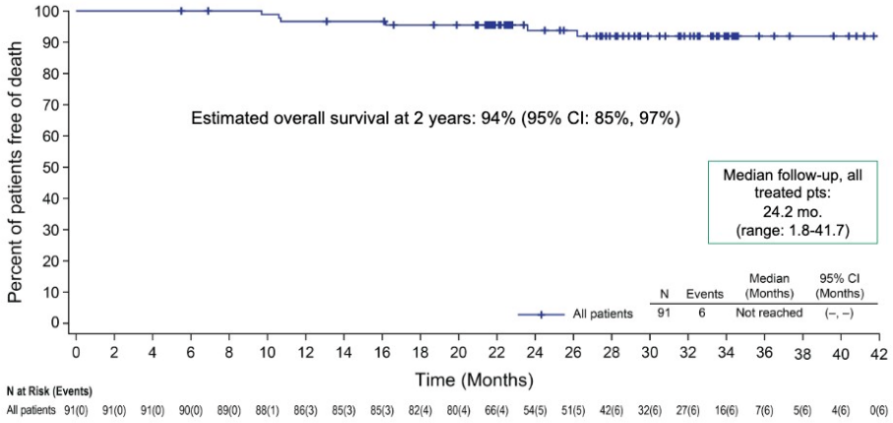
Best Responses per Investigator	Patients (N=19)[a] n (%)
Objective Response Rate (ORR) 95% confidence interval	**18 (95)** (74.0, 99.9)
Best Overall Response	
Complete response	13 (68)
Partial response	5 (26)
Stable disease	1 (5)
Progressive disease	0

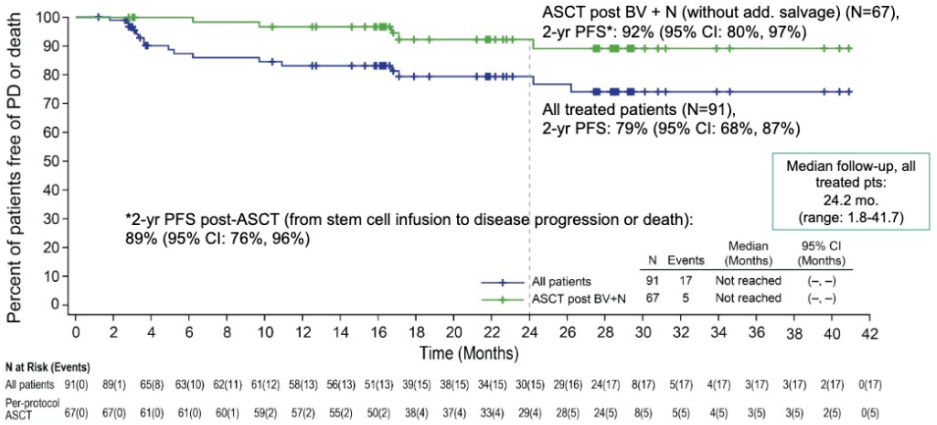
a Two patients did not have a post-baseline assessment, so response could not be determined

