



# HL multirefractario o recaído

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# CONFLICTS OF INTEREST

BMS – research

Beigene – research

Morphosys/Incyte – research

Morphosys – consultancy, speakers' bureau

SeaGen – consultancy, speakers' bureau

AstraZeneca – consultancy

ADC Therapeutics - consultancy

Novartis – consultancy

SyntheKine - consultancy

CTI – consultancy

# Outline

**Treatment Landscape of R/R HL**

**Chemorefractory disease may not be really chemorefractory**

**AutoHCT post PD-1 blockade**

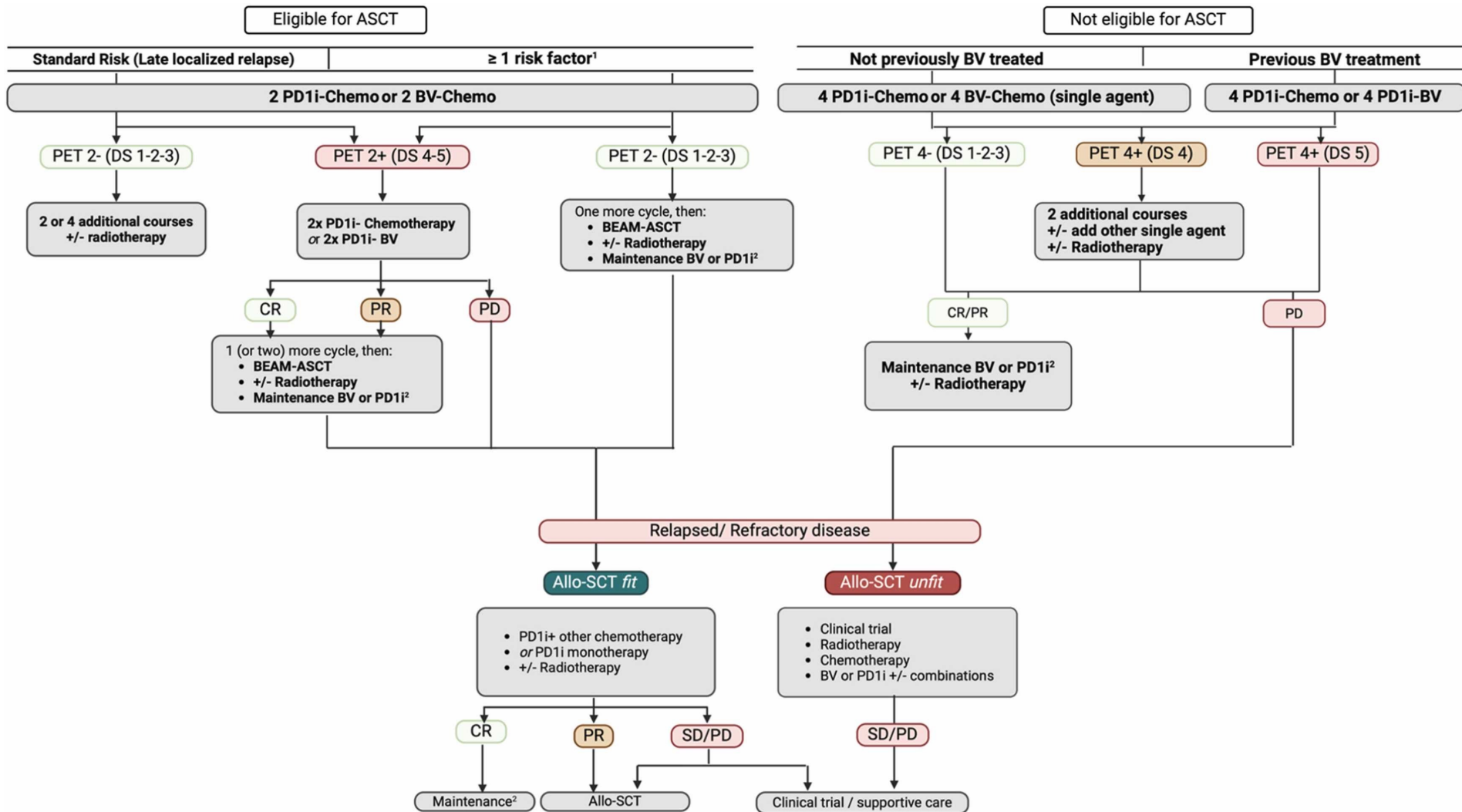
**PD-1 based combinations**

**Alternative immune checkpoints**

**CD30-targeted therapies beyond BV**

**Future directions**

# HL R/R

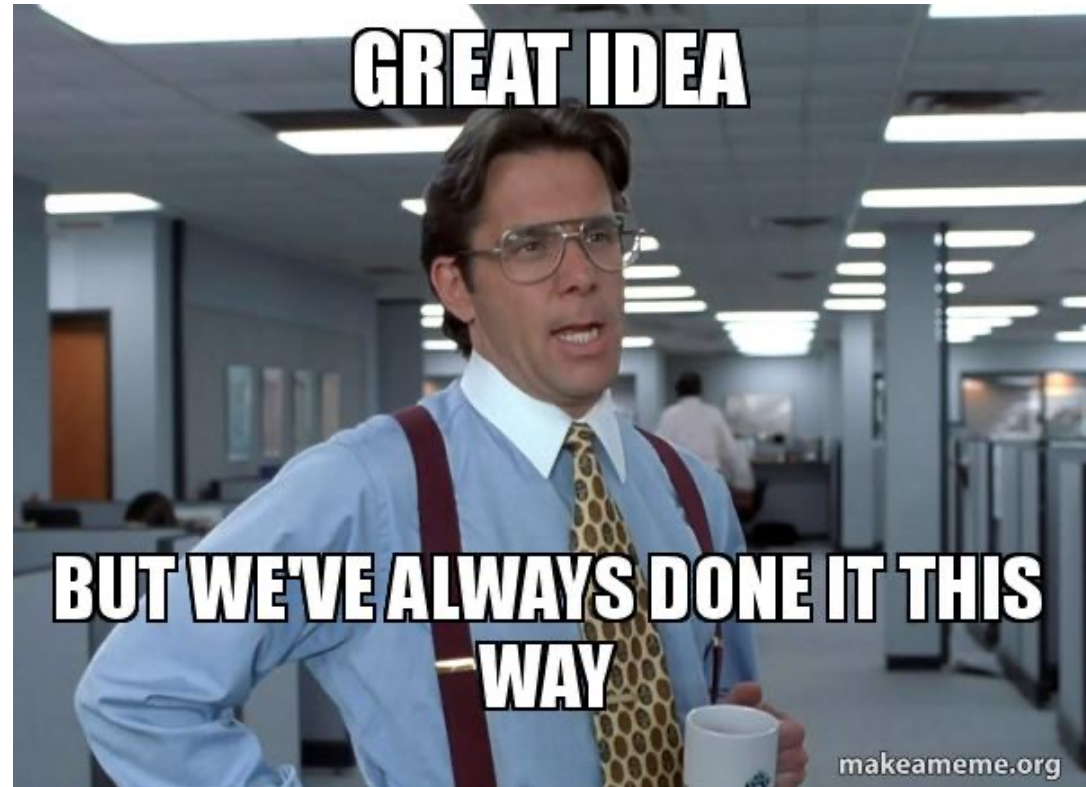


# CLINICAL CASE

25yo female

- 1L ABVD – PR
- 2L ICE – PD
- 3L IGEV - SD
- 4L BV – SD
- 5L Pembro – PR (near CR)

Is AutoHCT still feasible?



