

Optimal Management of Extensive SCLC (1st and 2nd Line)

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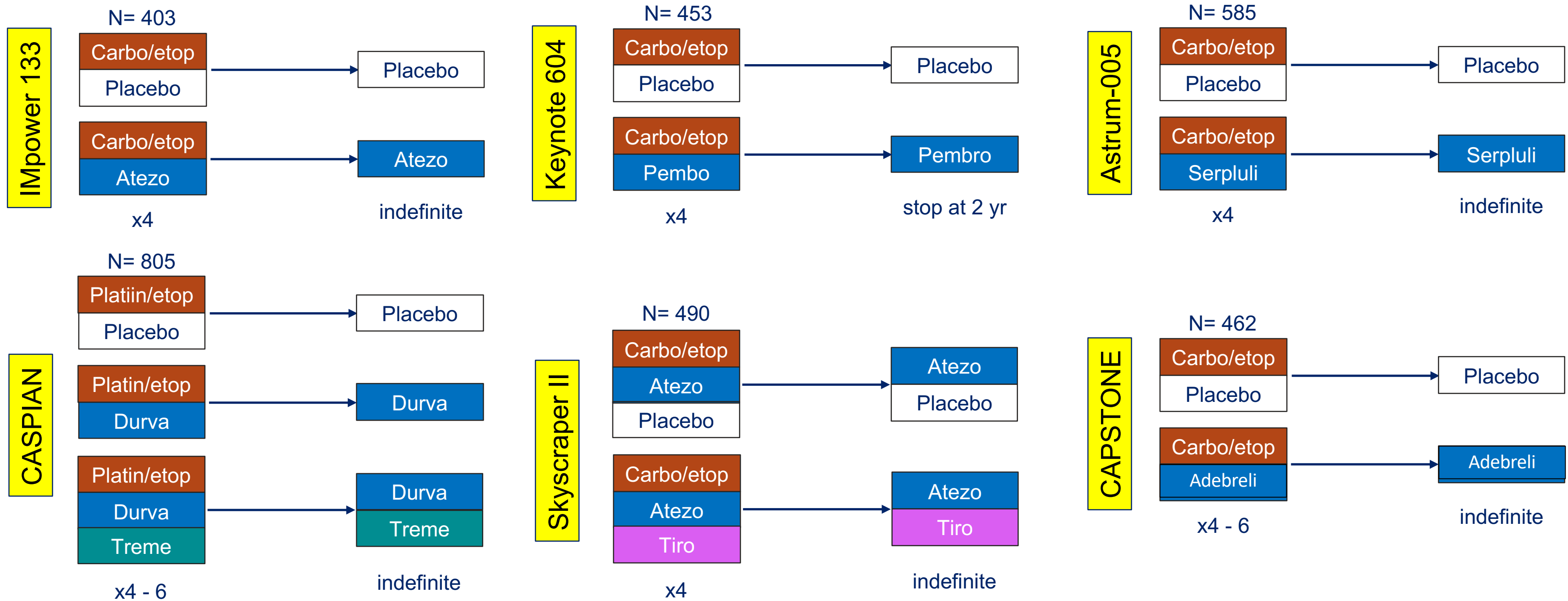


Memorial Sloan Kettering
Cancer Center

Are we making significant progress in treating SCLC?

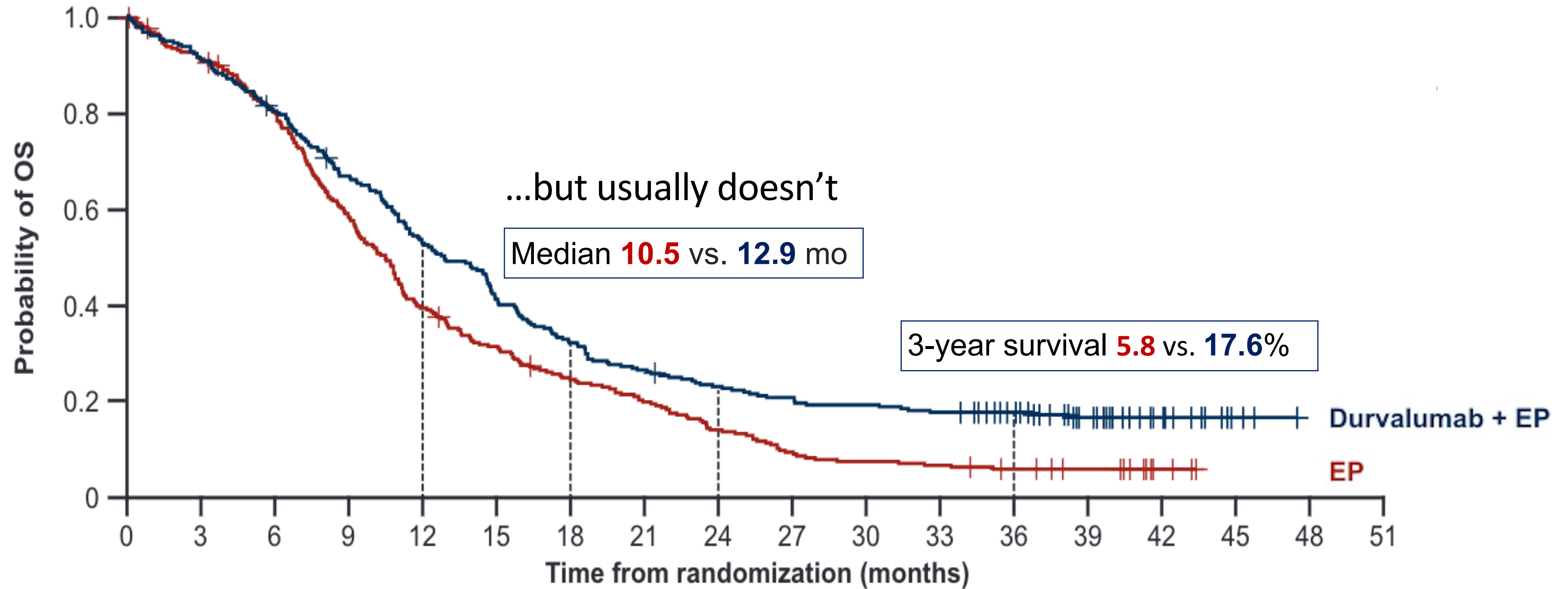
Yes and no...

Phase III clinical trials of ICI in SCLC (3198 patients... lessons?)



