Farmaci anti-PD-L1 e anti-PD-1: quali differenze?

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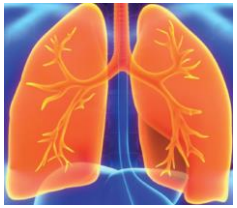
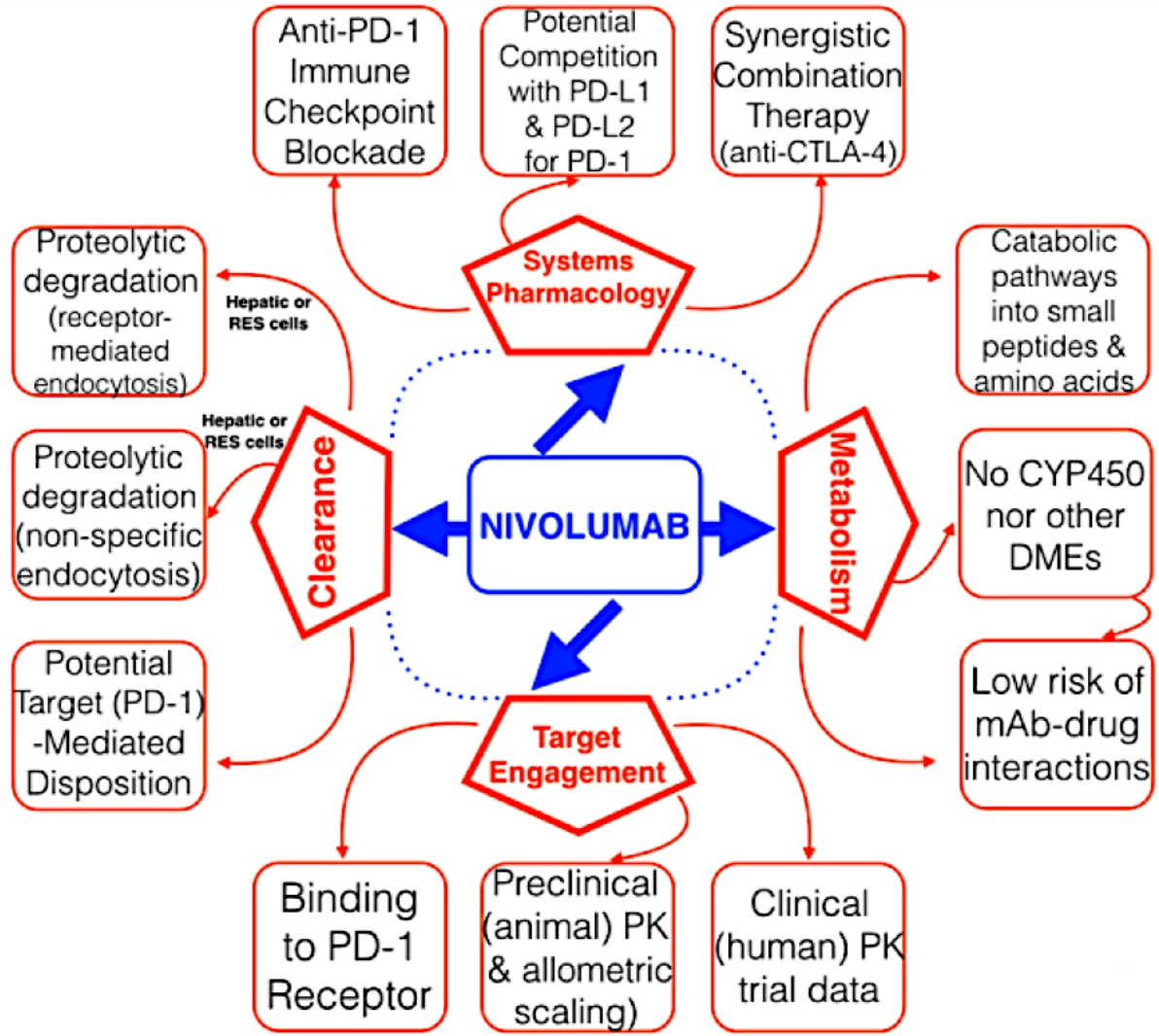


Pharmacometric variables in anticancer efficacy of immune checkpoint inhibitor nivolumab