# CLINICAL CASE

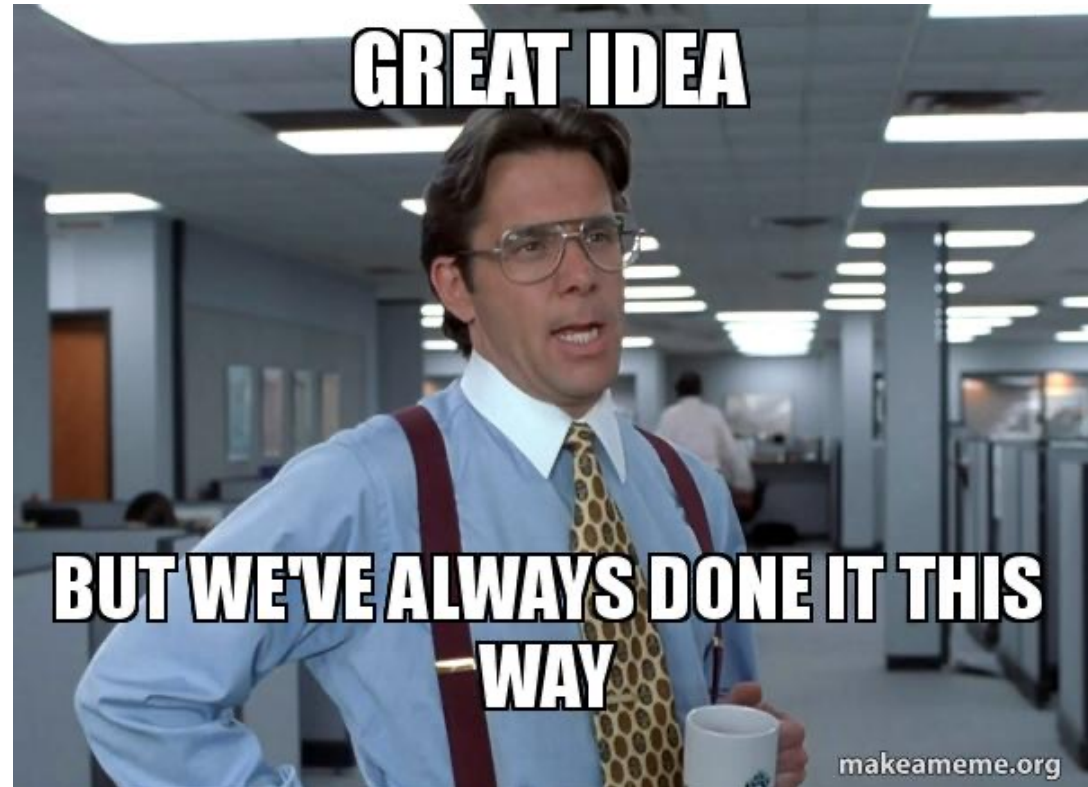
25yo female

- 1L ABVD – PR
- 2L ICE – PD
- 3L IGEV - SD
- 4L BV – SD
- 5L Pembro – PR (near CR)

Is AutoHCT still feasible?

AutoHCT with BEAM

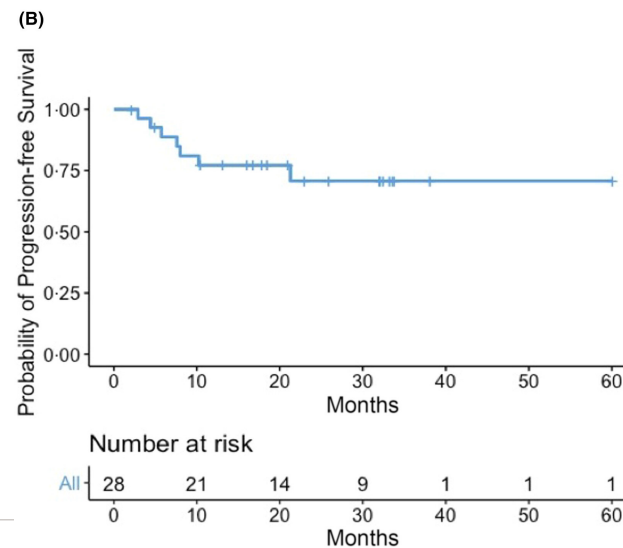
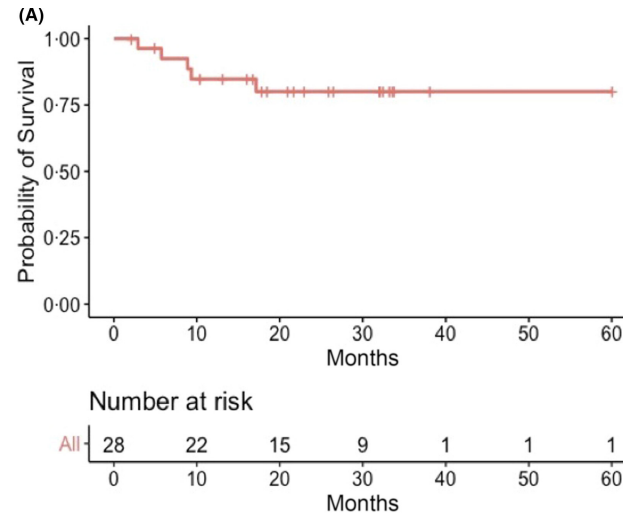
**Remains in long-term remission**



# CHEMO AFTER PD-1 BLOCKADE

N=28 patients with progression on PD-1 blockade who then received chemotherapy

- 64% prior auto, 100% prior BV
- ORR 93%, CR 82%
- 25 pts proceeded to allo
- 2y PFS 71%, 2y OS 80%



## Chemotherapy after PD-1 blockade highly effective

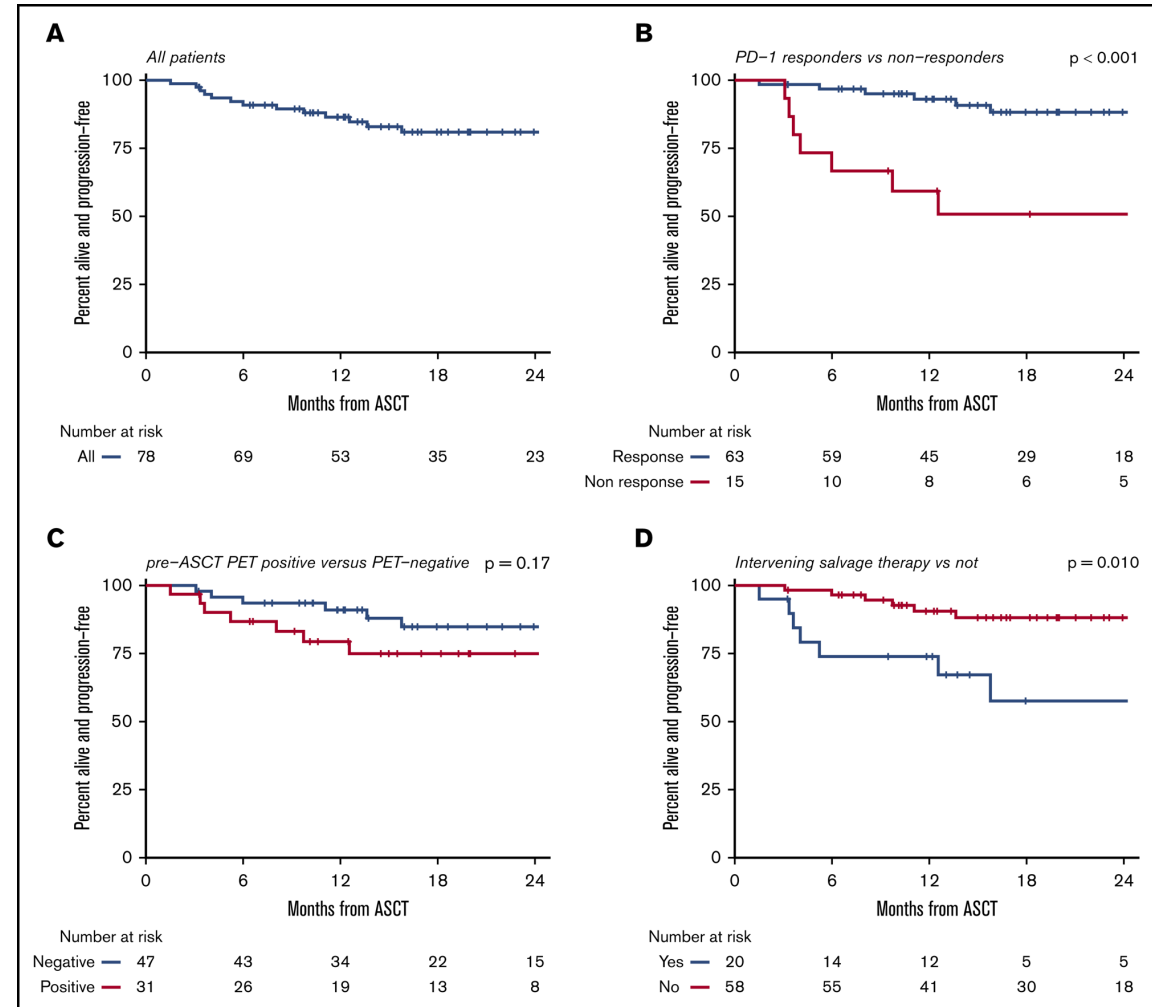
- Chemosensitization effect
- Could it apply to high-dose chemotherapy?

# AutoHCT post PD-1 blockade

## AutoHCT post PD-1 highly effective

Retrospective study (n=77) of ASCT post PD-1 blockade (PD-1 in 3L+)

- All patients ineligible for ASCT post 2L due to poor response
- **18m PFS 81%!**
- Pre-autoHCT PR vs. CR no difference! ( $p = 0.17$ )
- Response to PD-1 vs. no response to PD-1 blockade important ( $p < 0.001$ )



Merryman, et al. Blood Advances 2021.

