ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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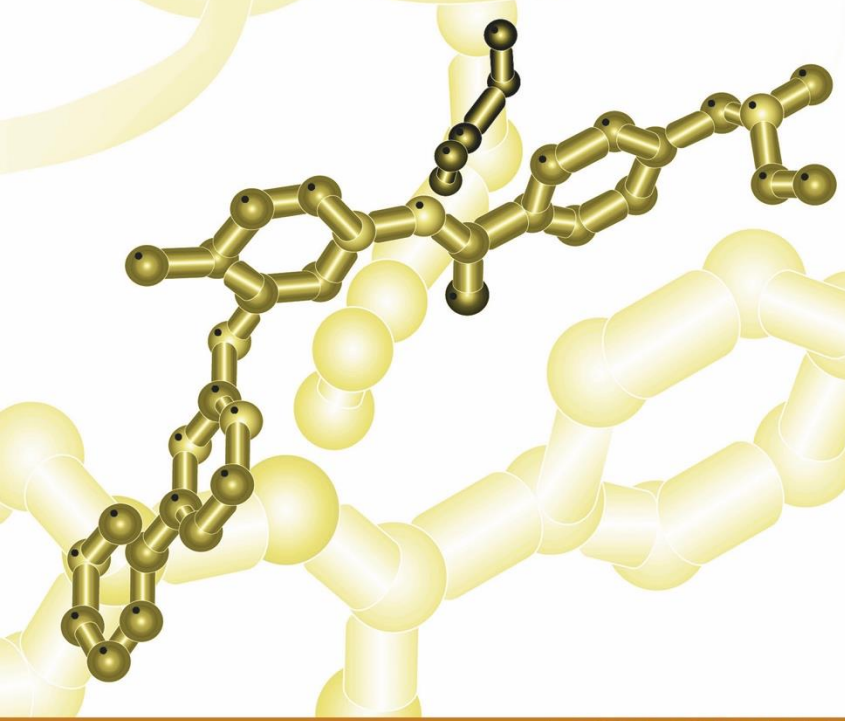


New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
January 15-17, 2024

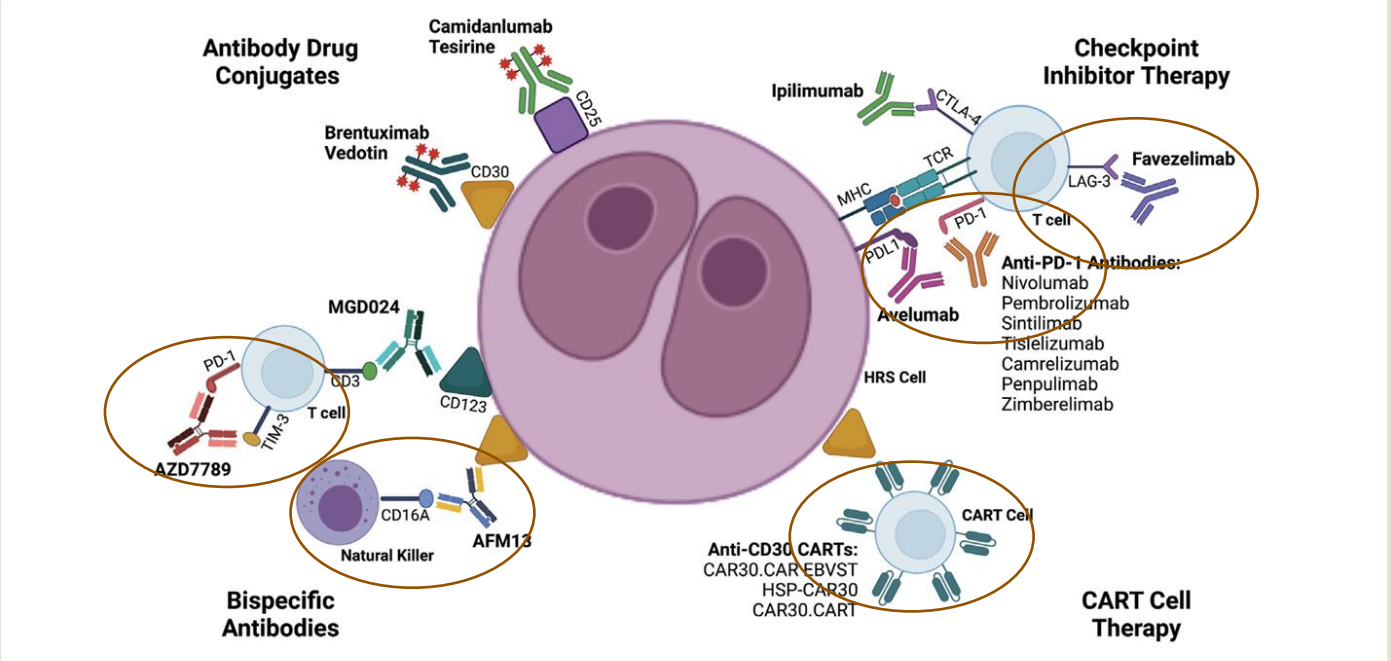
BOLOGNA BOLOGNA, ROYAL HOTEL CARLTON

Disclosures of Ann LaCasce

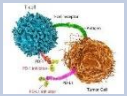
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Research to Practice					X		
Seagen						X	
Kite Pharna						X	