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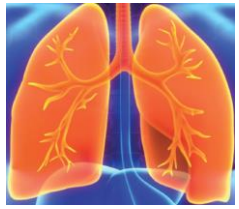
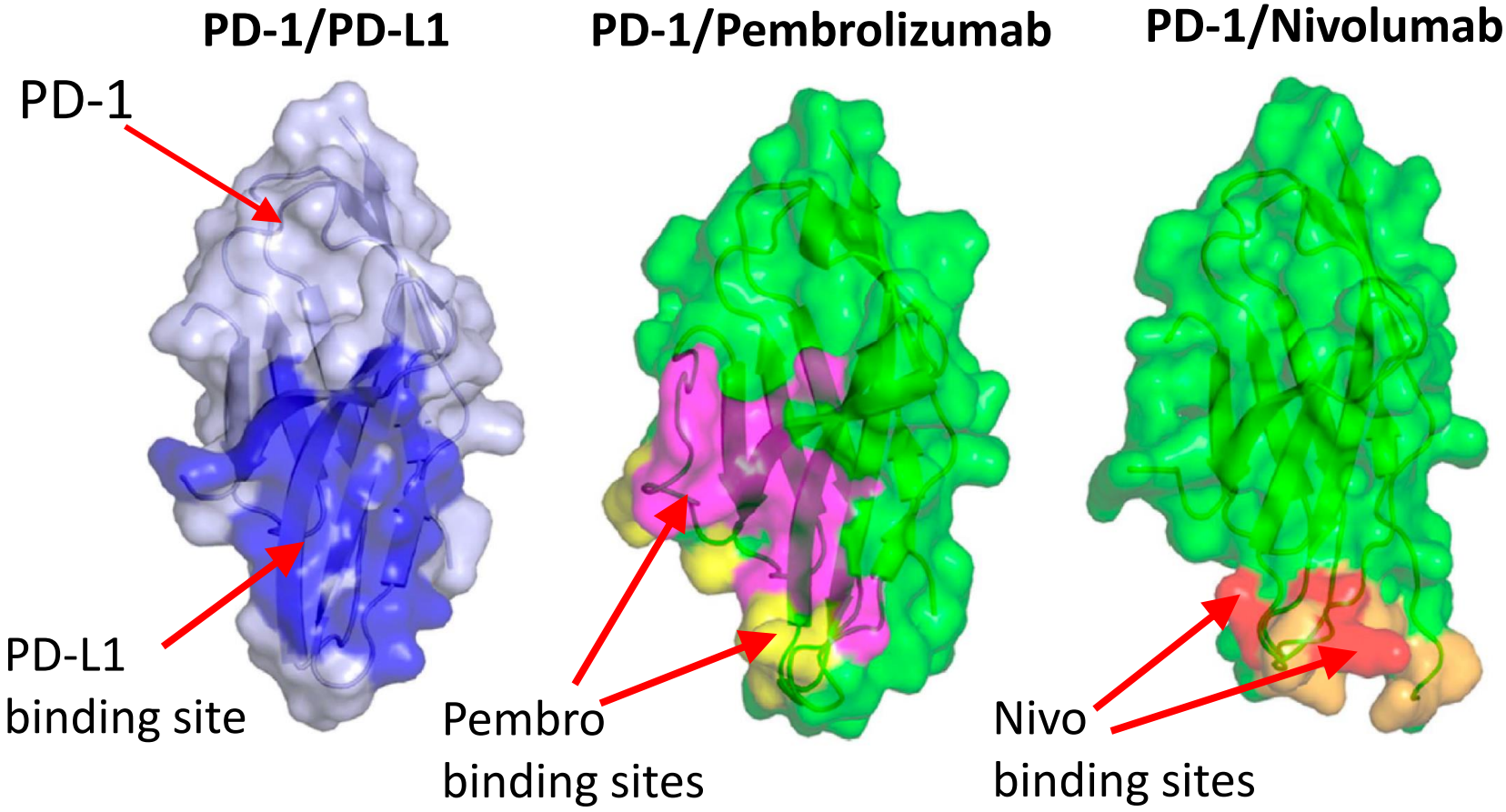


