Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Immune Checkpoint Blockade in Hodgkin and non-Hodgkin lymphoma

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Disclosures

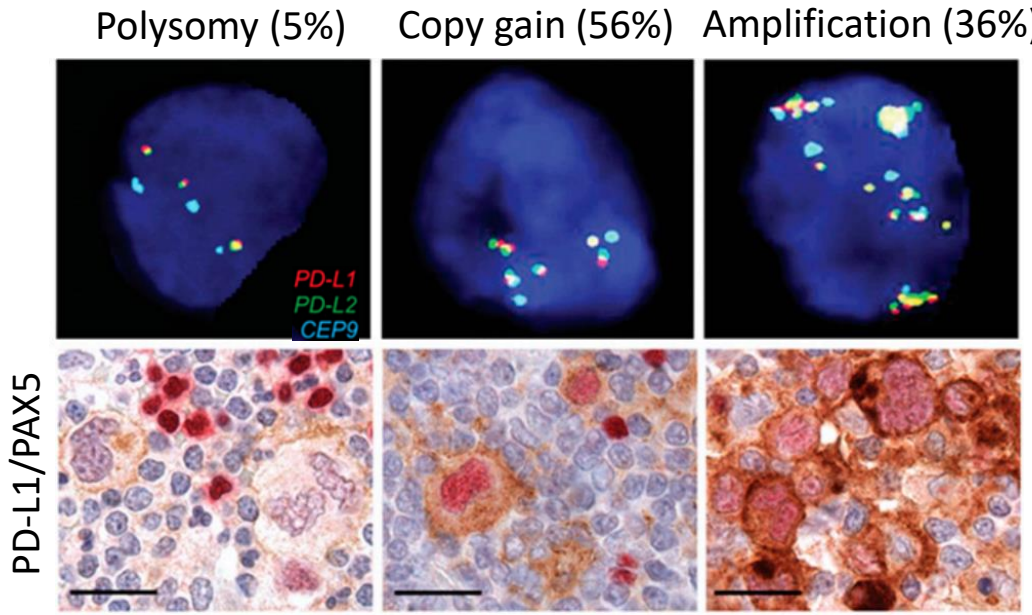
- No relevant financial disclosures

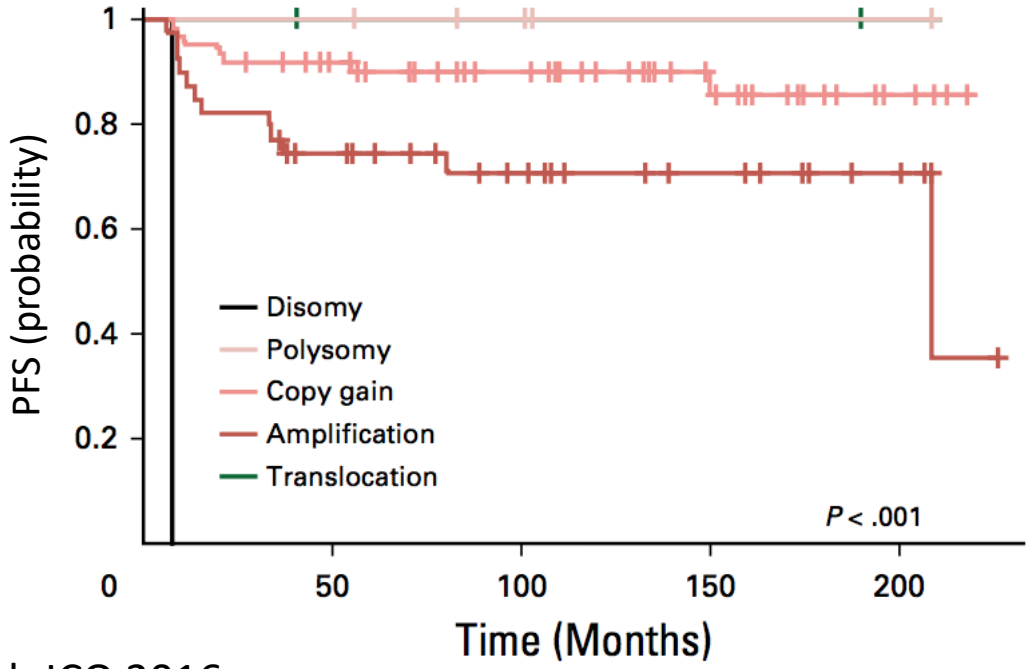
Objectives

- Review the biological basis for PD-1 blockade in classic Hodgkin lymphoma (cHL) and discuss biomarkers of response
- Discuss the role of PD-1 inhibitors in relapsed/refractory cHL and trials evaluating PD-1 inhibitors in the frontline setting
- Review trials of PD-1 inhibitors in B-cell and T-cell non-Hodgkin lymphoma (NHL)
- Highlight the CD47/SIRPa checkpoint and macrophage checkpoint inhibitors
- Discuss emerging checkpoint inhibitor combinations in cHL and NHL
  - ➢ Targeting PD-1 in combination with CTLA-4, LAG-3, or CD47

Biological basis for PD-1 blockade in classic Hodgkin lymphoma

- Hodgkin Reed-Sternberg cells have recurrent genetic alterations of chromosome 9p24.1, leading to overexpression of PD-L1, PD-L2, and JAK2
- Greater magnitude of 9p24.1 copy gain and higher PD-L1 expression are associated with inferior PFS





Roemer et al, JCO 2016

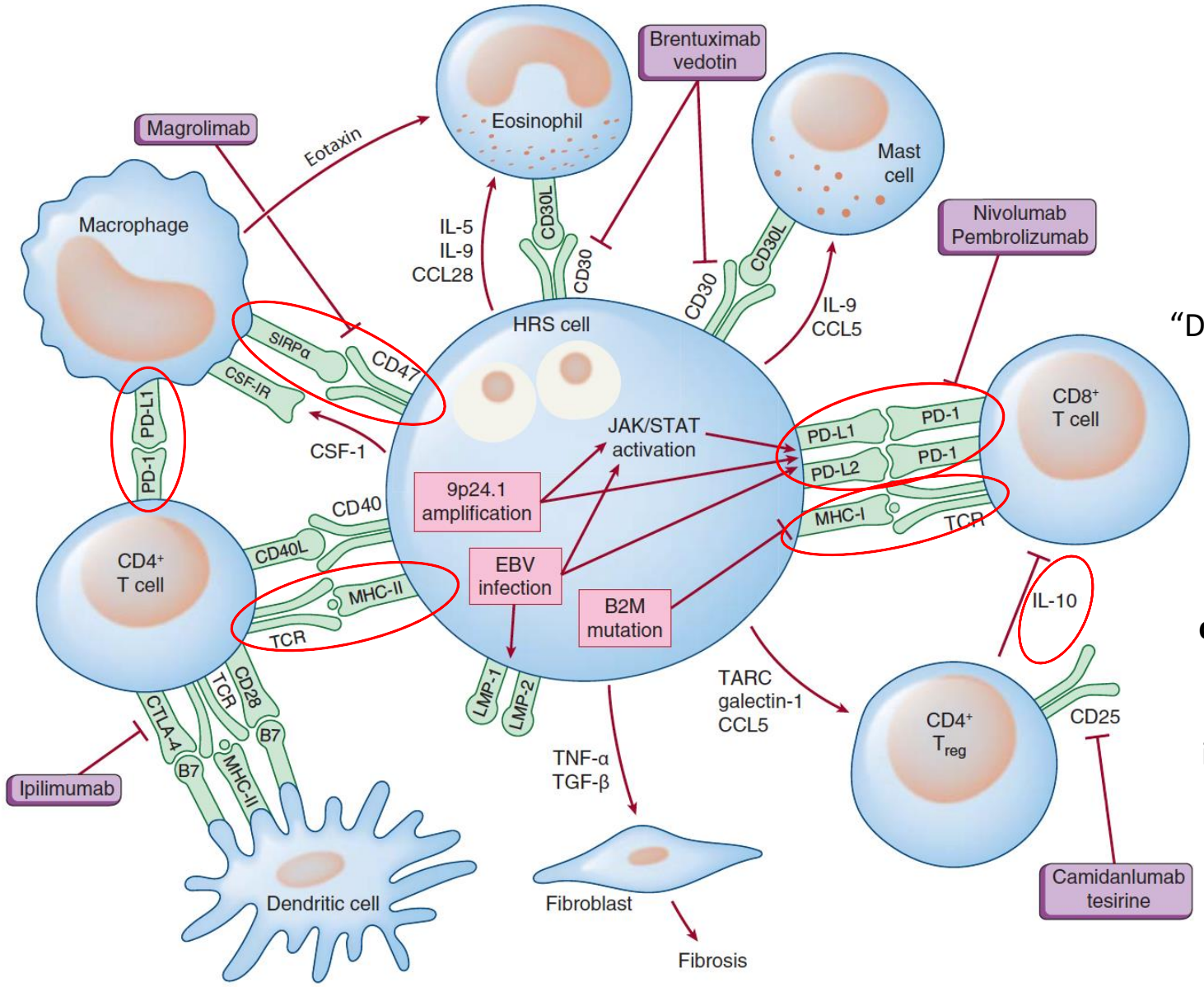
Hodgkin Reed-Sternberg cells evade the immune system through multiple mechanisms