Horn et al., *N Engl J Med* 2018; Paz-Ares et al., *ESMO Open* 2022; Rudin et al., *J Clin Oncol* 2021; Rudin et al., *ASCO* 2022; Cheng et al., *JAMA* 2022, Wang et al., *Lancet Oncol* 2022

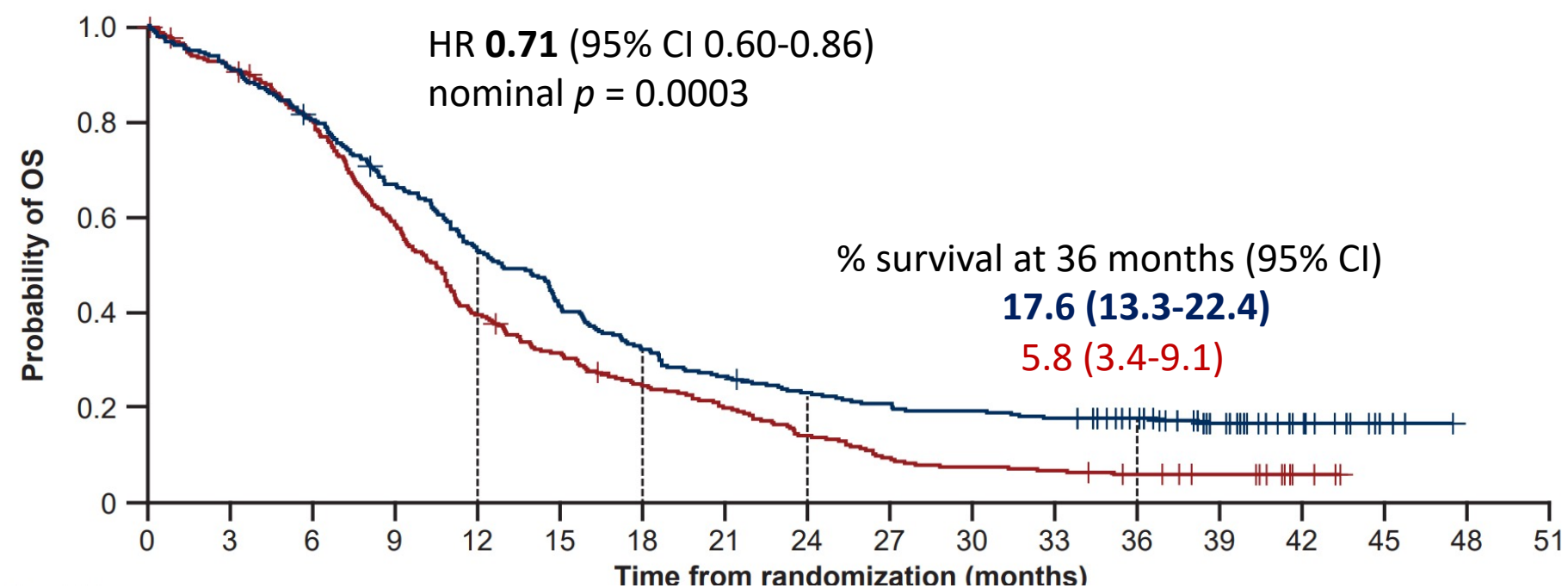
Immunotherapy can work...



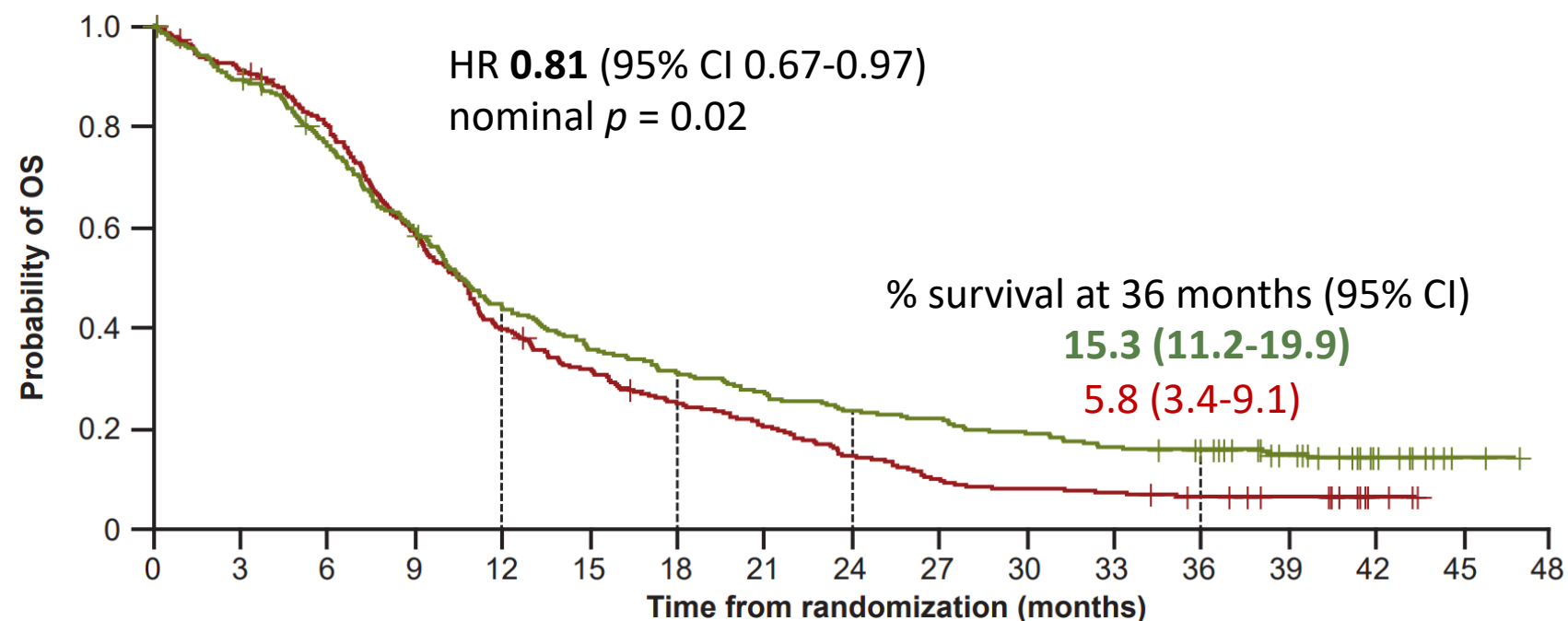
Blocking a second T cell checkpoints doesn't work