Interactions between PD-1 and anti-PD-1 drugs



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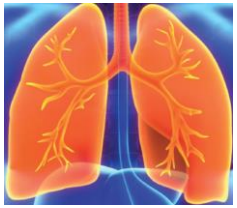
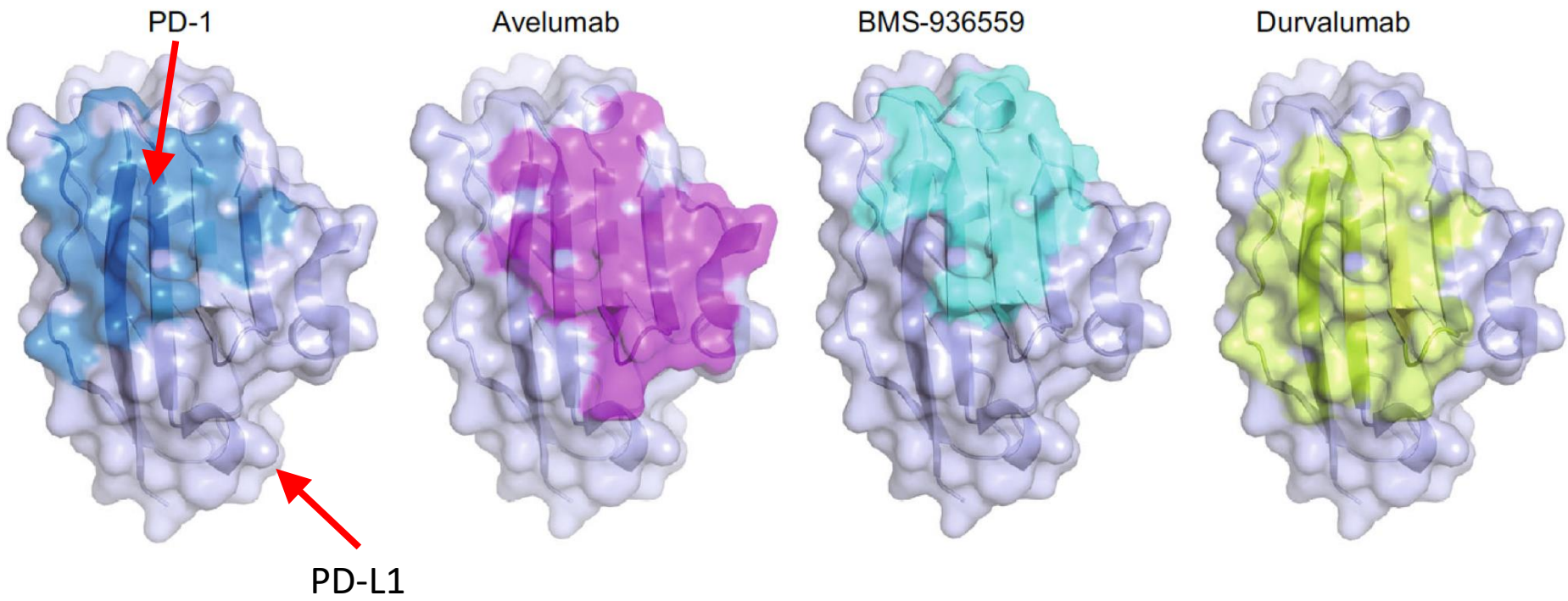
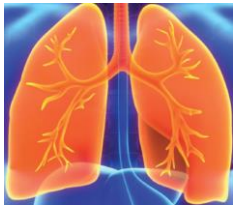


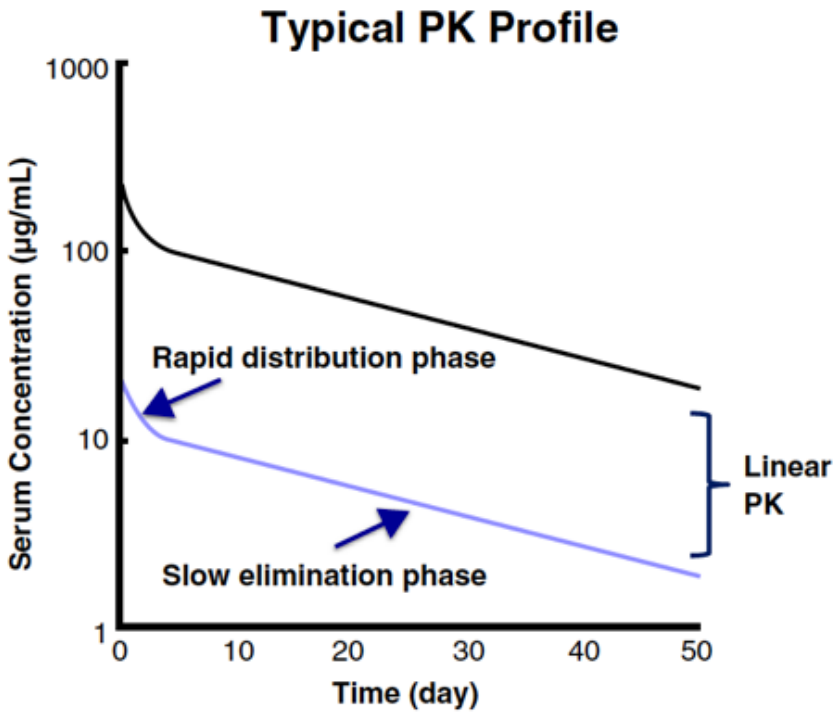
Binding surface of PD-1 and binding epitopes of avelumab, BMS-936559, and durvalumab on PD-L1