CD47 overexpression

"Don't eat me" signal

Decreased or absent MHC class I or II expression

Impaired antigen presentation



PD-L1 and PD-L2 overexpression

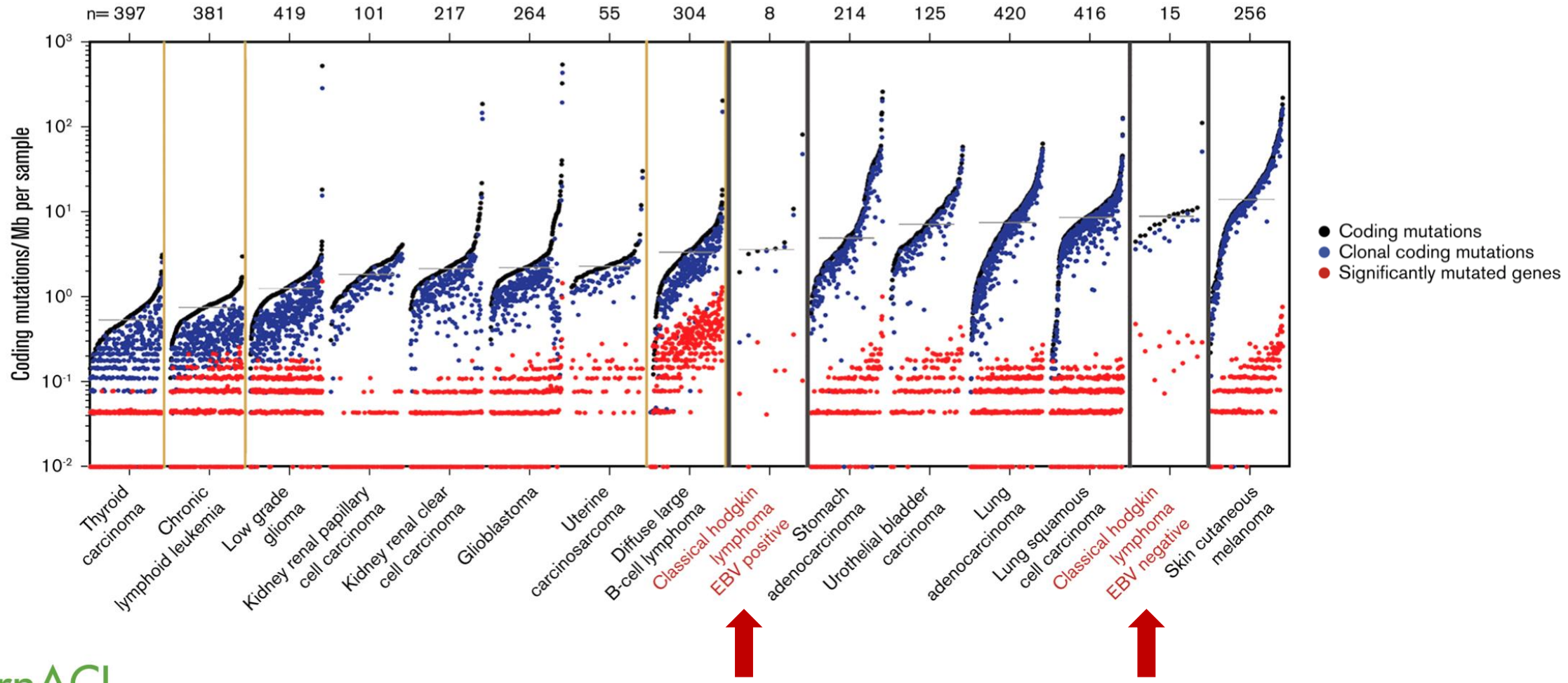
"Don't find me" signal

Anti-inflammatory cytokine production

Promoting an immunosuppressive microenvironment

Spinner MA, Mou E, Advani RH. Chapter 96. Hodgkin Lymphoma. Williams Hematology. 2021

Classic Hodgkin lymphoma has a high tumor mutational burden



Wienand et al, *Blood Adv* 2019

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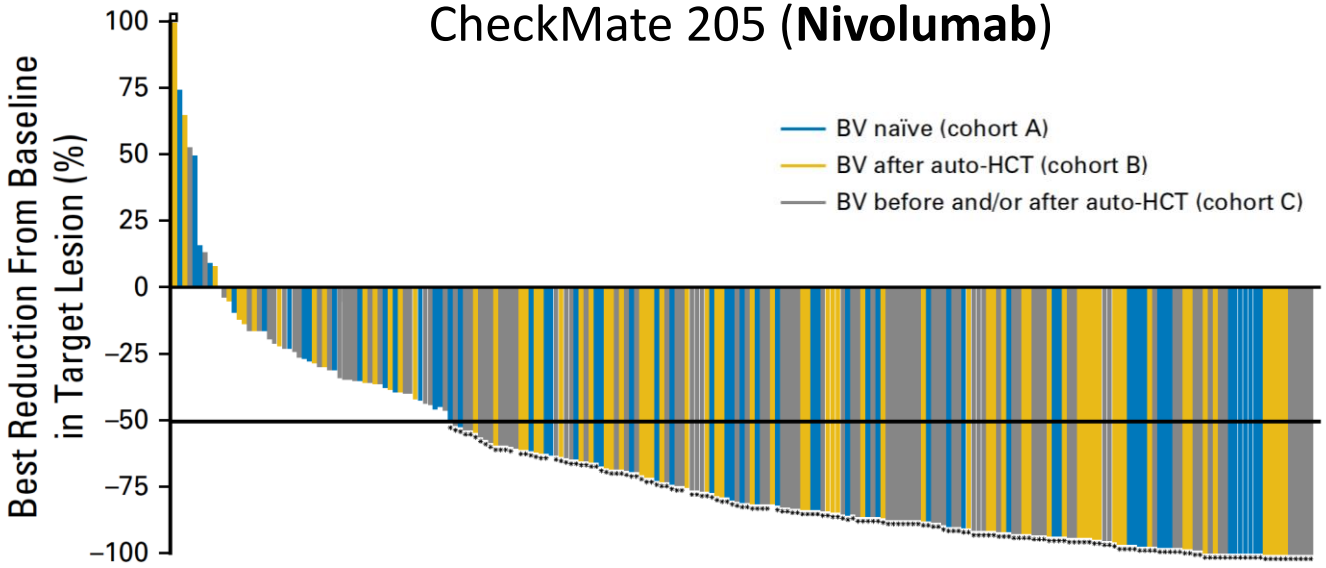
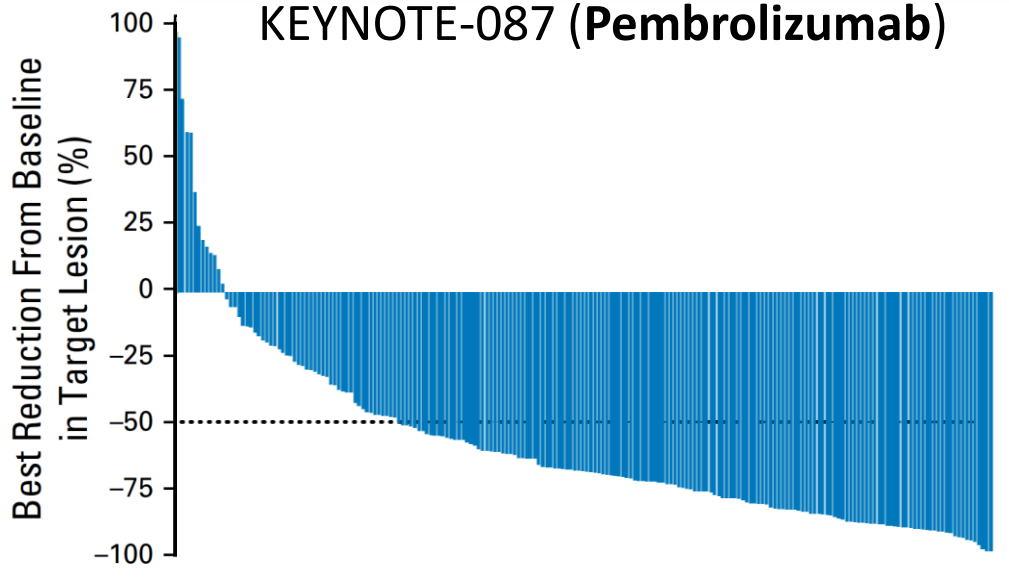
PD-1 inhibitors are highly active in relapsed/refractory cHL

