

Novel pharmacological paradigms in aggressive B-cell lymphomas

Giorgio Minotti

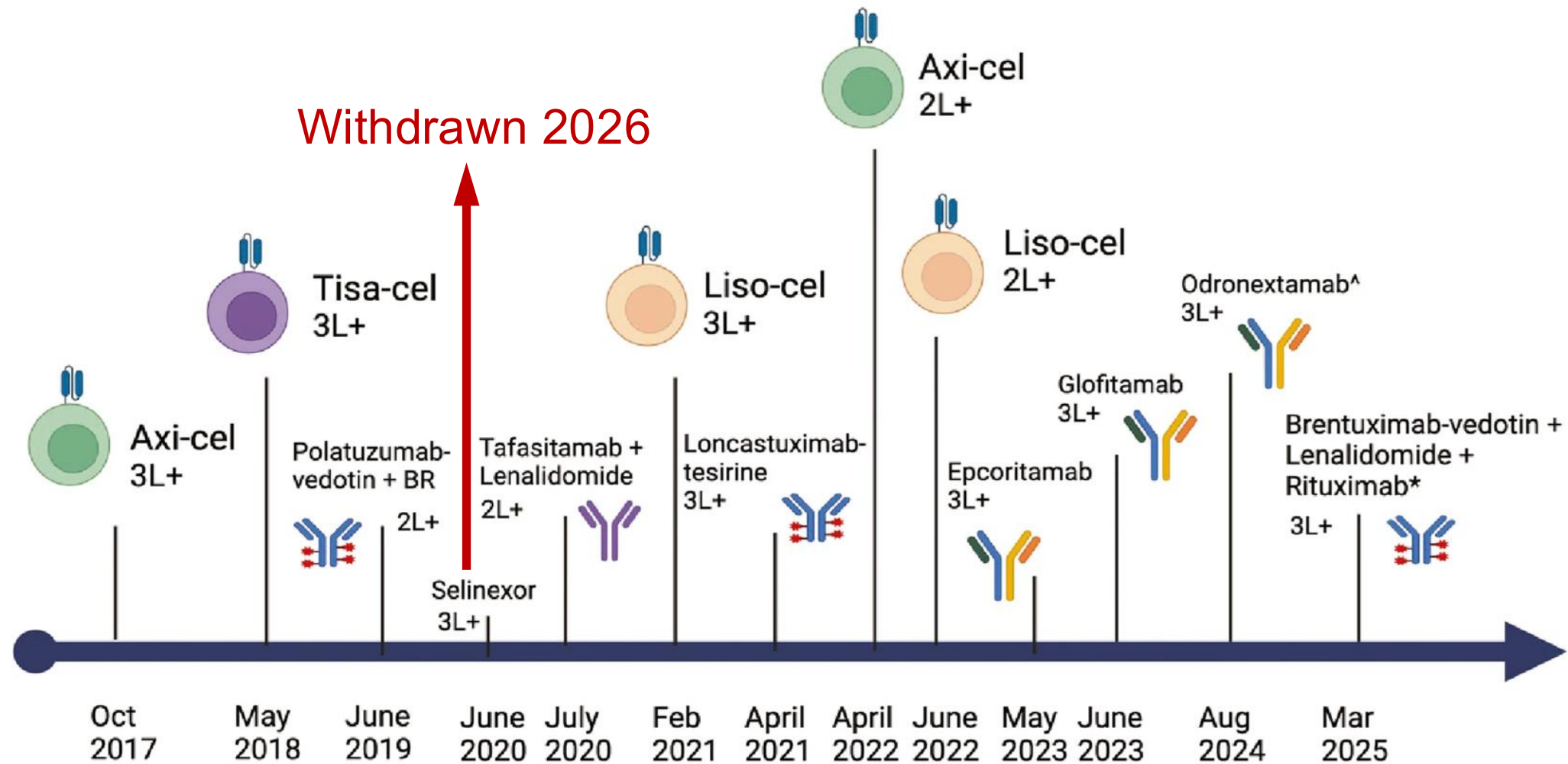
Università e Fondazione Policlinico Universitario
Campus Bio-Medico, Roma

16 ottobre 2026

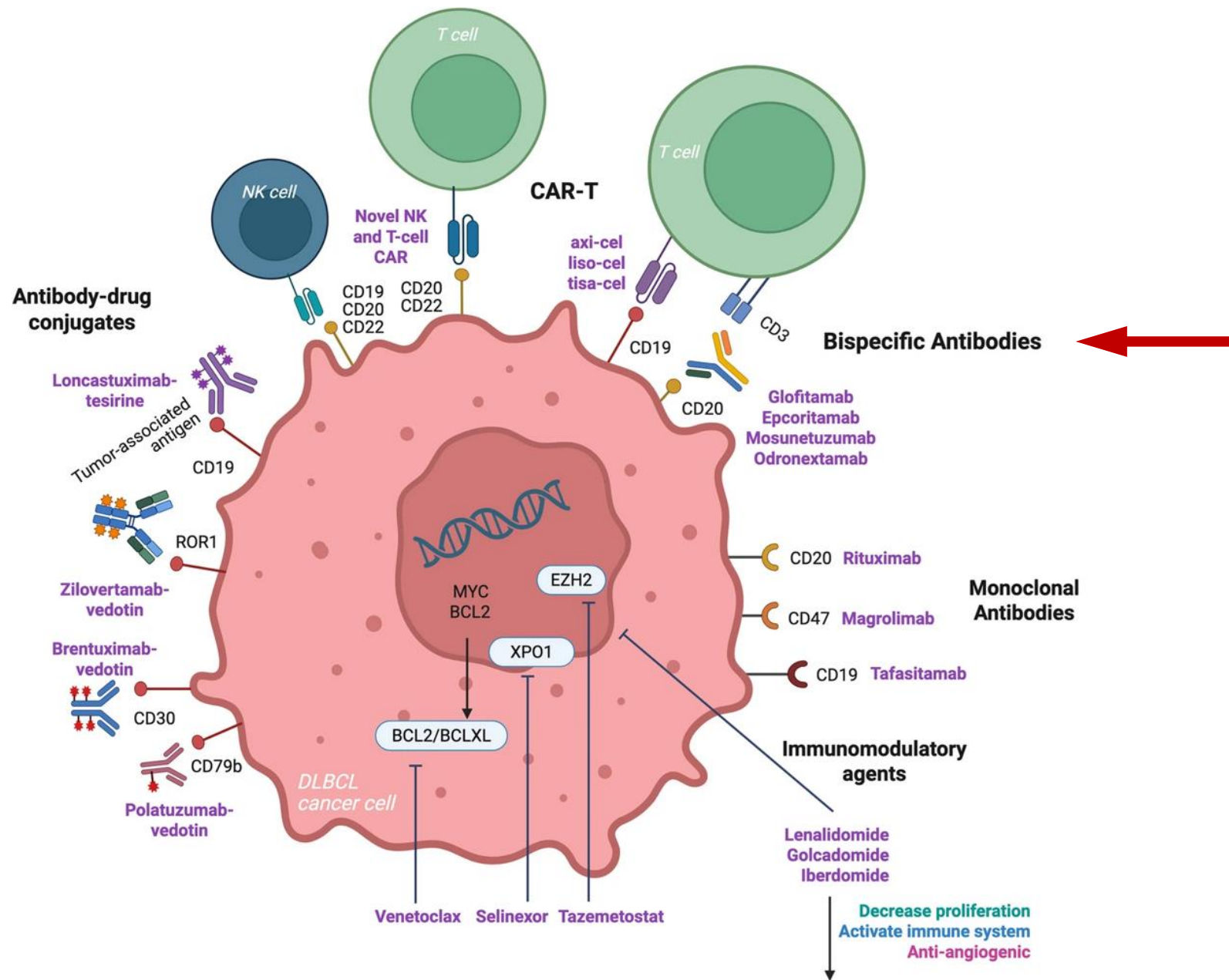
DISCLOSURES

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen			X		X	X	
Incyte	X		X			X	
BeiGene			X		X	X	
Servier			X			X	
Astellas	X						
Pfizer					X		
Gentili					X		
Lilly					X	X	

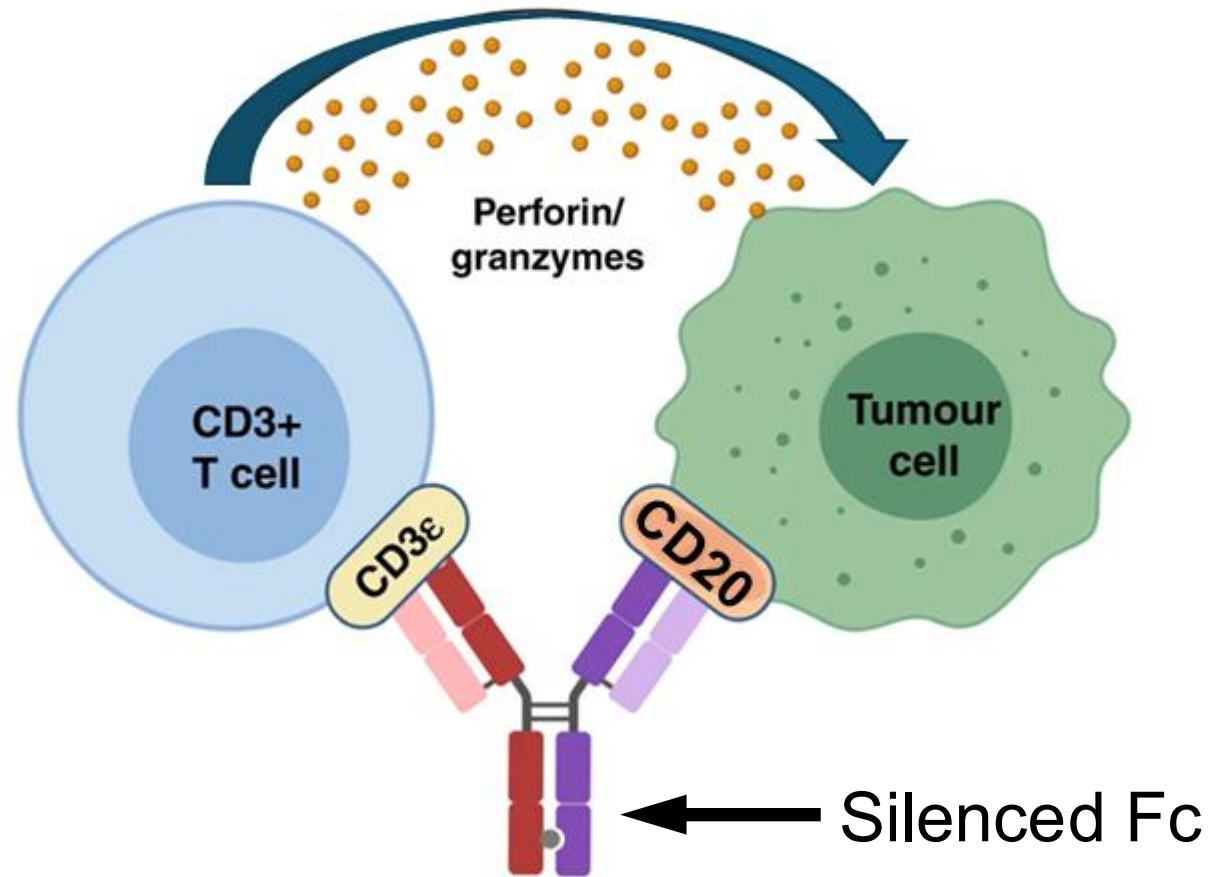
FDA & EMA APPROVALS IN R/R DLBCL



Abbreviations: axi-cel, Axicabtagene ciloleucel; liso-cel, Lisocabtagene maraleucel; tisa-cel, Tisagenlecleucel. 2L+, second line or later; 3L+, third line or later. *FDA approval only, ^EMA approval only.

