UNIVERSITY OF OXFORD

Oxford University Hospitals NHS
NHS Foundation Trust

Novel Checkpoint Inhibitors

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Disclosures

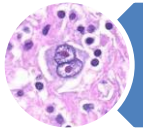
I have received honoraria from:

Takeda, Roche, ADC Therapeutics, Beigene, Incyte, MSD, Pfizer, Daiichi Sankyo, Gilead, Novartis, Celgene, SecuraBio, Astra Zeneca

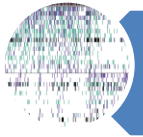
I have received research funding from:

BMS, MSD, Amgen, Pfizer, Beigene

Roadmap

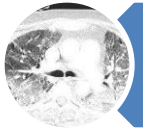


PD1 inhibitors



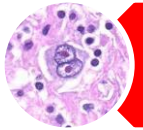
PDL1 inhibitors

Lag3 inhibitors

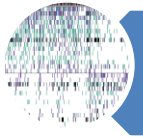


TIM3 inhibitors

CD47 / SIRP alpha inhibitors



PD1 inhibitors



PDL1 inhibitors

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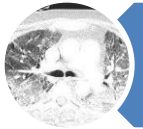
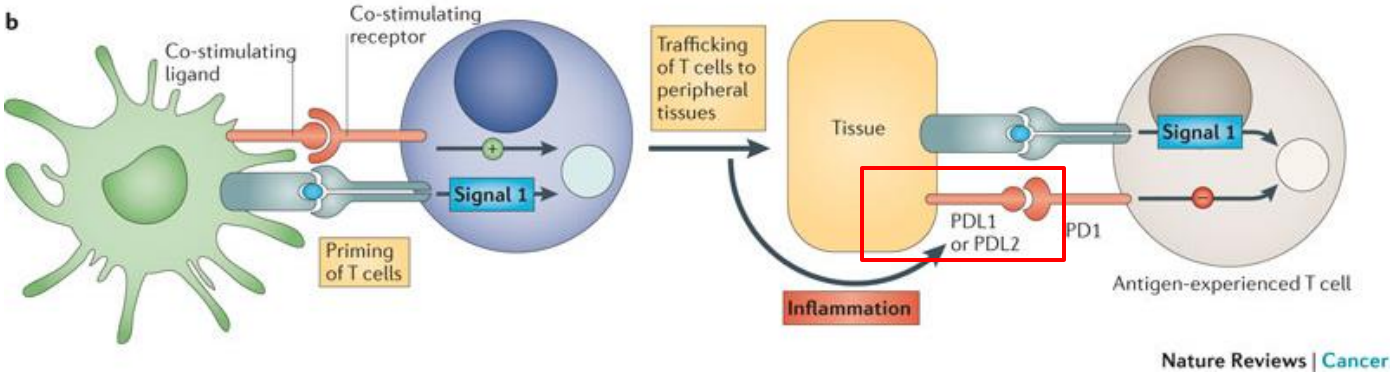


TIM3 inhibitors

CD47 / SIRP alpha inhibitors

Immunological Checkpoints – PD1

PDL1 is expressed by peripheral cells at the site of inflammation. It therefore prevents collateral damage from T-cells already activated



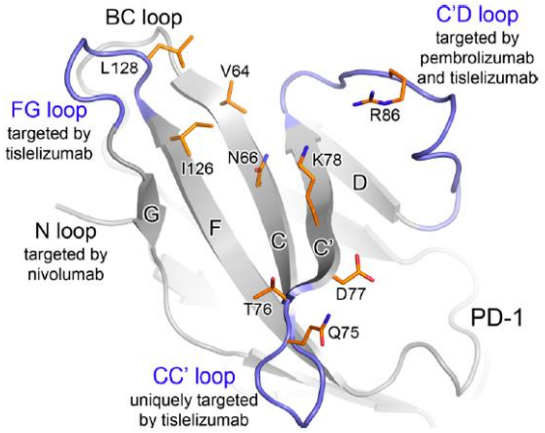
From: Pardoll (2012) Nature reviews cancer

PD1 inhibitor trials in Hodgkin

PD1 inhibitor	Phase	Population	ORR / CRR	PFS	Reference
Nivolumab	2	Relapse post ASCT BV naïve or BV exposed	69% / 16%	Med 14.7m	Armand (2018) JCO
Pembrolizumab	2	Relapse post ASCT with cohort prior; BV naïve or exposed	72% / 28%	Med 13.7m	Chen (2019) Blood
Avelumab	1	Relapse post ASCT or ASCT ineligible or post-alloSCT	41.9% / 19.4%	Not reported	Herrera (2021) Blood Advances
Sintilimab	2	Relapse post ASCT or ineligible	80.4% / 34%	6mo PFS 77%	Shi (2019) Lancet Haematol
Camralizumab	2	Relapse post ACST or ineligible	78% / 37%	6mo PFS 81%	Song (2019) Clin Cancer Res
Tislelizumab	2	Relapse post ASCT or ineligible	82% / 63%	6mo PFS 84%	Song (2020) Leukemia

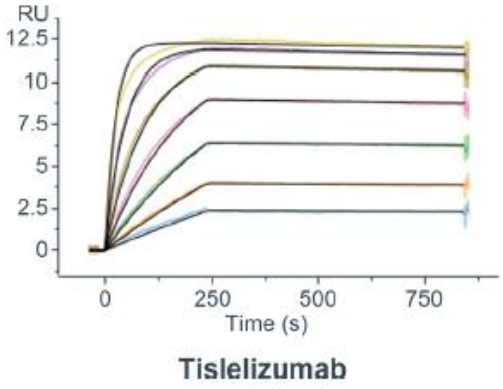
Acknowledgement: Desai & Ansell (2021) Leukemia and Lymphoma

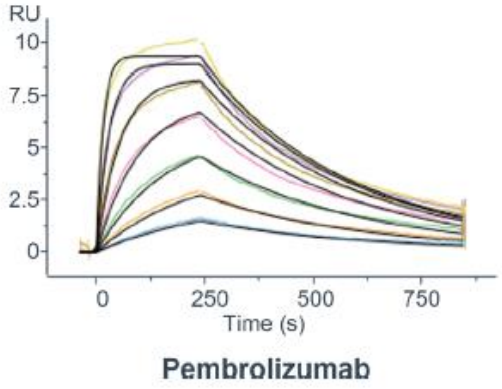
Are all PD1 inhibitors the same? No!

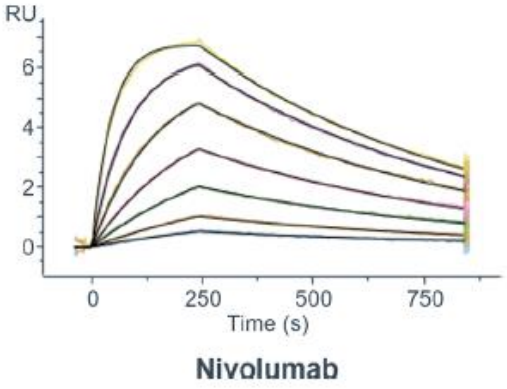


Hong et al (2021) FEBS Open Bio

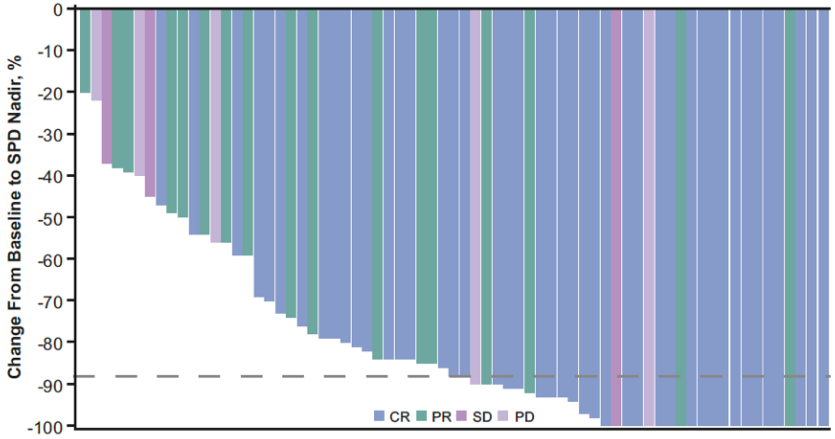
- Crystal structural studies of PD1-drug binding reveal some unique epitopes (note the CC' loop)
- Translates into different binding kinetics
- Tislelizumab has markedly prolonged dissociation rate