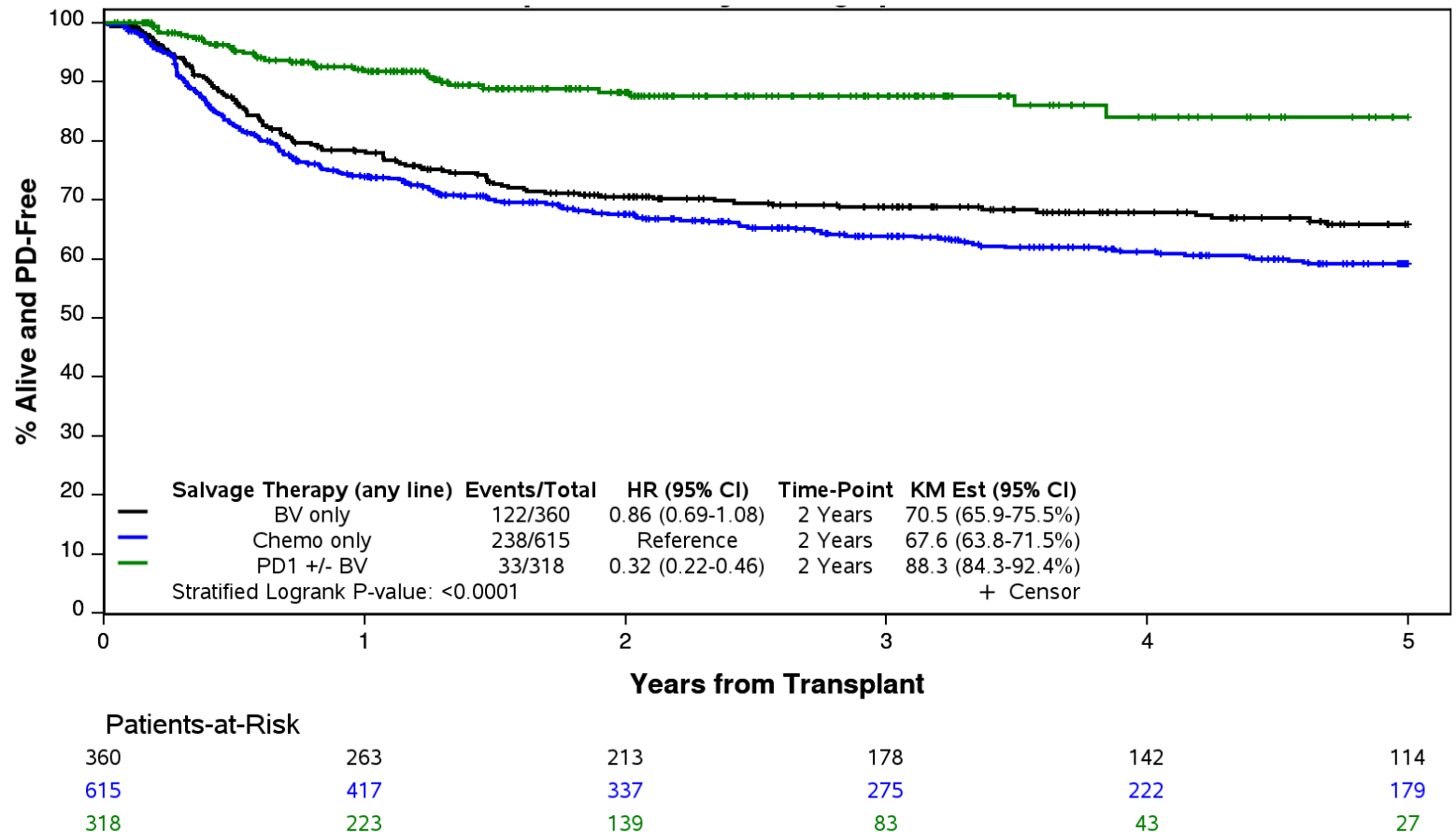
# Importance of PD-1 blockade pre-autoHCT

Retrospective study of 1293 patients with HL R/R post autoHCT

- 318 pts received PD-1 +/- BV pre-HCT
- 360 pts received BV WITHOUT PD-1 pre-HCT

## Improved PFS with PD-1 blockade pre-HCT

- Not just due to higher CR rate pre-HCT:
  - Effect maintained on MVA \*controlling\* for response



# PD-1 / BV refractory patients

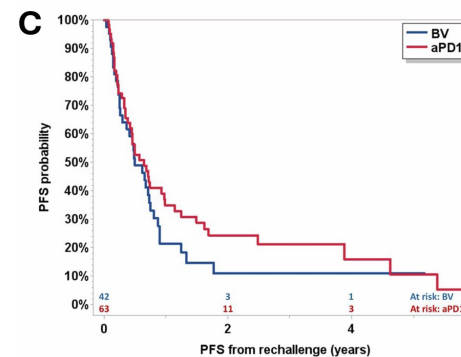
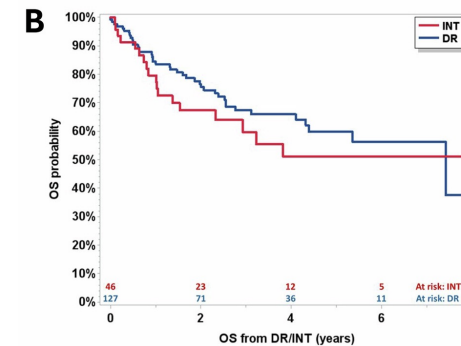
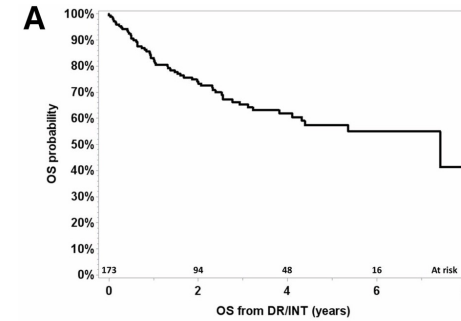
R/R HL patients eventually will become PD-1 and BV refractory (neither curative\*)

Retrospective study of 173 pts with R/R HL refractory or intolerant to BV + PD-1

- Median 3.4y from dx
- Median 5 lines of tx

Prognosis improved with time

- OS 7.4y from time of refractoriness
- ORR to PD-1 rechallenge 55%,
- ORR to BV rechallenge 62%



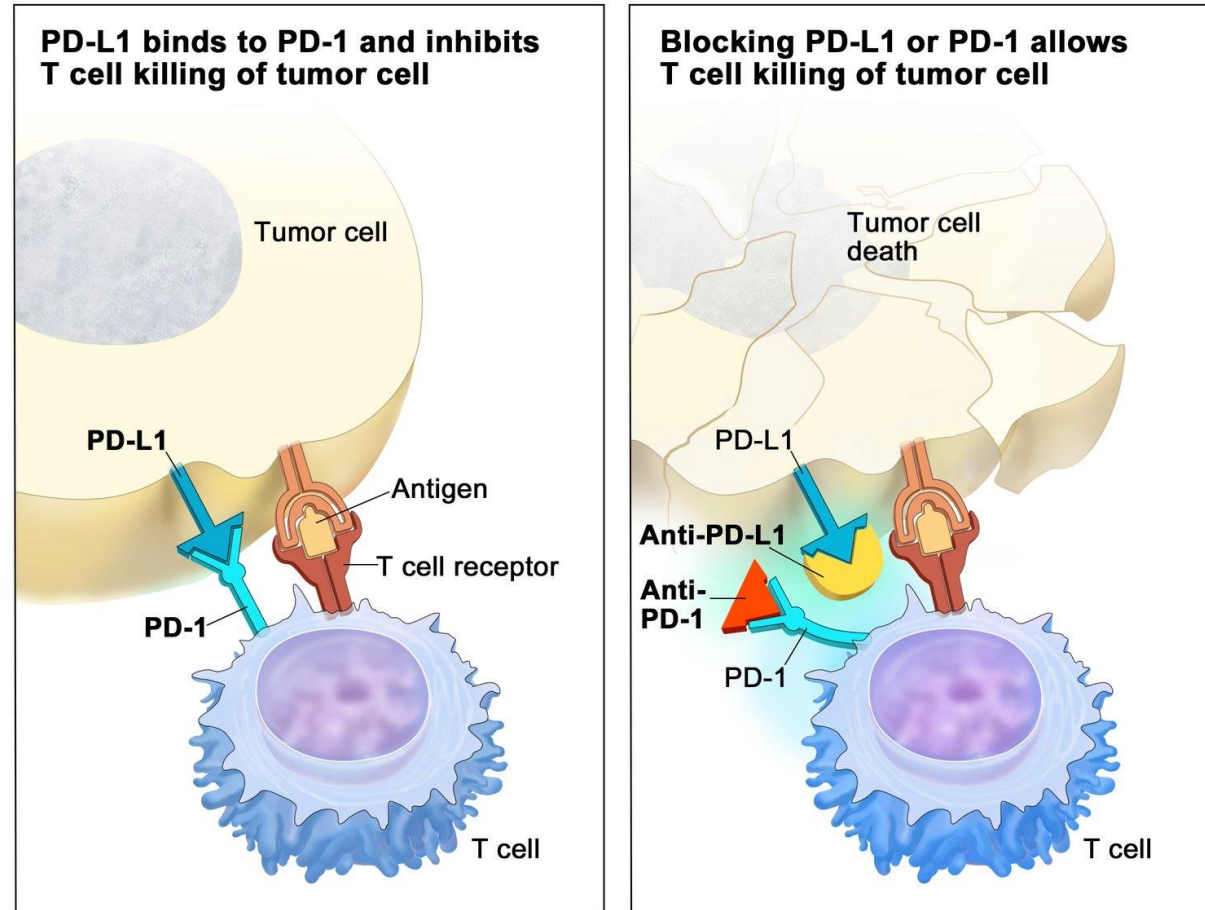
# Restoration of PD-1 sensitivity

## Can we restore PD-1 sensitivity?

- Would be useful – PD-1 blockade still most effective mechanism in R/R HL

## How does acquired resistance appear?

- May be an issue more with the immune system than the tumor
- Slow progression on PD-1 blockade common – can continue tx for months / years
- **How to reinvigorate the immune system?**