CA Yasenchak, ASH 2019

Phase 1/2 Trial Design Nivolumab + BV Second line treatment

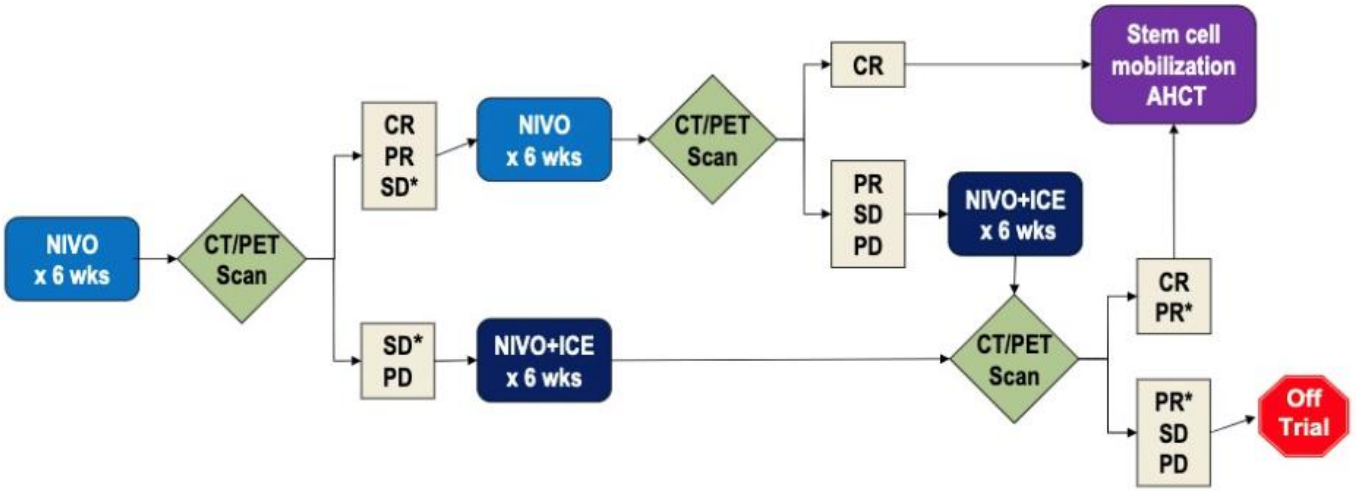




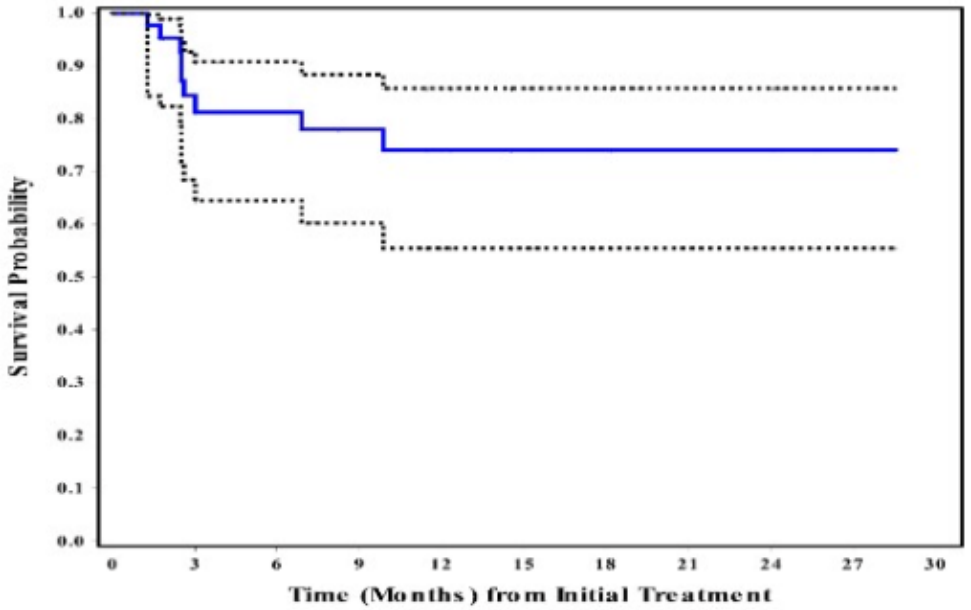


Herrera A, Blood 2017; Moskowitz A, ASH 2019.