CheckMate 205 (**Nivolumab**)



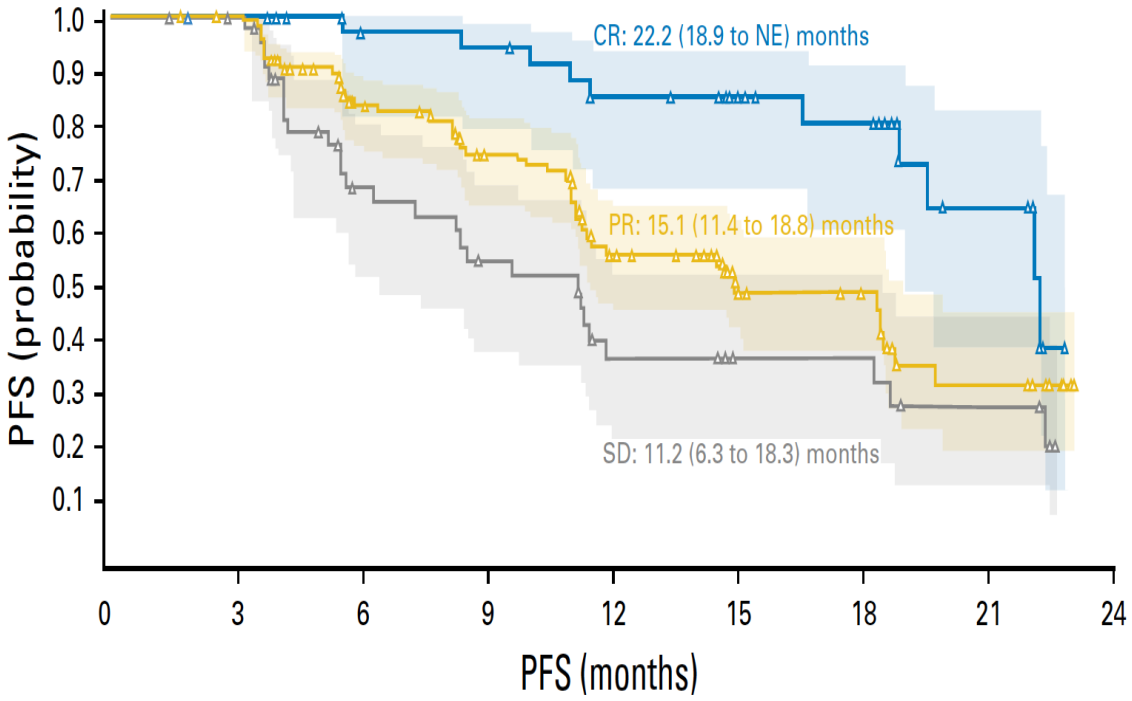
KEYNOTE-087 (**Pembrolizumab**)



Trial	Phase	PD-1 inhibitor	N	Median prior Tx	ORR	CR rate	Median PFS	Reference
CheckMate 205	2	Nivolumab	243	4	69%	16%	14.7 mo.	Armand et al, *J Clin Oncol* 2018
KEYNOTE-087	2	Pembrolizumab	210	4	72%	27%	13.7 mo.	Chen et al, *Blood* 2019
KEYNOTE-204	3	Pembrolizumab	151	2	67%	25%	13.2 mo.	Kuruvilla et al, *Lancet Oncol* 2021

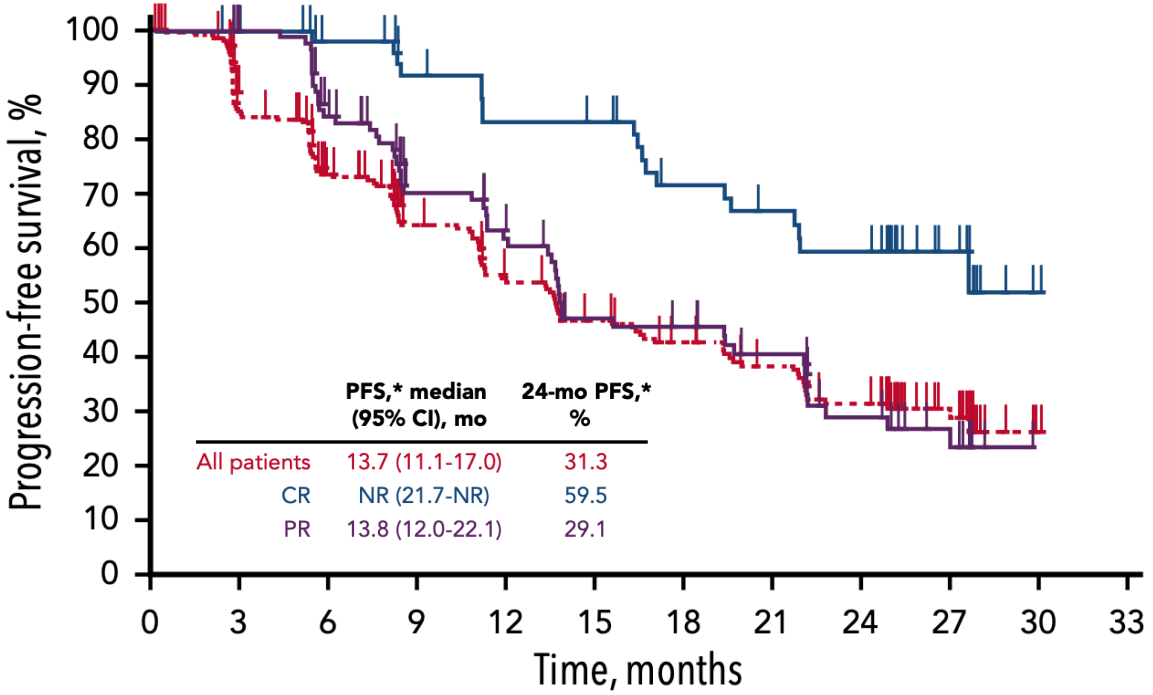
Deeper responses are associated with more durable remissions

CheckMate 205 (**Nivolumab**)



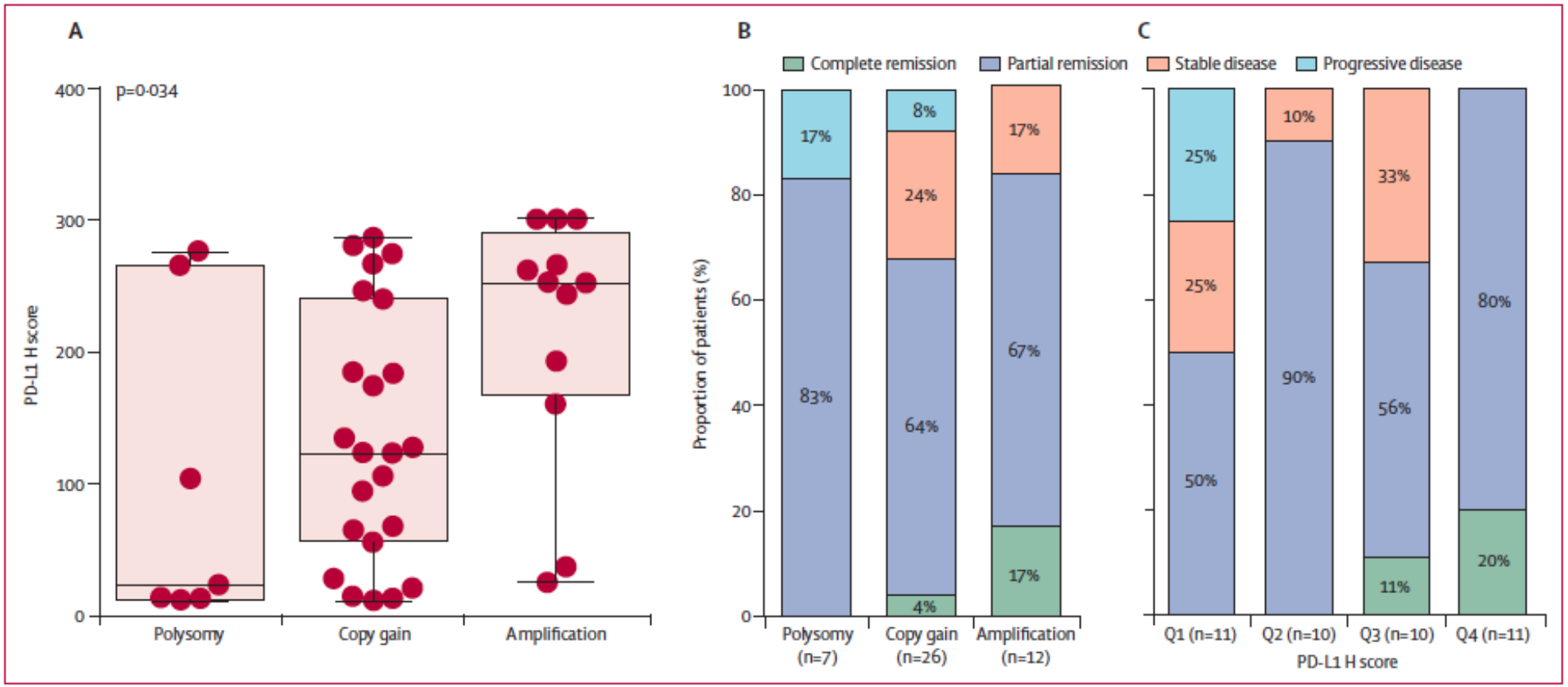
Armand et al, JCO 2018

KEYNOTE-087 (**Pembrolizumab**)