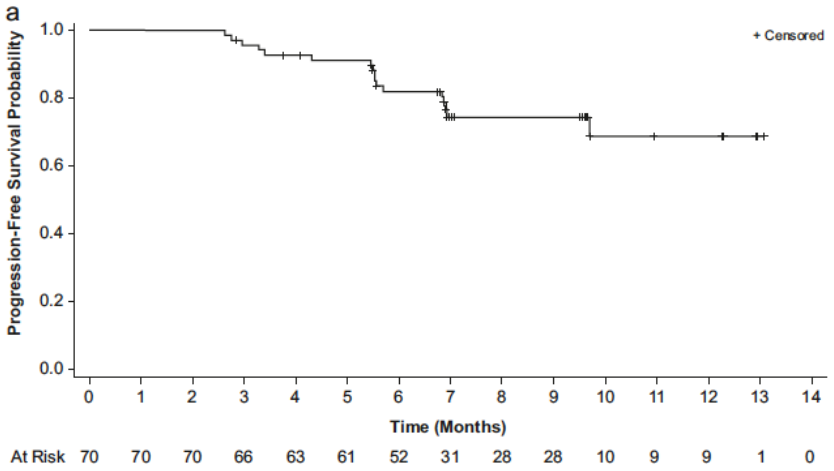






Tislelizumab clinical data





Song et al (2020) Leukemia

- 70 pts, median age 33y, median prior lines 3, mostly BV naïve, 52% refractory, 82% not suitable ASCT
- Median FU 9.8mo; 24% discontinued Rx
- ORR: 87%; CRR: 63% (52% CRR in primary refractory)
- Infusion reactions 36% (1 G3); 4 pts discontinued due to irAE (3 pneumonitis; 1 renal injury)

Reducing chemo in older patients

Newly diagnosed cHL > 60 chemo fit but for whom ABVD not recommended by the investigators

Tislelizumab x3

PET

Negative

Less chemotherapy than standard

Early

Single agent Tislelizumab

Intermediate

2x Tisle + AVD

Advanced

4x Tisle + AVD

Positive

Standard chemo with Tisle

Early and intermediate

4x Tisle + AVD

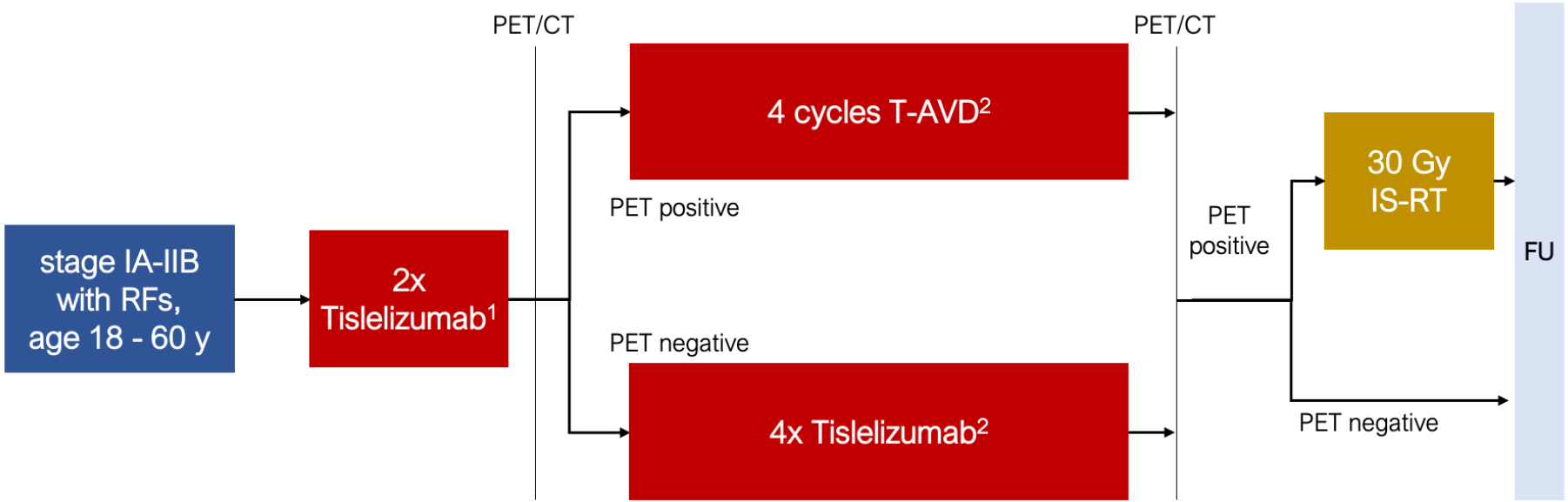
Advanced

6x Tisle + AVD

Radiotherapy as per institutional standard

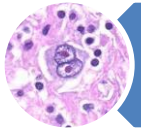
RATiFY

INDIE trial

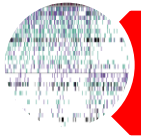


*chemotherapy should start as soon as central PET evaluation is available. Up to 1 further dose tislelizumab is allowed in case of severe delay of PET panel assessment. [1]Tislelizumab 200mg Q3W [2]Tislelizumab 300mg Q4W, on day 1 of each 28-day AVD cycle if combined with AVD. RFs: GHSG risk factors for early-stage unfavorable; y: years