CASPIAN

EP +/-
durvalumab

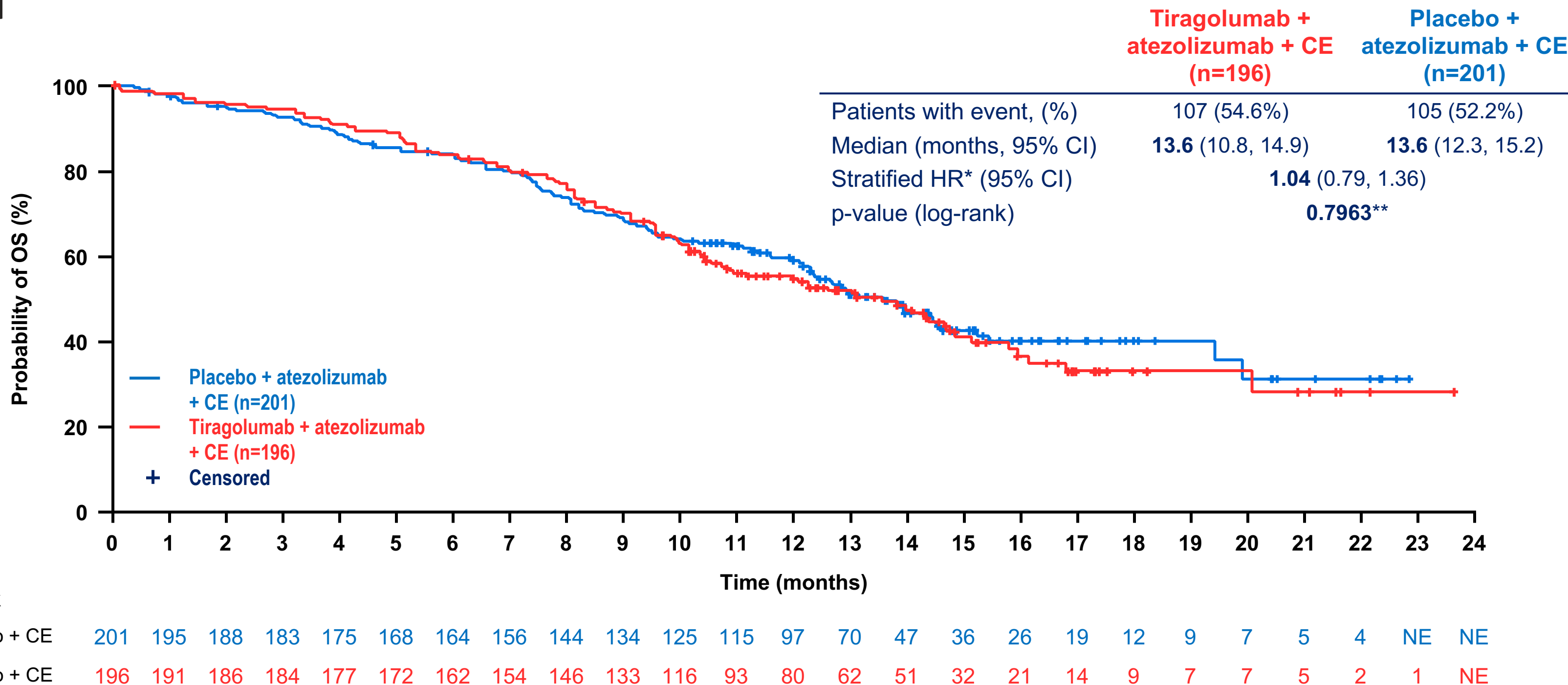


EP +/-
durvalumab/tremelimumab

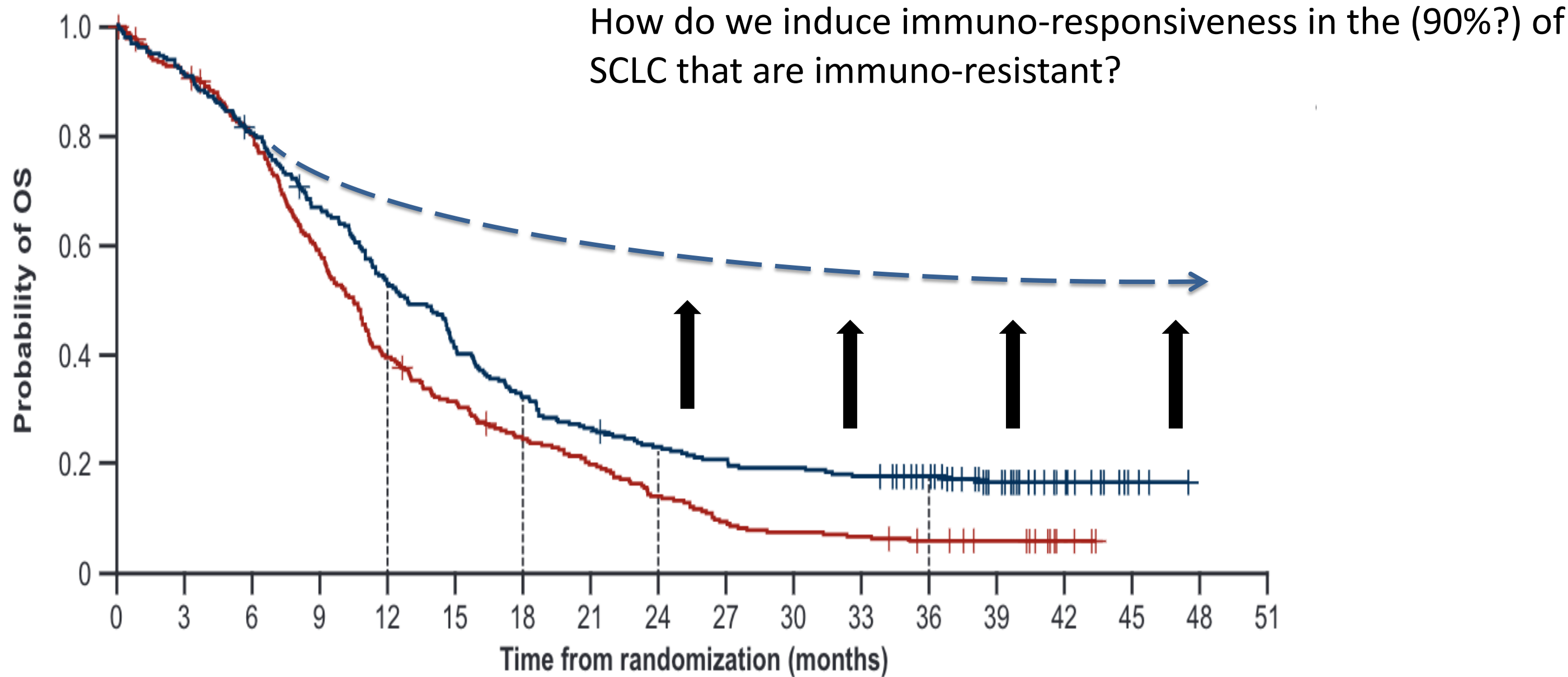


Blocking a third T cell checkpoints doesn't work