New Agents in Relapsed/Refractory Hodgkin Lymphoma

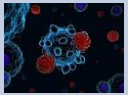
Ann S. LaCasce, MD, MMSc



Chohan and Ansell. Clin Lymphoma, Myeloma, Leuk 2023

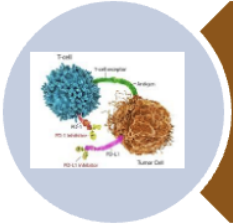


PD-1 combinations



Cellular therapy

Novel agents



PD-1 combinations

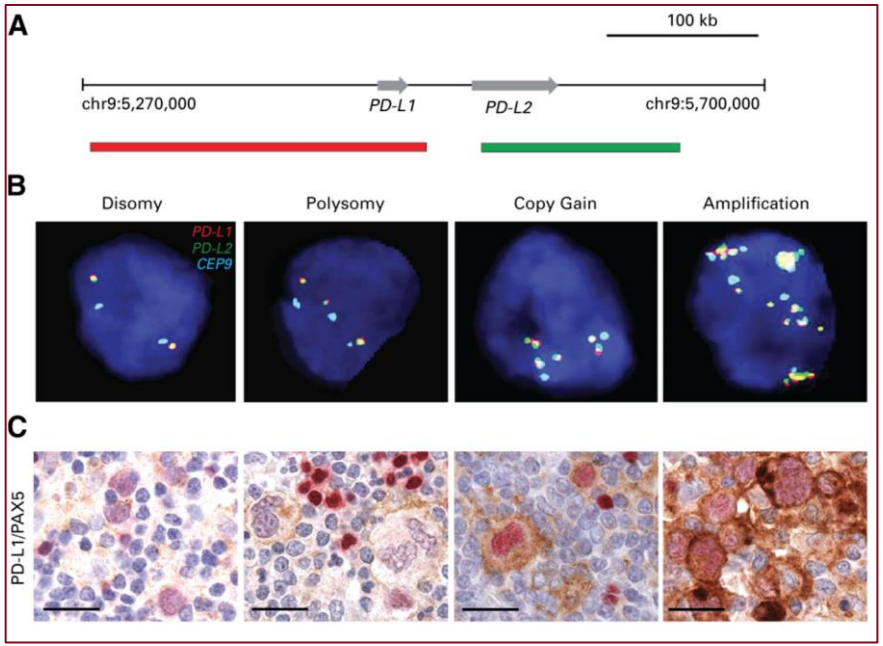
PD-1 inhibitors in cHL

Pembrolizumab
ORR 67-78%
CR 26-32%

Chen et al. Blood 2019

Nivolumab
ORR 65-73%
CR 12-29%

Armand et al JCO 2018

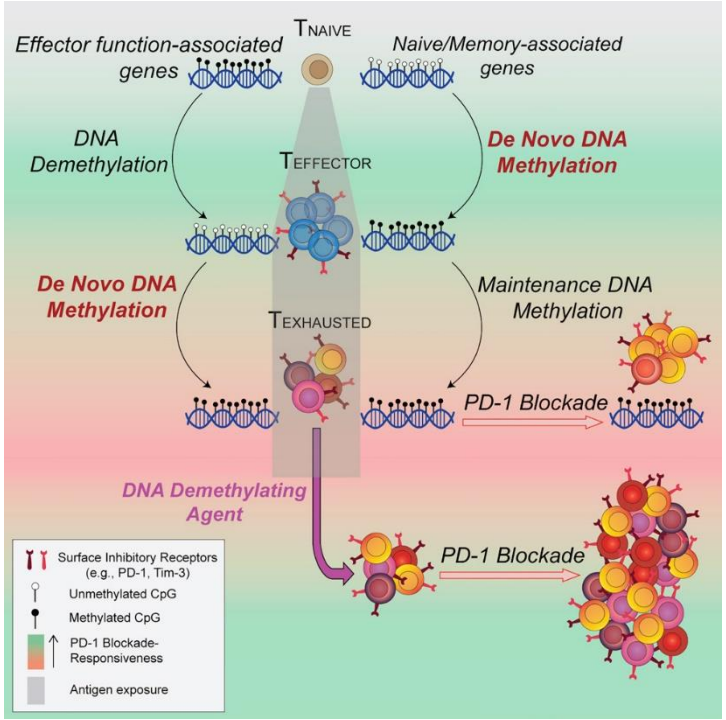


Grade 3-4 immune mediated AEs rare.

4-6% of patients discontinued therapy for toxicity.

Younes et al. Lancet Onc 2016

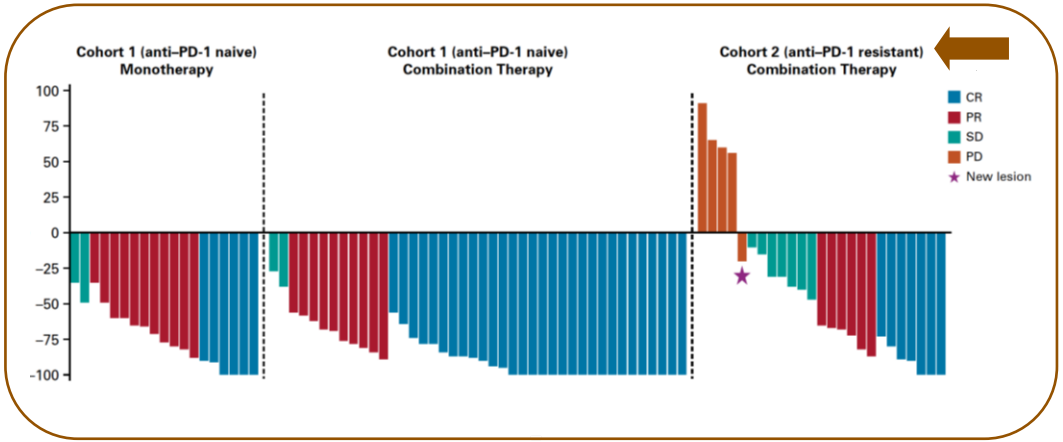
DNA methylation associated with T-cell exhaustion