Nivo-ICE



All participants (Intent-to-treat)



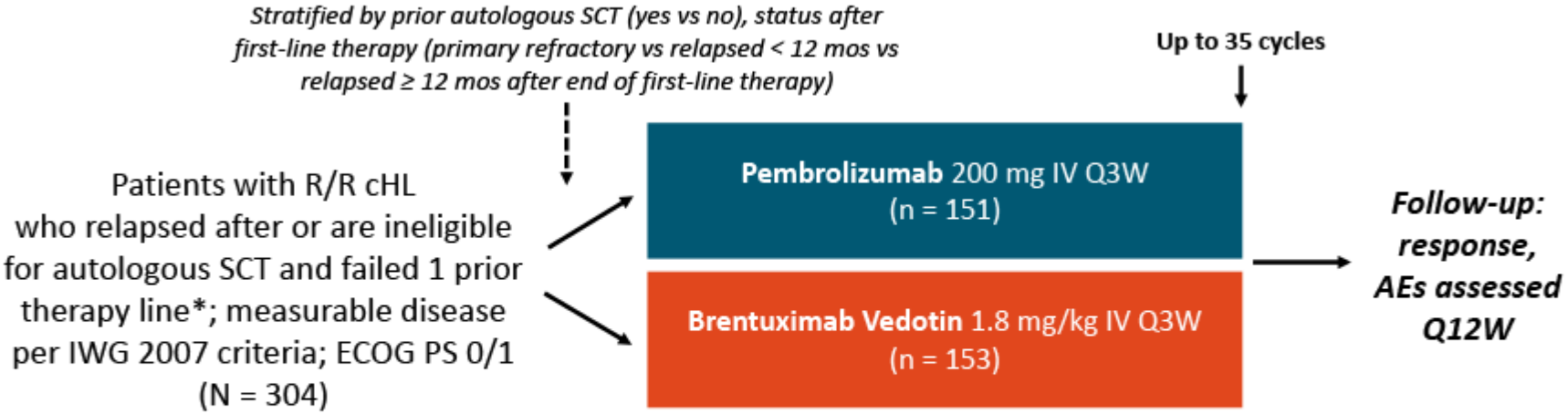
- Median follow-up: 12 months (range: 0.5-28.6)
- 1 year PFS: 74% (95% CI: 55 - 86)

Herrera A, ASH 2019.

Phase 3 Pembrolizumab vs Brentuximab Vedotin in R/R HL: KEYNOTE-204

Study Design

- Multicenter, randomized, open-label phase III study (data cutoff: January 16, 2020)