Credit: © Terese Winslow

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# Pembrolizumab + vorinostat

Vorinostat – various immunomodulatory effects.

Pembrolizumab + vorinostat:

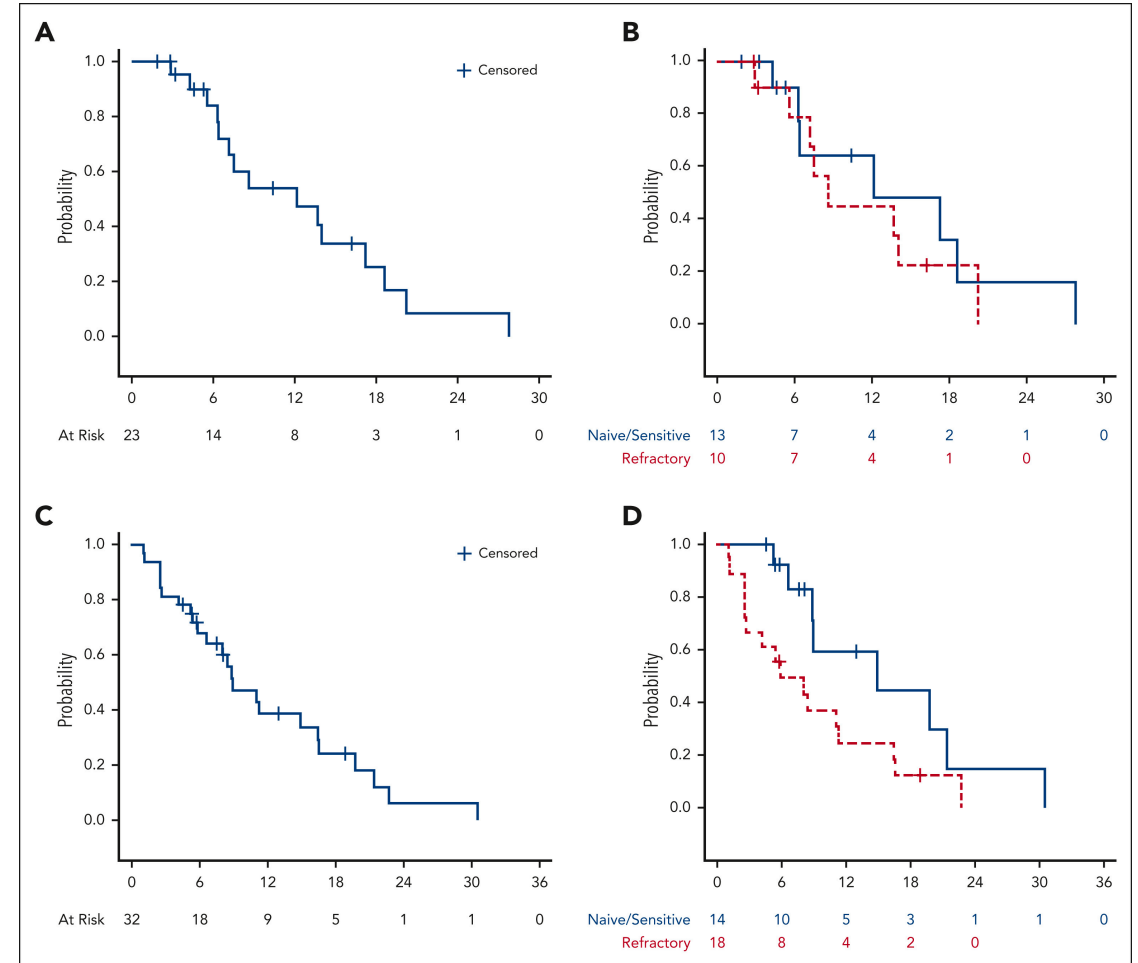
- **N=32 (18 PD-1 refractory)**
- **ORR 72% (56% in PD-1 refractory)**
- **DOR 12.2m (8.6m in PD-1 refractory)**

## PRINCIPLES OF SYSTEMIC THERAPY Relapsed or Refractory Disease

### Classic Hodgkin Lymphoma

- Consider the following when selecting re-induction or subsequent therapy:
  - ▶ Clinical trial enrollment
  - ▶ Referral to a center with expertise

Primary Refractory Disease or Relapse (within any time frame) (Candidate for or Not a Candidate for HDT/ASCR)	Additional Considerations for Relapsed/ Refractory CHL (Not a Candidate for HDT/ ASCR)
<b>Second-Line and Subsequent Therapy<sup>1,6</sup></b> (in alphabetical order)	<ul style="list-style-type: none"> <li>• Individualized treatment is necessary.</li> <li>• For localized relapse, consolidative ISRT should be strongly considered.</li> <li>• Refer to or consult a center with expertise.</li> <li>• Single-agent palliative therapy options include:                         <ul style="list-style-type: none"> <li>▶ CPI:                                 <ul style="list-style-type: none"> <li>◊ Nivolumab<sup>27,28</sup></li> <li>◊ Pembrolizumab<sup>29,30</sup></li> </ul> </li> <li>▶ Non-CPI containing regimen:                                 <ul style="list-style-type: none"> <li>◊ Bendamustine<sup>15</sup></li> <li>◊ BV<sup>5</sup></li> <li>◊ Everolimus<sup>20</sup></li> <li>◊ ISRT<sup>1</sup></li> <li>◊ Gemcitabine<sup>31</sup></li> <li>◊ Lenalidomide<sup>23</sup></li> <li>◊ Vinblastine<sup>24</sup></li> </ul> </li> </ul> </li> </ul>
<b>Therapy for Disease Refractory to at Least 3 Prior Lines of Subsequent Therapy (in alphabetical order)</b>	<ul style="list-style-type: none"> <li>• Bendamustine<sup>15</sup></li> <li>• Bendamustine-carboplatin-etoposide<sup>16</sup></li> <li>• Decitabine-pembrolizumab<sup>17,18,19</sup></li> <li>• GCD (gemcitabine, cisplatin, dexamethasone)<sup>21</sup></li> <li>• GEMOX (gemcitabine, oxaliplatin)<sup>22</sup></li> <li>• ISRT<sup>1</sup></li> <li>• <b>Vorinostat-pembrolizumab<sup>25</sup></b></li> </ul>
<b>Non-CPI-containing regimens</b> <ul style="list-style-type: none"> <li>• BV<sup>5</sup></li> <li>• BV-bendamustine<sup>6</sup></li> <li>• DHAP (dexamethasone, cisplatin, high-dose cytarabine)<sup>7,8</sup></li> <li>• Gemcitabine/bendamustine/vinorelbine<sup>9</sup></li> <li>• GVD (gemcitabine, vinorelbine, liposomal doxorubicin)<sup>10</sup></li> <li>• ICE (ifosfamide, carboplatin, etoposide)<sup>8,11,12</sup></li> <li>• ICE-BV<sup>13</sup></li> <li>• IGEV (ifosfamide, gemcitabine, vinorelbine)<sup>14</sup></li> </ul>	