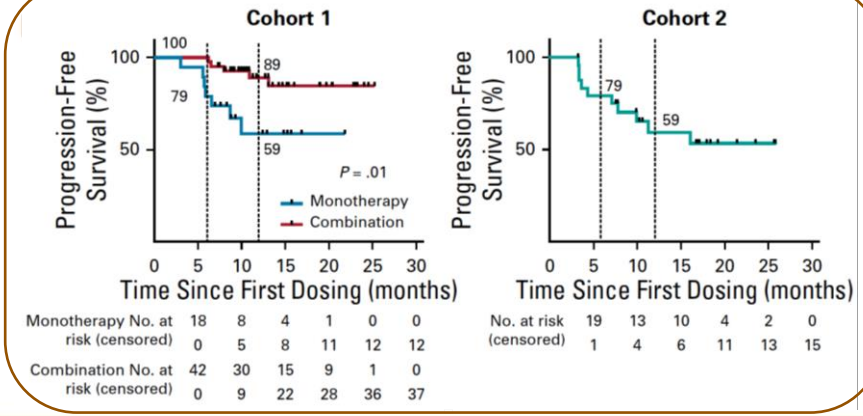
Ghoneim et al. Cell 2017

Synergy between hypomethylating agents and PD-1 blockade

Falci et al. J Hematol Oncol 2016



PD-1 inhibitor plus decitabine active in relapsed/ref HL



Grade 3-4 toxicities occurred in 37% of pts on combination therapy (37% leukocytopenia, 3% thrombocytopenia)

Nie et al. JCO 2019

On-going clinical trials of PD-1 inhibitors plus hypomethylating agents

Phase II Study of the Combination of Azacitidine and Pembrolizumab for Patients Relapsed/Refractory Hodgkin's Lymphoma (MDACC)

CC-486 and Nivolumab for the Treatment of Hodgkin Lymphoma Refractory to PD-1 Therapy or Relapsed (COH)

Testing the Combination of Nivolumab and ASTX727 (decitabine and cedazuridine) for Relapsed or Refractory B-Cell Lymphoma (multiple sites US)

IMM01 Plus Tislelizumab in Prior Anti-PD-1 Failed Classic Hodgkin Lymphoma: An Open Label, Multicenter, Phase 2 Study (IMM01-04) Evaluating Safety As Well As Preliminary Anti-Tumor Activity

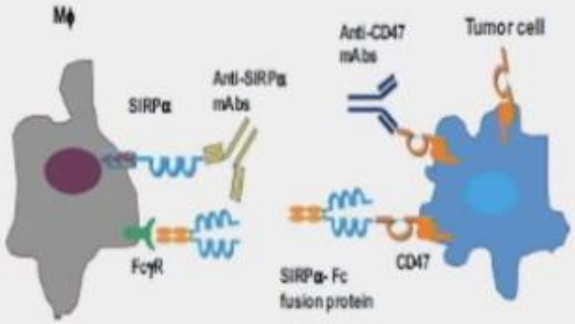


Fig.1 The mechanism of CD47-SIRP α

- CD47 is an innate immune checkpoint that binds signal regulatory protein alpha (SIRPα), and serves as immune surveillance evasion and macrophage phagocytosis suppression[1,2] (Fig.1).
- IMM01(**Timdarpacept**) is a recombinant SIRPα IgG1 fusion protein, that exerts anti-tumor activity by inducing antibody-dependent cellular phagocytosis (ADCP)[3] (Fig.2).
- Published data showed that CD47 is highly expressed on cHL, and high expression of CD47 may affect the efficacy of immunotherapy through the inhibition of macrophage phagocytosis. The expression level of CD47 is negatively correlated with prognosis[4].