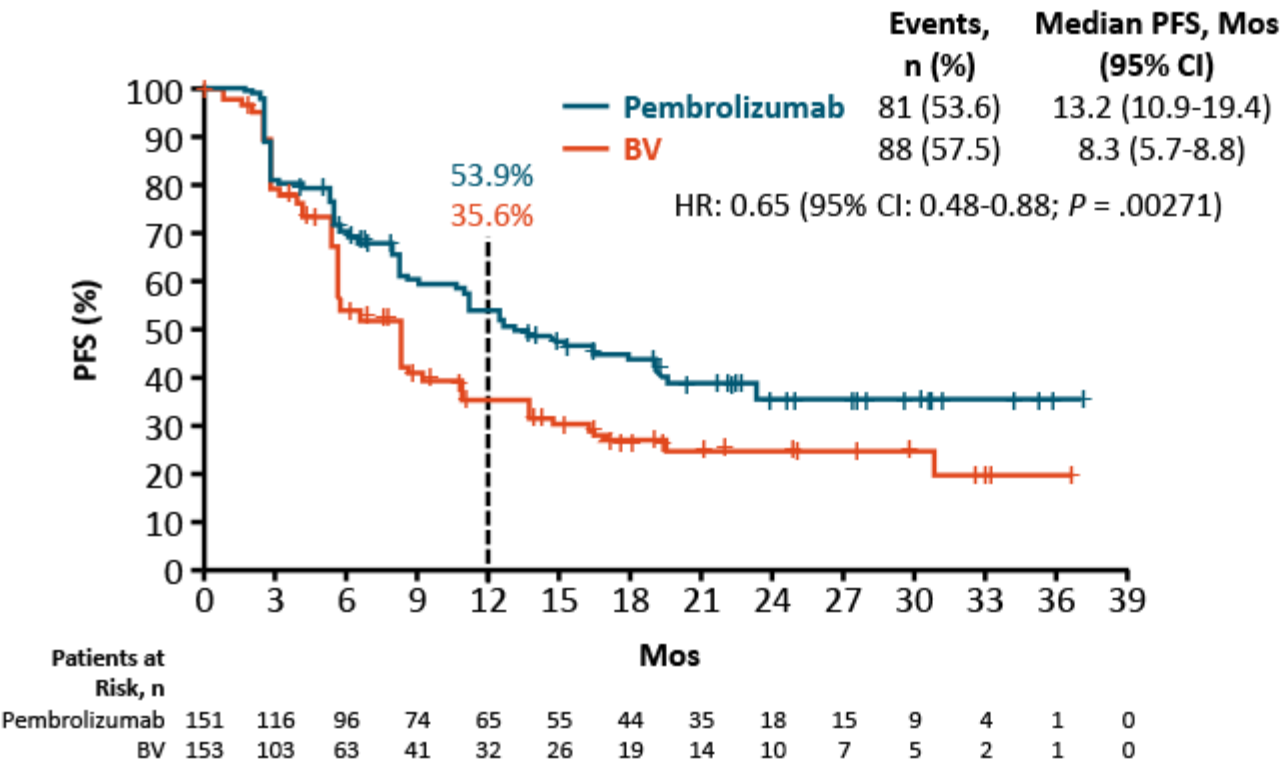


*Prior use of brentuximab vedotin permitted. AEs assessed Q3W during trial period.

- Primary endpoint: PFS by BICR per IWG 2007 criteria (including clinical and imaging data after autologous or allogeneic SCT), OS
- Secondary endpoints: PFS by BICR per IWG 2007 criteria (excluding clinical and imaging data after autologous or allogeneic SCT), ORR by BICR per IWG 2007, PFS per investigator review, DoR, safety

Kuruvilla, ASCO 2020; Zinzanni PL, EHA 2020

KEYNOTE-204: PFS by BICR with Post-SCT Clinical and Imaging Data (Primary Endpoint)



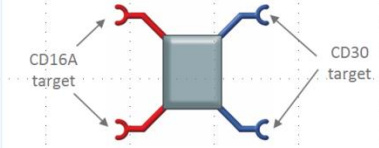
- Median PFS by BICR without post-SCT clinical and imaging data:
  - Pembrolizumab: 12.6 mos (95% CI: 8.7-19.2)
  - BV: 8.2 mos (95% CI: 5.6-8.6)
  - HR: 0.62 (95% CI: 0.46-0.85)
- Median PFS by investigator:
  - Pembrolizumab: 19.2 mos (95% CI: 13.8-28.1)
  - BV: 8.2 mos (95% CI: 5.7-8.6)
  - HR: 0.49 (95% CI: 0.36-0.67)

Kuruvilla, ASCO 2020; Zinzanni PL, EHA 2020

AFM13+Pembrolizumab

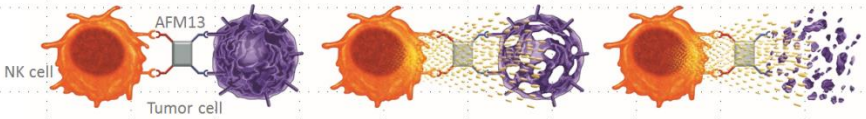
Background: AFM13

First-in-class CD30-directed innate cell engager



- Designed to activate NK cells and macrophages against CD30-expressing lymphomas
  - Potent binding of CD16A and NK cell activation
  - Enhanced antibody-dependent cellular cytotoxicity (ADCC)
- Preclinical efficacy of AFM13 in combination with anti-PD1
- Single agent activity in a Phase 1 study in patients with relapsed/refractory (R/R) Hodgkin lymphoma