Curtesy of Dr Paul Broeckelmann

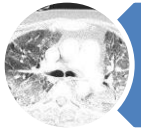


PD1 inhibitors



PDL1 inhibitors

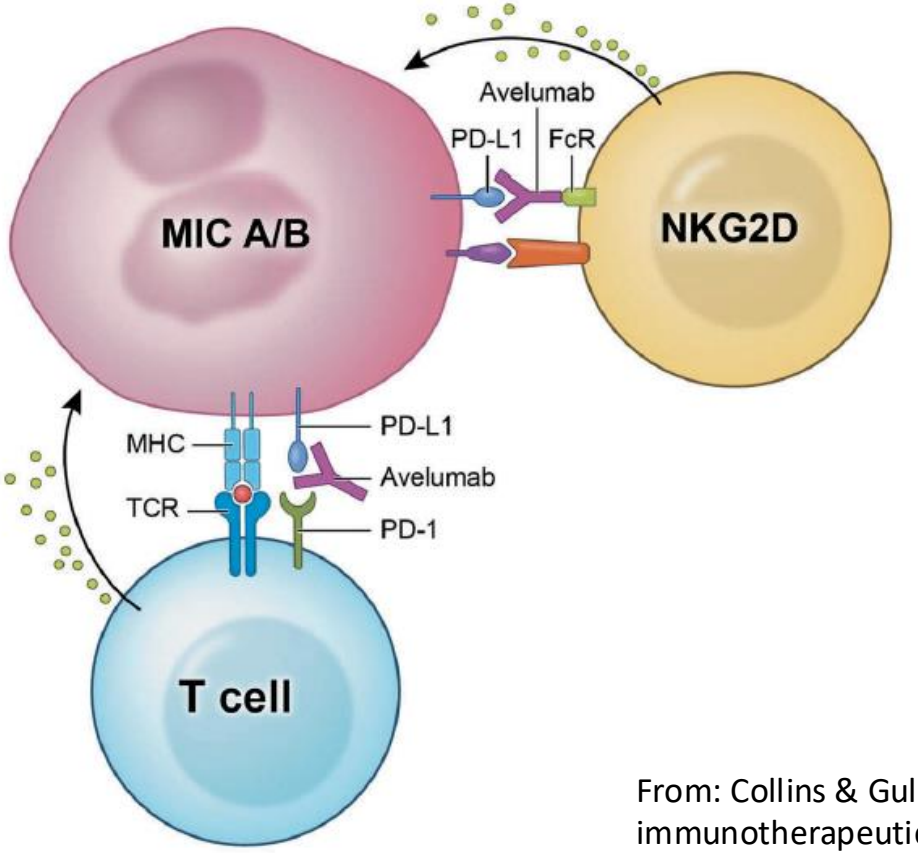
Lag3 inhibitors



TIM3 inhibitors

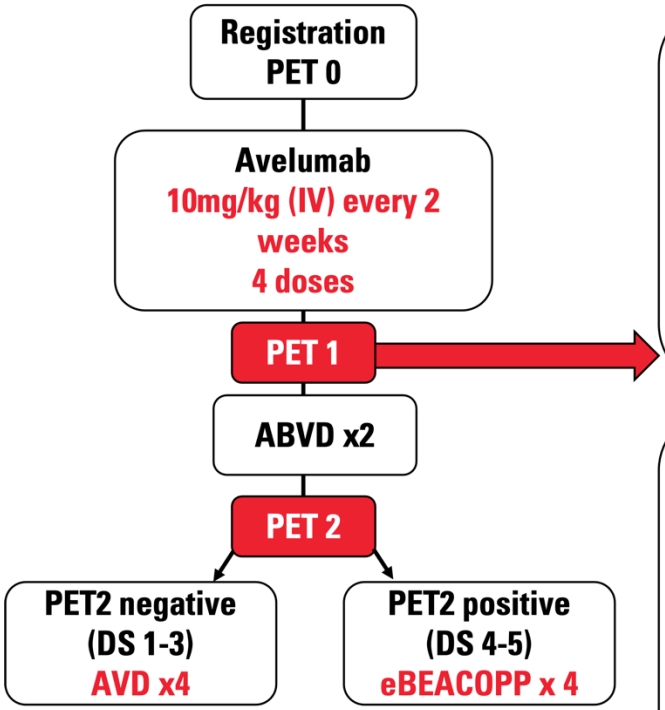
CD47 / SIRP alpha inhibitors

Avelumab: putative dual mechanism of action



From: Collins & Gulley (2019) Human vaccines & immunotherapeutics

AVENuE study



Primary endpoint:
ORR (CMR/PMR) at PET1

Worthy of further study: 40%
Unacceptable: <20%
5% (1-sided) alpha
90% power
Sample size: 47

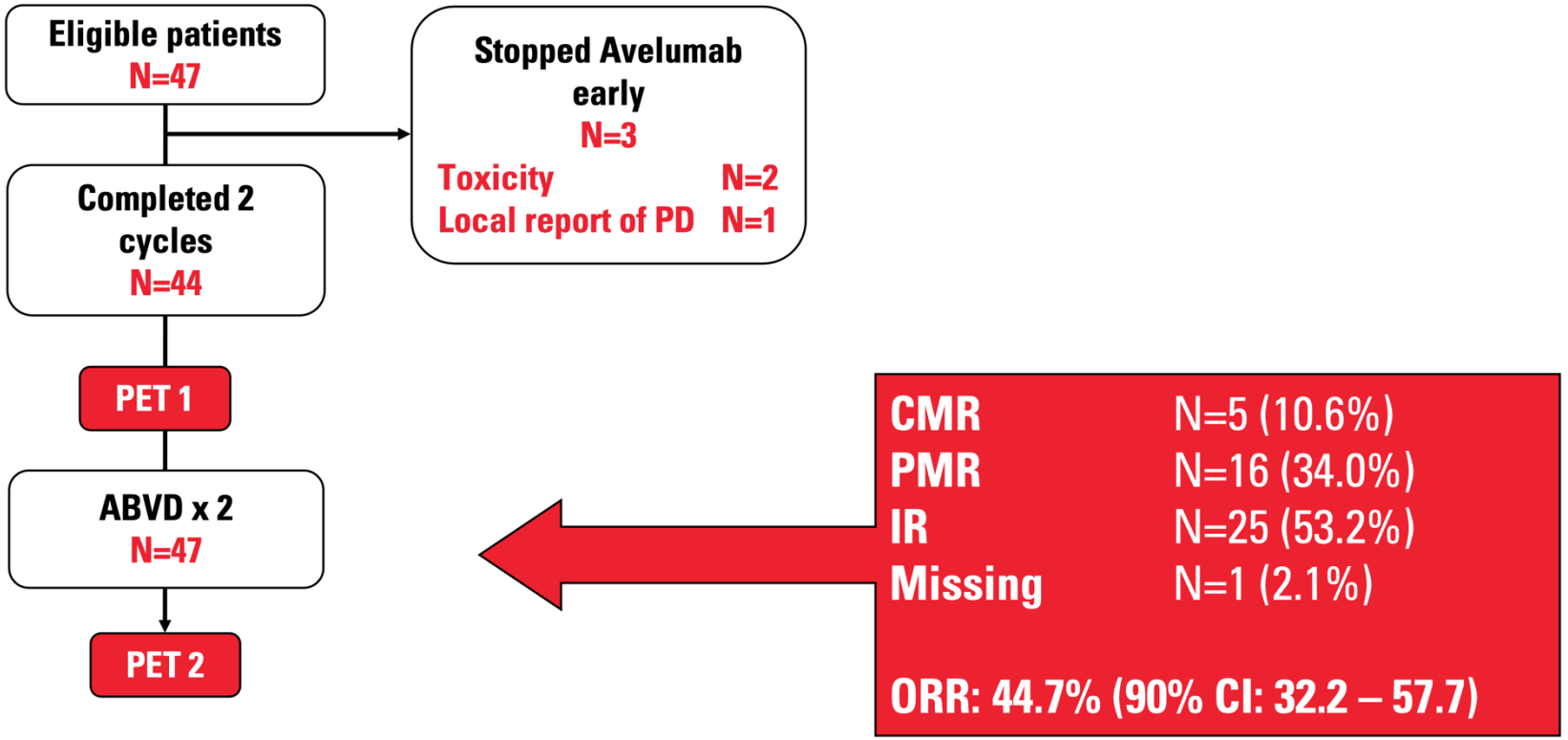
Secondary endpoints

CMR rate at PET2 (iPET)
Progression Free Survival
Overall Survival
Adverse events
Deliverability of subsequent chemotherapy

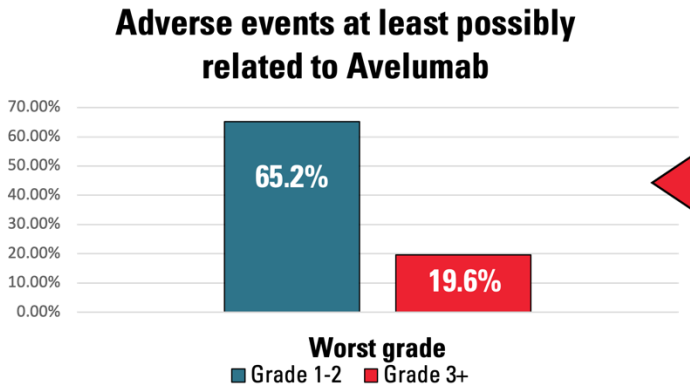
Baseline characteristics

		AVENuE N=47	RATHL N=1201
Age, median (range)		30.0 (17.0- 58.0)	33 (18-79)
Male, N(%)		30 (64%)	653 (54.4%)
Stage, N(%)			
	High risk stage II	11 (23.4%)	499 (41.5%)
	Stage III	12 (25.5%)	362 (30.1%)
	Stage IV	24 (51.1%)	340 (28.3%)
ECOG, N(%)			
	0	45 (91.8%)	888 (74.0%)
	1	4 (8.5%)	312 (26.06%)
	2-3 (excluded from AVENuE)	-	41 (3.4%)
B-symptoms, N(%)		28 (59.6%)	737 (61.4%)
IPS ≥3		19 (40.4%)	440 (36.8%)

Primary endpoint



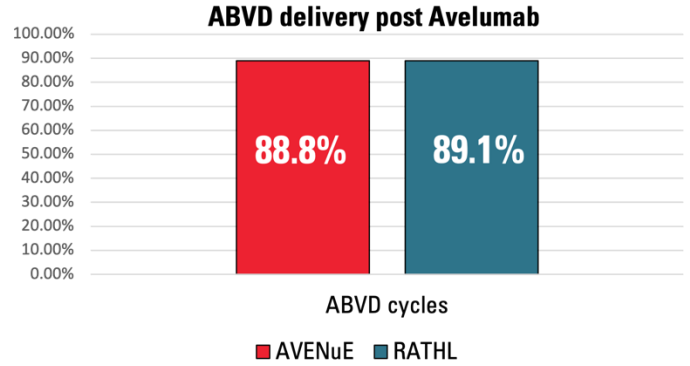
Adverse events and chemo deliverability



Nine patients with a grade 3-4 AE
Events included:
Colitis (N=1)
Pneumonitis (N=1)
Autoimmune hepatitis (N=1)
Renal tubular acidosis (N=1)
Tumour flare (N=2)

88.8% subsequent ABVD/AVD cycles were delivered without delay (compared with 89.1% in RATHL).

