

ASGO Webinar #53

ADCs in Gynecologic Cancers

Discussion

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10/31/2024

Questions

1. Patient selection and treatment setting?
2. Combination with other regimen? (chemo/ICIs/targeted therapy)
3. Can we move forward to 1st line treatment?
4. How to reduce the toxicities and deal with those unfamiliar AEs?

Phase II innovaTV 204

R/M cervical cancer

PD during/after doublet chemo with Bev (if eligible)

≤2 prior lines

PS ECOG 0-1

(N = 102, treated 101)

Phase III innovaTV 301

R/M cervical cancer

PD on/after chemo doublet ± Bev and anti-PD-(L)1

eligible and available

≤2 prior lines

(N = 502)

Phase II SORAYA Trial

HGS PROC (TFI_p >3-≤6m if 1 prior line, ≤6m if 2-3 prior lines)

1° platinum refractory (TFI_p ≤3m) excluded

FR_a high (≥75%, 2+-3+ membrane staining [Ventana]) [PS2+]

Prior Bev required

1-3 prior lines

Prior PARPi; *BRCA* mutations allowed

(N = 106, 105 evaluable)

Phase III MIRASOL Trial

HGS PROC (TFI_p ≤6m)

1° platinum refractory (TFI_p ≤3m) excluded

FR_a high (≥75%, 2+-3+ membrane staining [Ventana]) [PS2+]

1-3 prior lines

Prior Bev and PARPi; *BRCA* mutations allowed

(N = 453)

DESTINY-PanTumor02

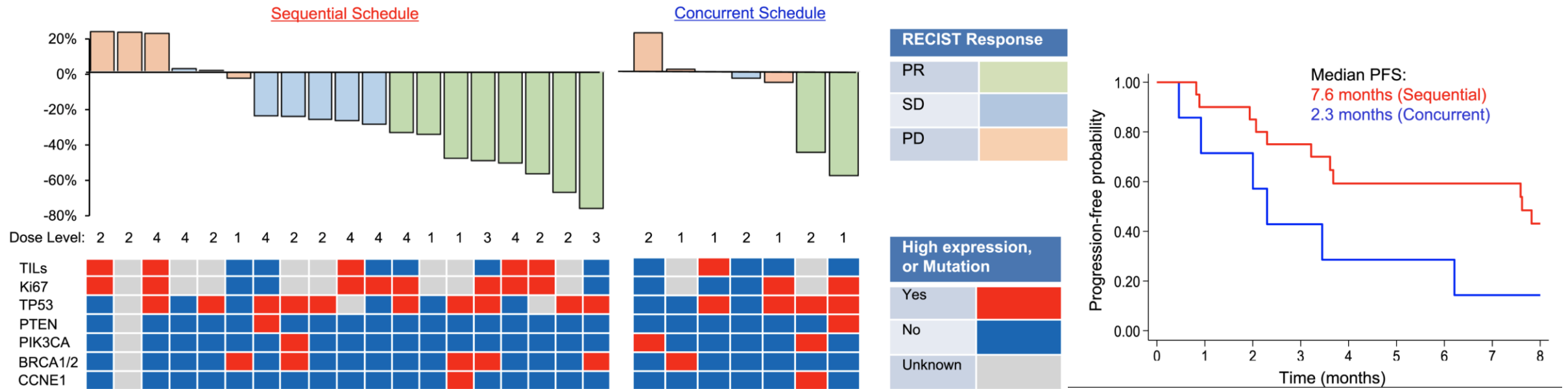
- Advanced solid tumors not eligible for curative therapy
- Second-line plus patient population
- HER2 expression (IHC 3+ or 2+)
 - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer scoring¹)*
 - Cervical cohort was expanded to include five IHC 1+ patients
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0-1

Recurrent/metastatic, heavily pretreated, refractory
Absolute PFS/OS improvement is limited