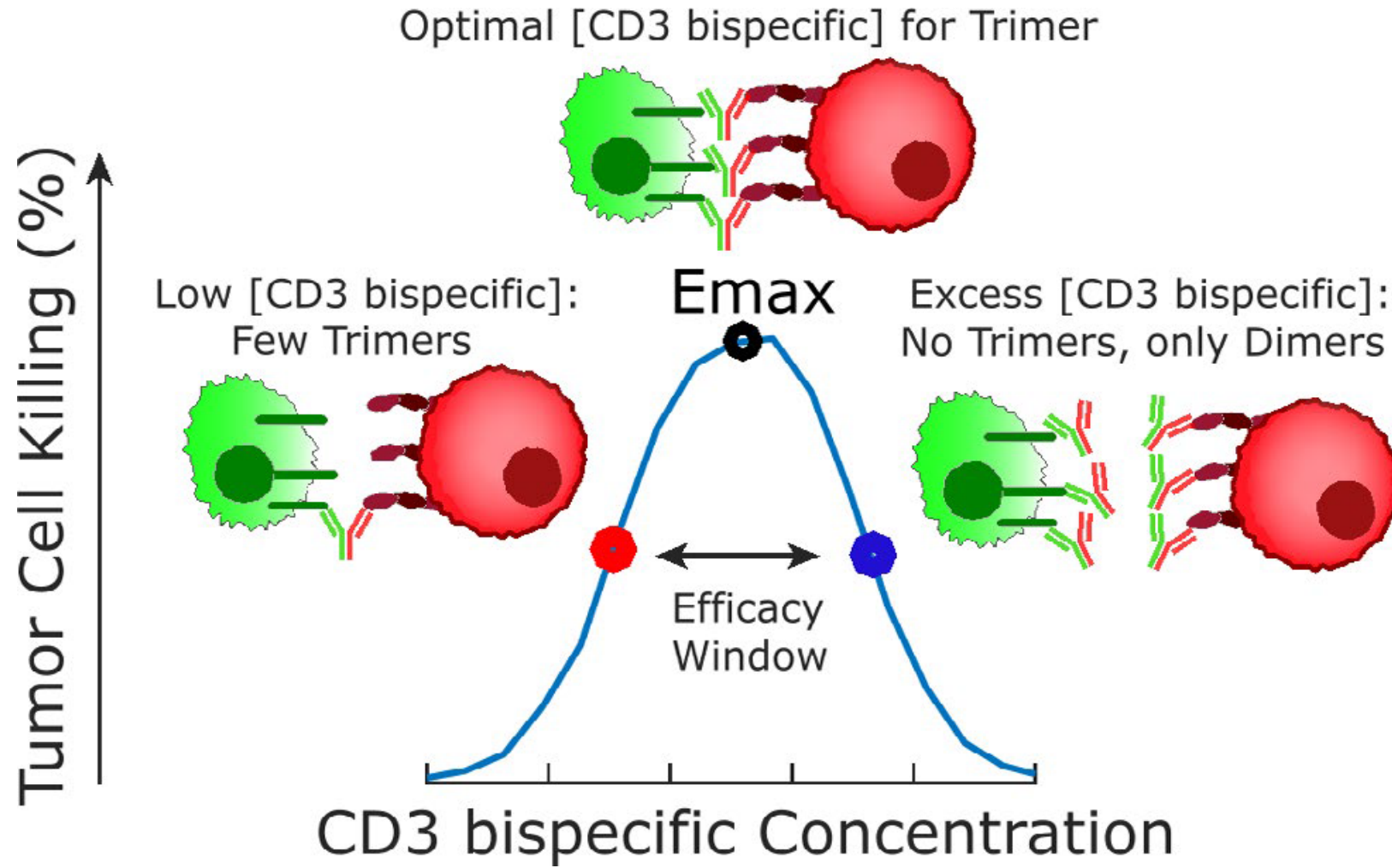


BiTEs and trimers

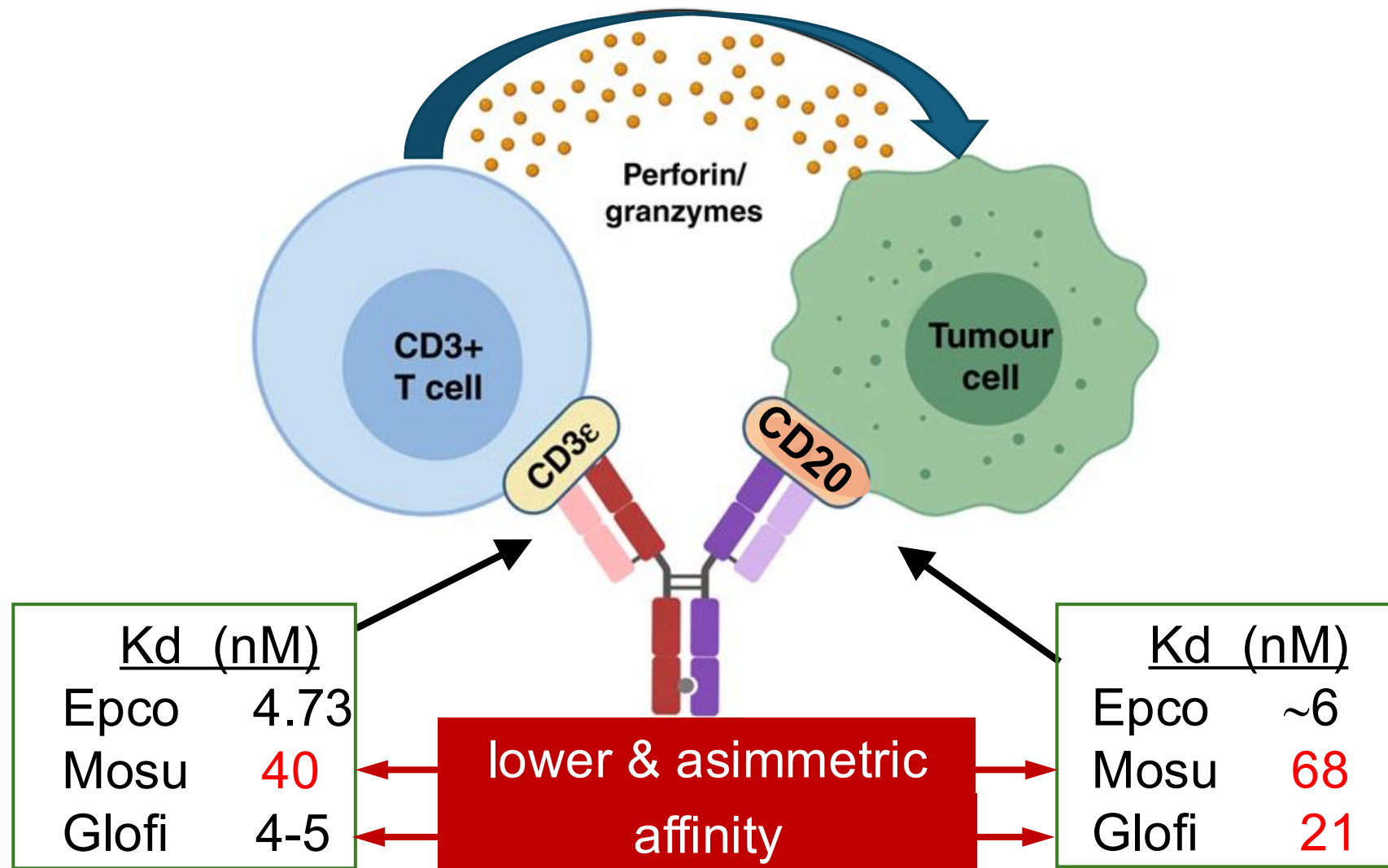


Modified after Singh et al. Br. J. Cancer (2021) 124:1037-1048

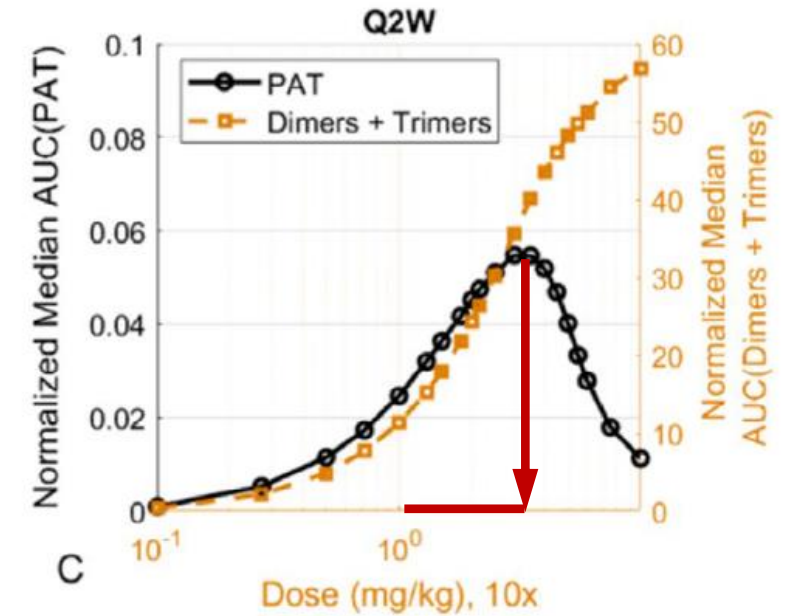
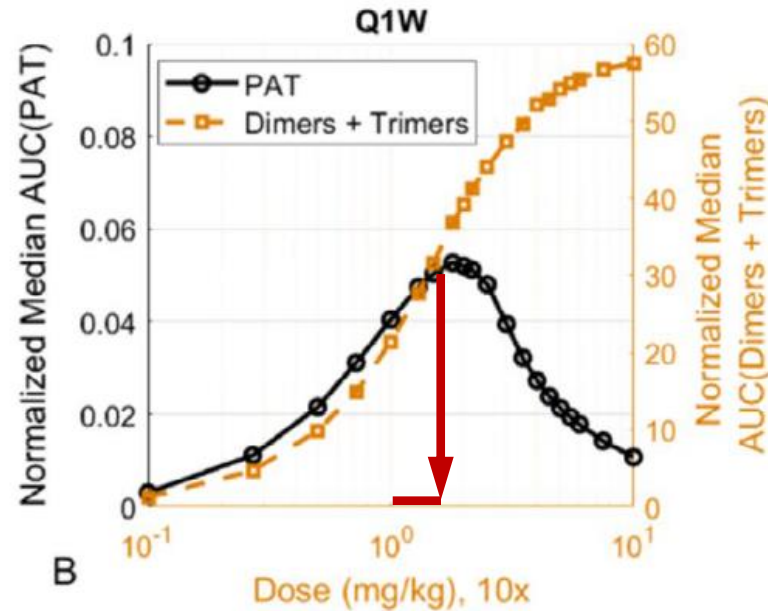
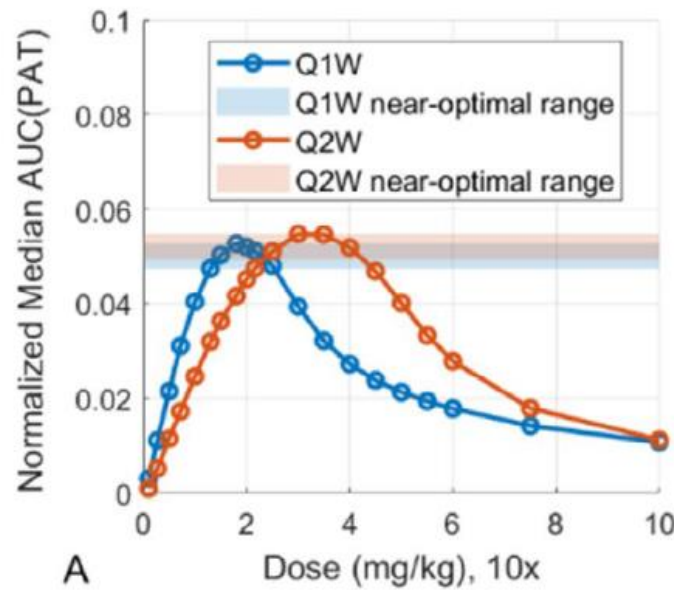
Trimers and efficacy window