Skyscraper II



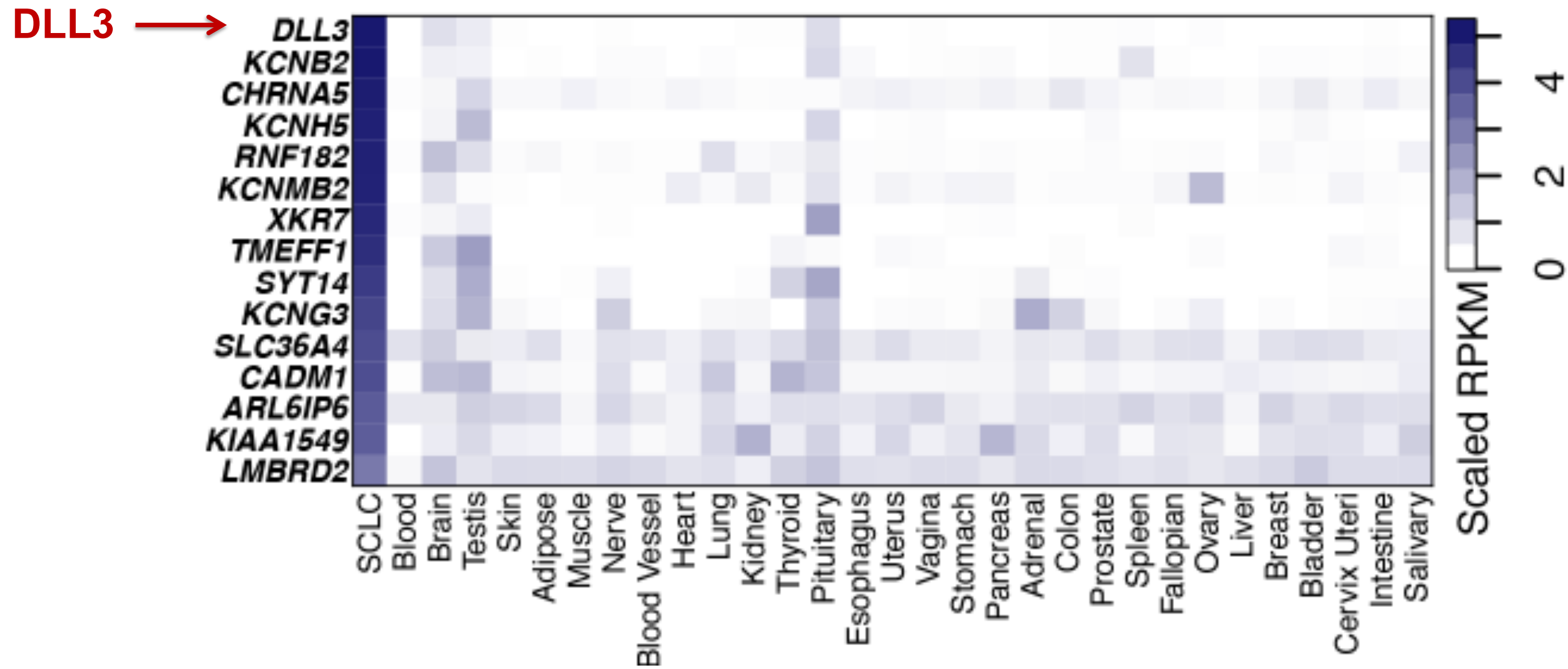
How do we raise the tail of this curve?



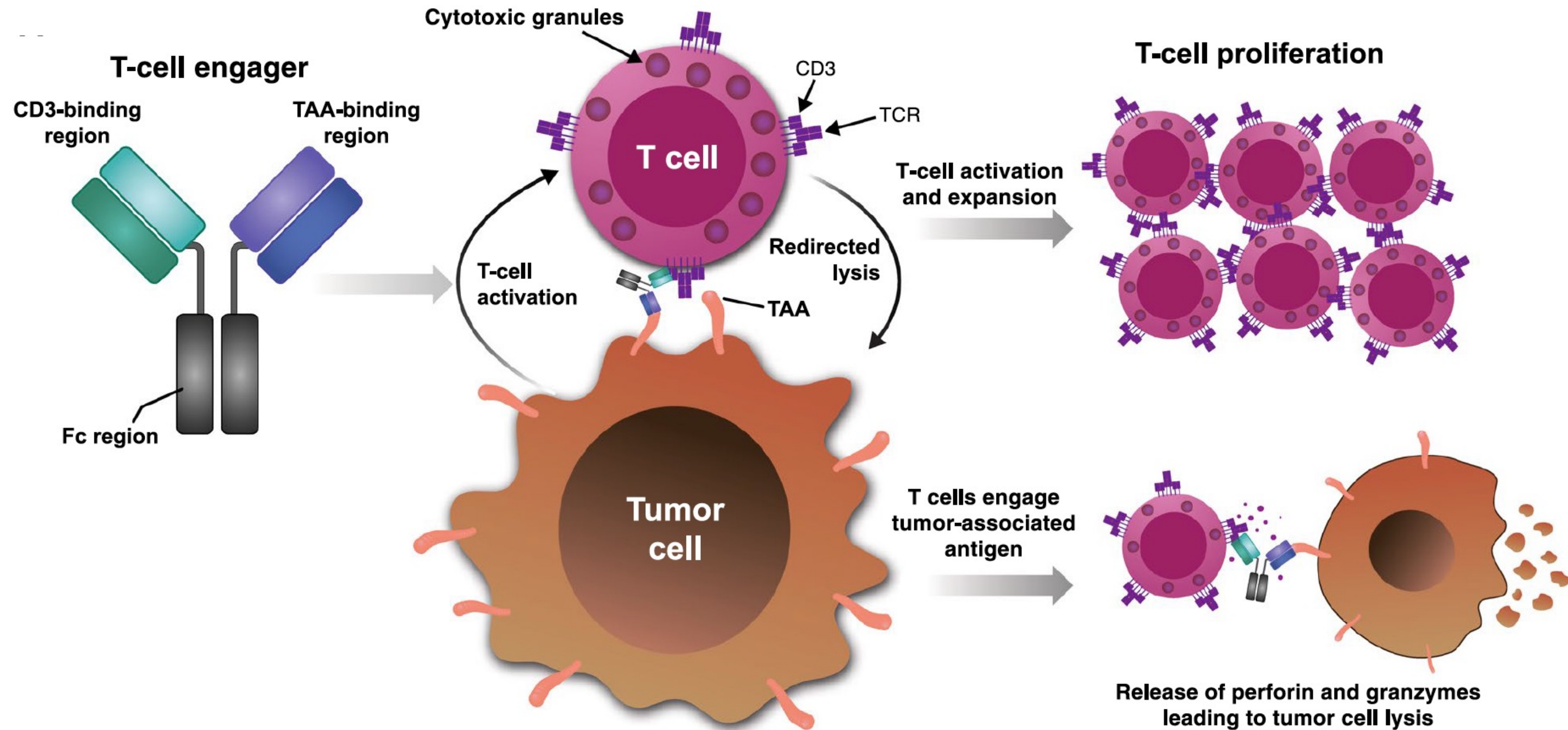
Antibody therapeutics targeting cell surface determinants of SCLC