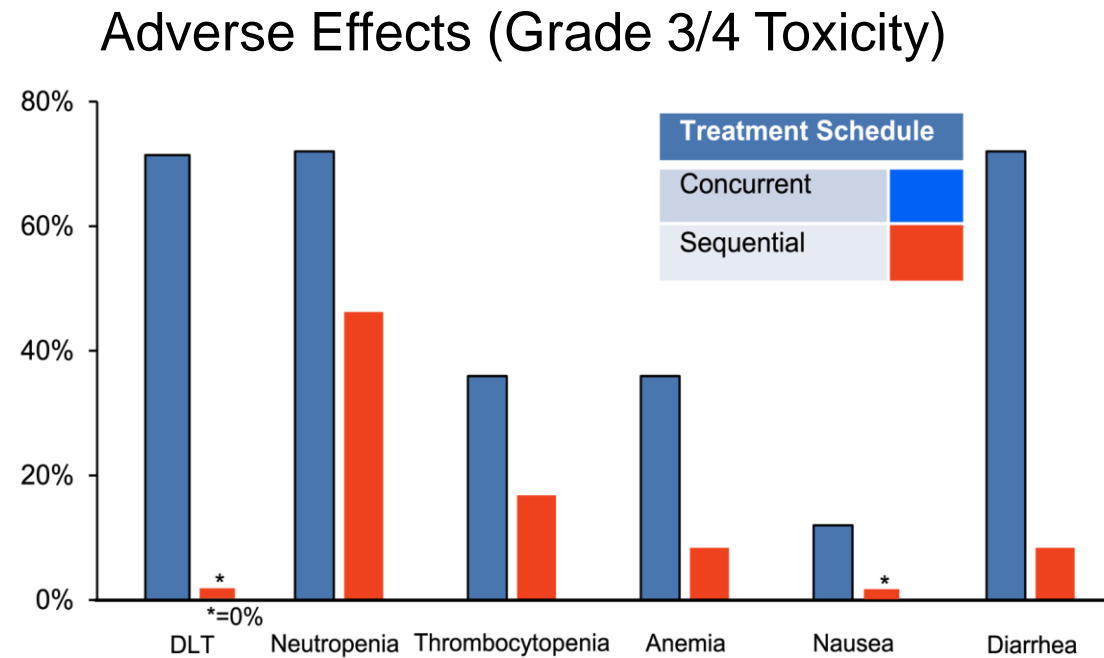
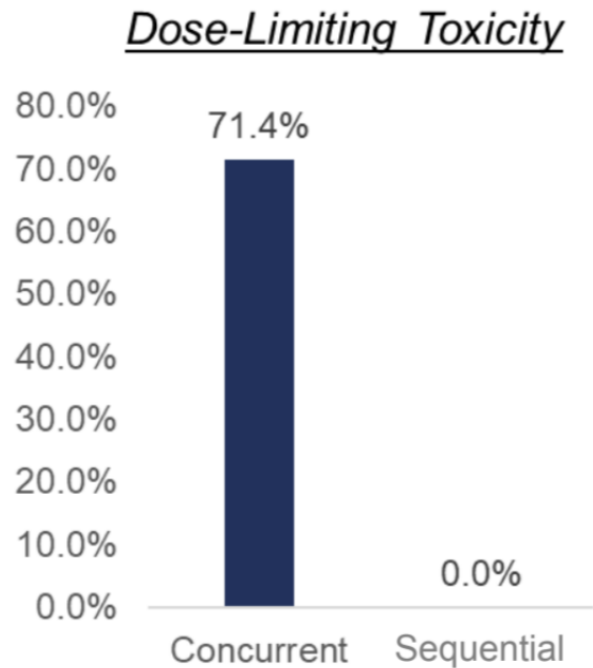
Sequential? Combination?

Research in Breast cancer

Sacituzumab Govitecan and Talazoparib efficacy of concurrent vs sequential schedule



Sacituzumab Govitecan and Talazoparib toxicity of concurrent vs sequential schedule