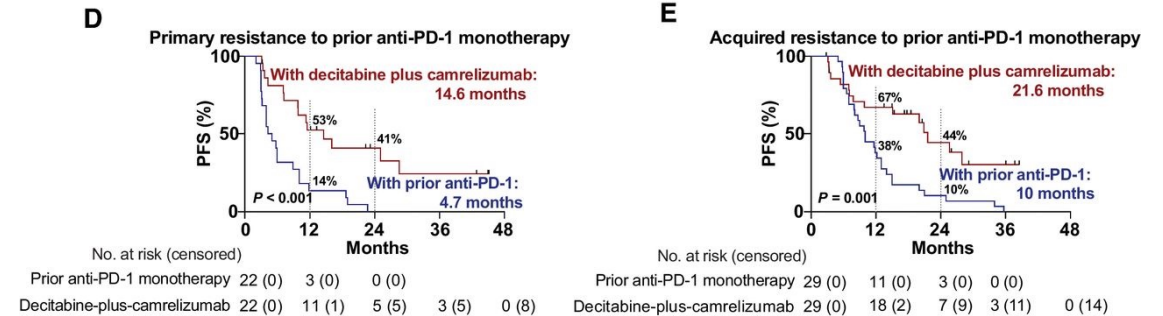
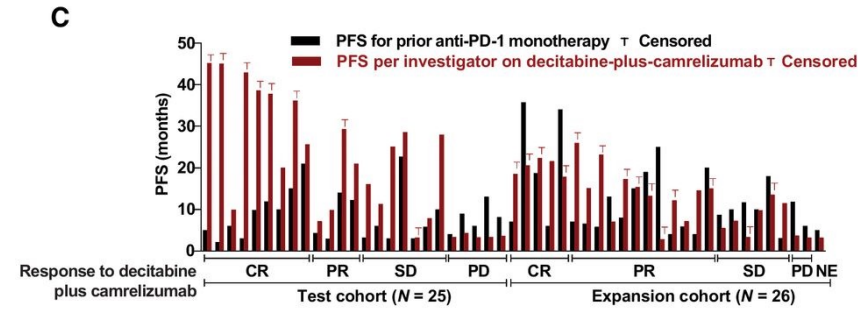
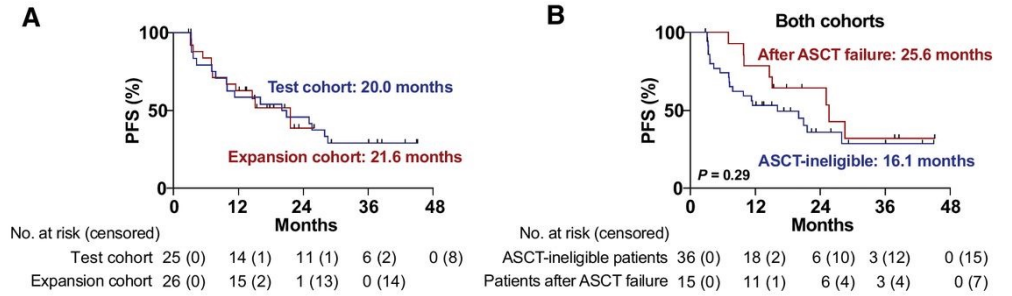
Mei M, et al. Blood 2023..

# Camrelizumab + decitabine

Decitabine 10 mg/day x 5,  
camrelizumab 200 mg IV D8  
q21d

## PD-1 experienced cohort:

- N=50
- ORR 62% (test cohort),  
80% (expansion cohort)
- DOR not reached



Wang C, et al. Cancer Res. 2021 May 15;27(10):2782-2791.

# PD-1 + HMA, cont'd

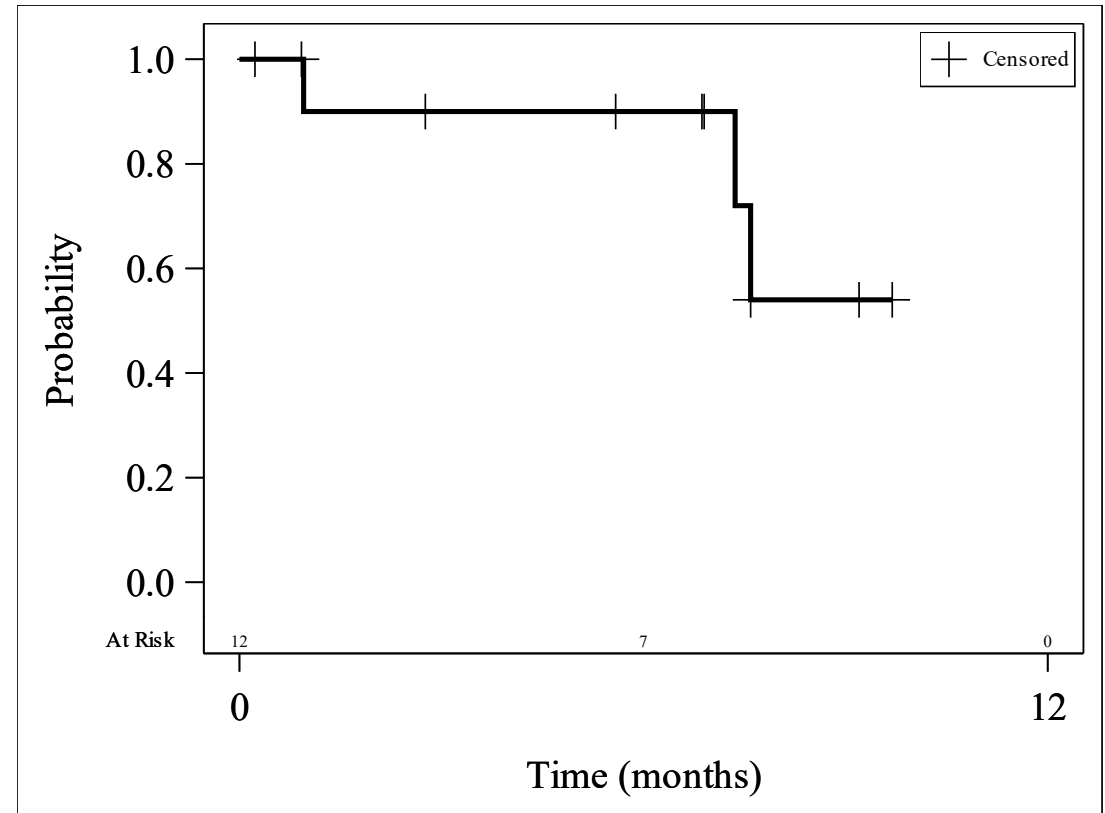
Nivolumab + CC-486  
(azacitidine oral) in R/R HL  
refractory to PD-1 blockade

CC-486 300 mg PO D1-7  
Nivolumab 480 mg IV D8  
Q28d

Preliminary analysis (ASH  
2023)

- 19 patients evaluable
- **ORR 63%**
- **PFS 11.3m (est)**

**Fully enrolled, data being  
analyzed**



Mei M, et al. ASH 2023

# PD-1 + HMA + HDACi

Phase 2 trial in China of chidamide (HDACi), decitabine, camrelizumab in patients previously exposed to PD-1 blockade

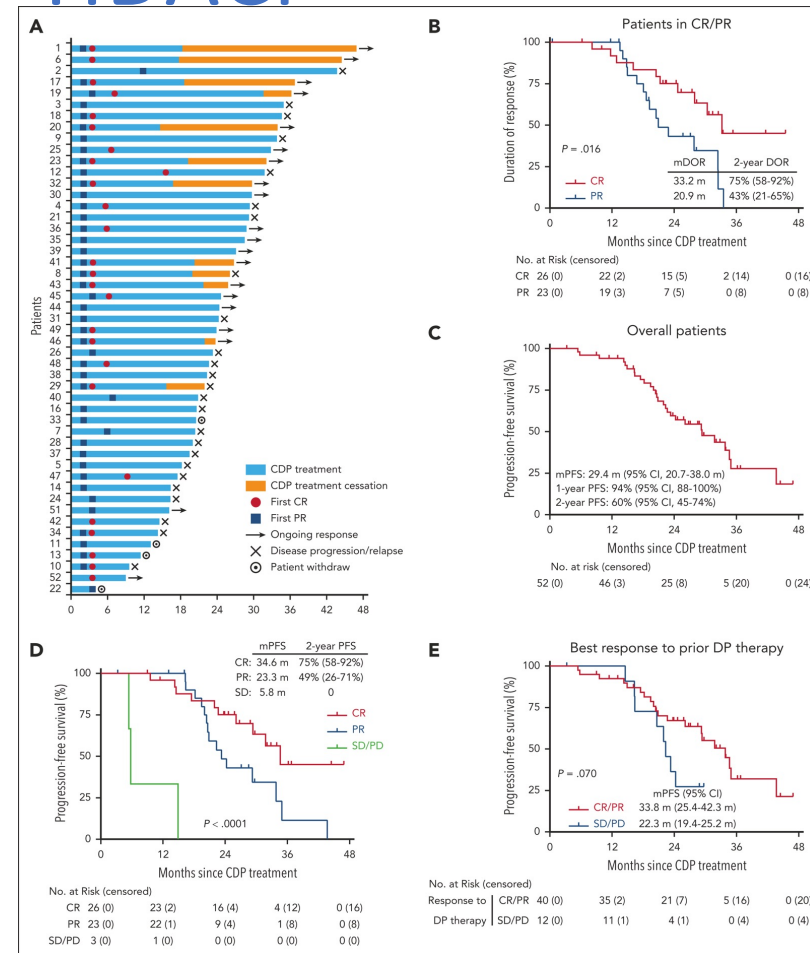
N=52, 5 median lines of tx

- Only 5 had prior BV, 12 prior autoHCT

ORR 94%, CR 50%, PFS 29.4m

12 patients in CR discontinued therapy, 9 remained in CR @ 1y

Chidamide PO 10 mg/day D1-4, 20 mg/day D8, 11, 15, 18  
Decitabine IV 10 mg/day D1-5  
Camrelizumab 200 mg IV D6  
q21d



Nie J, et al. Blood 2024.