Surface proteome of SCLC – DLL3 stands out

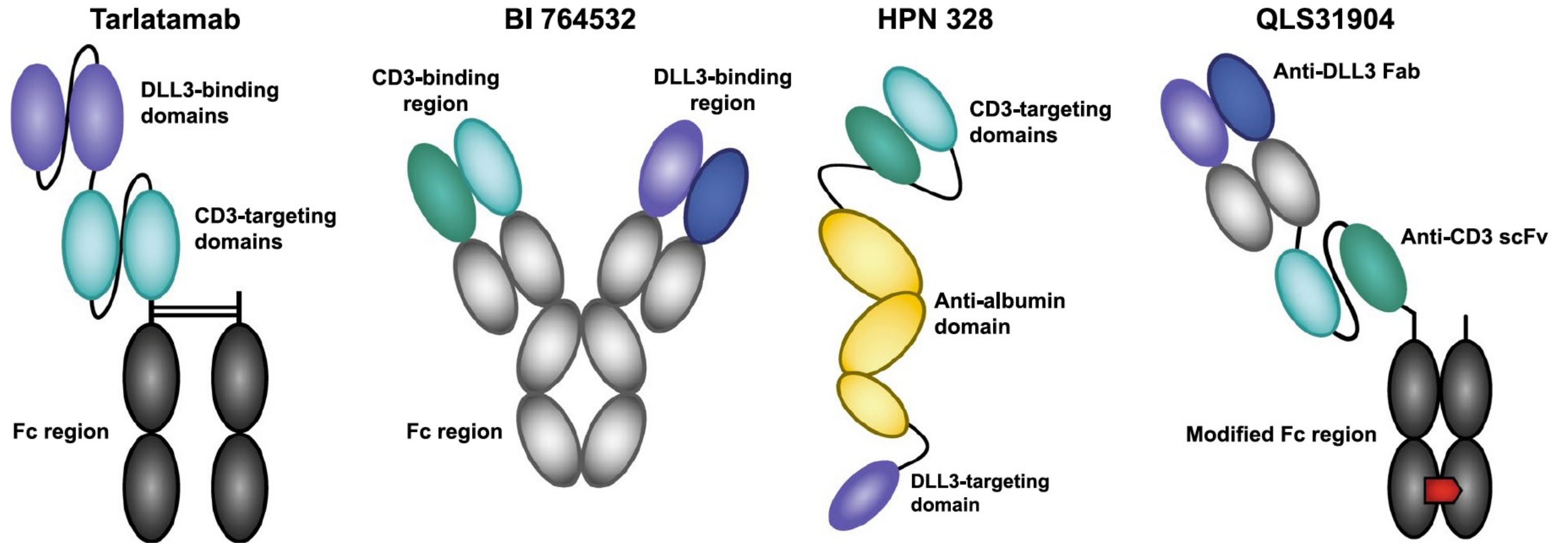
High tumor specificity of cell surface expression



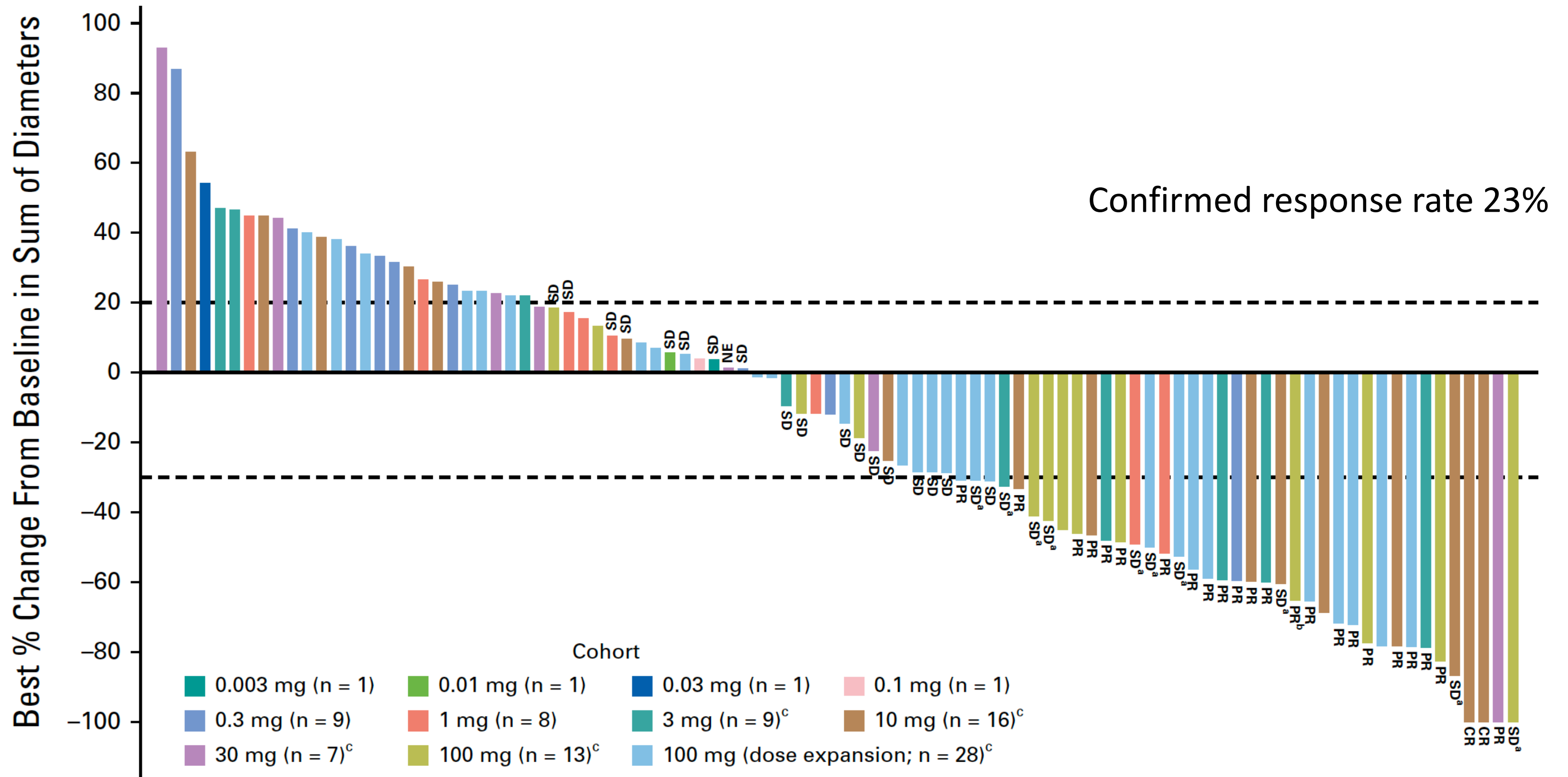
Bi-specific T-cell engagers (BiTEs): bringing the T cell to the tumor