Chen et al, Blood 2019

9p24.1 amplification and higher PD-L1 expression correlate with better responses to nivolumab



Younes et al, *Lancet Oncol* 2016

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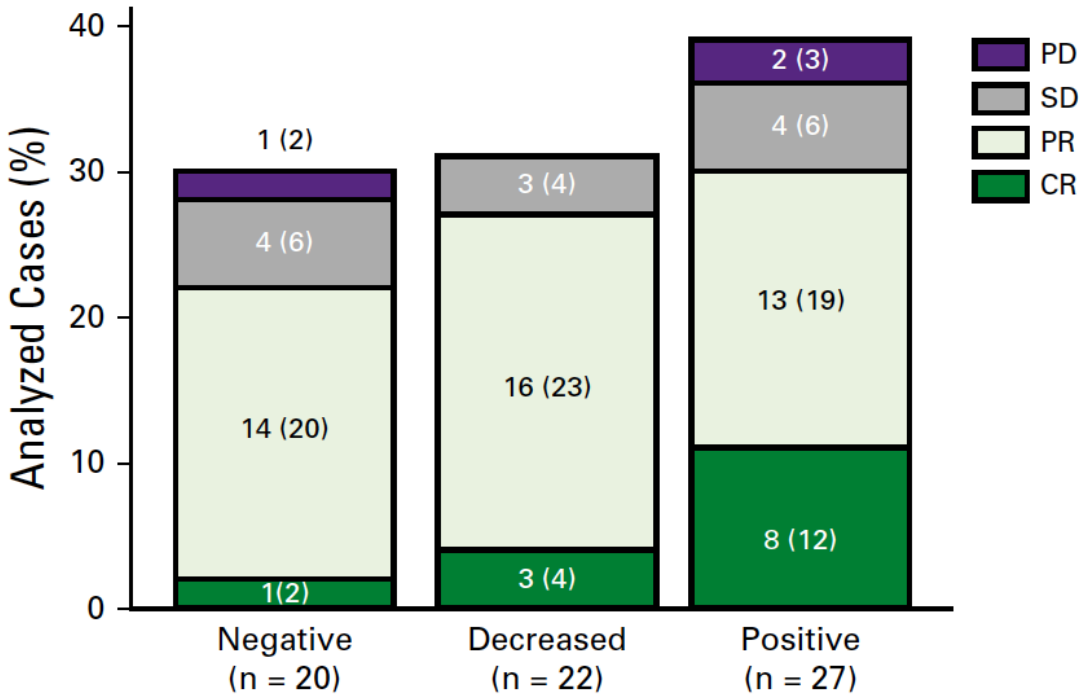
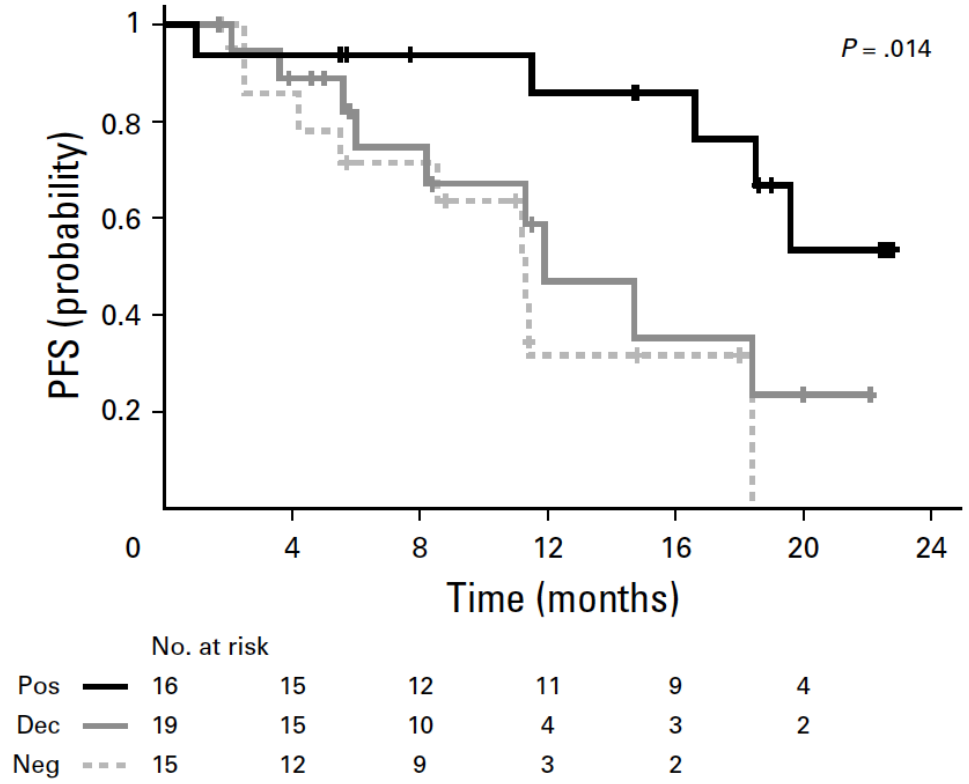
MHC class II expression correlates with better response to nivolumab



MHC class II expression in HRS cells



Roemer et al, *J Clin Oncol* 2018

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Novel salvage regimens combining PD-1 inhibitors with BV or chemotherapy have high CR rates and excellent PFS

Regimen	N	CR rate	PFS (All patients)	PFS (ASCT cohort)	Reference
Nivolumab + BV	91	67%	77% (3y)	91% (3y)	Advani et al, *Blood* 2021
Nivolumab + Ipilimumab + BV	22	84%	80% (1y)	NR	Diefenbach et al, *Lancet Haematol* 2020
Nivolumab + ICE	37	86%	79% (1y)	NR	Herrera et al, ASH 2019
Pembrolizumab + ICE	42	87%	88% (2y)	NR	Bryan et al, ASH 2021
Pembrolizumab + GVD	38	95%	100% (1y)	100% (1y)	Moskowitz et al, *J Clin Oncol* 2021