1st line setting – data from lung cancer

TROP2 ADCs with anti PD(L)1 mAbs

TROPION-Lung02

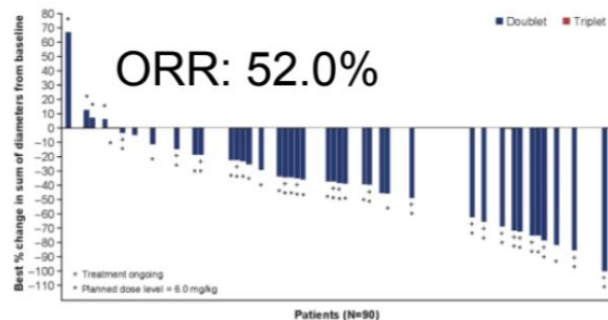
Key eligibility criteria

- Advanced/metastatic NSCLC
- Dose escalation^a: s2 lines of prior therapy^a
- Dose expansion: s1 line of platinum CT (cohorts 1 and 2)^a; Treatment-naïve (cohort 2, enrollment after June 30, 2022)^a; Treatment-naïve (cohorts 3–6)^a

Primary objectives: safety and tolerability

Secondary objectives: efficacy, PK, and antidrug antibodies

1L Patients Only	Dato-DXd (Q3W)	Pembro (Q3W)	Platinum CT (Q3W)	
Cohort 1 (n=2)	4 mg/kg	200 mg		Doublet 88% with PD-L1 <50%
Cohort 2 (n=40)	6 mg/kg	200 mg		
Cohort 3 (n=14)	4 mg/kg	200 mg	carboplatin AUC 5	Triplet
Cohort 4 (n=26)	6 mg/kg	200 mg	carboplatin AUC 5	
Cohort 5 (n=8)	4 mg/kg	200 mg	cisplatin 75 mg/m ²	
Cohort 6 (n=6)	6 mg/kg	200 mg	cisplatin 75 mg/m ²	



≥3 TRAEs 33%

EVOKE-02

Key eligibility criteria

- Squamous or nonsquamous stage IV NSCLC
- No known actionable genomic alterations
- Measurable disease per RECIST v1.1
- No prior treatment for mNSCLC
- ECOG PS 0–1
- PD-L1 TPS ≥50%

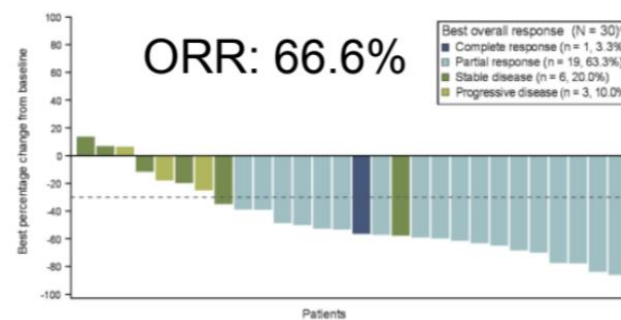
21-day cycles:

SG 10 mg/kg IV on day 1 and day 8 (until PD or unacceptable toxicity) + Pembro 200 mg IV on day 1 (up to 35 cycles)

End points

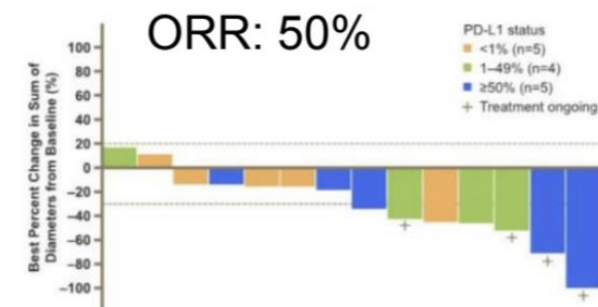
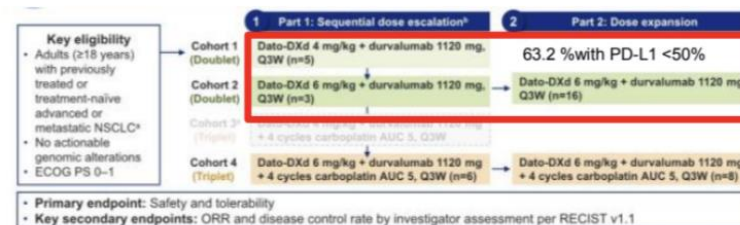
- Primary: ORR (IRC assessed)
- Secondary: PFS (IRC assessed), OS, DOR (IRC assessed), DCR (IRC assessed), and safety

^aPD-L1 status was determined locally or at the central laboratory by 22C3 assay. DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; IV, intravenous; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.