1 patient stopped treatment early (after 1 AVD), this was due to patient choice without clinical toxicity concern

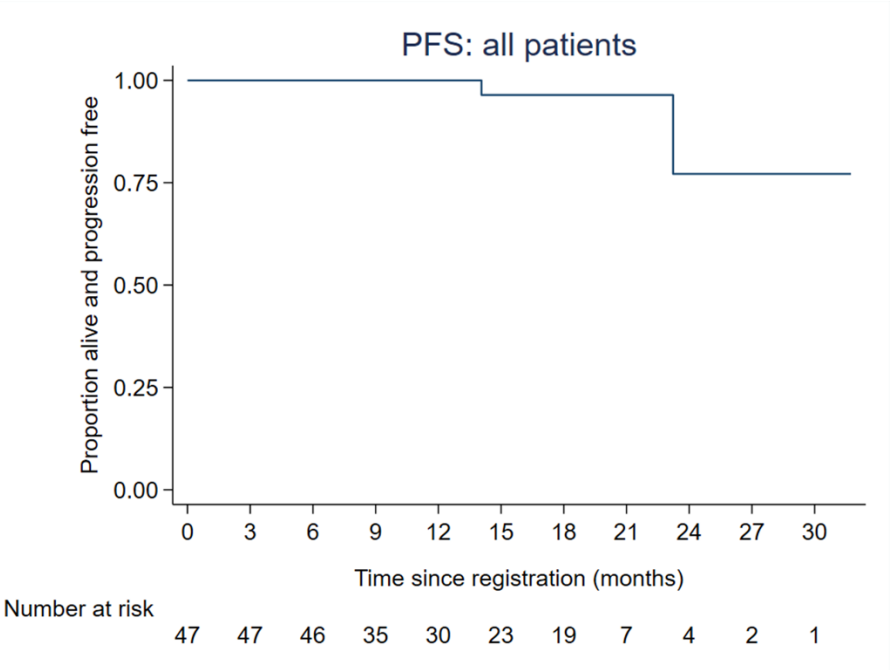


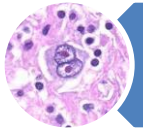
Progression free survival

PET2+ patients (N=5)
PET- post BEACOPP: N=4
PET+ post BEACOPP: N=1 (treated with consolidation RT alone, no PD reported)

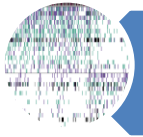
Median follow-up: 14 months (range: 4-32)

1-year PFS: 100%
Two progressions reported at 14 and 23 months



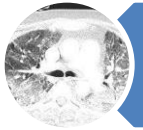


PD1 inhibitors



PDL1 inhibitors

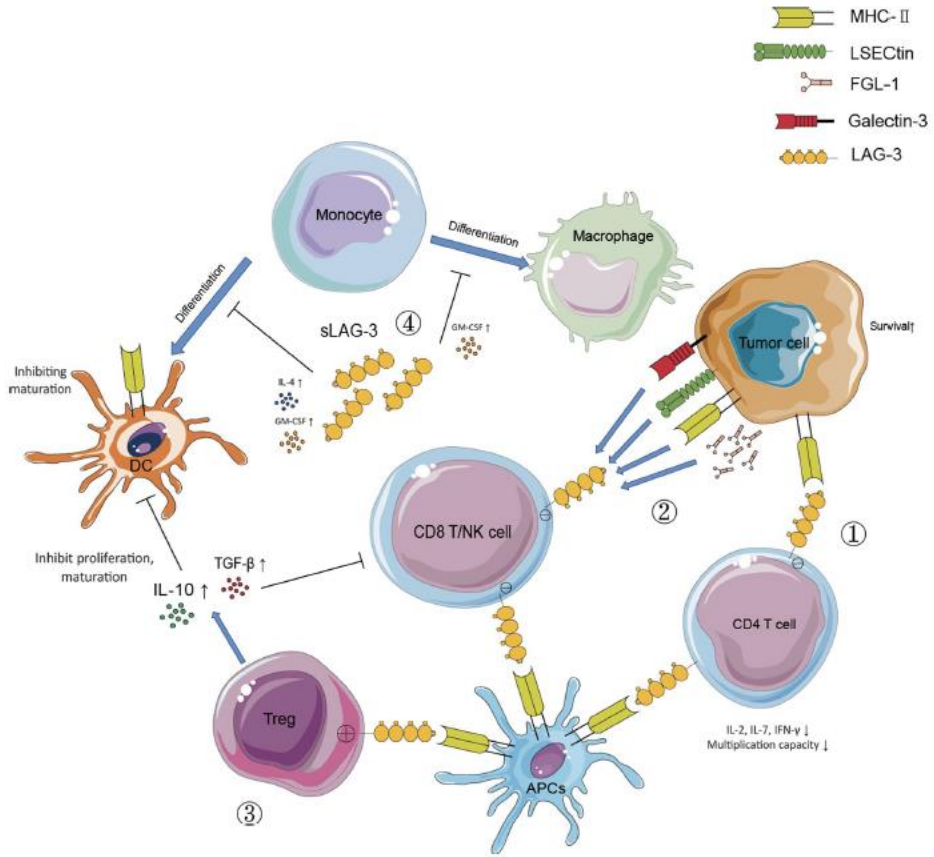
Lag3 inhibitors



TIM3 inhibitors

CD47 / SIRP alpha inhibitors

Immunological checkpoints – LAG3

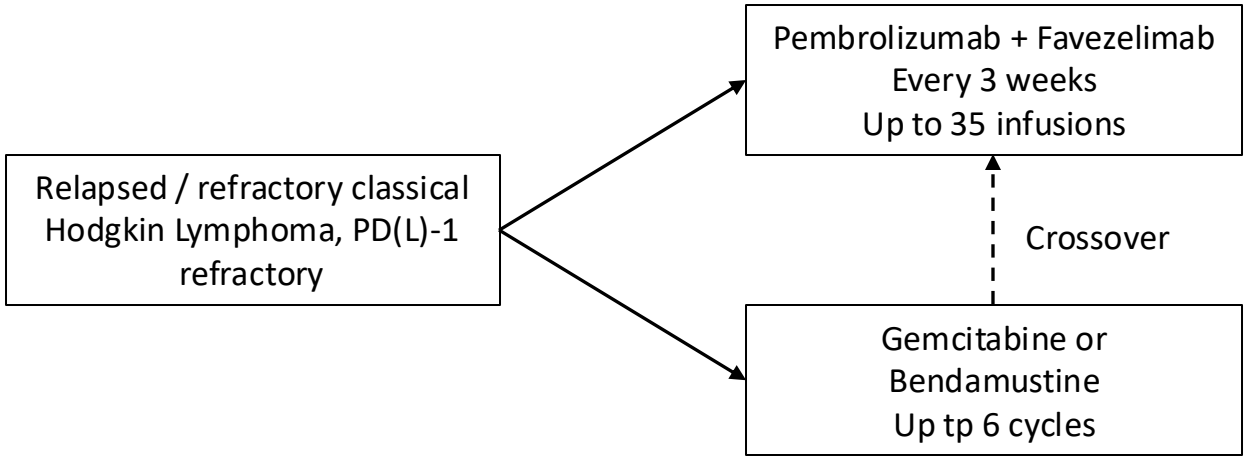


1. LAG3-MHCII interaction between T-cell and tumour cells suppresses T-cell
2. Same interaction may give survival signal to tumour cell
3. LAG3 on CD8 T-cell / NK cell suppresses activity when interacts with Galectin-3 / FGL-1 / LSECtin
4. LAG3 on Treg interacts with MHCII on APCs to enhance suppressor function
5. Soluble LAG3 inhibits monocyte derived dendritic cells