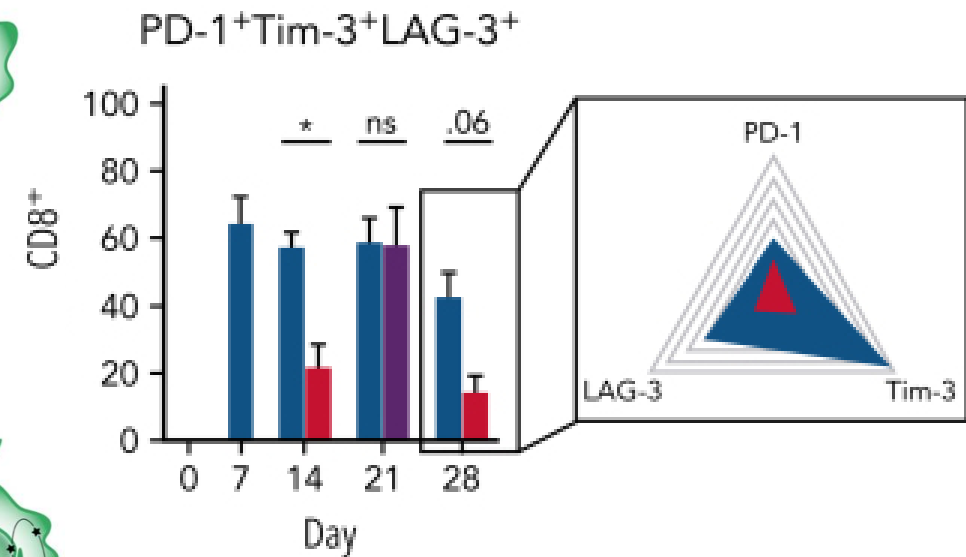
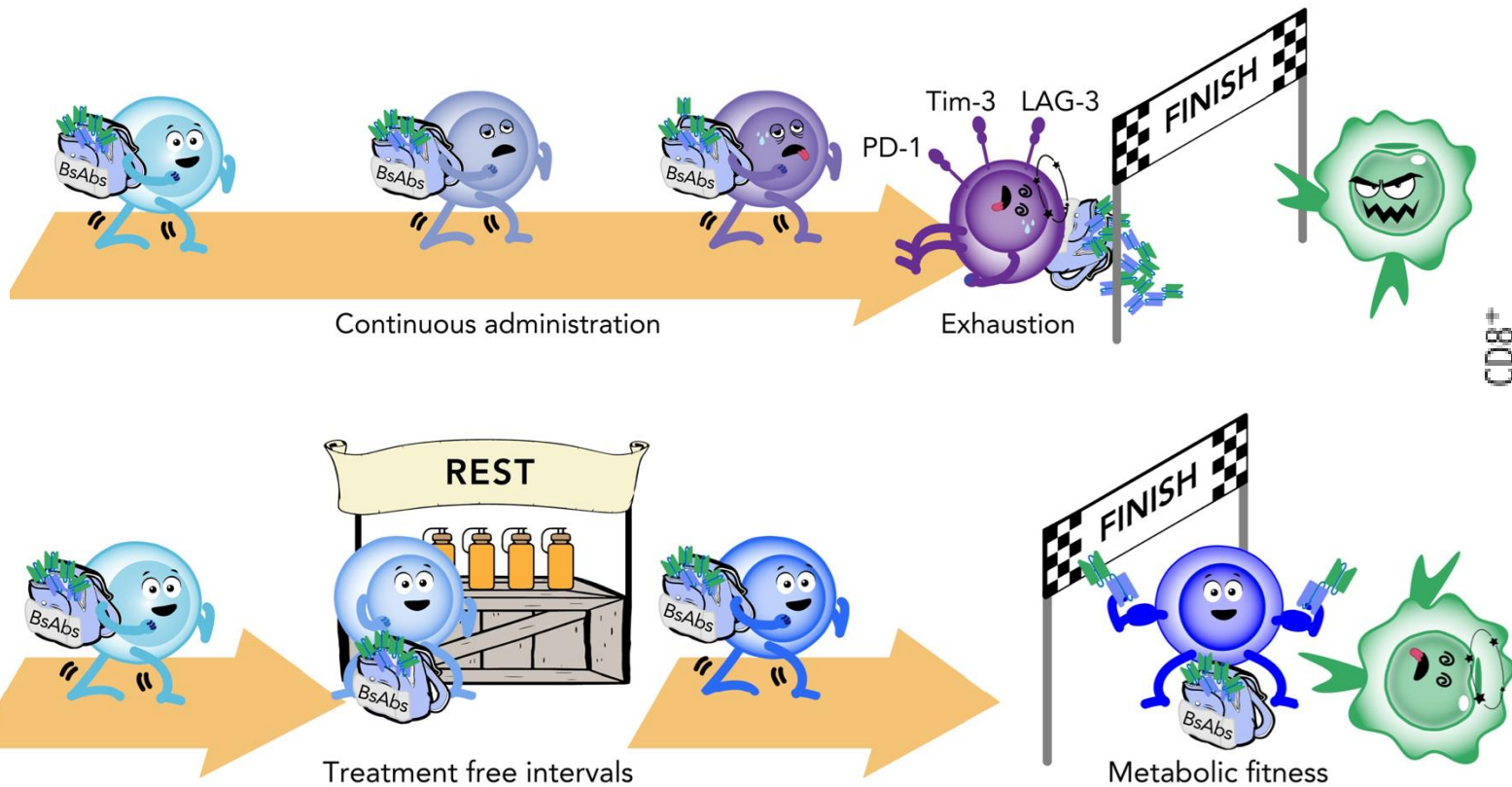
Not all trimers are identical



PK/PD INFORMING OF SCHEDULE



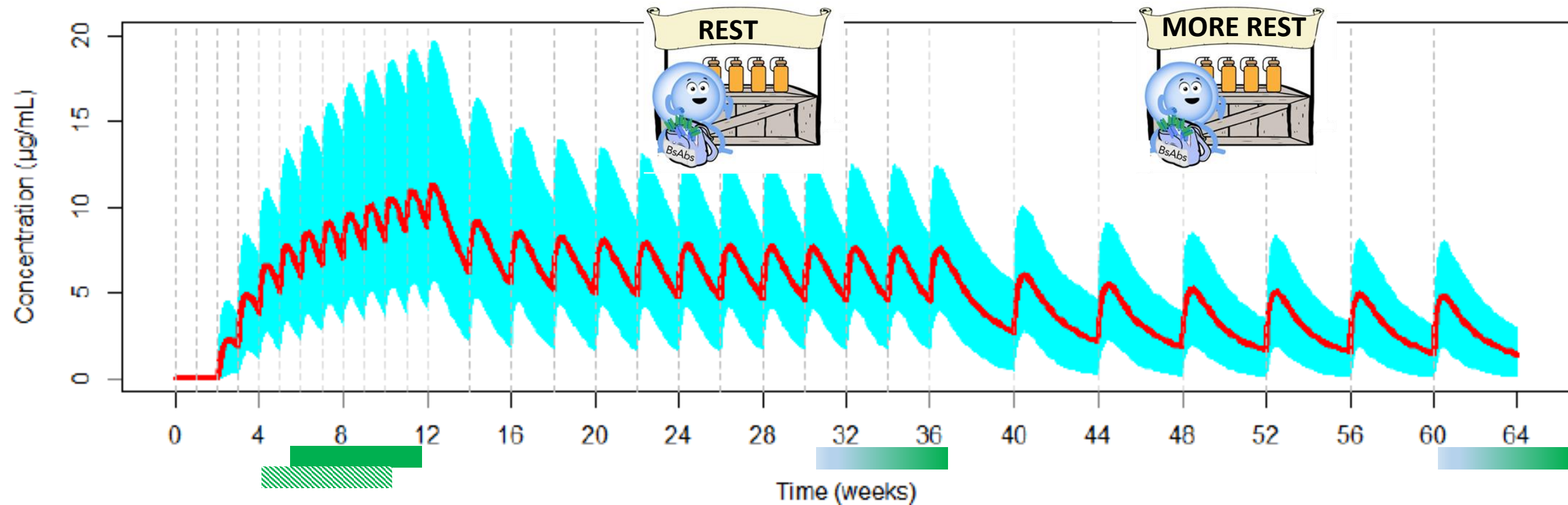
Treatment induced CD8+ exhaustion: give them a rest