≥3 TRAEs 40%

TROPION-Lung04



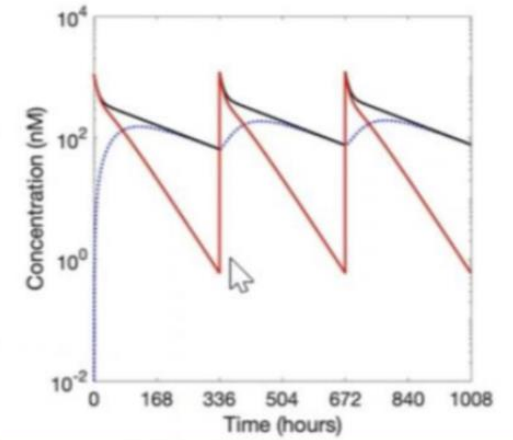
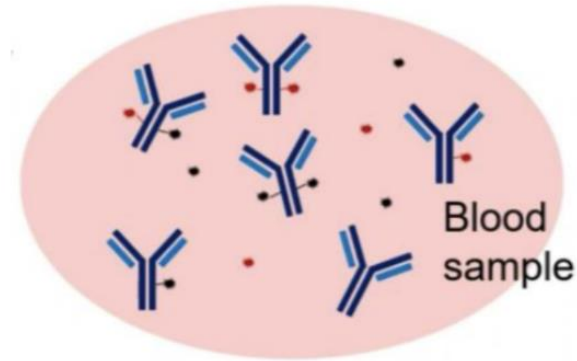
≥3 TRAEs 31.6%