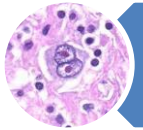
MK4280A - 008

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)

ClinicalTrials.gov ID NCT05508867



Aiming for 360 patients



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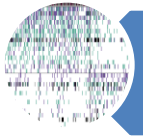
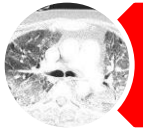


PDL1 inhibitors

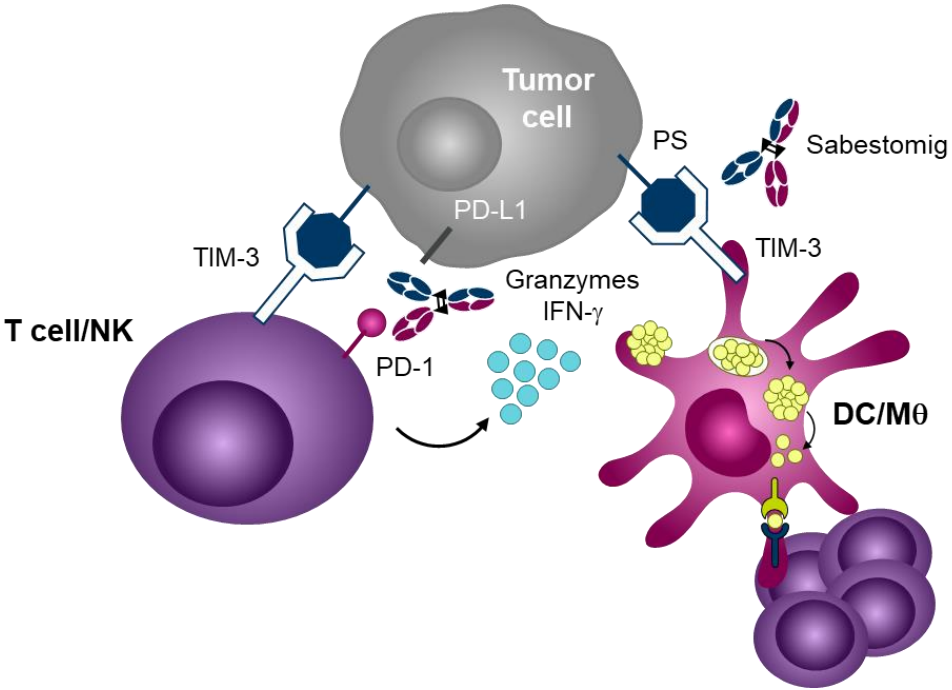
Lag3 inhibitors



TIM3 inhibitors

CD47 / SIRP alpha inhibitors

Immunological checkpoints – TIM3



- 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
  - Myeloid/dendritic cells: Targets TIM-3 to increase tumor cell phagocytosis and antigen presentation

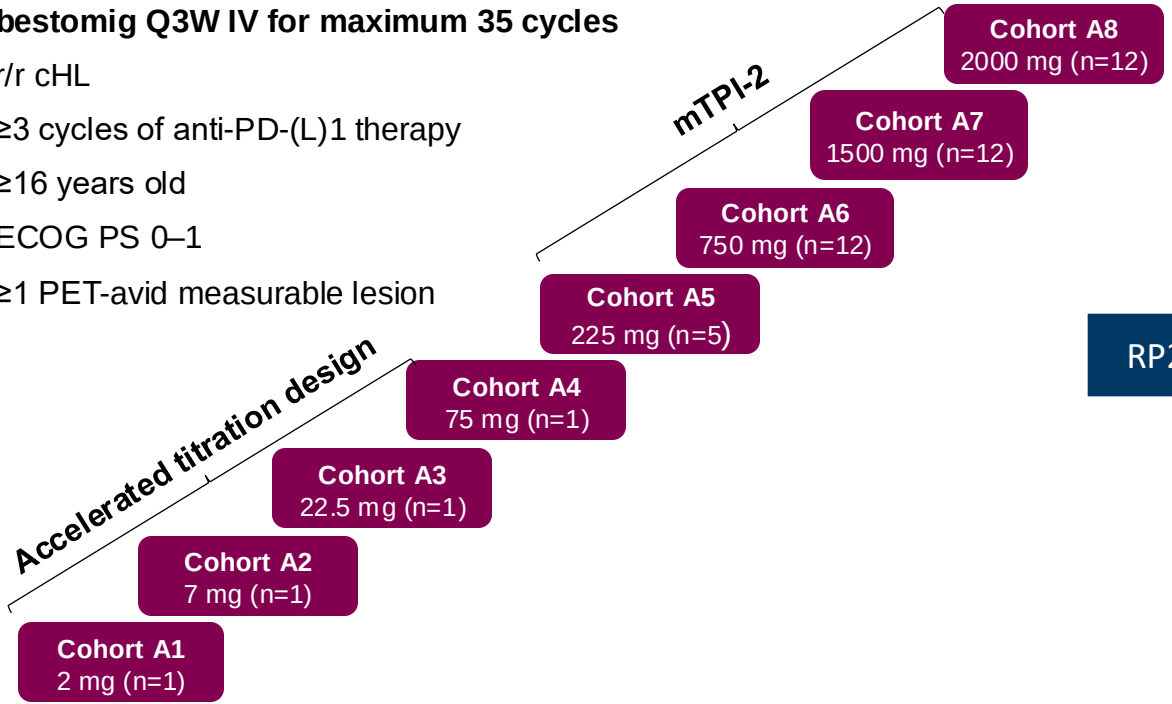
Myeloid/DC MOA:
Targets TIM-3 to increase phagocytosis, tumor antigen presentation, and antitumor T cell expansion

Trial design

Phase I: Dose Escalation
N=45*

Sabestomig Q3W IV for maximum 35 cycles

- r/r cHL
- ≥3 cycles of anti-PD-(L)1 therapy
- ≥16 years old
- ECOG PS 0–1
- ≥1 PET-avid measurable lesion



RP2D

Phase II: Dose Expansion

Cohort B1
Anti-PD-(L)1-exposed

Cohort B2
Anti-PD-(L)1-naïve

Selected baseline characteristics

	N=45
Median age (range), years	39.0 (21–80)
Male / female, n (%)	30 (66.7) / 15 (33.3)
Disease stage, n (%)	
I	1 (2.2)
II	7 (15.6)
III	11 (24.4)
IV	26 (57.8)
Hodgkin lymphoma status after last line of therapy, n (%)	
Relapsed	20 (44.4)
Refractory	24 (53.3)
Unknown	1 (2.2)
Median number of prior anticancer therapy lines (range)	5.0 (2–13)
Prior disease-related treatment modalities, n (%)	
Anti-PD-1	45 (100)
Anti-PD-L1	1 (2.2)
ASCT	25 (55.6)
Brentuximab	42 (93.3)

Safety summary

Safety, n (%)	N=45	
	Treatment emergent	Possibly related to sabestomig
Any AE	42 (93.3)	28 (62.2)
Grade ≥3 AE	9 (20.0)	3 (6.7)
AE with outcome of death	1 (2.2)	0
AE leading to discontinuation of sabestomig	1 (2.2)	0
SAE	7 (15.6)	4 (8.9)
AESI	17 (37.8)	12 (26.7)
ImAE*	7 (15.6)	7 (15.6)