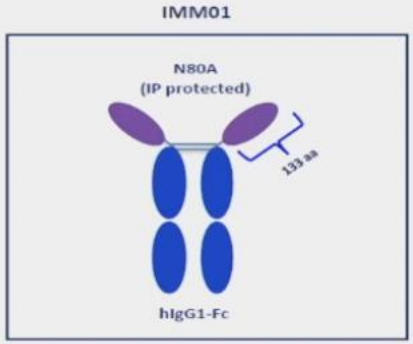


Fig.2 The Structure of IMM01

Zhou et al. ASH 2023

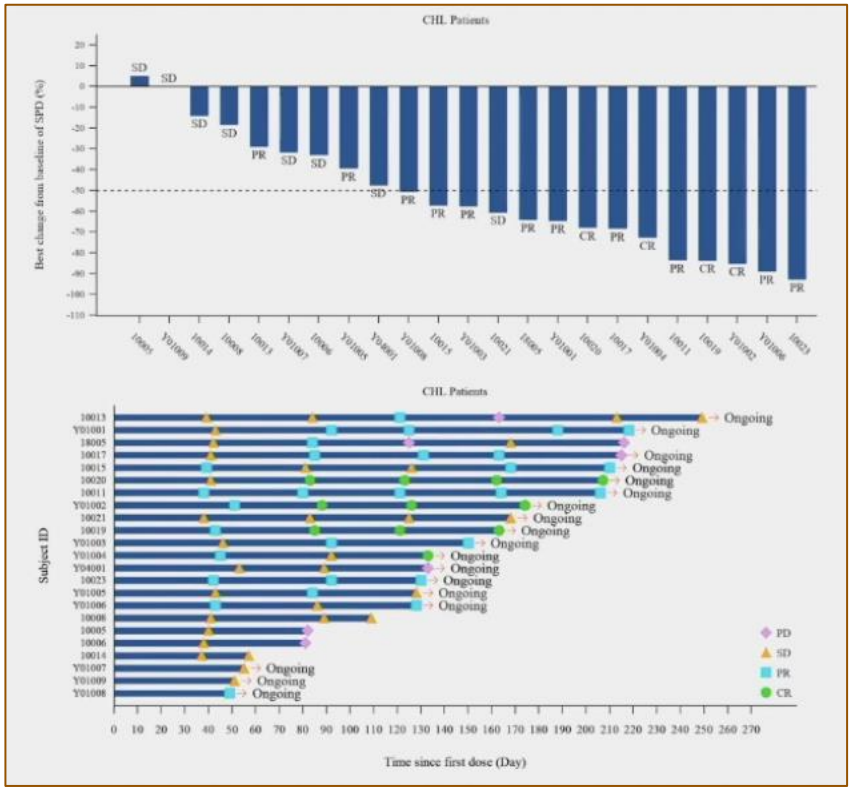
IMM01 Plus Tislelizumab: overall response rate 65%

- Of 23 efficacy-evaluable patients, median follow-up time was 5.32 months.
- Best overall response was 65.2%, with 4 CR, 11 PR, 8 SD.
- Median time to response (TTR) was 1.6 months.
- mDoR, mPFS, and mOS were not reached.

Best Response	Efficacy Evaluable (N=23)
CR, n (%)	4 (17.4)
PR, n (%)	11 (47.8)
SD, n (%)	8 (34.8)
PD, n (%)	0
ORR, n (%)	**15 (65.2)**
DCR, n (%)	**23 (100)**

Cut off date: Nov 20, 2023

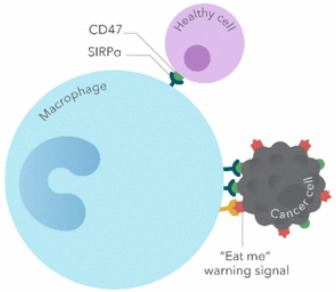
- The most common TRAEs were WBC decrease (54.5%), PLT decrease (45.5%), anemia (45.5%), lymphocytopenia (31.8%), and neutropenia (27.3%).
- 36.4% of patients had grade ≥3 TRAEs.
- No ≥G3 anemia or ≥ G4 Platelet decrease was reported.
- No TRAE leading to death or permanent treatment discontinuation reported.



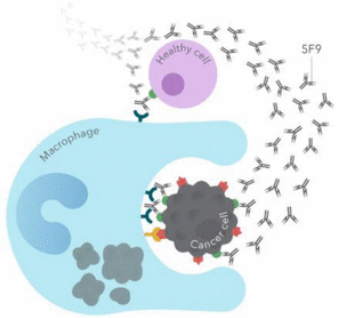
Zhou et al. ASH 2023

Study of Magrolimab and Pembrolizumab in Relapsed or Refractory Classic Hodgkin Lymphoma

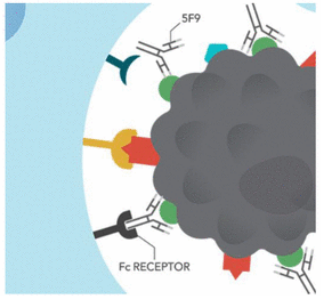
Magrolimab Overview



Macrophages use a signaling pathway to detect abnormal cells for elimination. When macrophages encounter healthy cells, the receptor SIRP-alpha binds to CD47, a "don't eat me" signal, preventing phagocytosis

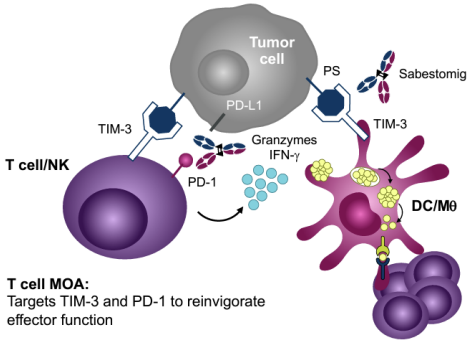


Magrolimab is an antibody that blocks the CD47 "don't eat me" signal, restoring the macrophages ability to detect and destroy cancer cells



In addition, the Fc region of magrolimab can bind the Fc receptor on macrophages providing an additional phagocytic "eat me" signal

Safety and Preliminary Efficacy of Sabestomig (AZD7789), an Anti-PD-1 and Anti-TIM-3 Bispecific Antibody, in Patients with R/R cHL Previously Treated with Anti-PD-1 Therapy

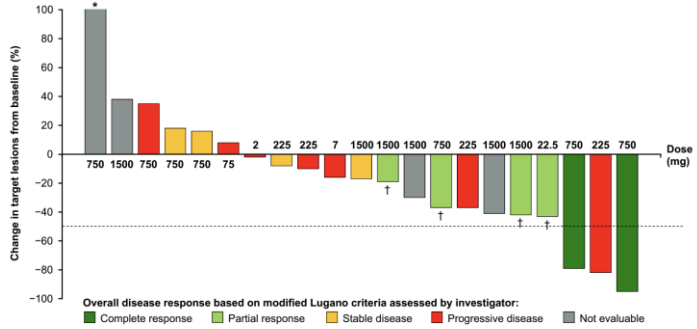


- Sabestomig binds to PD-1 and a unique TIM-3 epitope compared to other anti-TIM-3 molecules to unlock distinct biology.
- Two MOAs:
  - T cells: Targets PD-1 and TIM-3 to reinvigorate T cell function and improve antitumor immune response[9]
  - Myeloid/dendritic cells: Targets TIM-3 to increase tumor cell phagocytosis and antigen presentation[9]