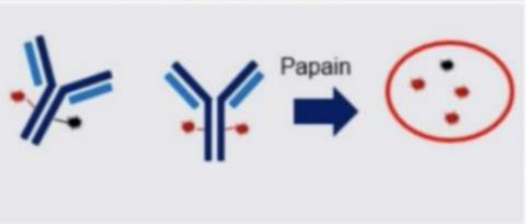

Adapted from Levy B, ASCO 2024; Patel JD, ASCO 2024; Papadopoulos KD, WCLC 2023

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Pharmacology

Assays and analytes overview

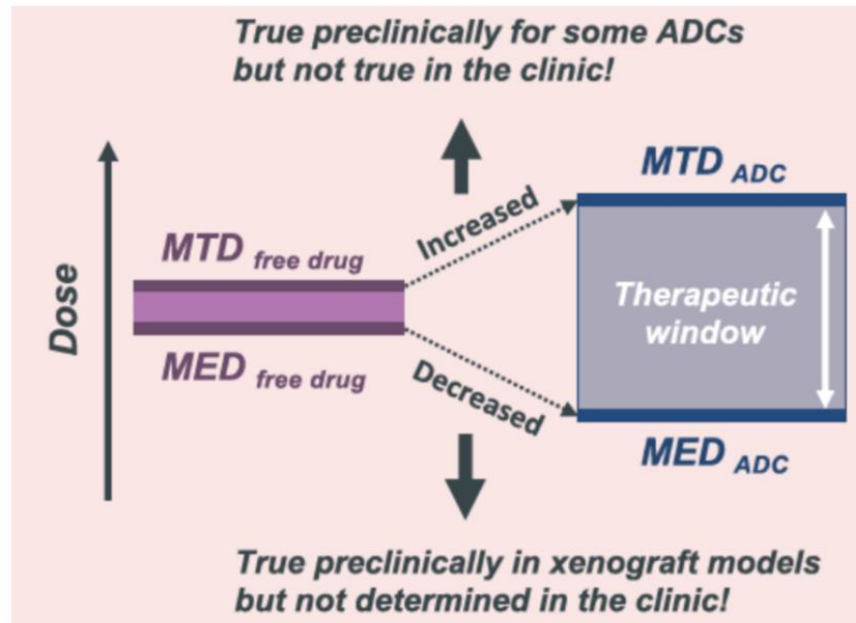


Assay Name	Matrix	Analytes	Assay principle	Importance
Total mAb	Serum		<ul style="list-style-type: none"> LBA Quantifying all mAb based material, independent of payload 	<ul style="list-style-type: none"> A measure for total drug related material in circulation, Regulatory requirement
PRA (conjugated payload)	Plasma		<ul style="list-style-type: none"> 3 Step Assay: <ol style="list-style-type: none"> Isolation of mAb related drug Incubation with papain Payload quantification by LC-MS/MS 	<ul style="list-style-type: none"> Direct and accurate measure of available active payload on the ADC, Should correlate with efficacy
Free (active) payload	Blood		<ul style="list-style-type: none"> Quantification of active unbound payload by LC-MS/MS, Blood is used based on the high blood:plasma distribution ratio 	<ul style="list-style-type: none"> May correlate with safety, Regulatory requirement

Preclinical data may not present the real clinical action

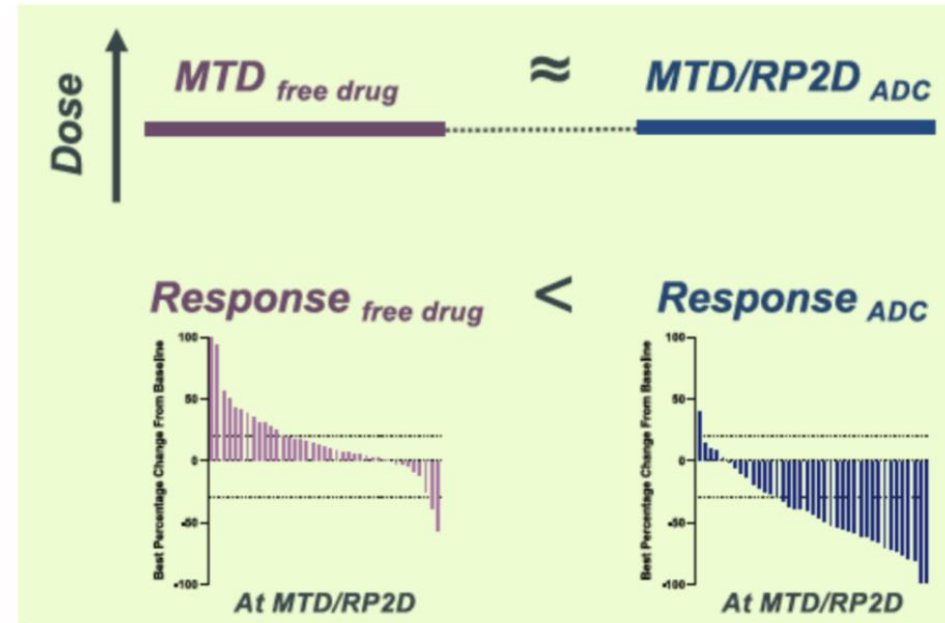
Revised representation of ADC therapeutic window

Current representation



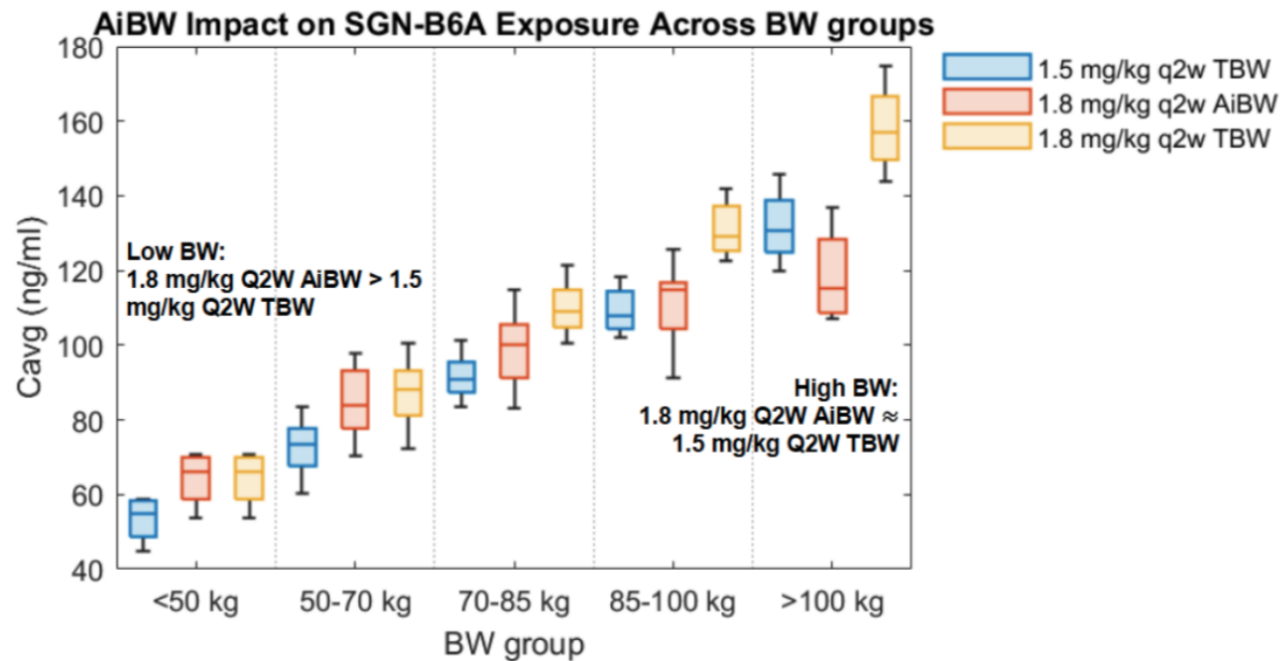
(based on preclinical data)