Many BiTEs, many flavors



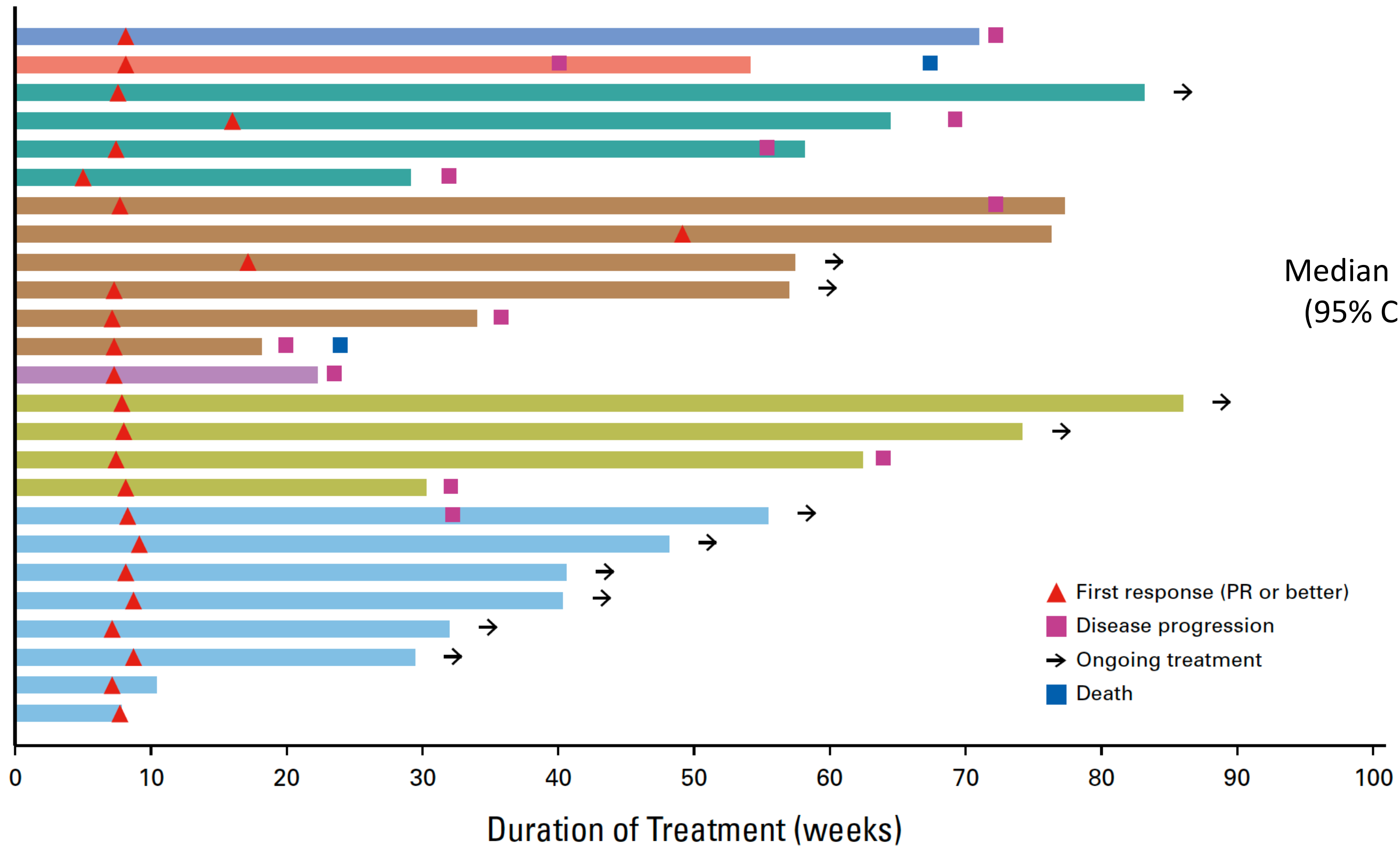
Tarlatamab response in patients with treated SCLC



Durability of tarlatamab responses in SCLC

Duration of Response in Confirmed Responders (n=25)

Median DOR 12.3 mo
(95% CI 6.6 – 14.9)



0.3 mg (n = 1) 1 mg (n = 1) 3 mg (n = 4)^c 10 mg (n = 6)^c
 30 mg (n = 1)^c 100 mg (n = 4)^c 100 mg (dose expansion; n = 8)^c