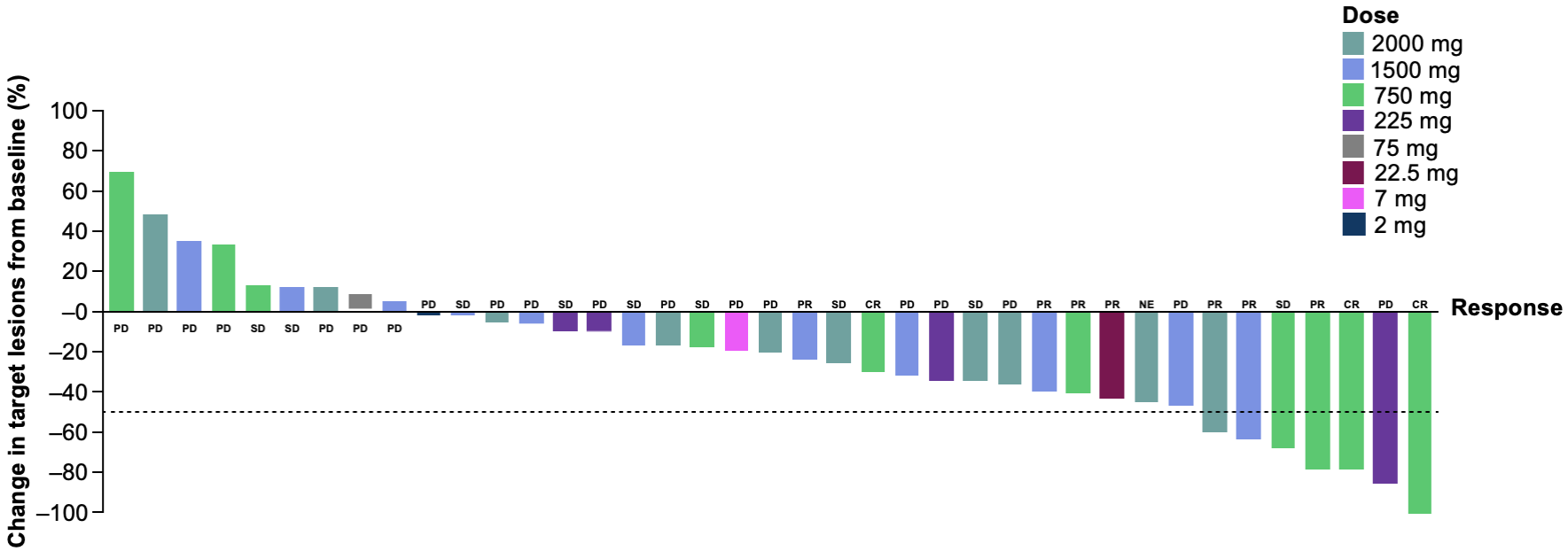
Best Overall Response

N (%)	2–75 mg N=4	225 mg N=5	750 mg N=12	1500 mg N=12	2000 mg N=12
ORR	1 (25.0)	0	6 (50.0)	3 (25.0)	2 (16.7)
CR	0	0	3 (25.0)	0	0
PR	1 (25.0)	0	3 (25.0)	3 (25.0)	2 (16.7)
SD	0	1 (20.0)	3 (25.0)	3 (25.0)	3 (25.0)
PD	3 (75.0)	3 (60)	2 (16.7)	6 (50.0)	6 (50.0)
NE/missing	0	1 (20)	1 (8.3)	0	1 (8.3)

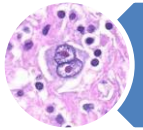
Of 45 patients:

- 12 objective responses
- 3 complete responses
- Best response rate seen in 750mg cohort

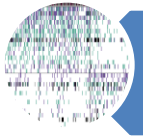
Waterfall plot



Decision made to terminate development in classical Hodgkin lymphoma

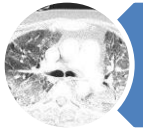


PD1 inhibitors

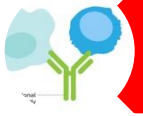


PDL1 inhibitors

Lag3 inhibitors

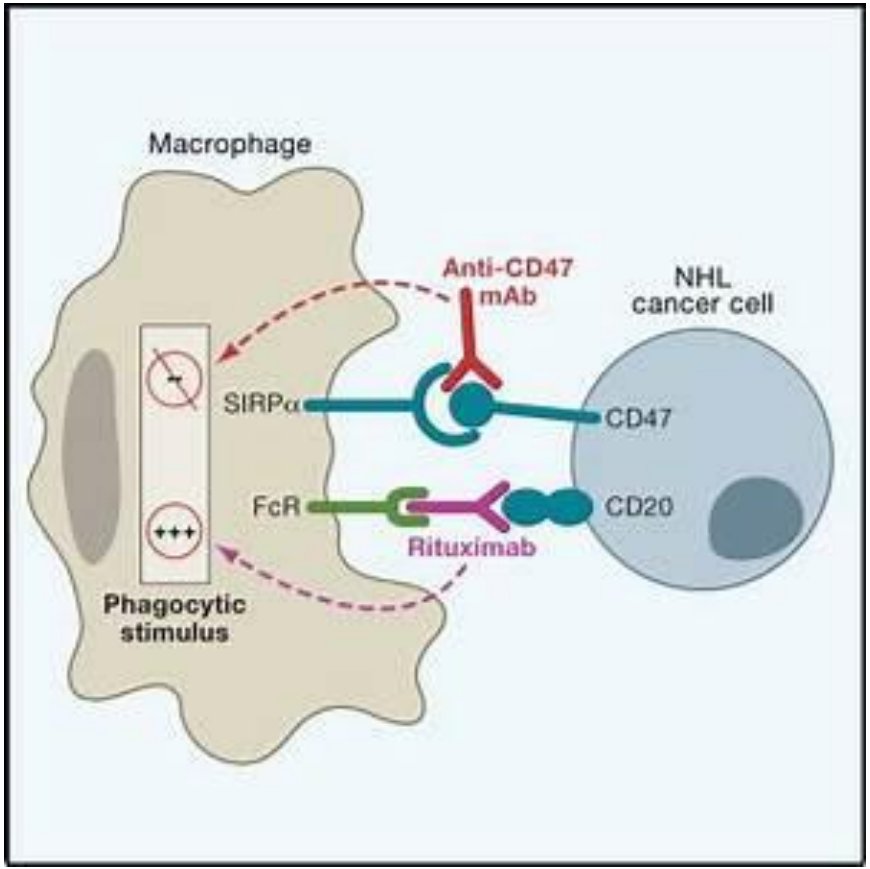


TIM3 inhibitors



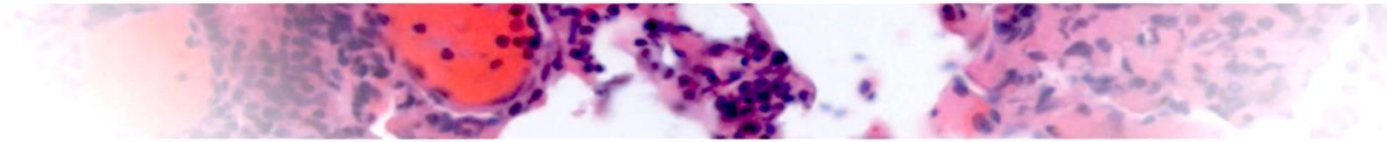
CD47 / SIRP alpha inhibitors

The macrophage checkpoint: CD47 - SIRPalpha



American Society *of* Hematology

Helping hematologists conquer blood diseases worldwide



Timdarpacept plus tislelizumab in prior anti-PD-1 failed R/R classical Hodgkin lymphoma: An open label, multicenter, phase 2 study (IMM01-04)