# ALTERNATIVE CHECKPOINT INHIBITION

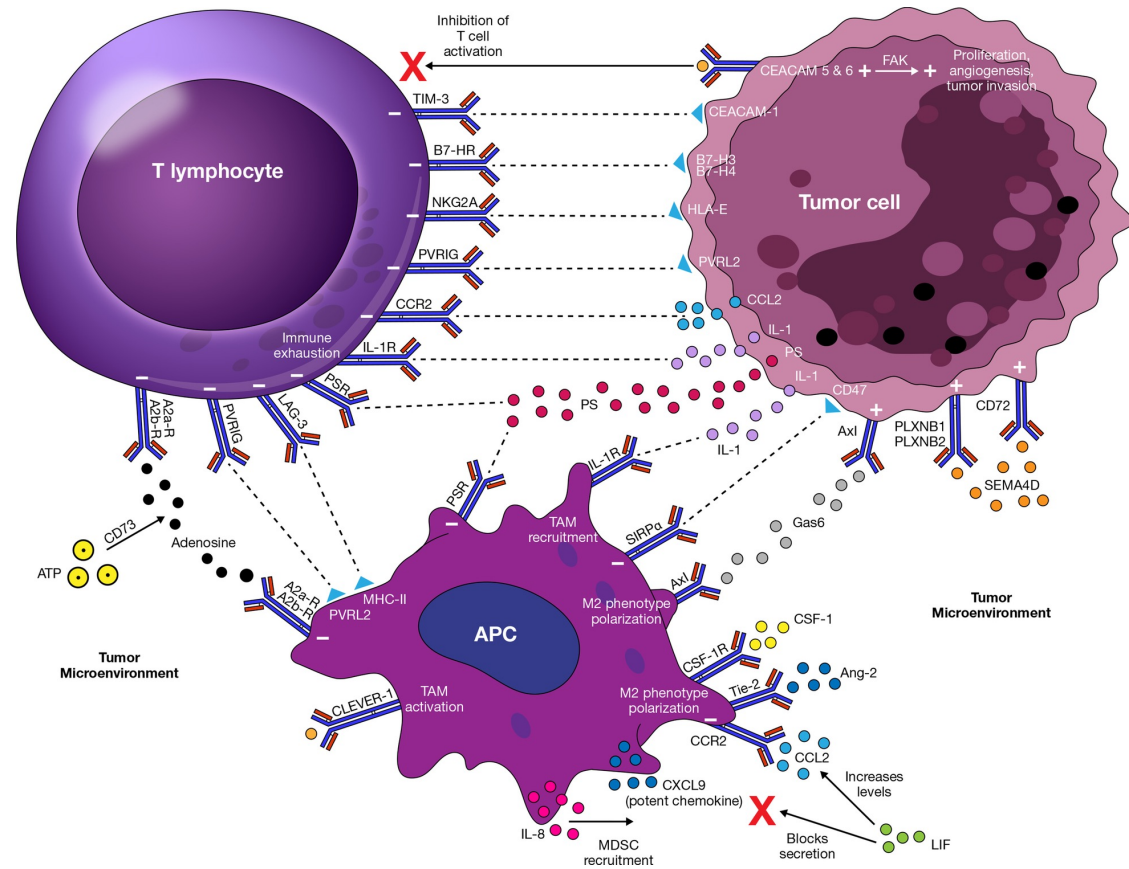
Many other immune checkpoints besides PD-1 / PD-L1 tried in HL

- CTLA-4
- CD47 / SIRP $\alpha$
- LAG3
- TIM3
- TIGIT

Little interest in HL

Discontinued in HL (trials COH involved in)

- TTI-621 (CD47i)
- Vibostolimab (anti-TIGIT mAb)
- Favezelimab (anti-LAG3 mAb) – ORR 29% to PD-1 refractory
- AZD7789 (PD1 / TIM3 BsAb)
- SEA-TGT (anti-TIGIT mAb)



Marin-Acevedo JA, et al. J Hematol Oncol 14, 45 (2021).

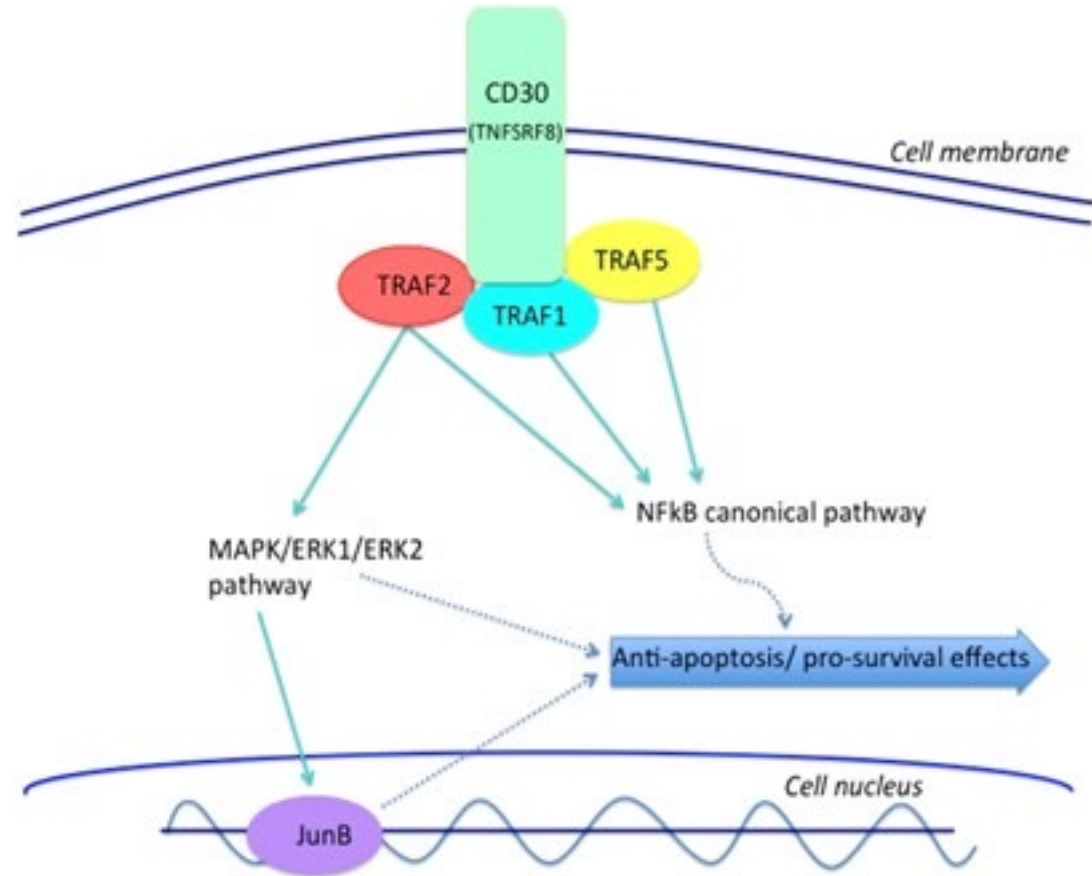


# CD30-DIRECTED THERAPY

## CD30 expressed in ~100% of HL

- Multiple downstream effects of activation
- BV active in cHL and PTCL (recently approved in DLBCL + R2)
- **CD30 antigen retained in BV-refractory cases**
  - BV + cyclosporine is active in BV-refractory HL (Chen R, et al. CCR 2020, Kambhampati S, et al. CLML 2024).

## What about other CD30-targeted therapies?



Van der Weyden CA, et al. Blood Cancer J 2017.