PD-1 inhibitor-based salvage regimens lead to excellent PFS post-ASCT

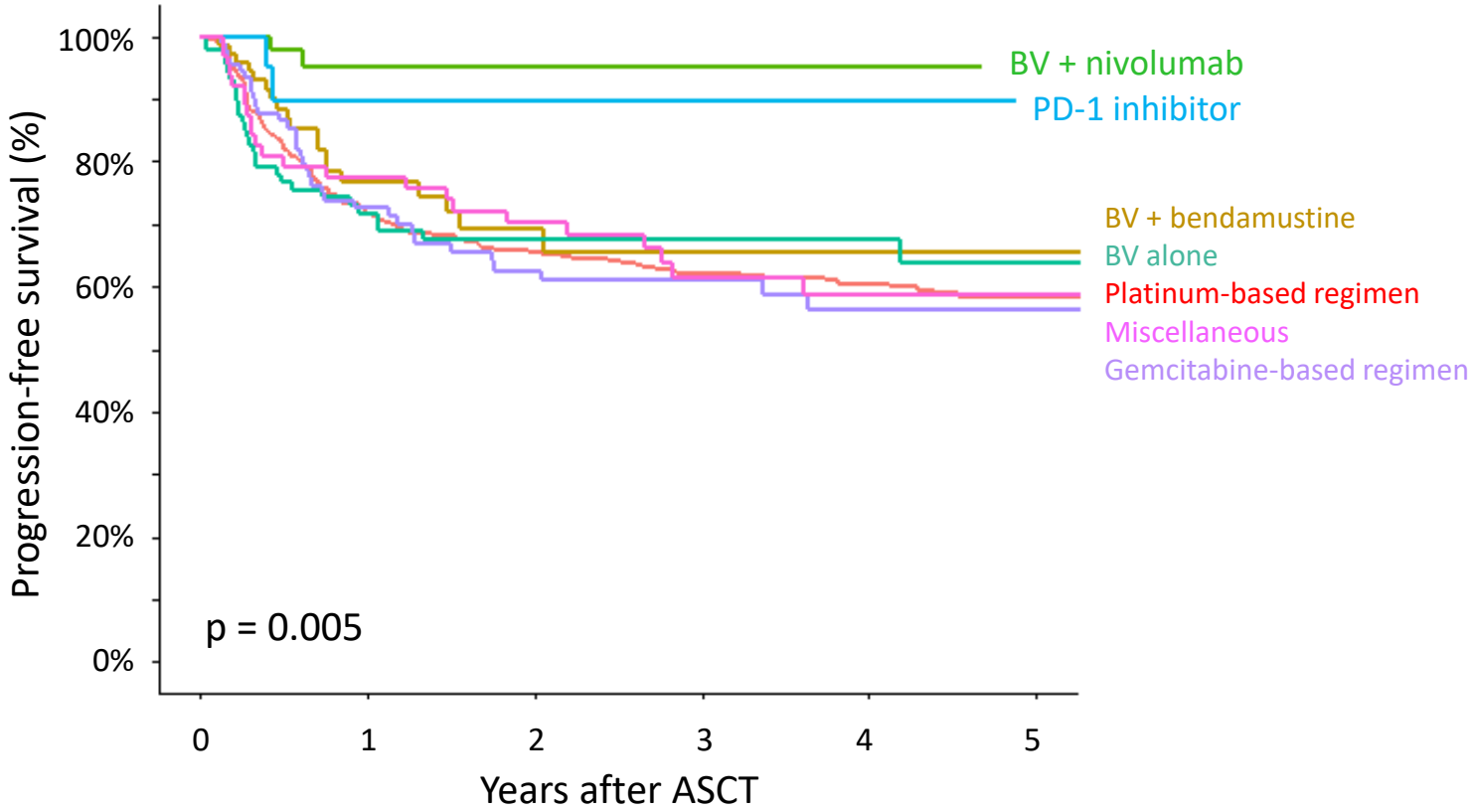
N = 853 patients at 12 U.S. centers

ASCT between 2010-2020

Outcomes compared by salvage regimen:

- Platinum-based regimen (N=451)
- Gemcitabine-based regimen (N=90)
- BV alone (N=87)
- BV + bendamustine (N=76)
- BV + nivolumab (N=48)
- PD-1 inhibitor (N=24)
- Miscellaneous (N=64)

Higher CR rate with BV+nivo (67%) vs platinum regimens (49%) (p<0.001)



Desai S, Spinner MA, David KA, et al, 2021 ASH Abstract #878

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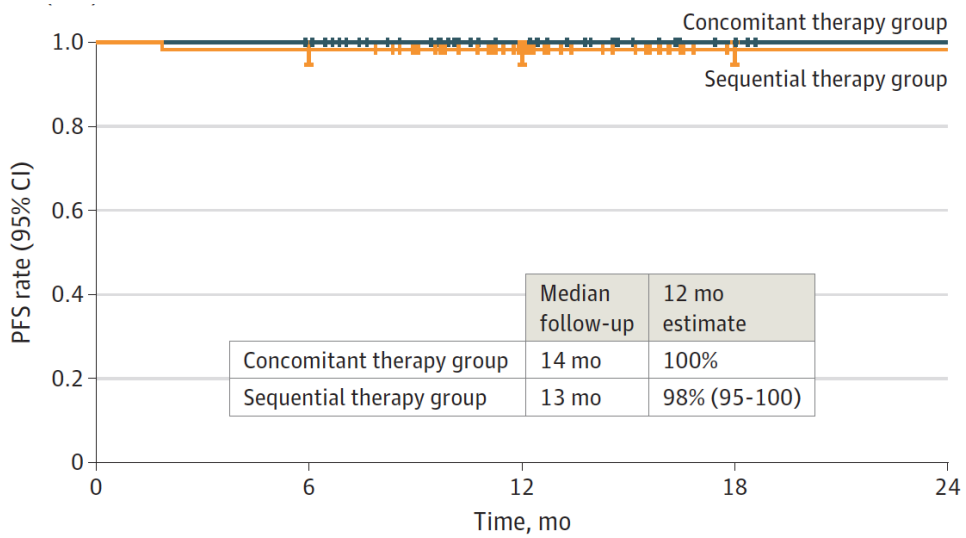
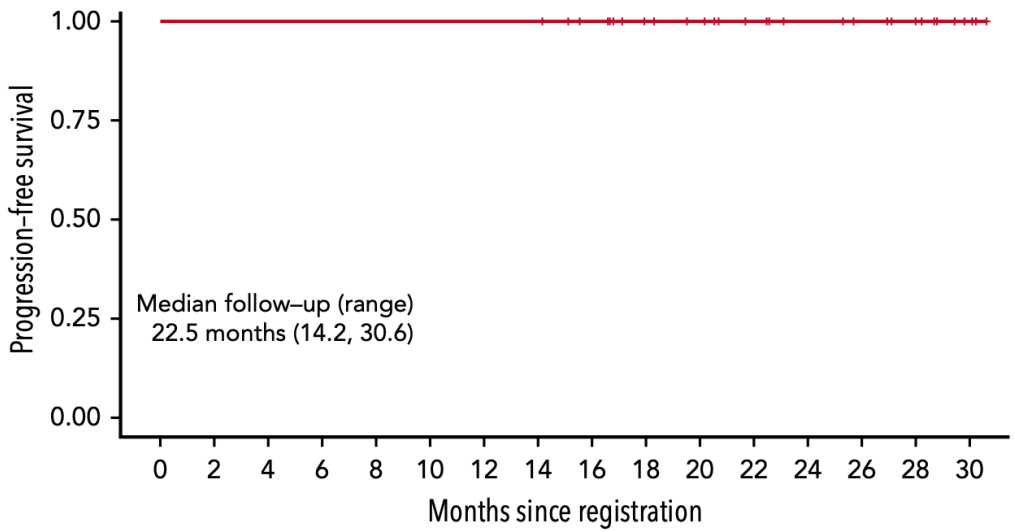
Integrating PD-1 inhibitors into frontline therapy for cHL

Nivo-AVD x 4 + 30 Gy ISRT (early unfavorable)



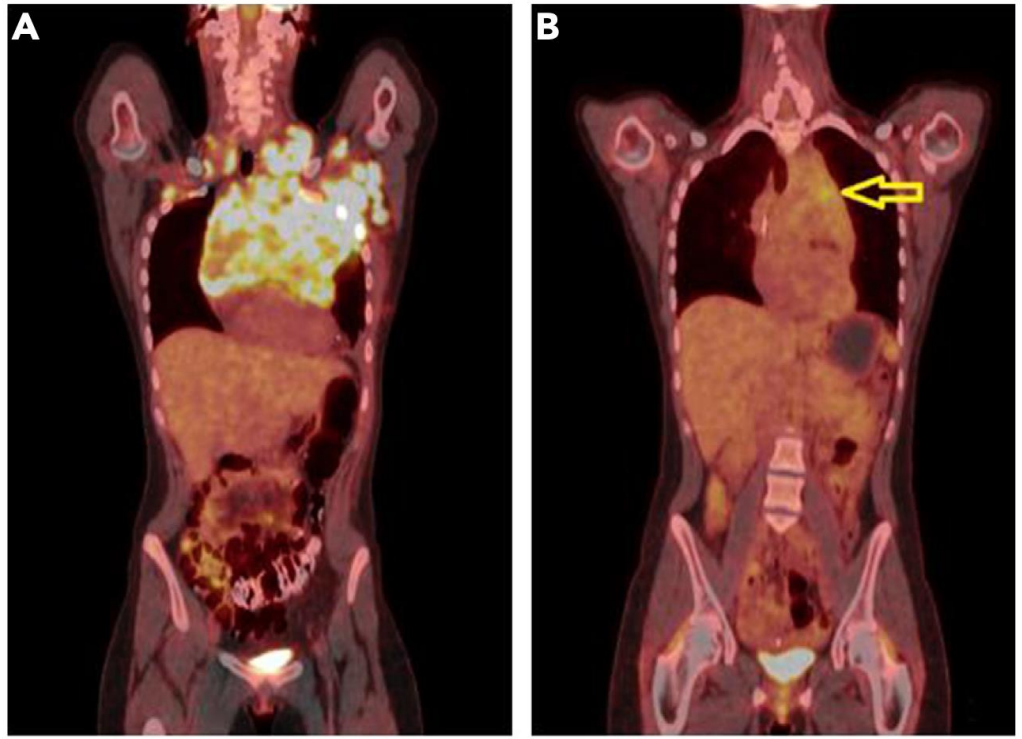
Pembro-AVD x 4-6 (early unfavorable & advanced)