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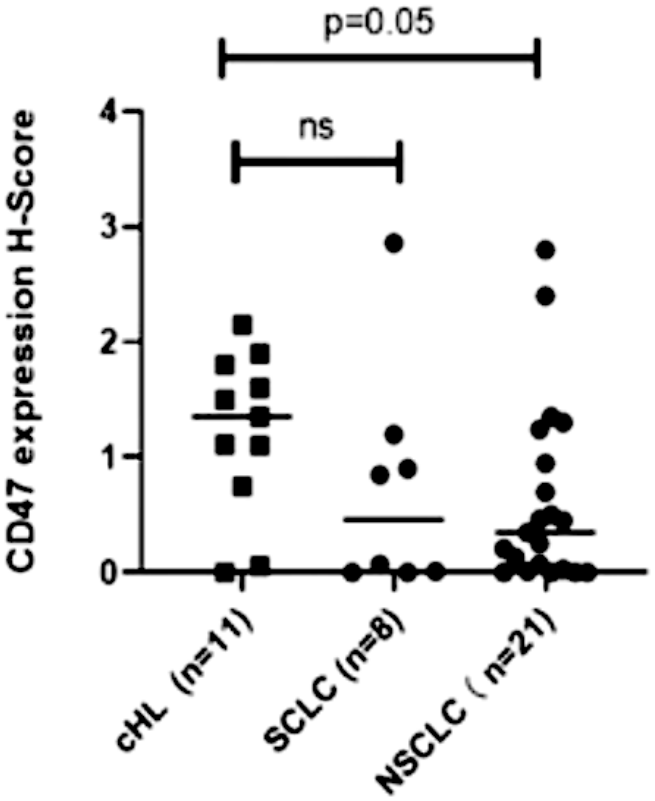
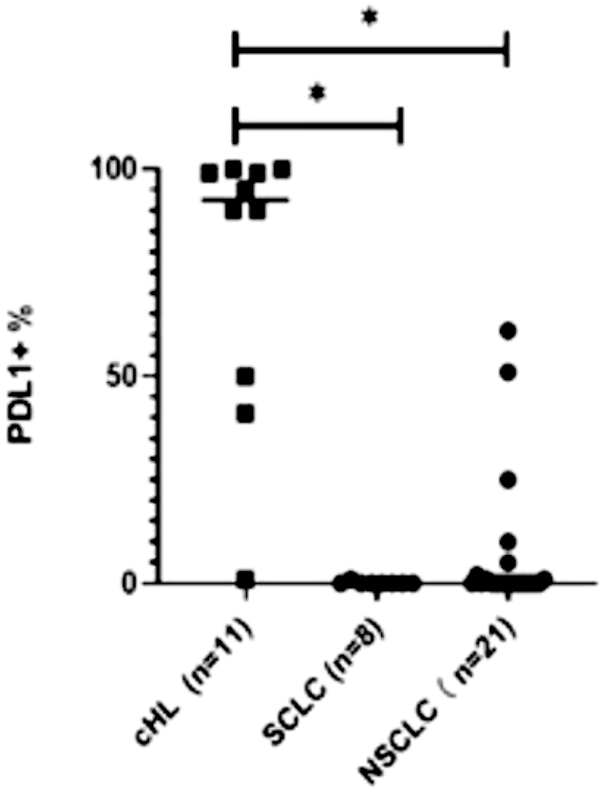
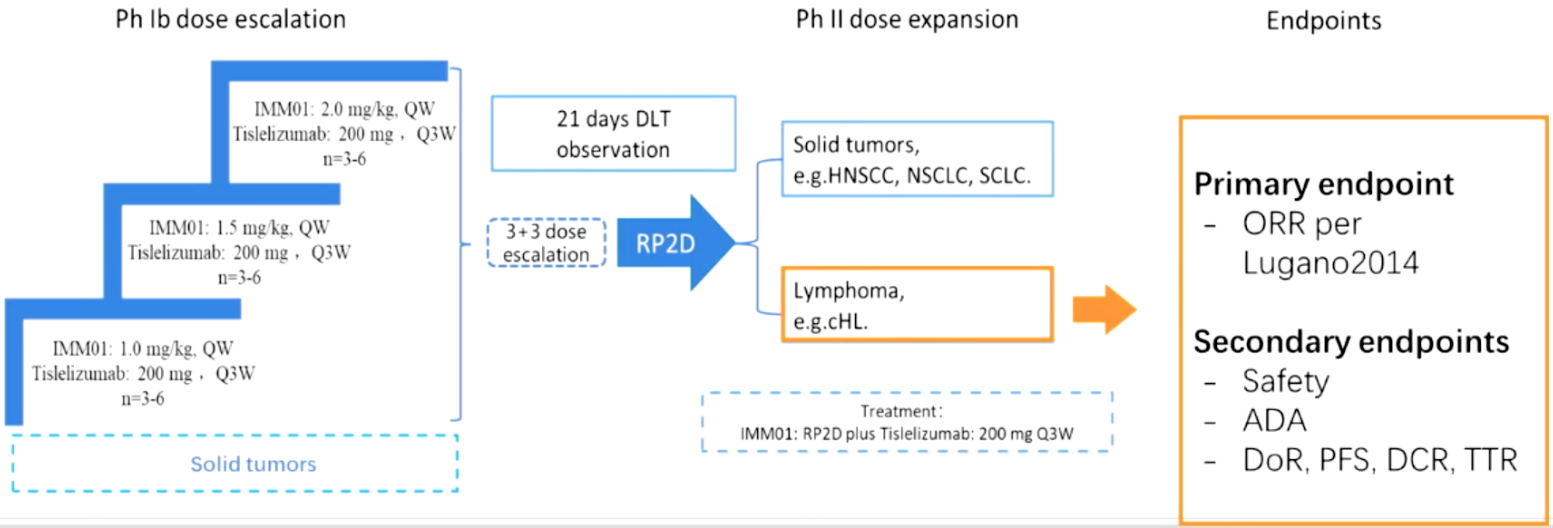
CD47 and PD1 expression in cHL





Study design

- IMM01-04 is a Phase Ib/II dose escalation & expansion study of timdarpacept plus tislelizumab in advanced solid tumors and lymphomas.
- 2.0mg/kg was determined as RP2D of timdarpacept; tislelizumab was given at a fixed dosage of 200mg.
- Preliminary results of **R/R cHL** in lymphoma cohort in Phases II study were reported as follows.



Baseline Characteristics

Characteristic	N=32
Age, years	
Median (range)	34.5 (19-77)
Gender, n (%)	
Male	22 (68.8)
Female	10 (31.2)
ECOG PS, n (%)	
0	21 (65.6)
1	11 (34.4)
Ann Arbor Staging, n (%)	
II	2 (6.3)
III	9 (28.1)
IV	21 (65.6)
Bulky (≥10cm), n (%)	
Yes	2 (6.3)
No	30 (93.7)
Prior systemic anti-cancer therapy, n (%)	
Median (range)	4 (2-12)
2L	5 (15.6)
3L	10 (31.3)
4L	4 (12.5)
≥5L	13 (40.6)
Prior auto-SCT (n, %)	5 (15.6)

- As of Nov 20, 2023, 32 patients with R/R cHL were treated with timdarpacept 2.0mg/kg QW plus tislelizumab 200mg Q3W.
- Heavily pre-treated patients, the median prior systemic therapy was 4 lines.
- All patients previously received at least one regimen containing anti-PD-1.

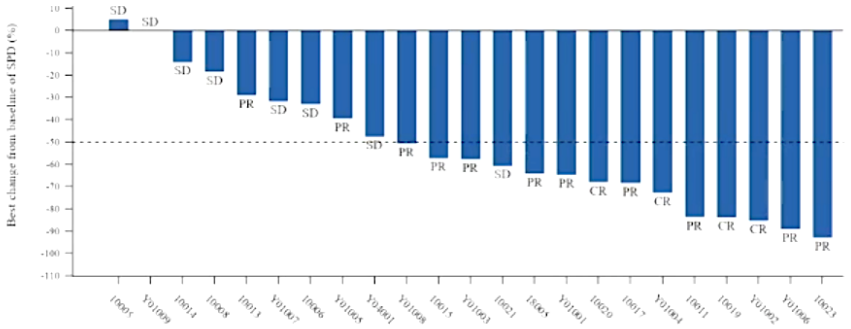
Cut off date: Nov 20, 2023

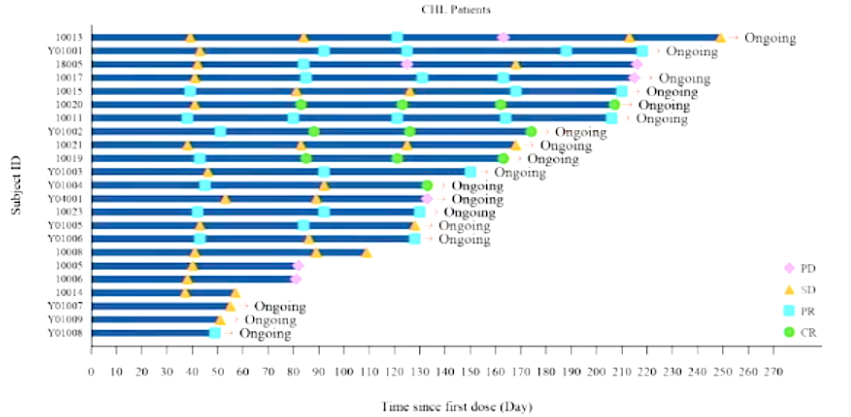
Efficacy

- 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





Benefit seen across all PD1-failed subgroups

In 23 efficacy-evaluable patients:

- Patients can benefit from timdarpacept combined with tislelizumab regardless of whether they were primary or secondary resistant to tislelizumab treatment, other PD-1-containing regimens (non-tislelizumab), or CD30-ADC treatment.