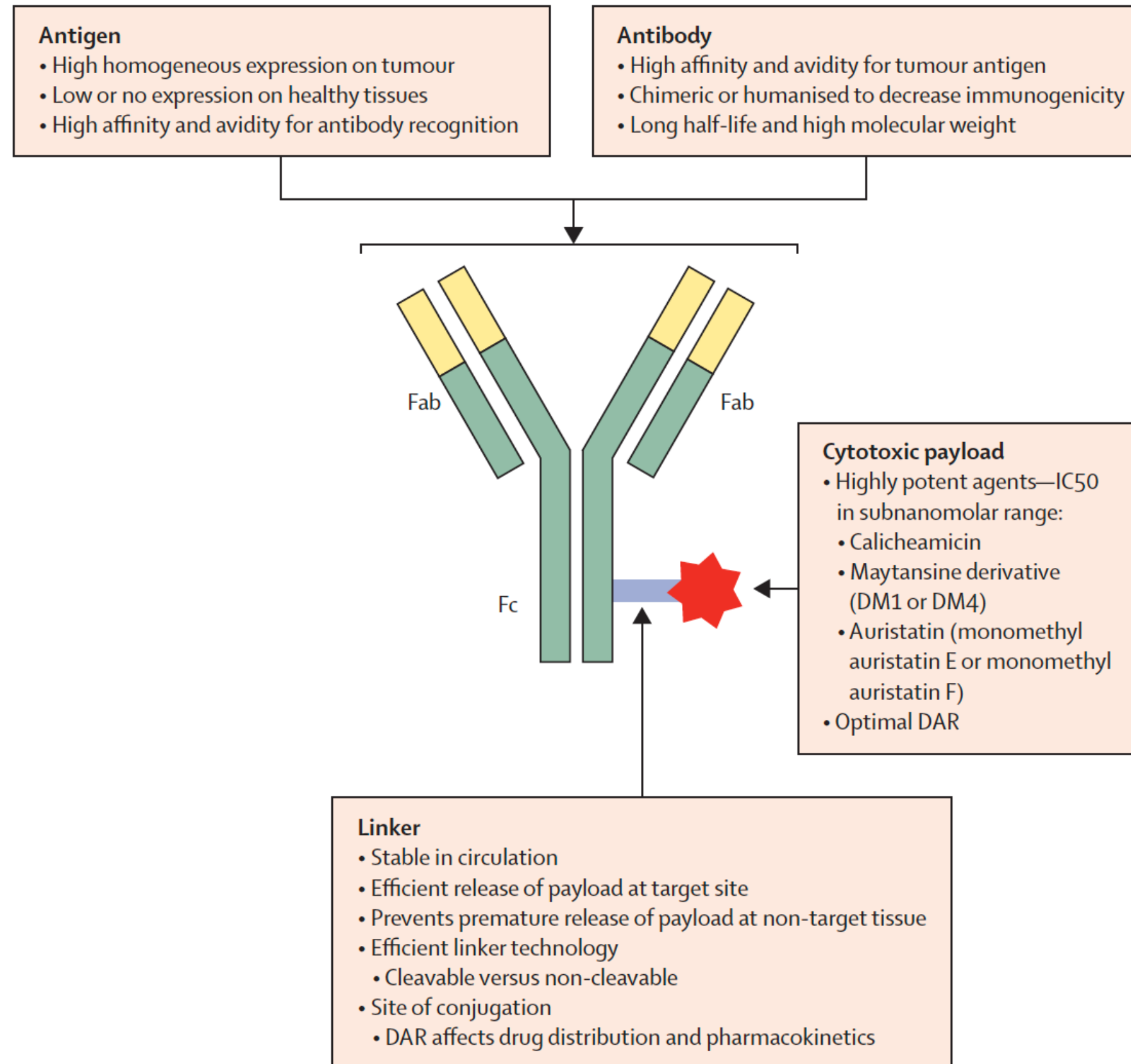
Antibody-based DLL3-targeted therapies in development for SCLC

Agent	Mechanism of action	Status
Antibody-drug conjugates		
Rovalpituzumab tesirine	ADC targeting DLL3	Terminated
SC-002	ADC targeting DLL3	Terminated
Chimeric antigen receptors		
DLL3-CAR-NK cells	Anti-DLL3-transduced natural killer cells	Recruiting (Phase 1)
AMG 119	Anti-DLL3 transduced autologous T cells	Suspended (Phase 1)
T-cell engagers		
Tarlatamab	DLL3/CD3 BiTE	Recruiting (Phase 2)
BI 764532	DLL3/CD3 BiTE	Recruiting (Phase 1)
HPN328	DLL3/CD3/Albumin TriTAC	Recruiting (Phase 1/2)
RO7616789	DLL3/CD3/CD137 TriTAC	Recruiting (Phase 1)
PT217	DLL3/CD47 BiTE	Not yet recruiting
QLS31904	DLL3/CD3 BiTE	Not yet recruiting