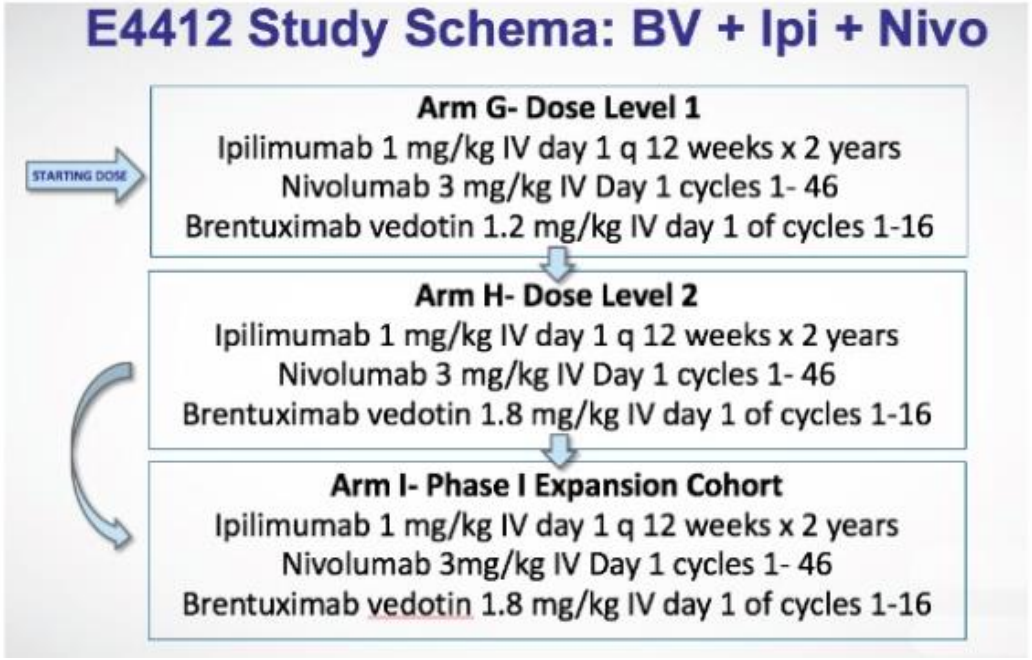
Mechanism of action for AFM13

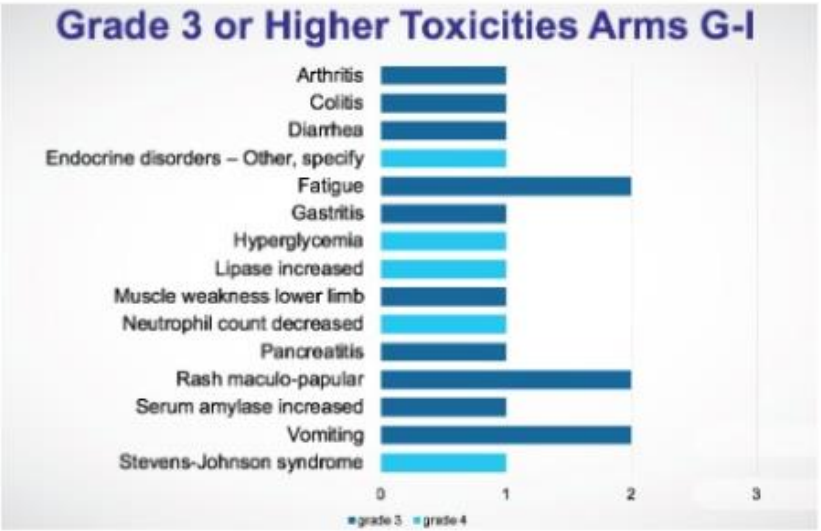


		Complete Metabolic Response (%)	Partial Metabolic Response (%)	No Metabolic Response (%)	Progressive Disease (%)	Overall Response Rate (%)
Investigator assessment	Cohorts 1 and 2 (N=6)	1 (17%)	3 (50%)	0 (0%)	2 (33%)	4 (67%)
	Cohort 3 + Extension (N=24)	10 (42%)	11 (46%)	2 (8%)	1 (3%)	21 (88%)
	ITT (N=30)	11 (37%)	14 (47%)	2 (7%)	3 (10%)	25 (83%)
Independent assessment	Cohorts 1 and 2 (N=6)	1 (17%)	3 (50%)	2 (33%)	0 (0%)	4 (67%)
	Cohort 3 + Extension (N=24)	11 (46%)	10 (42%)	1 (4%)	2 (8%)	21 (88%)
	ITT (N=30)	12 (40%)	13 (43%)	3 (10%)	2 (7%)	25 (83%)

S Ansell, ASH 2019; NL Barlett, Blood 2020

Phase 1/2 ACRIN trial triplet combination: BV + ipilumumab + nivolumab





ORR: 76% (95% CI 53–92)
CR: 57% (95% CI 34–78%)
Median follow-up of 2·6 years (IQR 1·8–2·9)
Median PFS is 1.2 years (95% CI 1·7–not reached)
Median OS not reached

CS Diefenbach, ASH 2018; CS Diefenbach, Lancet Haem 2020

Immune checkpoints in other hematological malignancies

- PD-1 blockade can re-invigorate a T cell mediated anti-tumor immune response.
- **Multiple Myeloma:**
  - PD-1 blockade may synergize with other antimyeloma therapy (IMiDs)
  - Phase II Study of Anti PD-1 Antibody Pembrolizumab, Pomalidomide and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma (RRMM). Badros A. ASH 2016
  - Pembrolizumab in Combination with Lenalidomide and Low-Dose Dexamethasone for Relapsed/Refractory Multiple Myeloma (RRMM): Keynote-023. San Miguel A. ASH 2015
- **Myelodisplasic syndrome**:
  - Several immune mechanisms have been identified in MDS, suggesting that immune dysregulation might be at least partially implicated in its pathogenesis