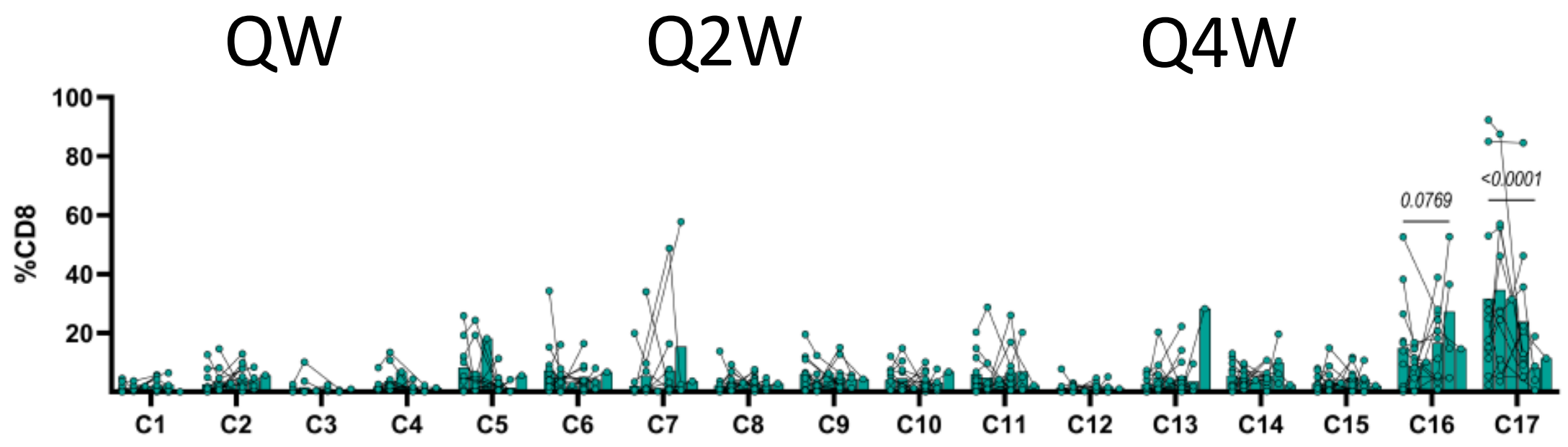
QW

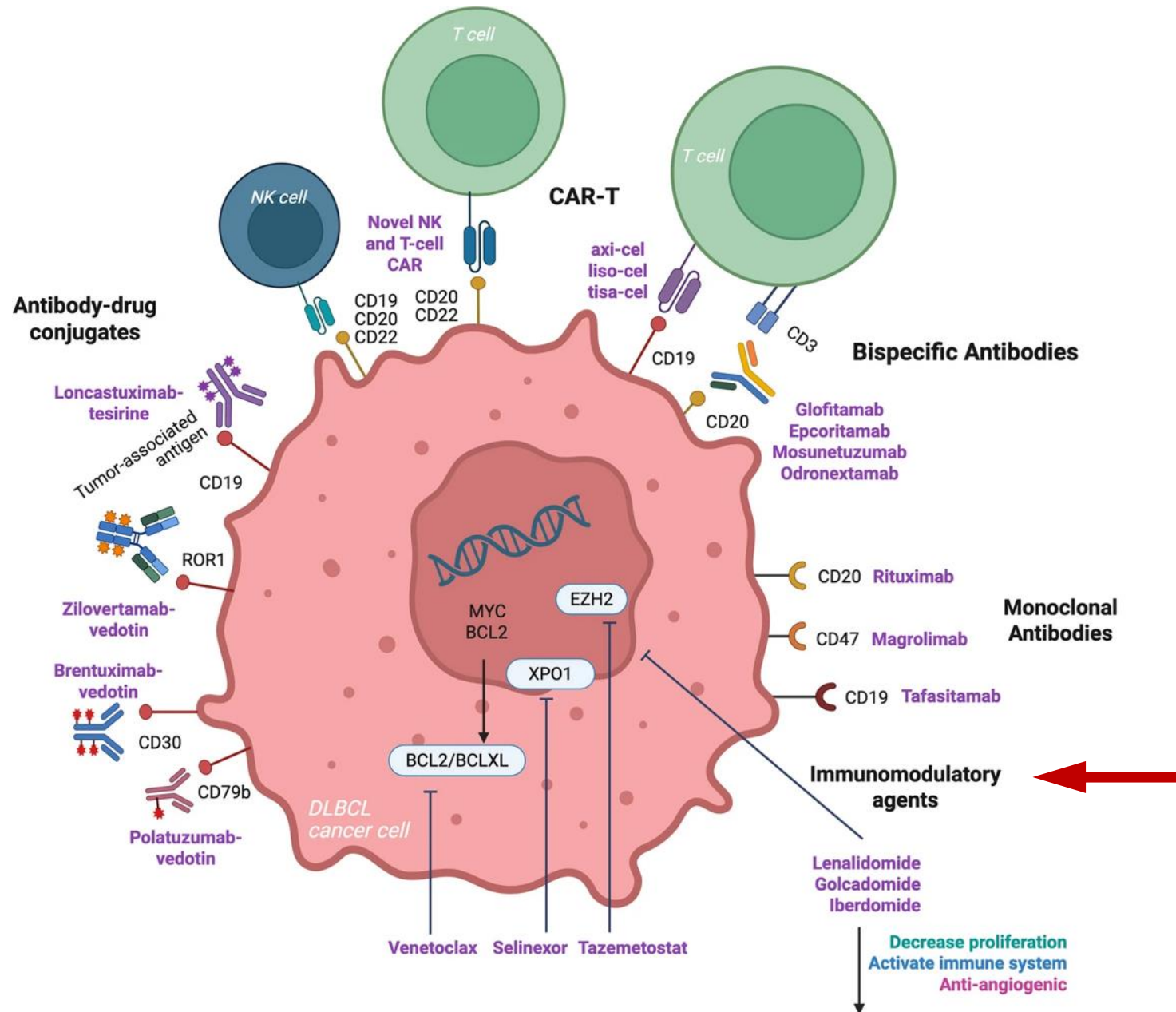
Q2W

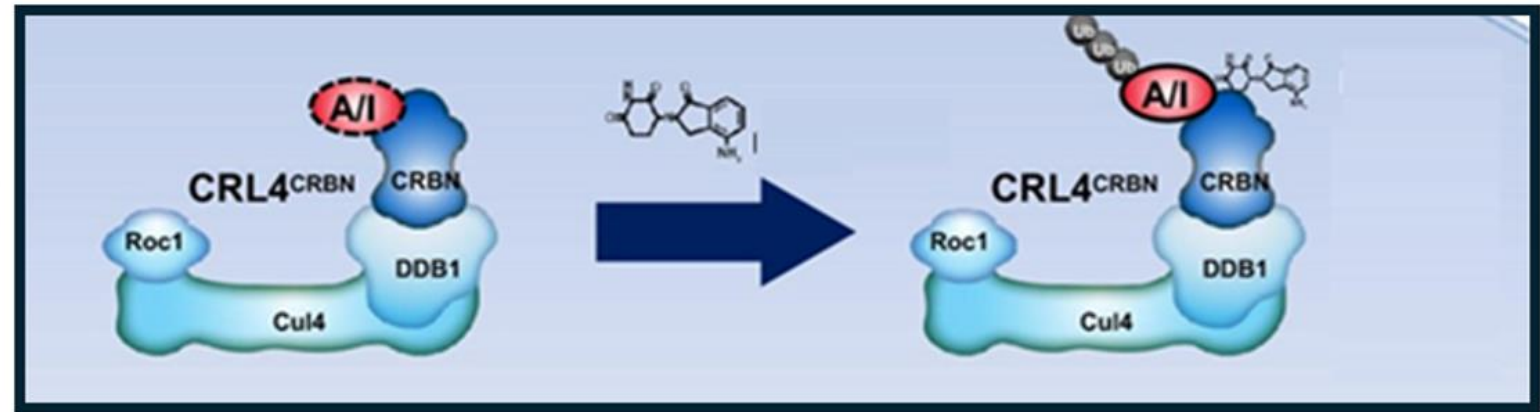
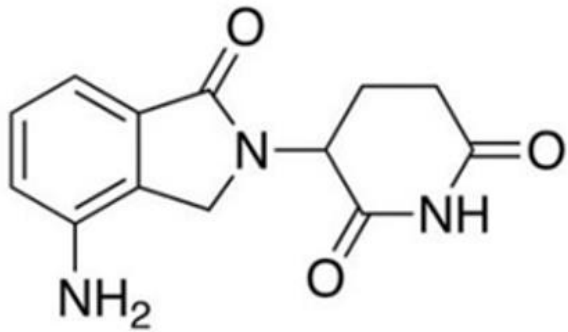
Q4W



ACTIVATED EFFECTOR MEMORY CD8+ T CELLS DURING Q4W

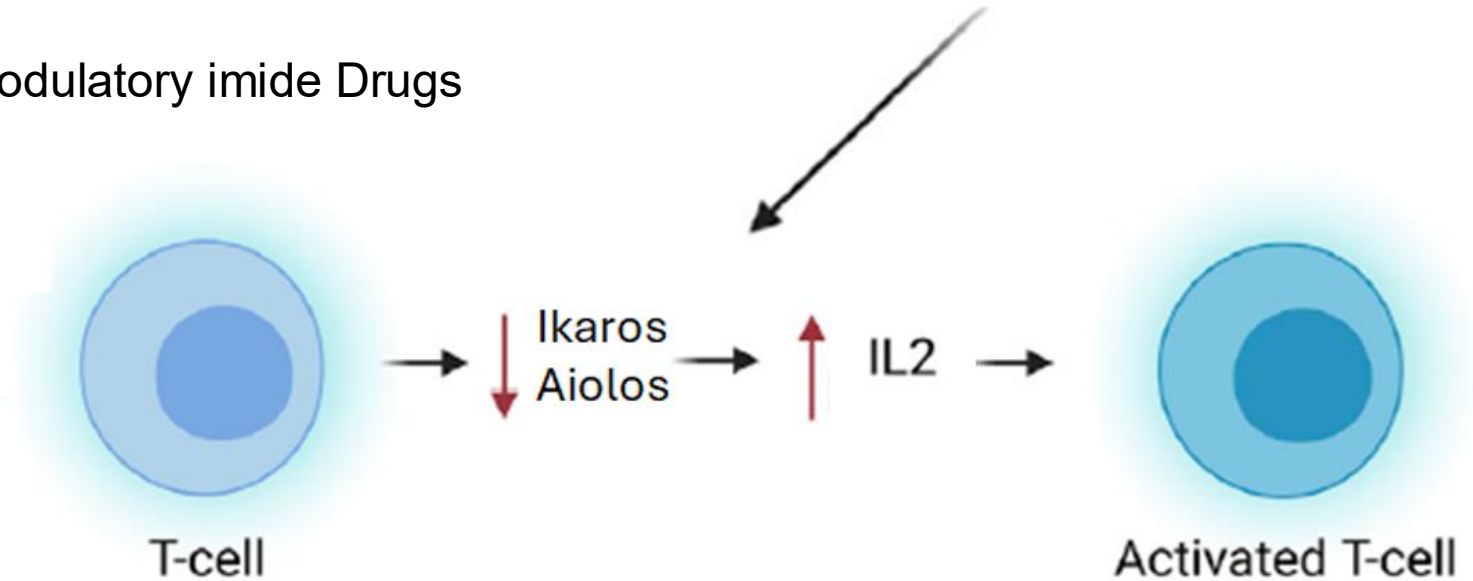


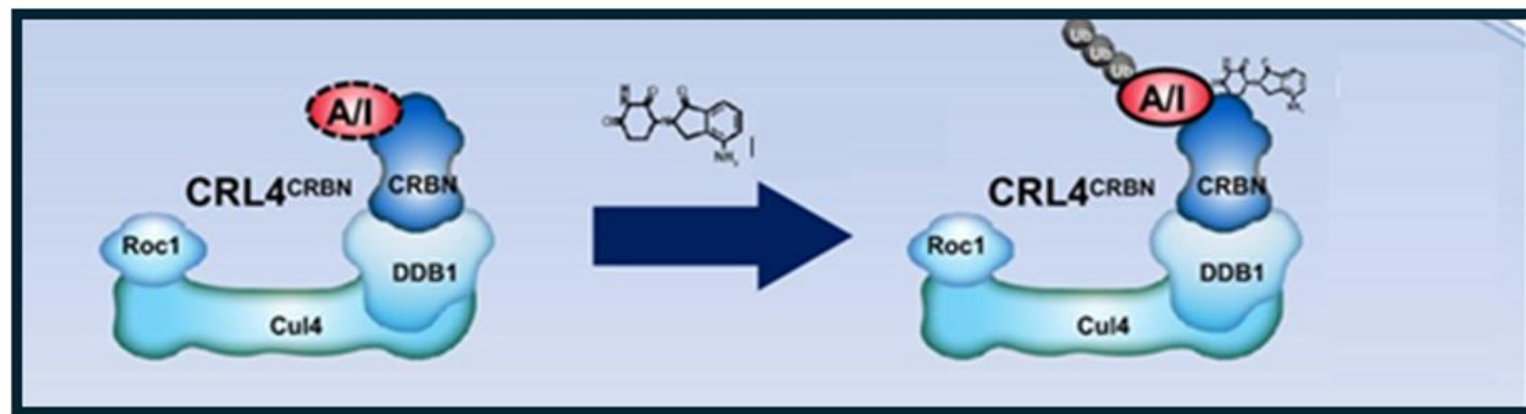
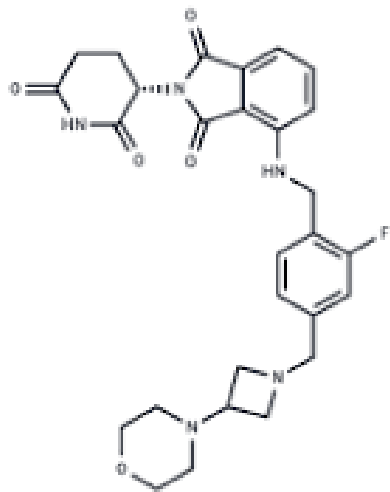




IMiDs:

Cereblon-targeting ImmunoModulatory imide Drugs



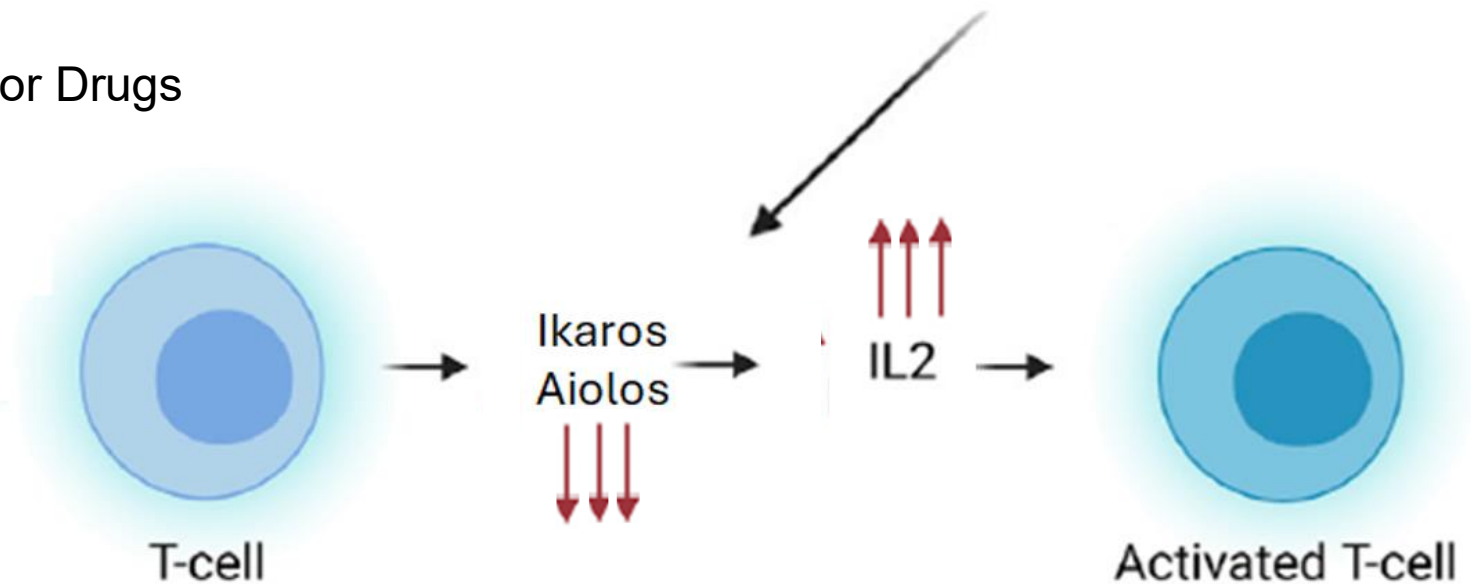


CELMoDs:

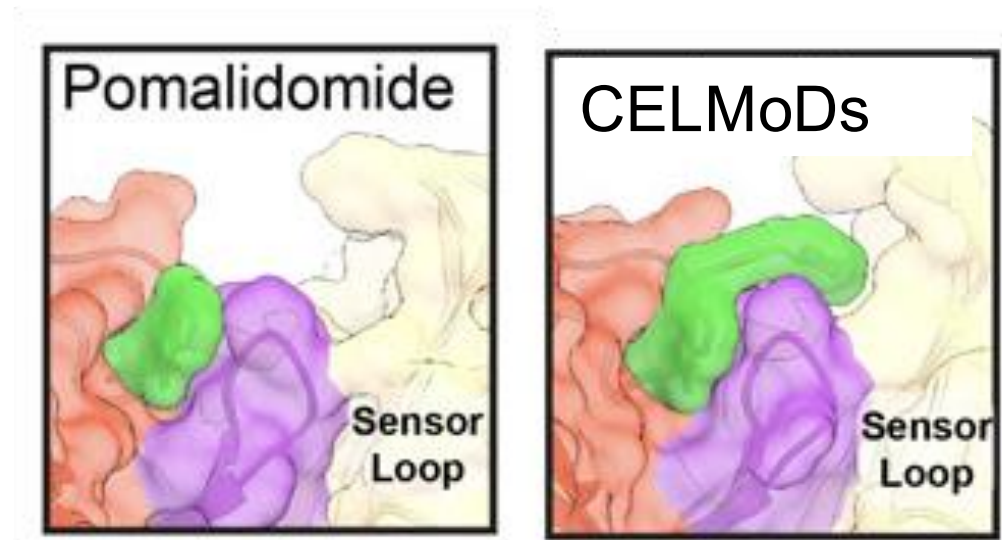
Cereblon E3 Ligase Modulator Drugs

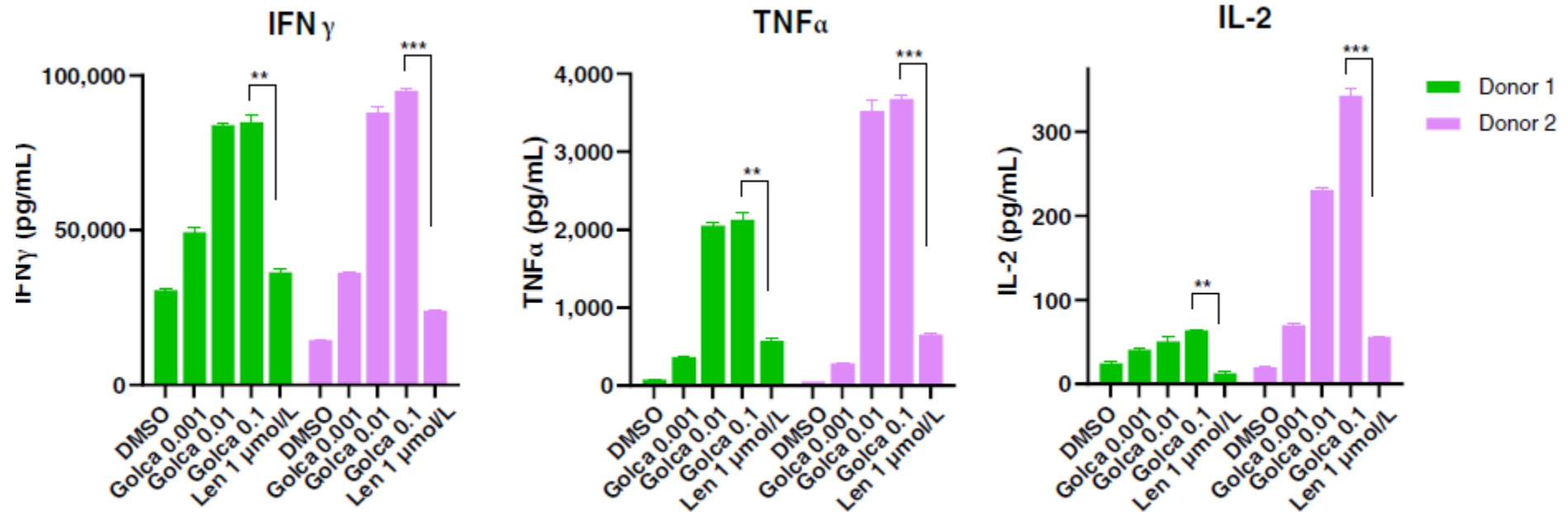
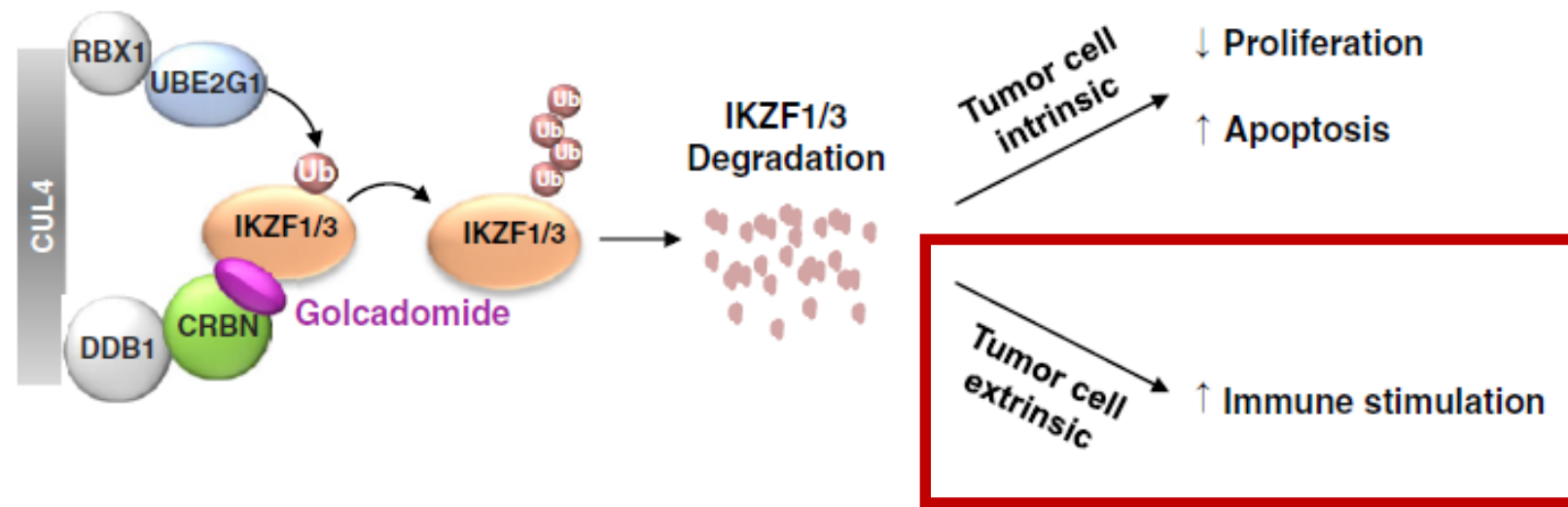
~10-20-fold higher affinity