# CD30 CAR-T

## Initial phase 1 promising

(Ramos CA, et al. JCO 2020)

N=41, median 7 prior lines of tx

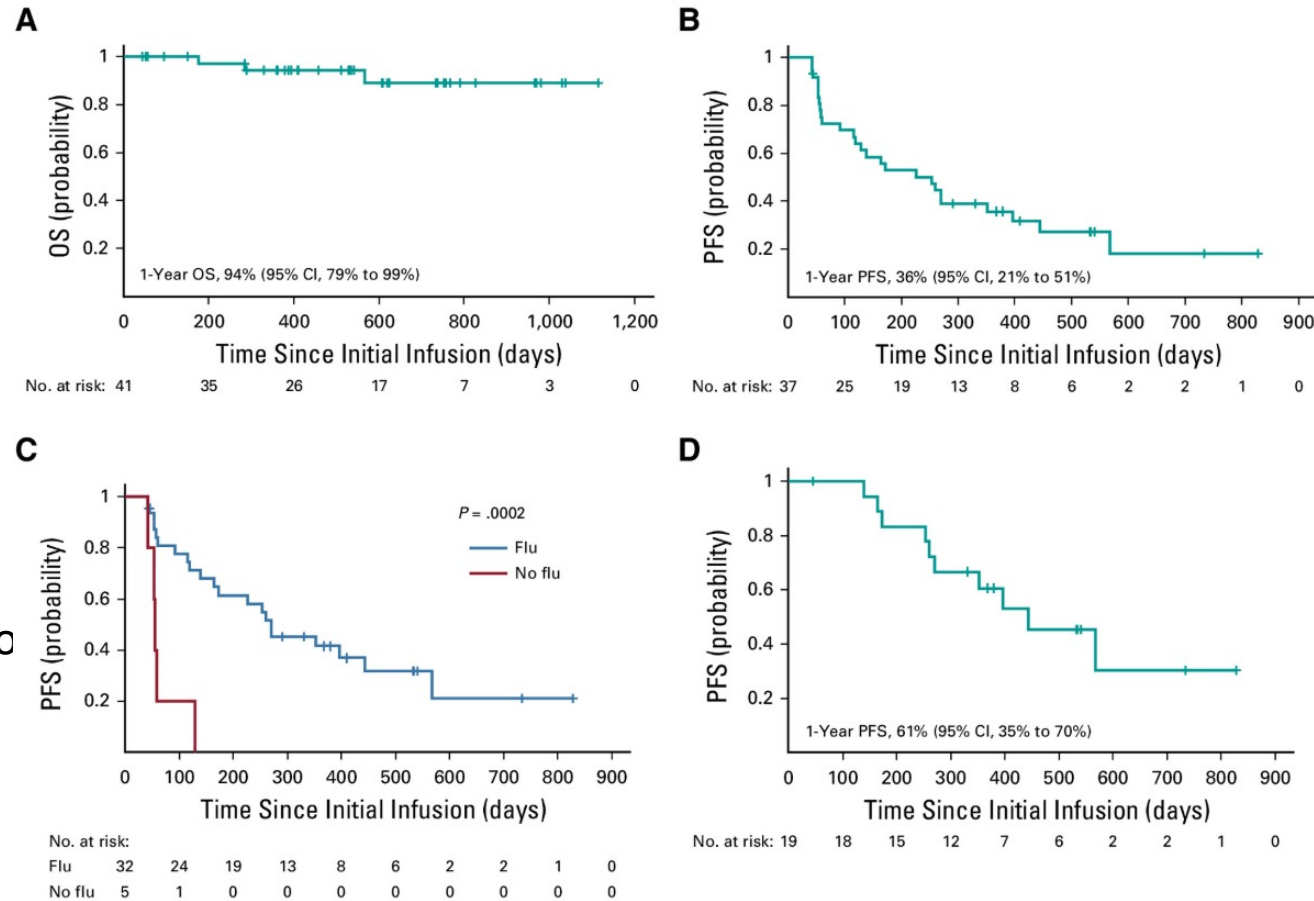
ORR 72%, CR 59%

1y PFS 36%

## Very safe!

- CRS in 10/41 pts – all G1
- No ICANS

Tessa Therapeutics obtained the rights to develop this CAR-T further...



Ramos CA, et al. JCO 2020.

# CD30 CAR-T, CD30 BsAb

## Phase 2 monotherapy (CHARIOT)

- Production difficulties – delayed > 1y
- 1y PFS 20% (3/15)

## Phase 2 in 2L + nivolumab (ACTION)

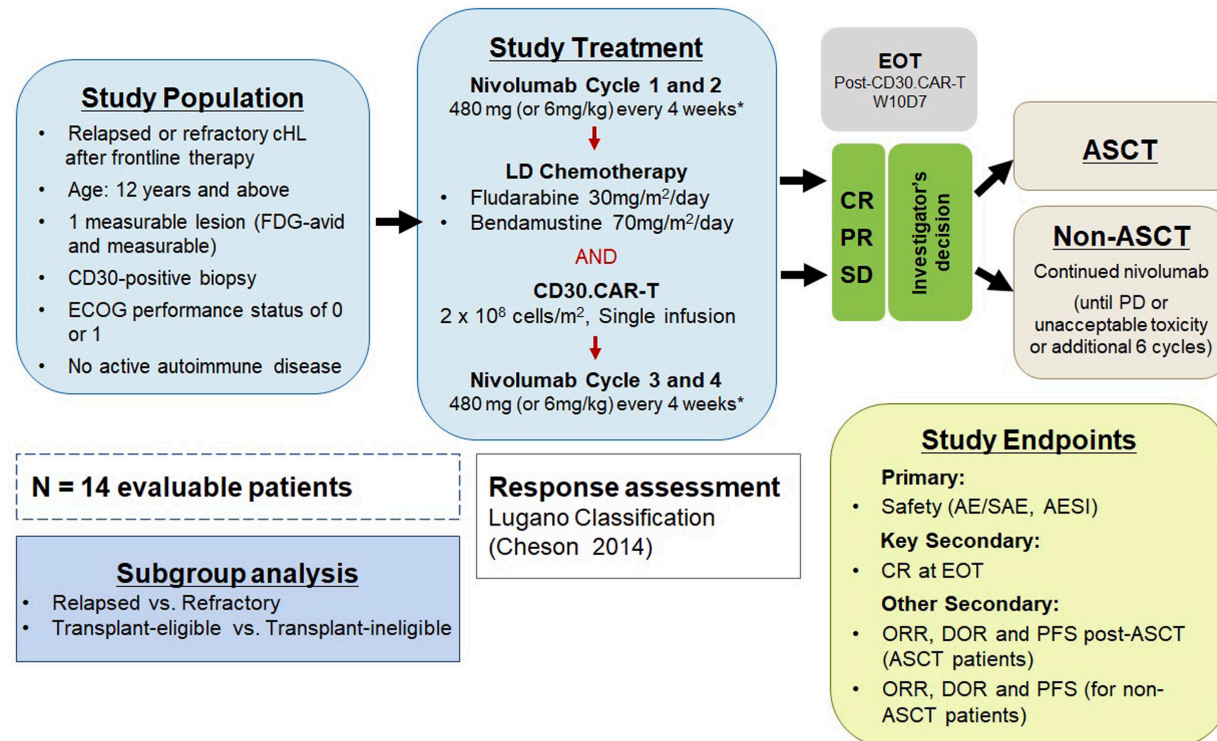
- Nivo x 2 + CD30 CAR-T + nivo x 2
- Then nivo x 6 vs. ASCT (Investigator choice)

**Company went bankrupt, CD30.CAR.T development halted**

Another CD30 CAR-T 5F11-28Z halted due to toxicity (Brudno JN, et al. Blood Adv 2024).

**GEN3017 (CD30 BsAb, Genmab) discontinued**

Figure 1: Overview of Study Design



\* Adults: Nivolumab 480 mg Q4W; Pediatric patients (aged 12-17 years and weighing ≥ 40 kg): Nivolumab 480 mg Q4W; Pediatric patients (aged 12-17 years and weighing < 40 kg): Nivolumab 6 mg/kg Q4W.