  - A Phase II Study of Nivolumab or Ipilimumab with or without Azacitidine for Patients with Myelodysplastic Syndrome (MDS). Garcia-Manero ASH 2018
  - Preliminary Results from a Phase II Study of the Combination of Azacitidine and Pembrolizumab in Patients with Higher-Risk Myelodysplastic Syndrome. Chien K. ASH 2018
- **Primary mediastinal lymphoma**→ Pembrolizumab monotherapy in R/R. ORR:41% + 35% SD. Median follow-up 11.2 m, OS and PFS not reached*. Fda aproved.

Zinnzanni PL, Blood 2017.

Preguntas abiertas

- Tenemos que tratar a todos los pacientes con inhibidores de checkpoint? Podemos identificar aquellos pacientes que se van a beneficiar más de esta estrategia terapéutica?
  - PET scan
  - Ct DNA
  - 9p24.1 amplificacion
- Pueden estos tratamientos resensibilizar o incrementar la respuesta de tratamientos posteriores?
- El incremento de RC se correlaciona con una mejora de la PFS o OS?
- Se deben utilizar estos tratamientos en combinación o de manera secuencial?

Conclusiones

- El tratamiento con inhibidores de checkpoint en pacientes con LH R/R ha demostrado una alta tasa de respuestas duraderas, independientemente de la profundidad de respuesta, exposición previa a BV o refractariedad a previos tratamientos, con un perfil de seguridad aceptable
- Monitorización de posibles toxicidades autoinmunes
- La combinación de inhibidores de checkpoint con otros agentes quimioterápicos podría ser una estrategia en el futuro para poder utilizarlo en líneas más precoces de la enfermedad.
- El futuro de estos fármacos se amplia al tratamiento de neoplasias hematológicas que no expresan pd1, aprovechando un efecto sinérgico con fármacos inmunomoduladores y como modificadores del microambiente tumoral.

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Gracias

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