T cell MOA:
Targets TIM-3 and PD-1 to reinvigorate effector function

Myeloid/DC MOA:
Targets TIM-3 to increase phagocytosis, tumor antigen presentation, and antitumor T cell expansion

DC, dendritic cell; IFN-γ, interferon gamma; MΦ, macrophage; MOA, mechanism of action; NK, natural killer cell; PD-(L)1, programmed cell death (ligand)-1; PS, phosphatidylserine; TIM-3, T cell immunoglobulin and mucin-domain containing protein-3
Adapted with permission from Besse et al. ESMO 2023[10]



*Percentage change from baseline was >100%; †Partial metabolic response by positron emission tomography

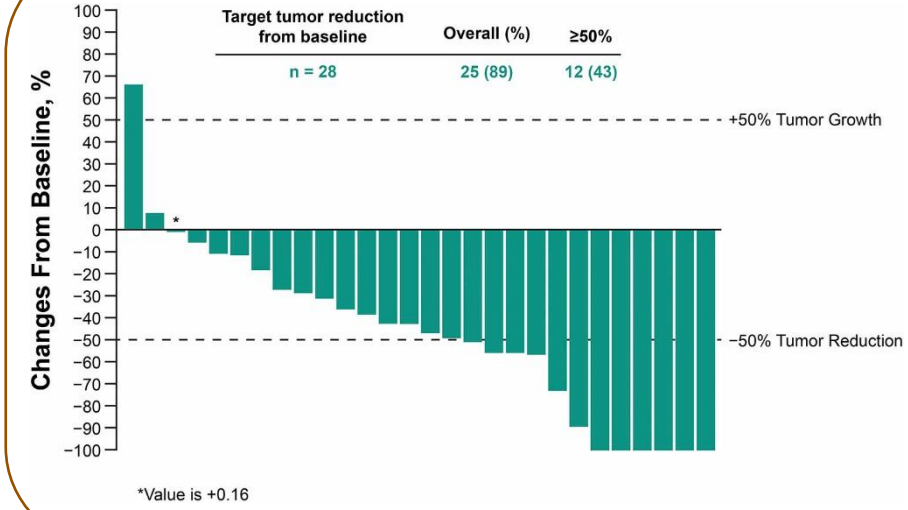
32 patients (median 5.5 prior lines of therapy) treated in the first 7 cohorts:

- **4 pts dosed at 2-75mg in cohorts 1-4**
- **5 pts dosed at 225 mg in cohort 5**
- **12 pts dosed at 750 mg in cohort 6**
- **11 pts dosed at 1500 mg in cohort 7**

No Grade ≥3 TRAEs
No immune-mediated AEs were reported
No AEs led to treatment discontinuation.

Mei et al. ASH 2023

Updated Results from an Open-Label Phase 1/2 Study of Favezelimab (anti-LAG-3) Plus Pembrolizumab in Relapsed or Refractory Classical Hodgkin Lymphoma after Anti-PD-1



n=28
ORR 29% CR 9% PR 21%
med DOR 19.4 m
med PFS 10.7 m
12 m PFS 39%

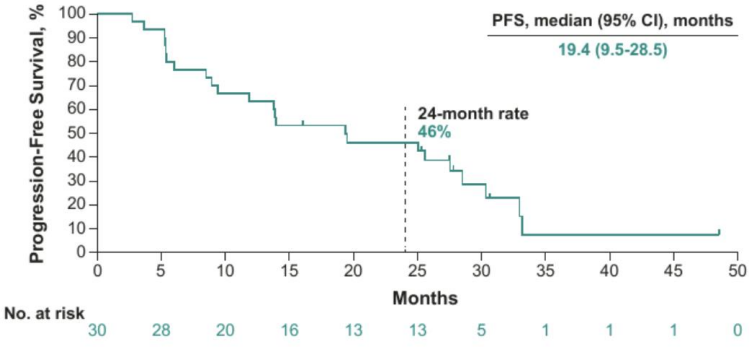
TRAE hypothyroidism 18%
Gr 3/4 18%:
autoimmune hyponatremia, encephalitis, hepatitis, neutropenia, diabetic ketoacidosis

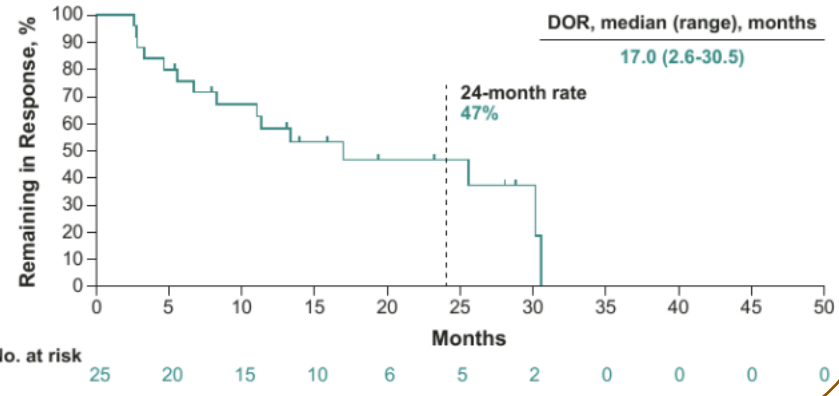
Timmerman et al. ASH 2022

Favezelimab in Combination with Pembrolizumab in Patients with Anti-PD-1 Naive Relapsed Refractory Classical Hodgkin Lymphoma: Updated Analysis of an Open Label Phase 1/2 Study

	Cohort 1 N = 30
ORR (CR + PR), n (%) [95% CI]	25 (83) [65-94]
Best overall response, n (%)	
CR	11 (37)
PR	14 (47)
SD	3 (10)
PD	2 (7)

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.