Regimen	Stage	N	CRR	PFS	Med f/u	Reference
Nivolumab x 4 → Nivo-AVD x 6	IIB-IV	51	75%	83% (2y)	24 mo.	Ansell et al, ICML 2019
Nivo-AVD x 4 (sequential) + 30 Gy ISRT	I-II unfavorable	54	94%	98% (1y)	13 mo.	Brockelmann et al, *JAMA Oncol* 2020
Nivo-AVD x 4 (concurrent) + 30 Gy ISRT	I-II unfavorable	55	90%	100% (1y)	14 mo.	Brockelmann et al, *JAMA Oncol* 2020
Pembro-AVD x 4-6 (sequential)	IIA-IV	30	100%	100% (2y)	33 mo.	Allen et al, ASH 2021
Pembro-AVD x 4-6 (concurrent)	I-IV	30	68%	96% (1y)	10 mo.	Lynch et al, ASH 2021

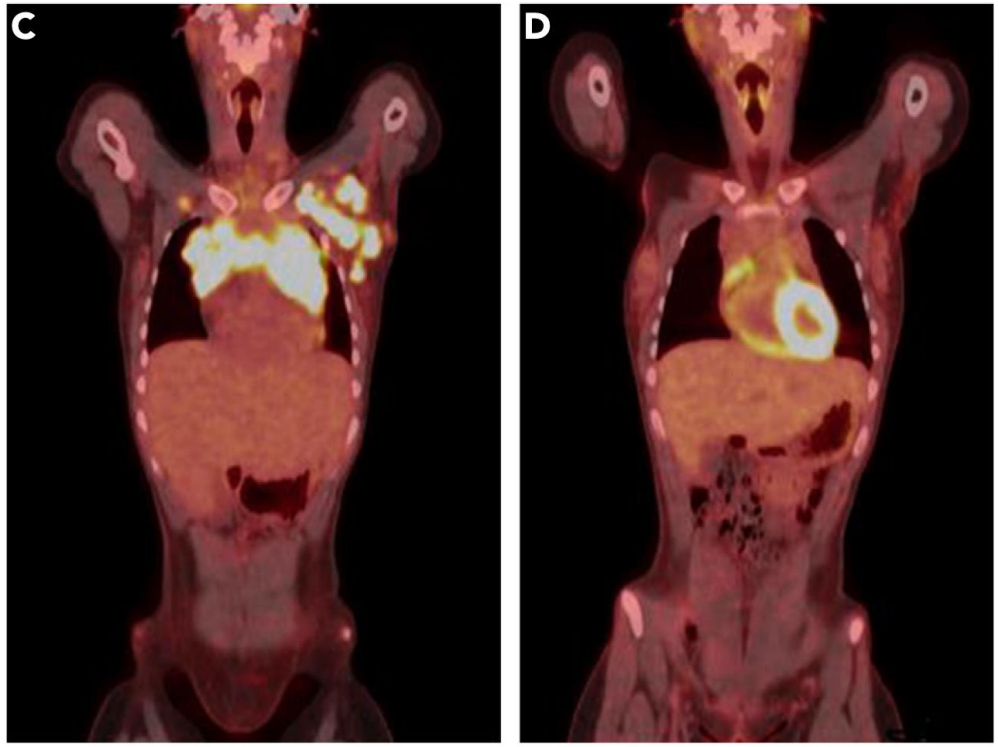
PET responses to pembrolizumab in newly diagnosed cHL

s/p pembrolizumab x 3



Deauville score 4

s/p pembrolizumab x 3

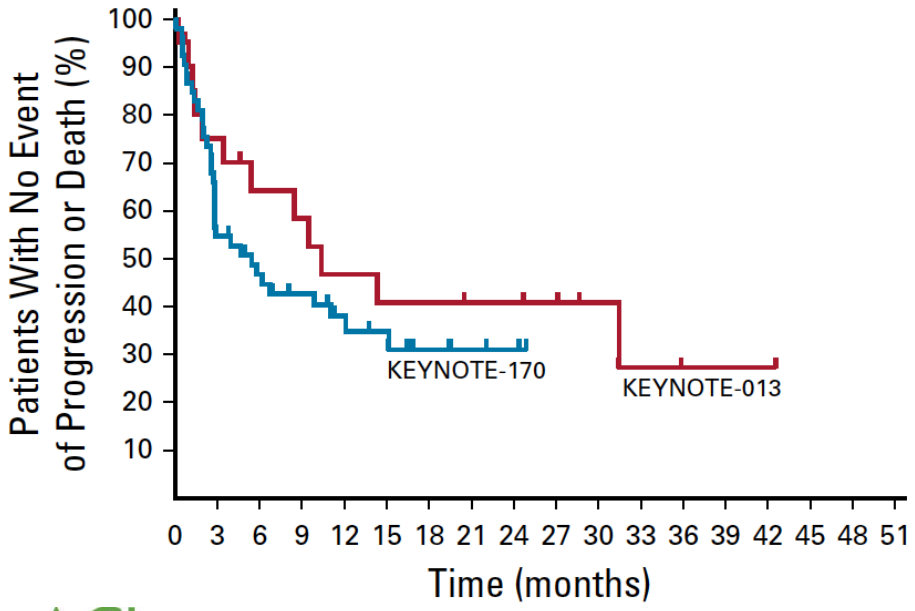


Deauville score 3

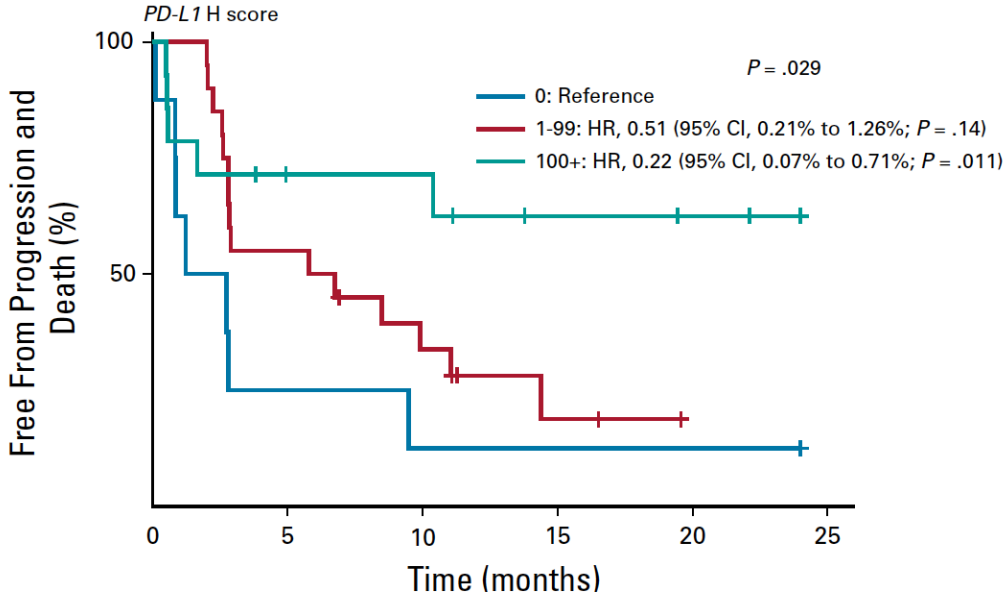
Allen et al, *Blood* 2021

PD-1 blockade in primary mediastinal B-cell lymphoma (PMBL)

- PMBL frequently harbors 9p24.1 copy gain or amplification
- Pembrolizumab is active in multiply R/R PMBL (ORR 48%, CR rate 33%, median PFS 10.4 months)
  - ➢ FDA approved in 2018 for R/R PMBL after 2 or more therapies
- Higher PD-L1 expression correlates with improved response and PFS