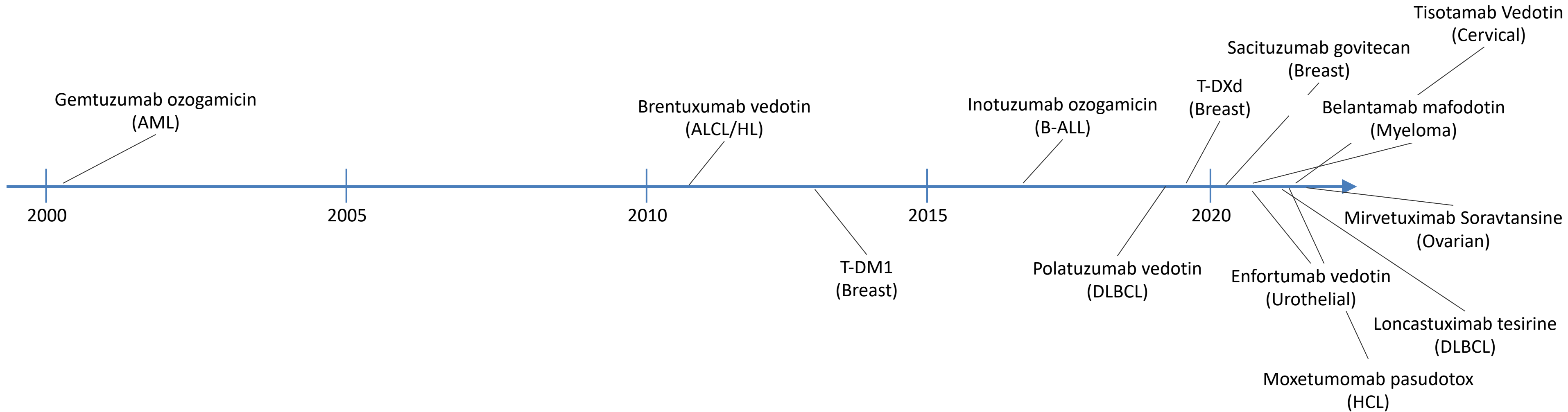
Antibody drug conjugates

- Antibody drug conjugates assessed in SCLC

- anti-DLL3
- anti-CD56
- anti-TROP2
- anti-CD276
- anti-SEZ6

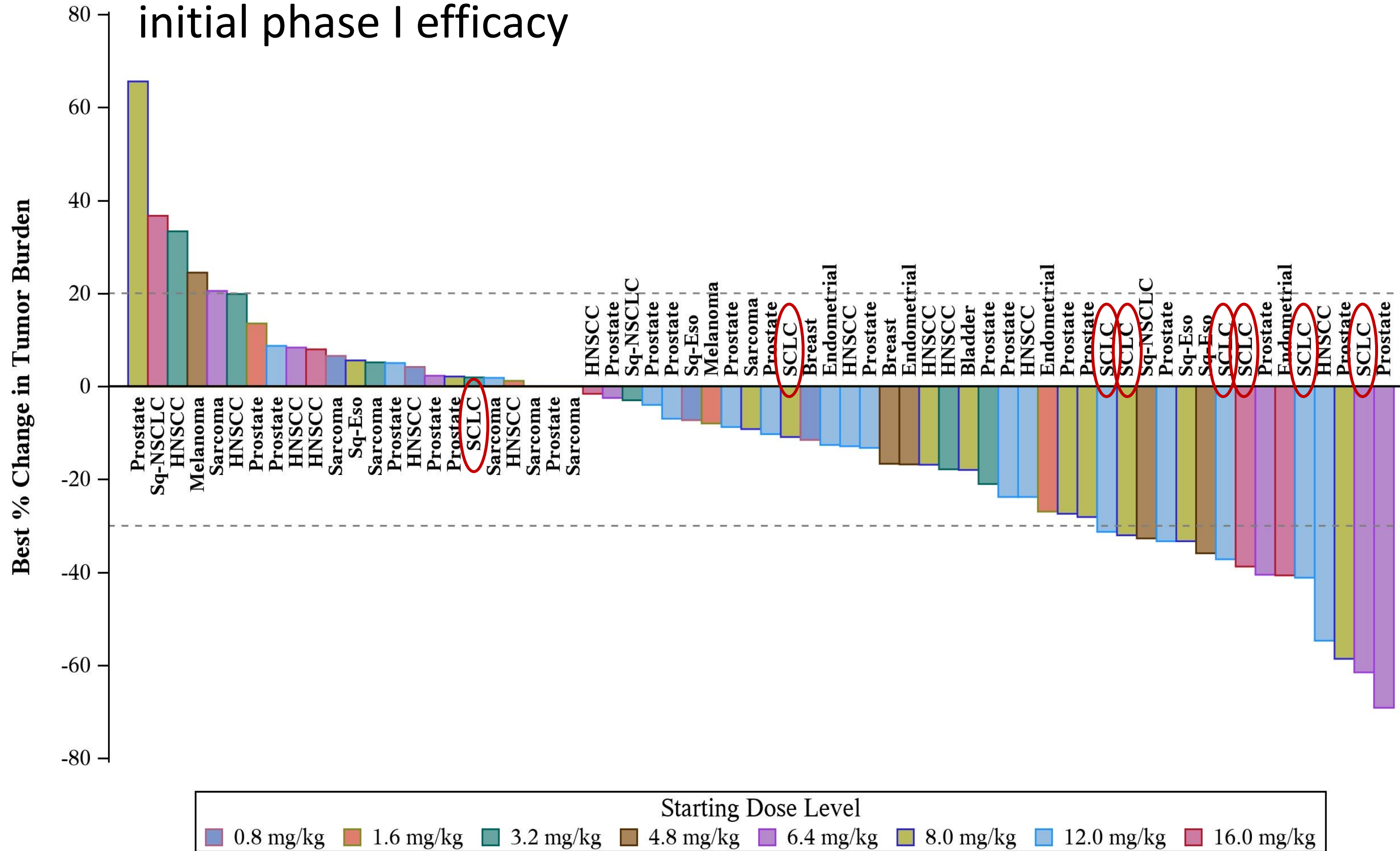


ADCs are having a moment...

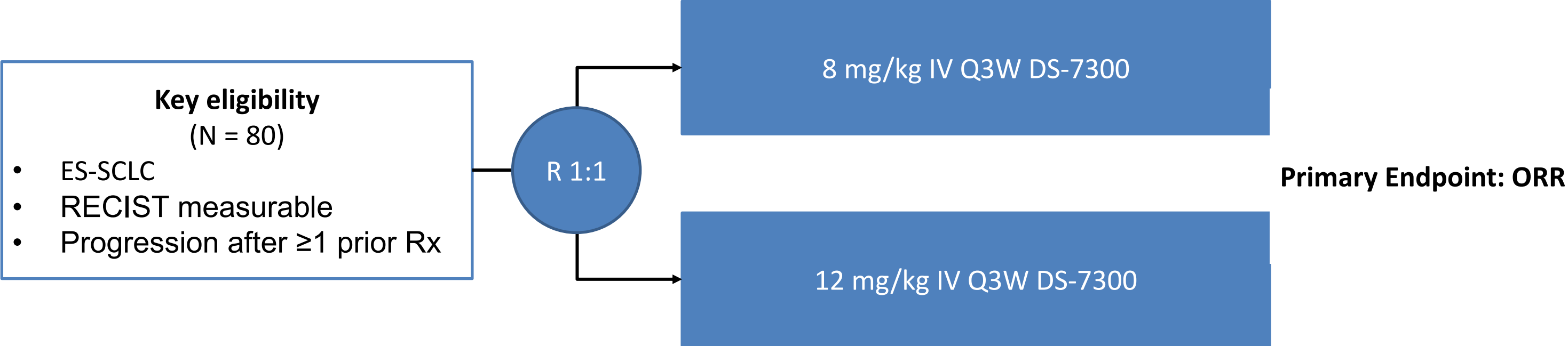


Over **300** ADCs are in preclinical/clinical development

CD276 (B7-H3)-directed ADC DS-7300: initial phase I efficacy



DS-7300 dose-finding study in patients with recurrent SCLC



Take home

- Anti-PD-(L)1 blockade has changed our first-line standard of care for ES-SCLC
 - Targeting T-cell checkpoints CTLA4 or TIGIT has not provided additional benefit
- Multiple classes of antibody-based therapies are in the clinic, with more on the way
 - Blocking antibodies
 - Antibody-drug conjugates
 - T cell engagers
 - CAR T constructs
 - Radioimmunoconjugates
- ADCs and TCEs are showing promising activity in patients with recurrent SCLC