Prior Treatments (anti-PD-1, CD30 ADC)	CR n, %	PR n, %	SD n, %	PD n, %	ORR n, %	DCR n, %
Resistance to tislelizumab (N=12)	1 (8.3)	7 (58.3)	4 (33.3)	0	**8 (66.7)**	12 (100)
• Primary resistance to tislelizumab (N=4)	1 (25.0)	2 (50.0)	1 (25.0)	0	**3 (75.0)**	4 (100)
Resistance to other PD-1 (N=12)	3 (25.0)	4 (33.3)	5 (41.7)	0	**7 (58.3)**	12 (100)
• Primary resistance to other PD-1 (N=4)	0	0	4 (100)	0	**0**	4 (100)
CD30 ADC (N=5)	1 (20.0)	1 (20.0)	3 (60.0)	0	**2 (40.0)**	5 (100)

Cut off date: Nov 20, 2023

Benefit seen across all PD1-failed subgroups

In 23 efficacy-evaluable patients:

- Patients can benefit from timdarpacept combined with tislelizumab regardless of the intervals from last dose of PD-1 Ab to first dose of timdarpacept + tislelizumab, within less than 6 months, 6-12 months, or more than 12 months.

	Intervals from last dose of anti-PD1 Ab to first dose of timdarpacept + tislelizumab		
	< 6 months N=8	6-12 months N=4	12 months N=11
BOR，n (%)			
CR	0	1 (25.0)	3 (27.3)
PR	5 (62.5)	3 (75.0)	3 (27.3)
SD	3 (37.5)	0	5 (45.5)
PD	0	0	0
ORR, n (%)	**5 (62.5)**	**4 (100)**	**6 (54.5)**
DCR，n (%)	8 (100)	4 (100)	11 (100)

Cut off date: Nov 20, 2023

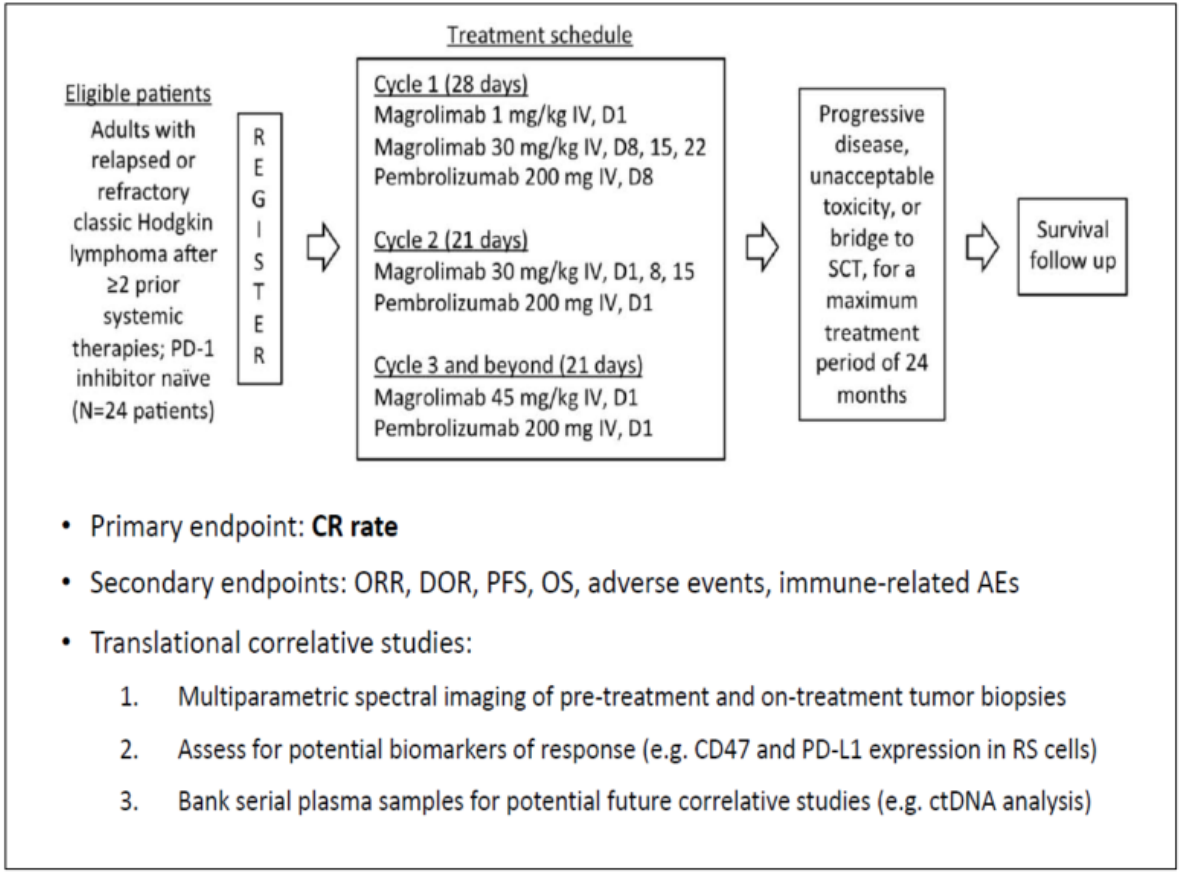
Well tolerated safety profile

Any grade TRAEs with incidence of ≥10%		
SOC, PT n(%)	**Patients（n=22）**	
	All Grades	**G3-4**
TRAE	22 (100)	8 (36.4)
White blood cell count decreased	**12 (54.5)**	**2 (9.1)**
Platelet count decreased	**10 (45.5)**	**2 (9.1)**
Anemia	**10 (45.5)**	0
Lymphocyte count decreased	**7 (31.8)**	**7 (31.8)**
Neutrophil count decreased	**6 (27.3)**	1 (4.5)
Gamma-glutamyl transferase increased	4 (18.2)	0
Anti-erythrocyte antibody positive	4 (18.2)	0
Blood bilirubin increased	4 (18.2)	0
Infusion related reaction	3 (13.6)	0
Electrocardiogram ST-T change	3 (13.6)	0

Overview of TRAE	n(%)
All grade TRAE	22 (100)
≥ G3 TRAE	8 (36.4)
TRAE leading to dose interruption	**7 (31.8)**
TRAE leading to permanent treatment discontinuation	**0**
Treatment-related SAE	1 (4.5)
TRAE leading to death	0
≥ G3 irAE	0
≥ G3 IRR	0

- 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.

Pembro + Magrolimab phase II



- Primary endpoint: **CR rate**
- Secondary endpoints: ORR, DOR, PFS, OS, adverse events, immune-related AEs
- Translational correlative studies:
  1. Multiparametric spectral imaging of pre-treatment and on-treatment tumor biopsies
  2. Assess for potential biomarkers of response (e.g. CD47 and PD-L1 expression in RS cells)
  3. Bank serial plasma samples for potential future correlative studies (e.g. ctDNA analysis)

Courtesy of Dr Ranjana Advani

Conclusions

- Not all PD1 inhibitors are the same: different epitopes and binding kinetics
- PDL1 inhibition does not appear to add any clinical benefit
- Randomised trial of PD1i + LAG3i is ongoing
- Sabestomig (PD1i / TIM3i) showed modest benefit – development terminated
- PD1i and CD47i shows very interesting activity
- Drug development in Hodgkin is a challenge: R/R is now rare and hard pathway to license

Thank you for listening

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NHS Foundation Trust

Oxford Lymphoid Disorders Study Group

Uniting Researchers, Fighting Lymphoid Cancers