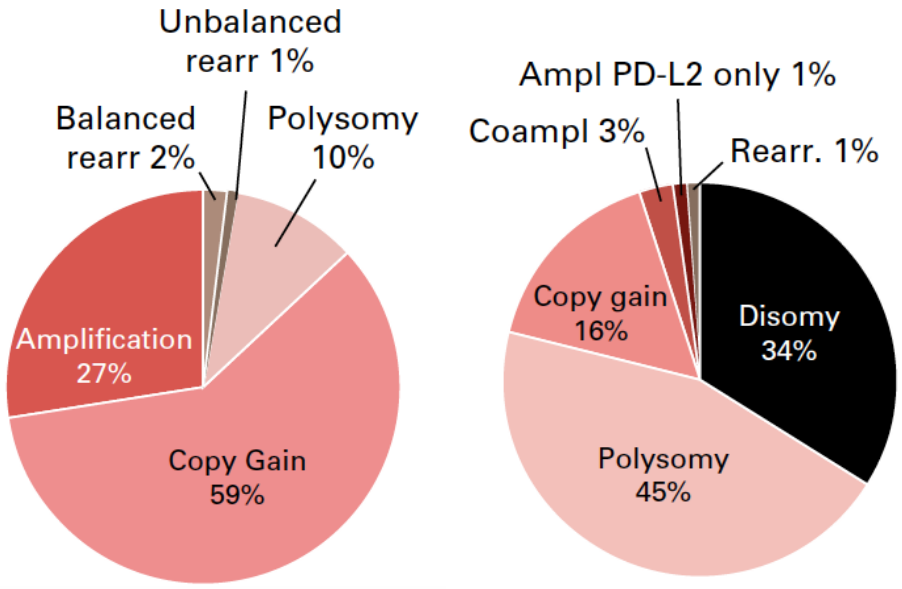
Armand et al, JCO 2019



Zinzani et al, ASH 2021 Abstract #306

PD-1 blockade in other B-cell non-Hodgkin lymphomas

- 9p24.1 copy gain and amplification are uncommon in most other B-cell NHL subtypes
- PD-1 inhibitors have minimal activity in R/R follicular lymphoma and DLBCL, NOS
- Response rates are higher in EBV+ DLBCL, Richter syndrome, and inflamed lymphomas (TCRLBCL)



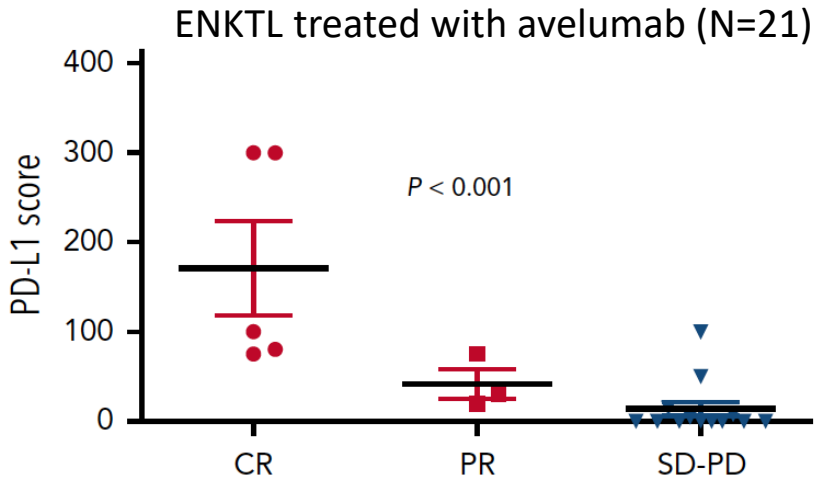
cHL **DLBCL**

Ansell et al, JCO 2019

NHL subtype	PD-1 inhibitor	N	ORR	CR	Median PFS	Reference
Follicular lymphoma	Nivo	92	4%	1%	2.2 mo.	Armand et al, *Blood* 2021
DLBCL, NOS	Nivo	87	10%	3%	1.9 mo.	Ansell et al, JCO 2019
Richter syndrome	Pembro	9	44%	11%	5.4 mo.	Ding et al, *Blood* 2017

PD-1 inhibitors have mixed results in T-cell lymphomas

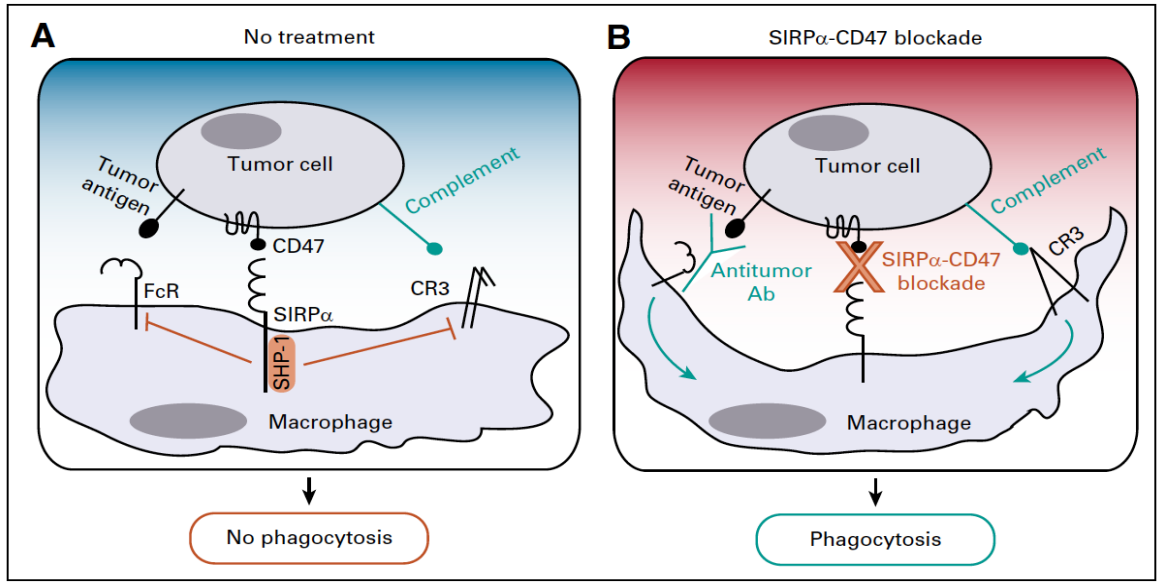
- Modest responses in PTCL, but hyperprogression also reported
- Some durable responses observed in advanced CTCL
- Highly active in extranodal NK/T-cell lymphoma, nasal type
  - ➢ High PD-L1 expression correlates with treatment response

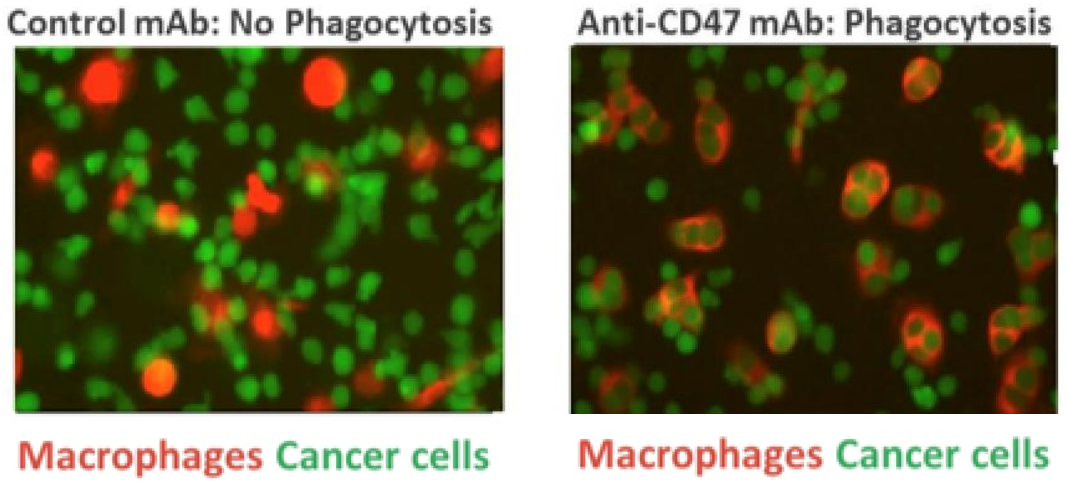


T-cell lymphoma subtype	PD-(L)1 inhibitor	N	ORR	CR rate	Median PFS	Reference
PTCL, NOS / TFH / AITL	Pembrolizumab	13	33%	27%	3.2 months	Barta et al, CLML 2019
Advanced MF / SS	Pembrolizumab	24	38%	8%	Not reached	Khodadoust et al, JCO 2019
ENKTL, nasal type	Pembrolizumab	7	100%	71%	Not reached	Kwong et al, *Blood* 2017
ENKTL, nasal type	Avelumab	21	38%	24%	2.7 months	Kim et al, *Blood* 2020

Activating macrophages through CD47/SIRPa checkpoint blockade

- CD47 is a ”don’t eat me” signal expressed by many cancers to evade phagocytosis by macrophages[1]
- Magrolimab (Hu5F9-G4) is an anti-CD47 antibody which promotes phagocytic elimination of multiple lymphoma subtypes in preclinical models[2,3]