Revised representation

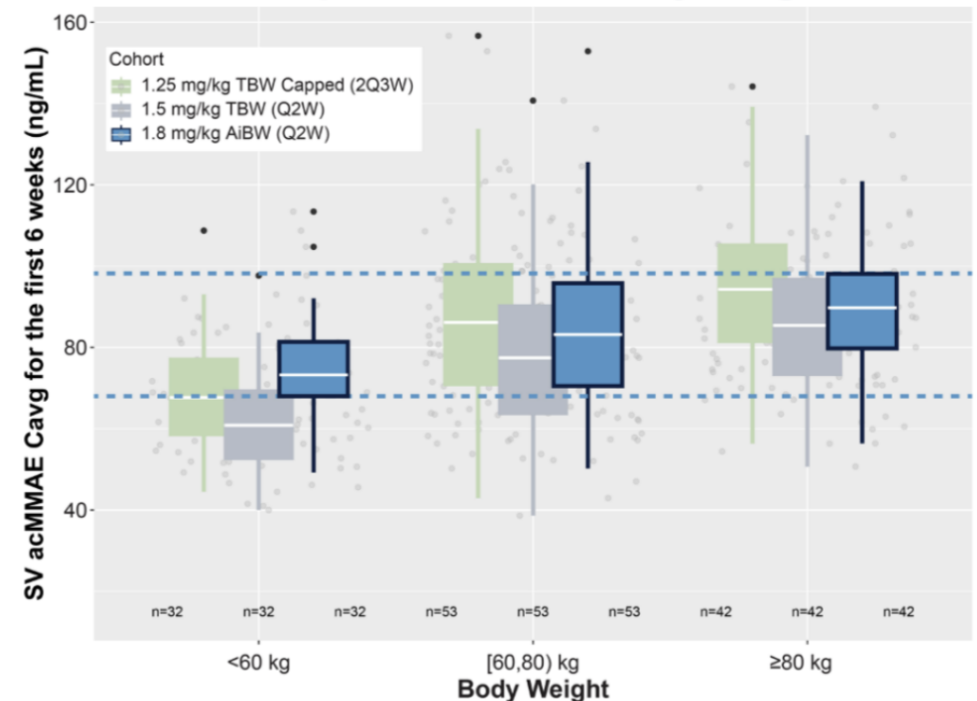


(based on emerging clinical data)

Dose adjustment need further evaluation. Clinical response is a consideration



Modeled SV Exposure Across Body Weight



Conclusions

- Treatment setting and patient selection is key to better response
- Combo and sequential treatment studies are warranted
- 1st line setting may be beneficial
- Efficacy and resistance mechanisms to ADCs are likely to be diverse given their multi-faceted mechanisms
- Joint clinical and translational research are in need to understand the MOA of ADCs, in term of treatment refinement and better outcomes