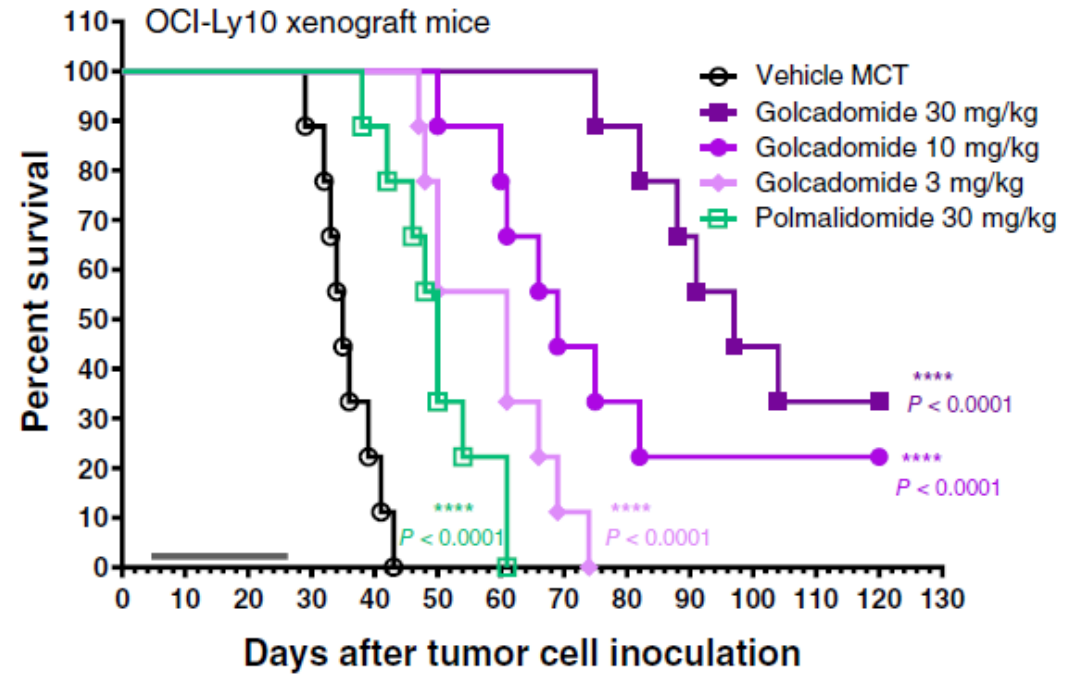
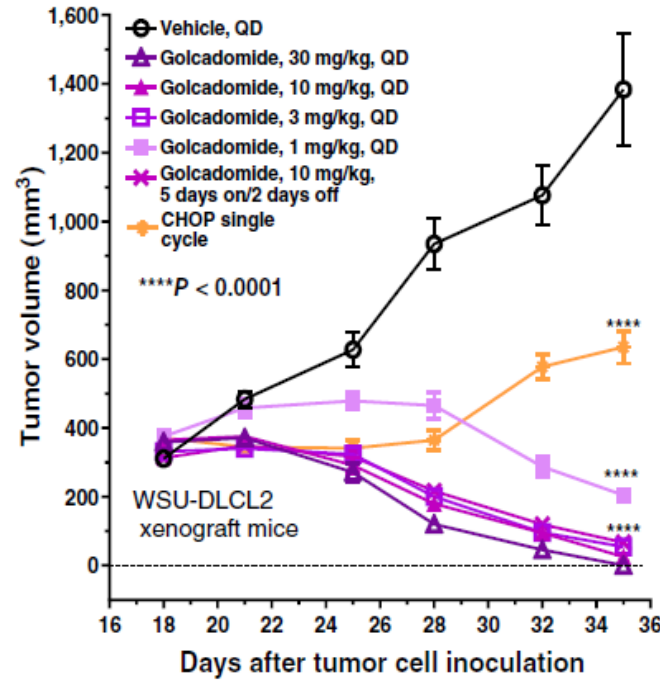
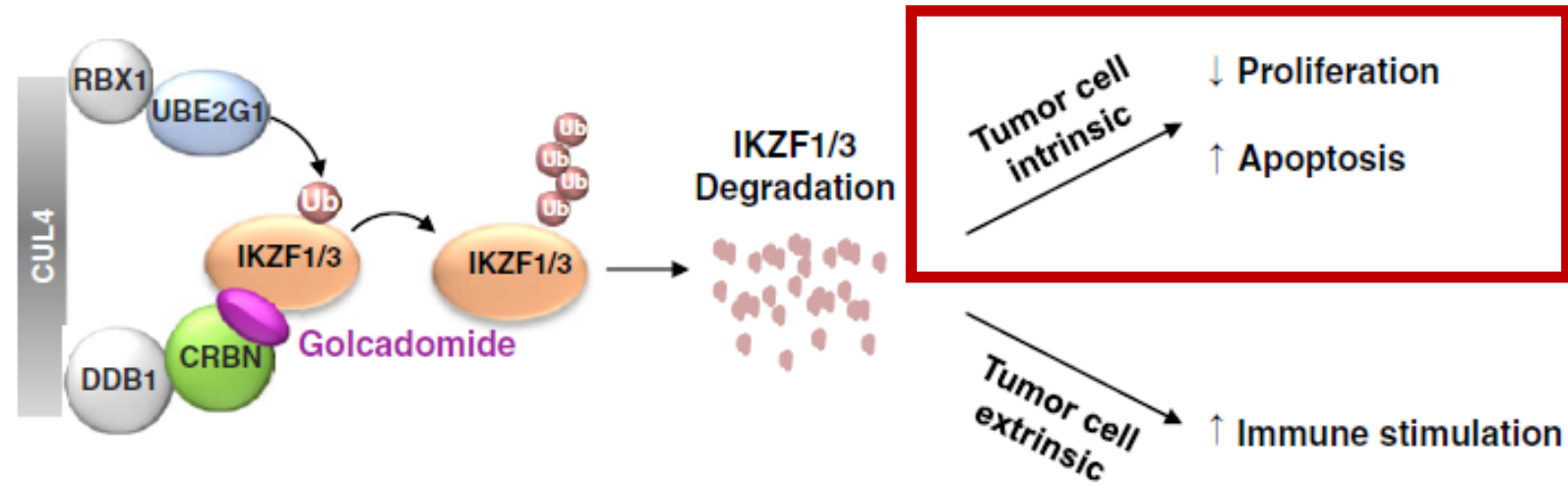
~10-100 fold potency



Potency of CELMoDs in the induction of Ikaros degradation compared to classical IMiDs:
golcadomide > iberdomide > avadomide >
pomalidomide > lenalidomide.









Blood 146 (2025) 66–68



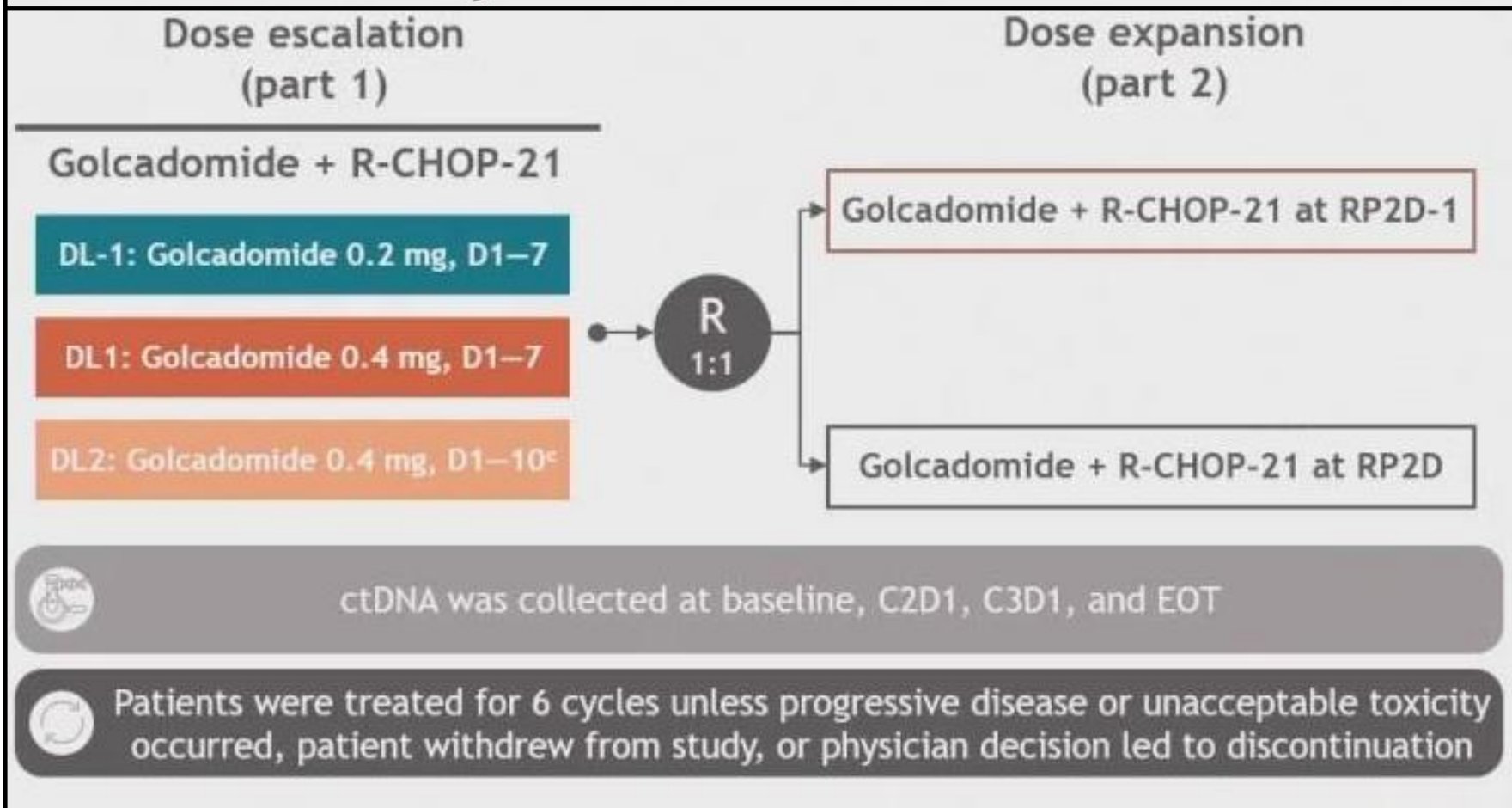
The 67th ASH Annual Meeting Abstracts

ORAL

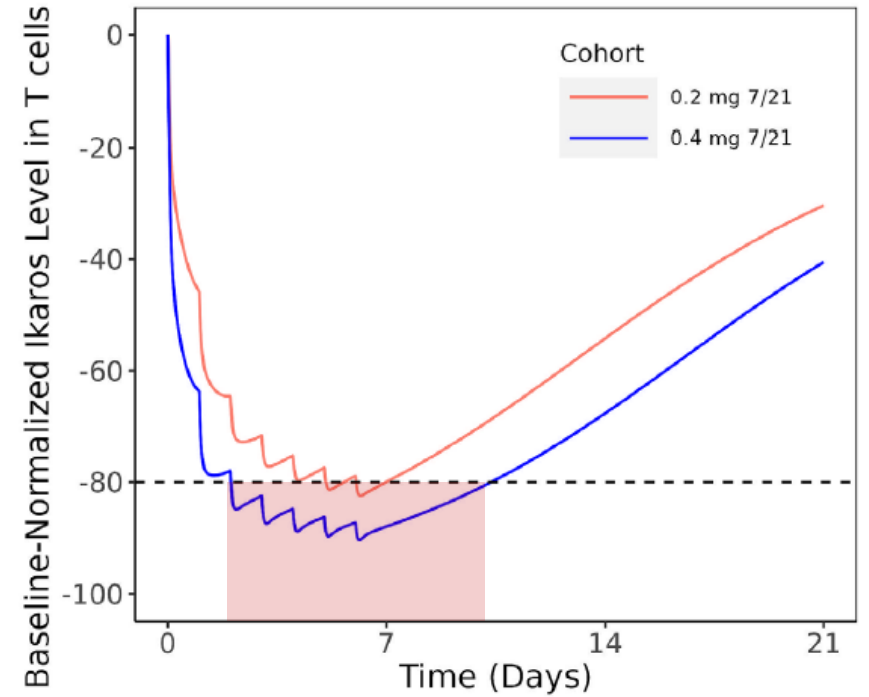
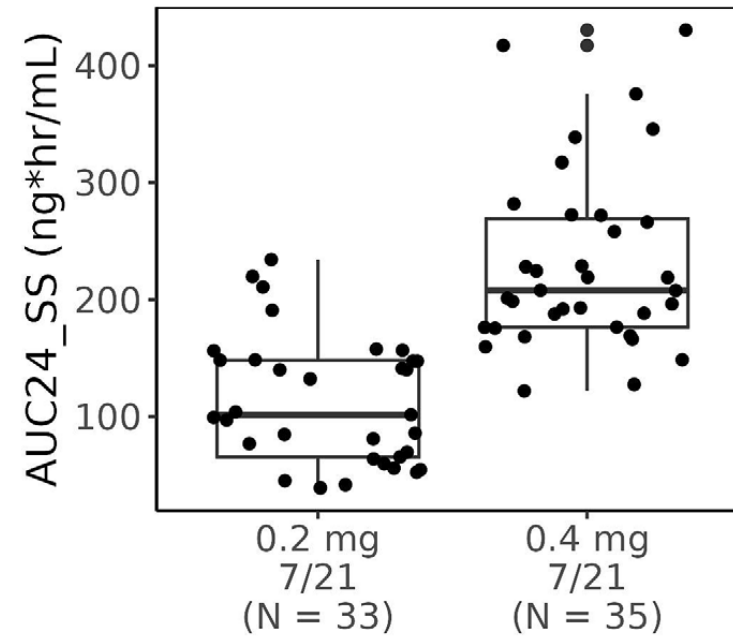
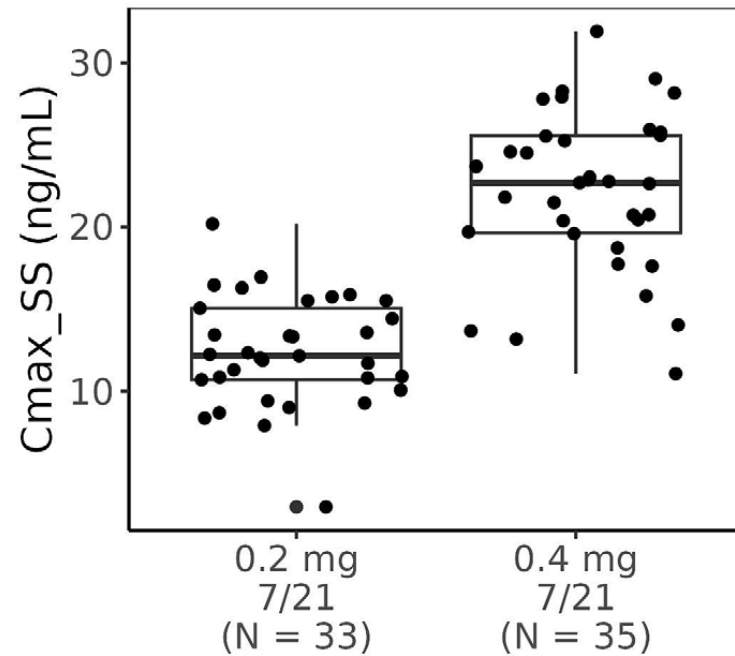
629. AGGRESSIVE LYMPHOMAS, IMMUNOTHERAPY INCLUDING BISPECIFIC ANTIBODIES