- A total of 20 patients (67%) had ≥1 AE of clinical interest; 3 patients (10%) had grade 3 events (colitis, pneumonitis, severe skin reactions) and 1 patient (3%) had a grade 4 event (hepatitis)

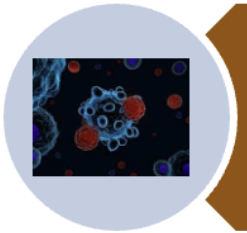
Johnson et al. ASH 2023

A Study of Coformulated Favezelimab/Pembrolizumab (MK-4280A) Versus Physician's Choice Chemotherapy in PD-(L)1-refractory, Relapsed or Refractory Classical Hodgkin Lymphoma (MK-4280A-008)

Phase 3 n=360

R/R cHL, s/p BV and progressed on anti-PD-1
MK-4280A (co-formulated favezelimab 800 mg/pembrolizumab 200 mg IV Q3W for up to 35 cycles) vs bendamustine or gemcitabine

Primary endpoint PFS
Secondary endpoint OS, ORR, DOR

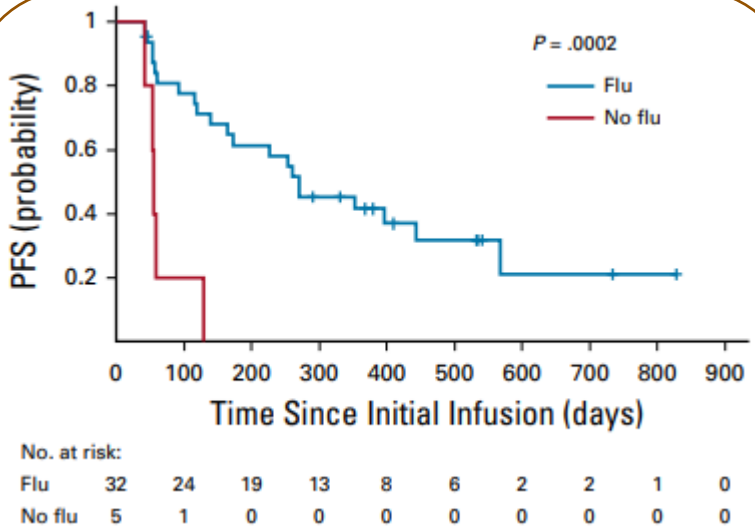


Cellular therapy

CD30 CAR T Cells, Relapsed CD30 Expressing Lymphoma

Response	All Patients (N = 37)	Benda (n = 5)	Benda-Flu (n = 15)	Cy-Flu (n = 17)
ORR				
CR + PR	23 (62)	0 (0)	12 (80)	11 (65)
Response rate				
CR	19 (51)	0 (0)	11 (73)	8 (47)
PR	4 (11)	0 (0)	1 (7)	3 (18)
SD	4 (11)	1 (20)	1 (7)	2 (11)
PD	10 (27)	4 (80)	2 (13)	4 (24)

AEs:
Rash (48%)
Cytopenias



Ramos et al. JCO 2020

Allogeneic CD30.CAR-EBVSTs in Patients With Relapsed or Refractory CD30-Positive Lymphomas

N=16 patients

Median 5 prior lines of therapy

ORR 75% (CR 38%)

Persistence of CAR-T approx. 1 week despite lymphodepletion

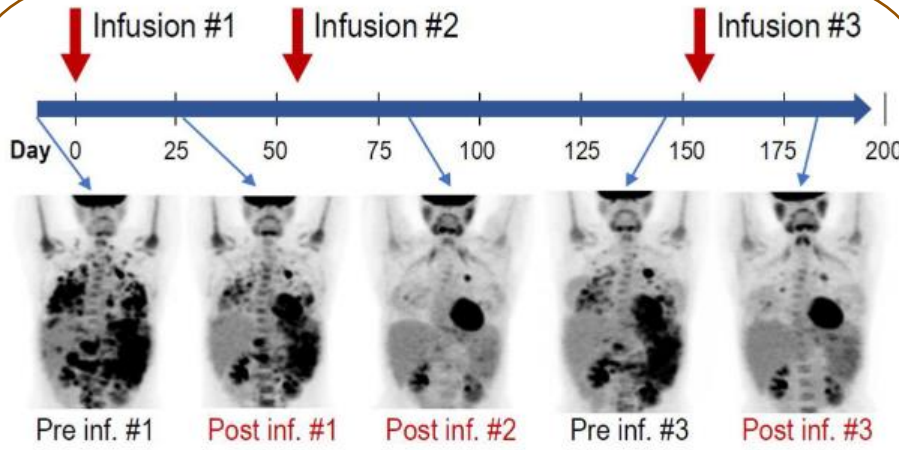
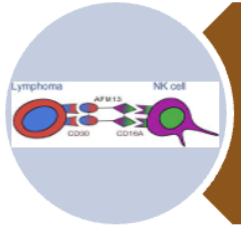


Figure 1. Clinical responses in patient who had high tumor burden and received 3 CD30.CAR-EBVST infusions at DL3. The timeline shows timing of infusions and diagnostic PET/CT scans, evidencing PR after each infusion.