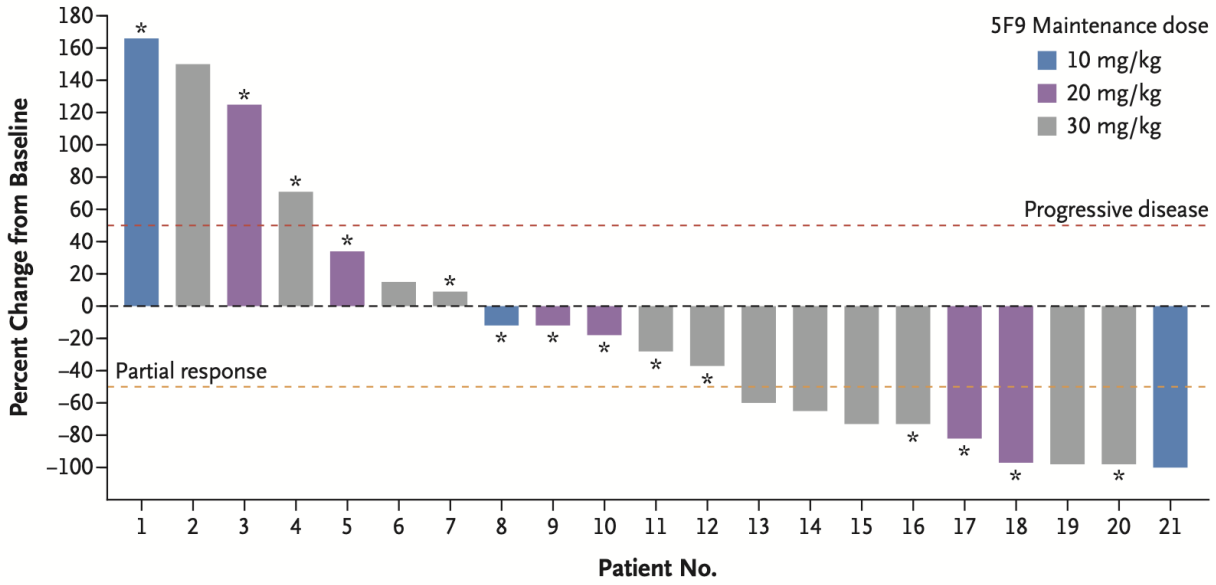
[1]Veillette and Tang, JCO 2019

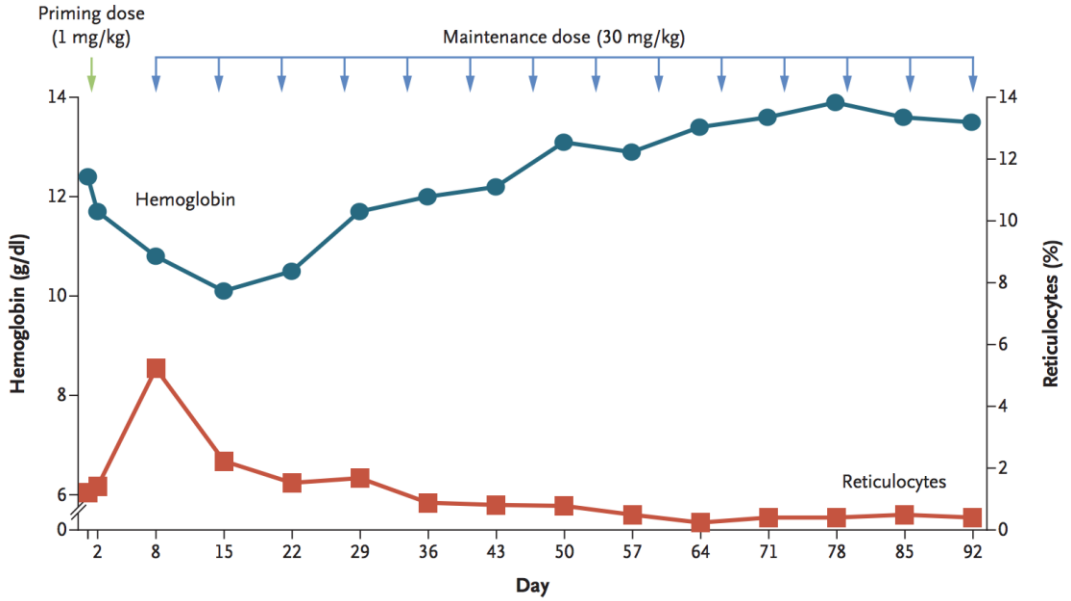
[2]Chao et al, *Cell* 2010

[3]Liu et al, *PLoS One* 2015

Magrolimab + rituximab in relapsed/refractory B-cell NHL

- Magrolimab + rituximab combination was active and synergistic in heavily pretreated follicular lymphoma (ORR 71%, CR 43%) and DLBCL (ORR 40%, CR 33%)
- Magrolimab led to transient anemia, mitigated by using a priming/maintenance dose schedule

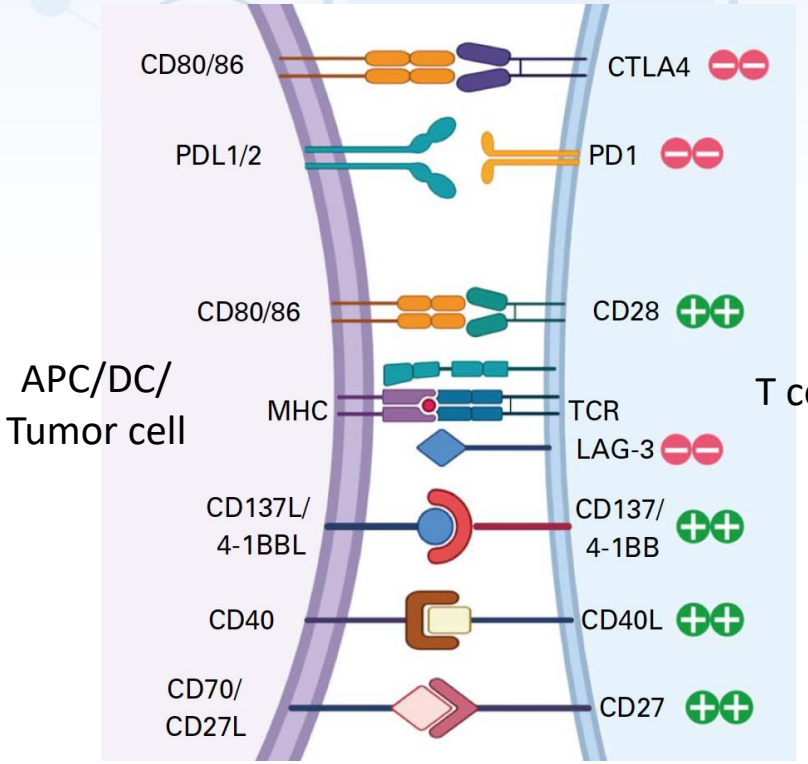




Advani et al, NEJM 2018

Novel immunotherapy combinations in lymphoma

- Numerous checkpoints modulate T-cell function in lymphoma
- Combining PD-1 inhibitors with other checkpoint inhibitors may enhance antitumor immune responses:
  - Enhancing T-cell immune responses (CTLA-4, LAG-3 antibodies)
  - Activating NK cells (CD30/CD16 bispecific antibody)
  - Activating macrophages (CD47/SIRPa blockade)



*cHL cohort

Ansell SM, JCO 2021

Immunotherapy combination	Therapeutic targets	Disease group	N*	ORR*	CR*	Reference / NCT number
Nivolumab + ipilimumab	PD-1 + CTLA-4	cHL, DLBCL, FL	31	74%	23%	Armand et al, *Leukemia* 2021
Nivolumab + lirilumab	PD-1 + KIR	cHL, DLBCL, FL	21	76%	24%	Armand et al, *Leukemia* 2021
Pembrolizumab + AFM-13	PD-1 + CD30/CD16 bispecific	cHL	24	88%	46%	Bartlett et al, *Blood* 2020
Pembrolizumab + magrolimab	PD-1 + CD47	cHL	Trial ongoing			NCT04788043
Pembrolizumab + MK-4280	PD-1 + LAG-3	cHL, DLBCL, FL	Trial ongoing			NCT03598608

Conclusions

- PD-1 inhibitors are highly active in cHL, PMBL, and some subtypes of T-cell lymphoma (extranodal NK/T-cell lymphoma, nasal type)
- 9p24.1 amplification, higher PD-L1 expression, EBV+ disease, and intact MHC class II expression are associated with better responses to PD-1 inhibitors
- PD-1 inhibitors are moving into earlier lines of therapy in cHL, including as first salvage and in the frontline setting in combination with chemotherapy with encouraging results
- PD-1 inhibitors can produce durable remissions but are not curative as single agents
- Future studies will focus on rational immunotherapy combinations to enhance T-cell responses and activate other immune effectors including NK cells and macrophages

Thank you!

- Questions?