Mosunetuzumab (Mosun) or glofitamab (Glofit) in combination with golcadomide (Golca) demonstrates a manageable safety profile and encouraging efficacy in patients with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL)

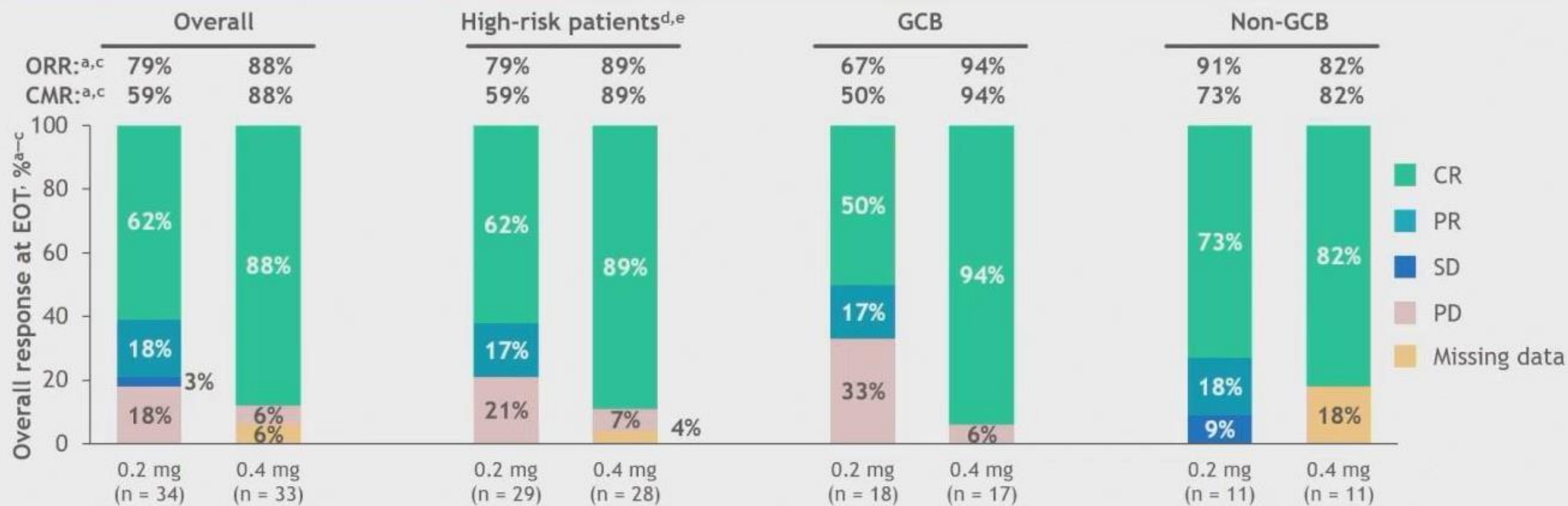
Golcadomide, a Potential, First-In-Class, Oral CELMoD™ Agent, Plus R-CHOP in Patients With Previously Untreated Aggressive B-Cell Lymphoma: 24-Month Efficacy Results



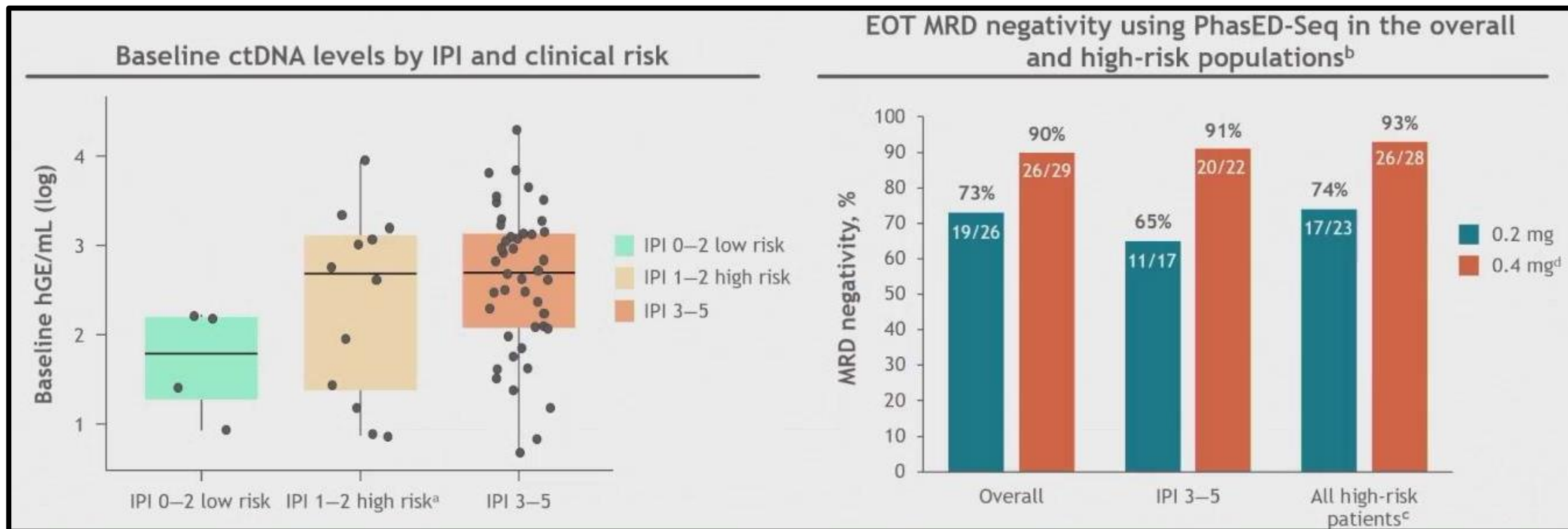
PK/PD informing of GOLCA dose



Golcadomide 0.4 mg + R-CHOP resulted in high complete response rates



Median (range) follow-up: 24.1 (0.7–34.4) months



GOLSEEK-1 Phase 3 Study Design.



Patients
N ≈ 850

Key eligibility criteria

- Age 18-80 years
- Previously untreated LBCL by WHO 2022 classification^a
- Ann Arbor stage II-IV disease
- IPI score
 - ≥ 3
 - 1 or 2 with LDH $> 1.3 \times$ ULN and/or bulky disease^b
- Measurable disease by Lugano classification^c
- No other lymphoma subtypes
- No lymphoma involvement in CNS

Screening:
 ≤ 4 weeks

R
1:1

Stratified by:

- IPI score
 - IPI 1-2 (with high-risk factors) + IPI 3
 - IPI 4-5
- Bulky disease
 - ≥ 7 cm
 - < 7 cm

Golcadomide + R-CHOP

× 6 cycles

(golcadomide 0.4 mg;
day 1-7 of each 21-day cycle)

Placebo + R-CHOP

× 6 cycles

(placebo; day 1-7 of each
21-day cycle)



Primary endpoint

- PFS by investigator based on Lugano Response Criteria



Key secondary endpoints

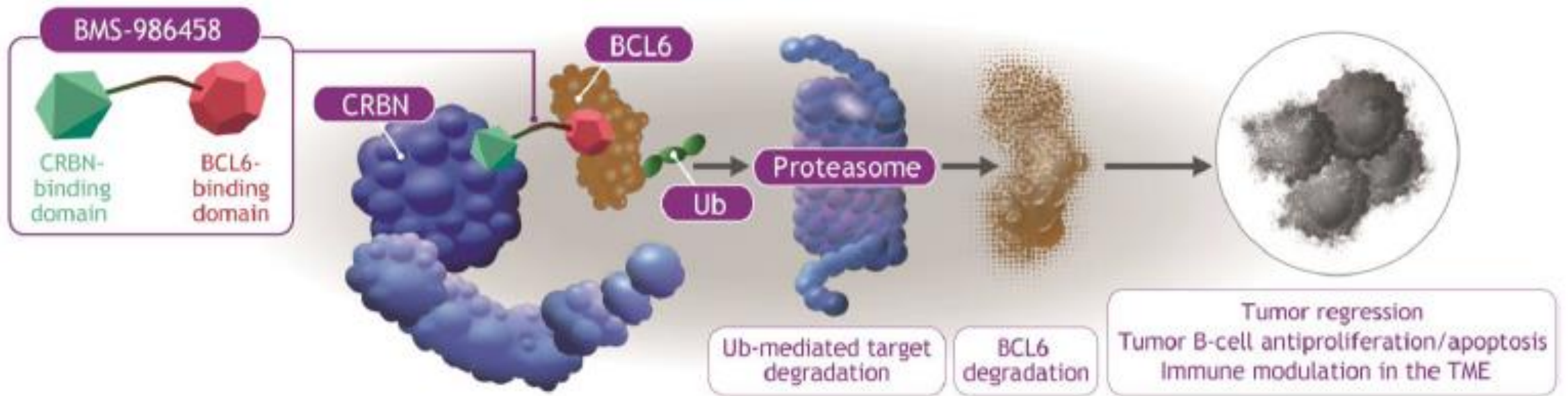
- PFS (non-high-grade BCL)
- OS
- EFS by investigator
- CMR by IRAC
- MRD-negativity rate (PhaseED-Seq)