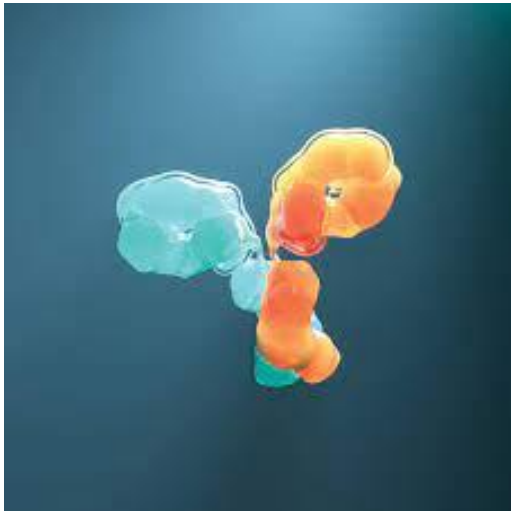
Ramos et al. ICML 2023



Novel agents

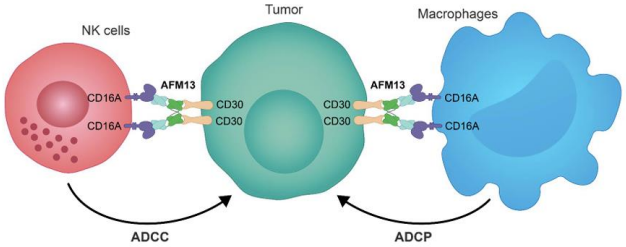
A First-in-human Trial of GEN3017 in Hodgkin Lymphoma and Non-Hodgkin Lymphoma

GEN-3017 (DuoBody-CD3xCD30) is under development for the treatment of Hodgkin lymphoma and t-cell lymphoma. The therapeutic candidate is a Fc-silenced IgG1 bi-specific monoclonal antibody T-cell engager, created by controlled Fab-arm exchange of a humanized CD3 epsilon and a human CD30 monoclonal antibody. It is being developed based on DuoBody platform. It is administered through subcutaneous route.