Abbreviations: AE: adverse event; AESI: adverse event of special interest; ASCT: autologous stem cell transplant; CAR-T: CD30.CAR-T; cHL: classical Hodgkin lymphoma; CR: complete response; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; EOT: End of Treatment; FDG: fluorodeoxyglucose; LD: lymphodepletion; ORR: overall response rate, PD: progressive disease; PFS: progression-free survival; PR: partial response; SAE: serious adverse event; SD: stable disease

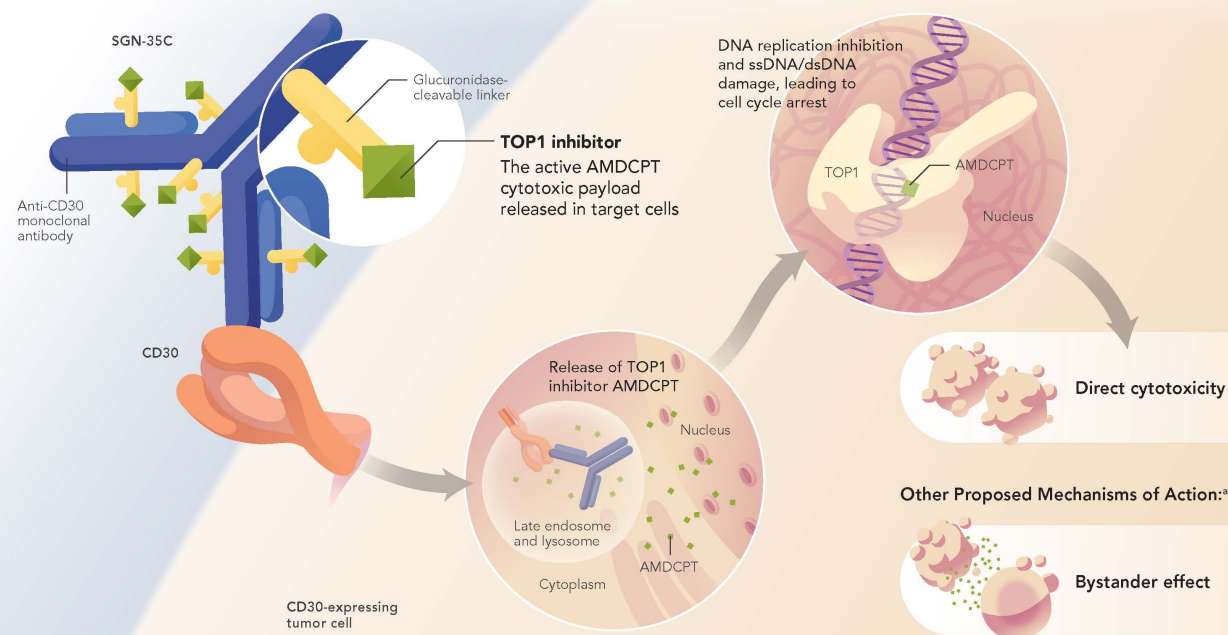
# SGN-35C

## Novel ADC with camptothecin payload

- Phase 1 trial ongoing
- 11 patients treated @ COH
- No neuropathy

## PF-08046044 | SGN-35C

Proposed Mechanism of Action of a CD30-directed, Next-Generation Antibody-Drug Conjugate With Novel Topoisomerase 1 Inhibitor Payload\*



AMDCPT: 7-aminomethyl-10,11-methenedioxycamptothecin; CD30: cluster of differentiation 30; dsDNA: double-stranded DNA; ssDNA: single-stranded DNA; TOP1: topoisomerase 1  
\*Additional mechanisms of action and their potential to complement the direct cytotoxicity of some camptothecin-based antibody-drug conjugates are currently under investigation.

\*SGN-35C is an investigational agent, and its safety and efficacy have not been established.  
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# CD16/CD30 BsAb

## Acimtamig (AFM13)

- CD16/CD30 BsAb
- Monotherapy with ORR < 20% (Sasse S, et al. Leuk Lymphoma 2022)
- AFM13 + pembro: 83% ORR in PD-1 naïve
  - Unclear if more effective than PD-1 alone

## AFM13-NK

- AFM13 with preactivated NK cell given after LD chemo
- ORR 97%, CR 77%, 63% in ongoing response @ 6m

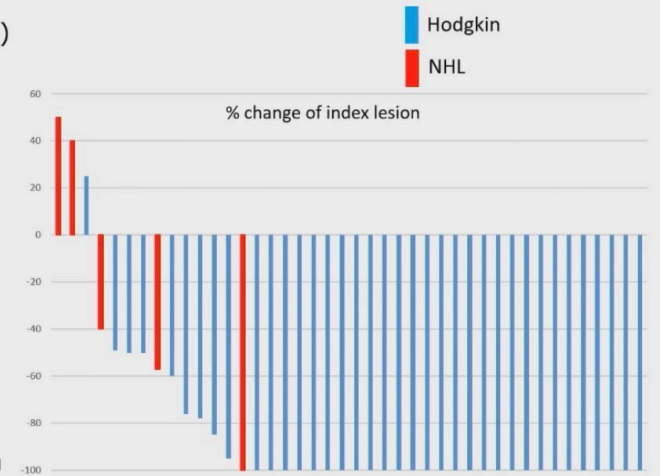
## Current trial:

AFM13 + AB101 (off the shelf NK cell)

- ORR 86%, CR 55%

## Antitumor Activity

- 39/42 responses (ORR 93%, 67% CR)
- Among 36 patients treated at the RP2D:
  - **94% ORR**
  - **72% CR**
- Among 32 cHL patients treated at the RP2D:
  - **97% ORR**
  - **78% CR**
- 10 patients in PR after C1 converted to a CR after C2
- All 4 patients who had previously experienced PD with CAR-T had a CR
- 7 patients had a CR consolidated with a SCT (4 allo, 3 auto)
  - 6 of them remain in CR at >1 year



# AlloHCT in HL

## Curative in R/R HL including after prior auto

- PTCy appears to be very important

## When to proceed?

- At first best response post auto?
- After exhausting PD-1 blockade / BV?

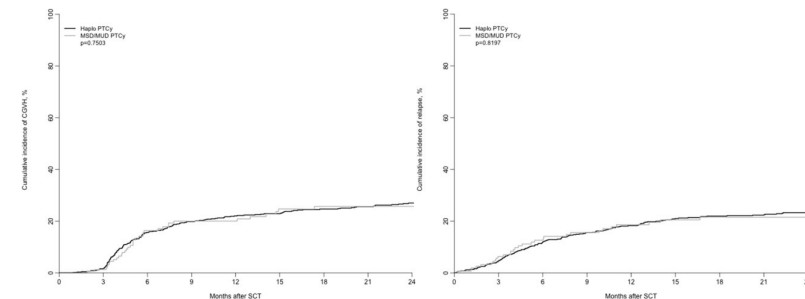
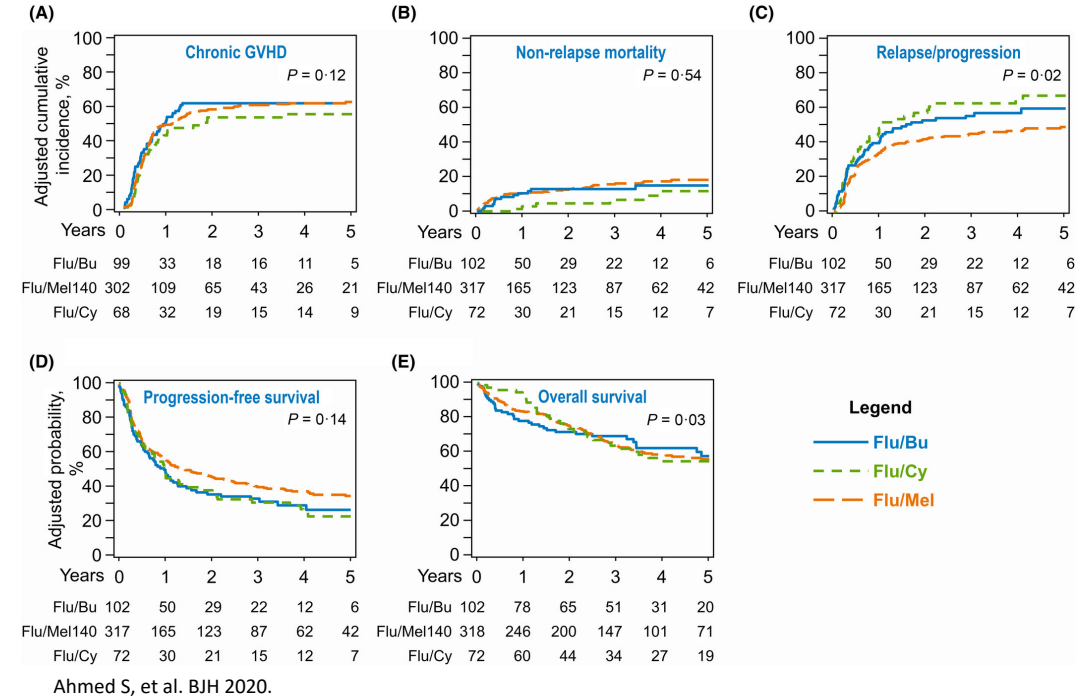
Ex:

Post-auto relapse

CR/PR with pembrolizumab

Proceed to allo now after wash-out? Or wait for relapse and retreat?

**My personal preference – wait until slow progression on PD-1 blockade and then add chemo -> allo.**



Montoro J, et al. TCT 2024.

# FUTURE DIRECTIONS

## Many challenges:

- Perception of HL as “solved” (nivo-AVD)
  - However, refractory patients are more difficult to salvage
- Difficult path to regulatory approval
- Low incentive for pharmaceutical companies
- No new mechanisms besides PD-1, CD30 targeting with ADC
  - Alternative checkpoints disappointing
  - CD30 CAR-T, CD30 BsAb disappointing

**Most current efforts are in optimizing 1L, 2L tx.**

# Thank you!

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