Other (select) secondary endpoints

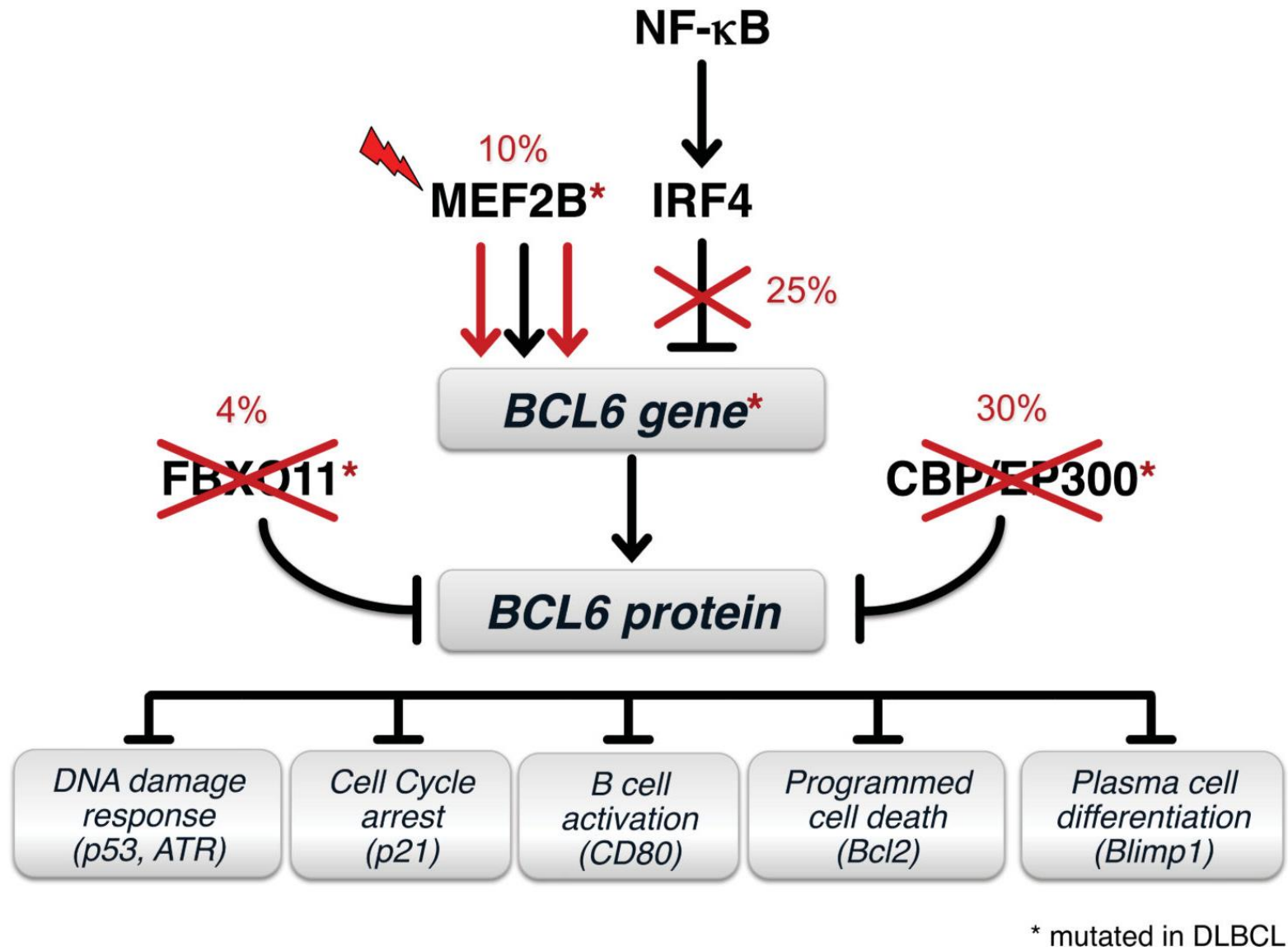
- PFS by IRAC
- OR by investigator
- CMR by investigator
- DOR
- HRQoL
- Safety

PROTAC

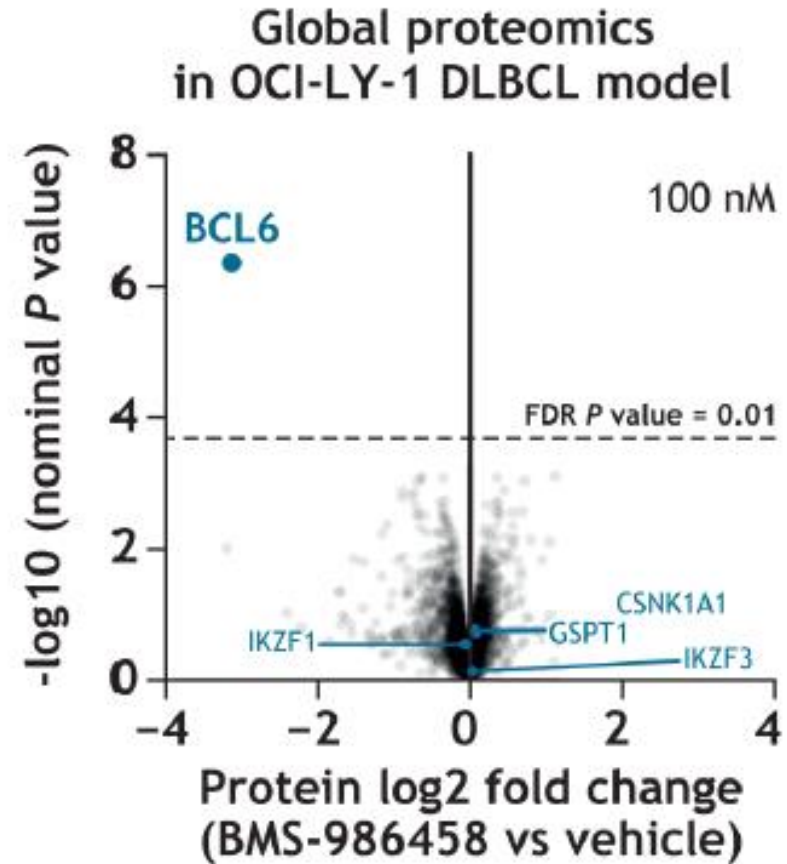
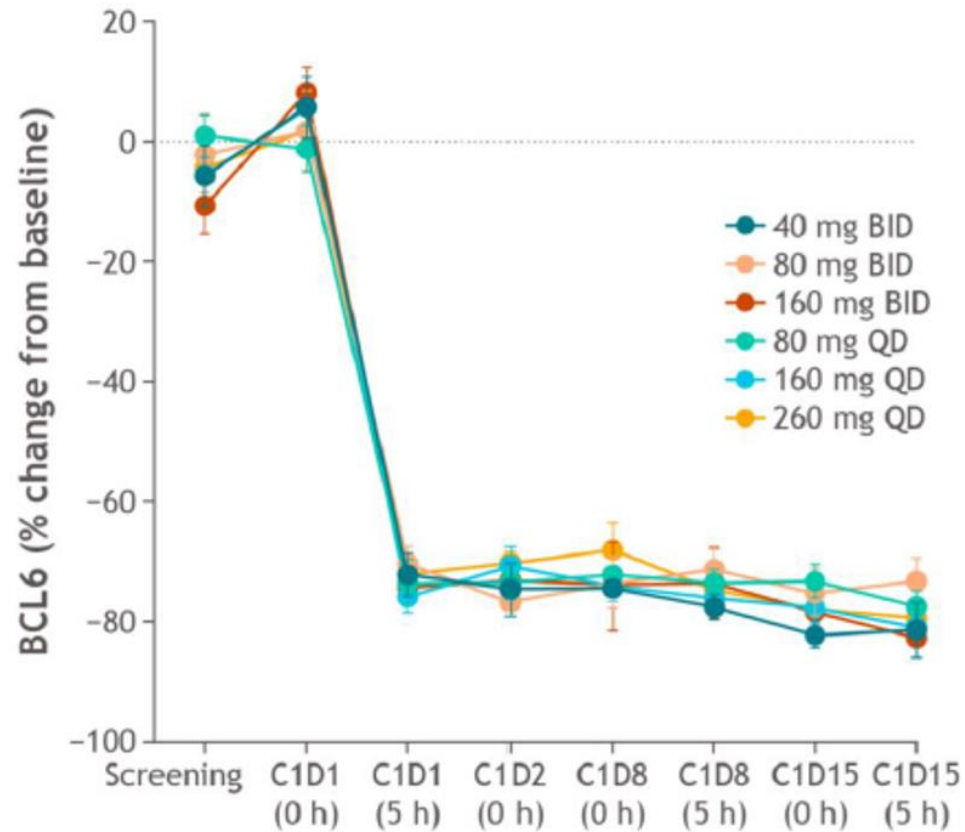
(PROteolysis-TArgeting Chimera)



Morschhauser et al. ASH 2025



PD INFORMING OF SELECTIVITY

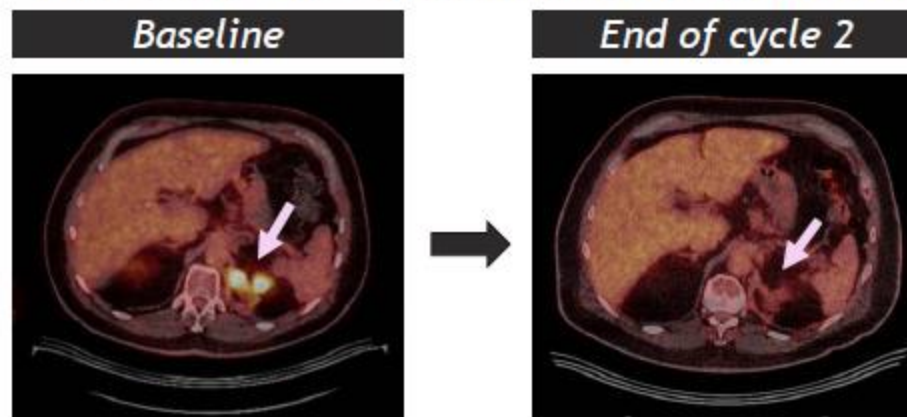


Morschhauser et al. ASH 2025

Example of metabolic responses in DLBCL

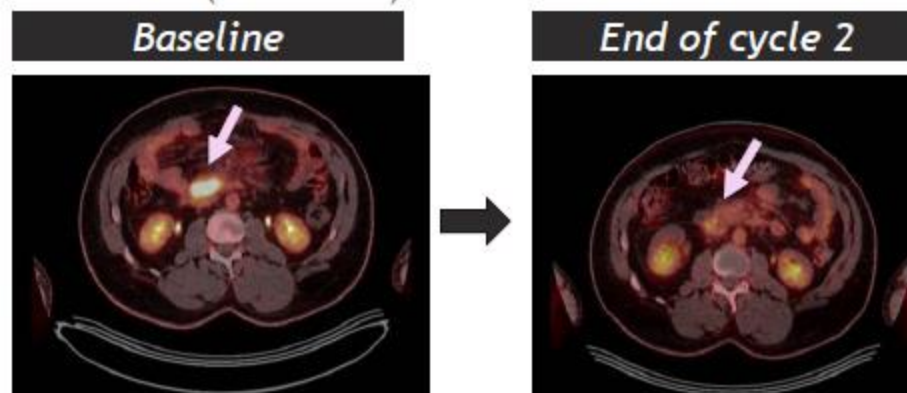
R/R DLBCL, 260 mg QD, 4 prior lines of therapy

- Liso-cel (BOR: CMR), glofitamab (BOR: PMR)



R/R DLBCL, 260 mg QD, 3 prior lines of therapy

- Axi-cel (BOR: PD)



Some conclusions

- Patients vs drugs : exhaustion
- Degrade old targets with new immunomodulators
- Degrade novel targets with new drugs
- PK/PD informing of schedule, dose & selectivity