AFM13: CD30 x CD16 bi-specific antibody

AFM13 mediates interaction of NK cells and macrophages to kill tumor cells



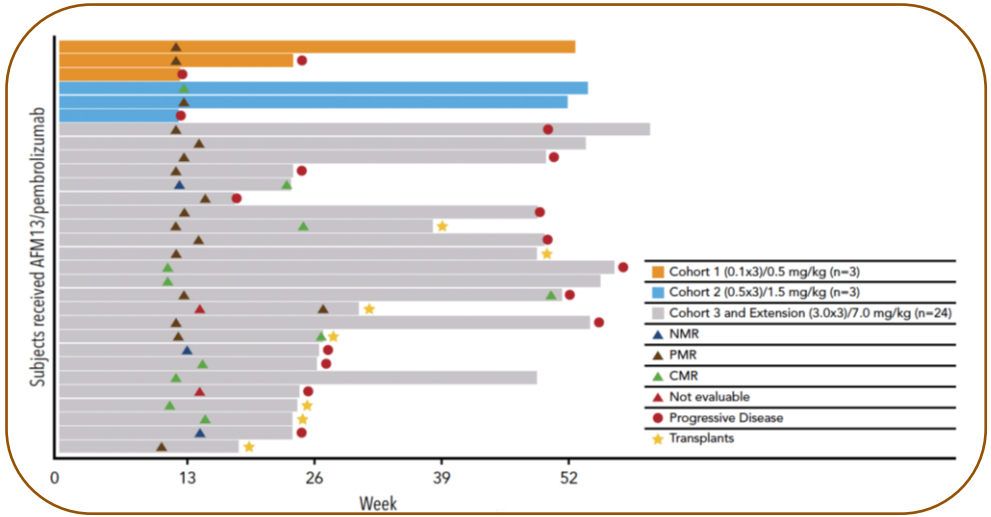
AFM13 single agent

n=25 (3 schedules)
ORR 16.7% 12 m PFS 12.6%

Sasse et al. Leuk Lymphoma 2022

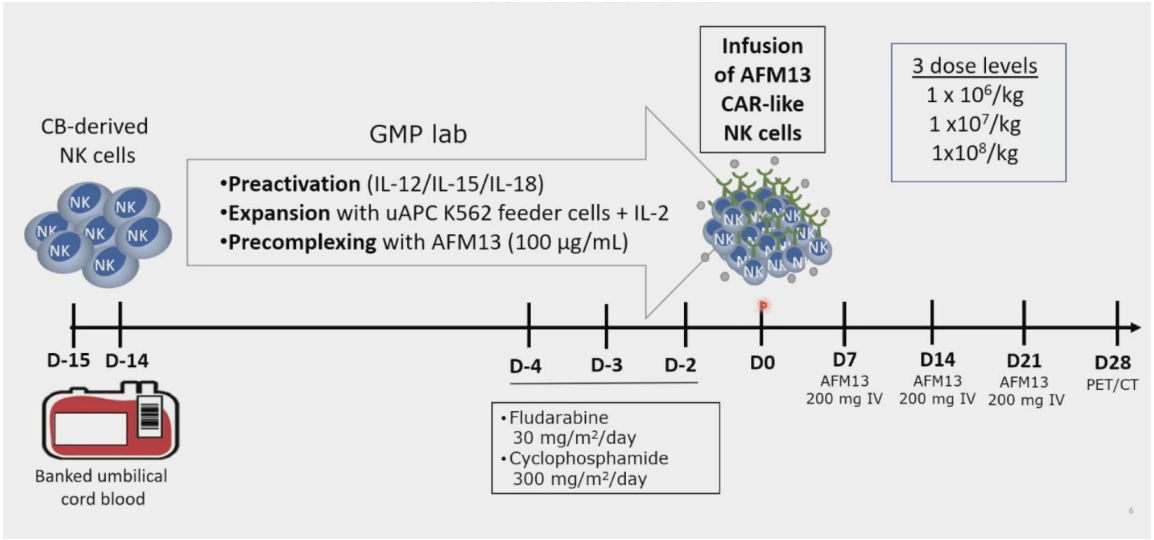
AFM13 with pembrolizumab

n=30
ORR 83% CR 47%



Bartlett et al. Blood 2020

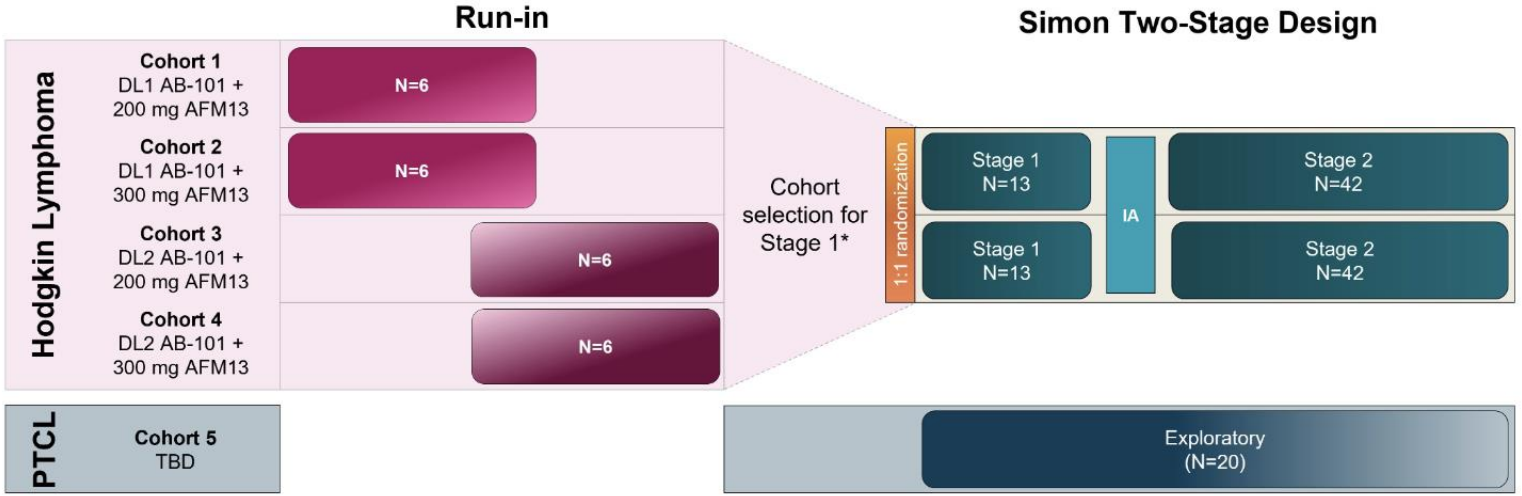
AFM-13 complexed cord blood derived NK cell in R/R CD30+ lymphoma

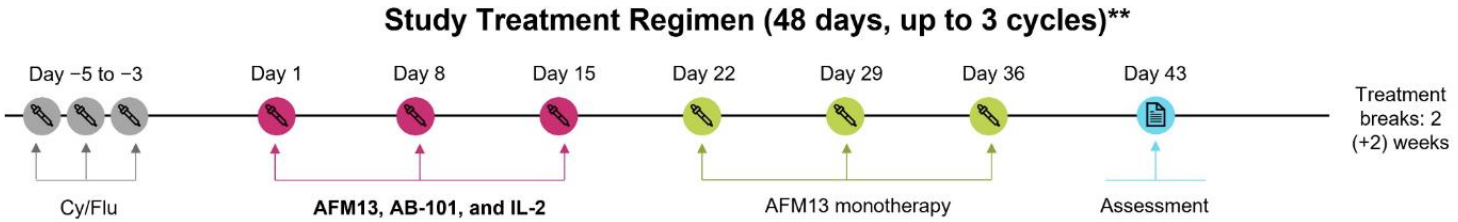


- well tolerated without CRS, NT, GVHD
- donor NK cells trafficked to nodal sites
- ORR 94% CR 72% (n=42)
- ORR 97% CR 78% (n= 37 cHL)
- m EFS 10 months
- 30% disease free at 1 year
- 7 pts proceeded to transplant

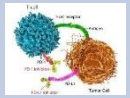
Nieto et al. ASH 2023

AFM13 in combination with AB-101 (allogeneic NK cells)



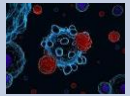


Moskowitz et al. ASH 2023



PD-1 combinations

Hypomethylating agents promising.
? benefit of adding LAG-3/TIM3 to PD-1



CAR-T cell therapy

Reasonable responses though durability unclear

Novel agents

CD30xCD3 and AFM-13 plus allogeneic NK: more to come

At this point, allogeneic transplantation remains the only potentially curative therapy in relapsed/refractory cHL