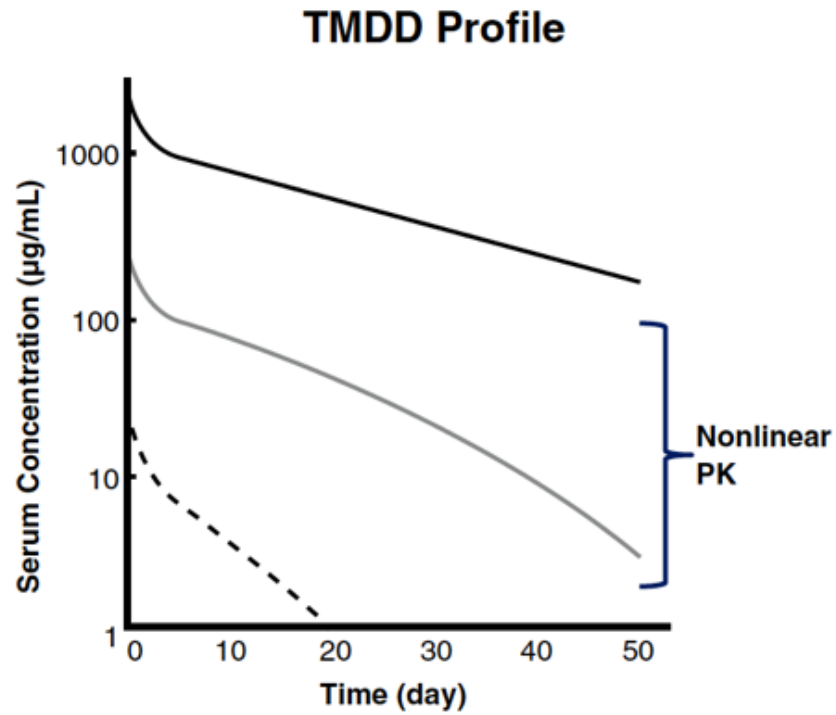


Shuguang Tan et al., Protein Cell DOI 10.1007/s13238-017-0412-8



Pharmacokinetic profile of moAbs





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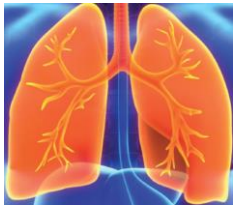
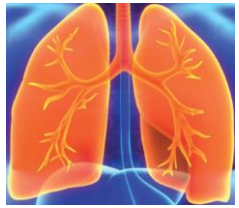


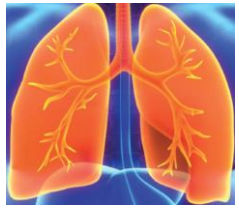
Comparison table of moAbs anti-PD-1

	Nivolumab	Pembrolizumab	Pidilizumab	AMP-224
Humanized	--	✓	✓	--
Fully human	✓	--	--	--
Ig subclass	IgG4	IgG4	IgG1	Fusion protein
ADCC/CDC	--	--	✓	✓
PD-1 affinity	+/++	+++	+	?
PD-1 engagement	50 µg/ml (75%)	10 µg/ml (60%)	NA	NA
Half-life	26.7 days	26 days	/	/
Vd	8 L	7.5 L	/	/
Clearance	9.4 ml/h	9.2 ml/h	/	/

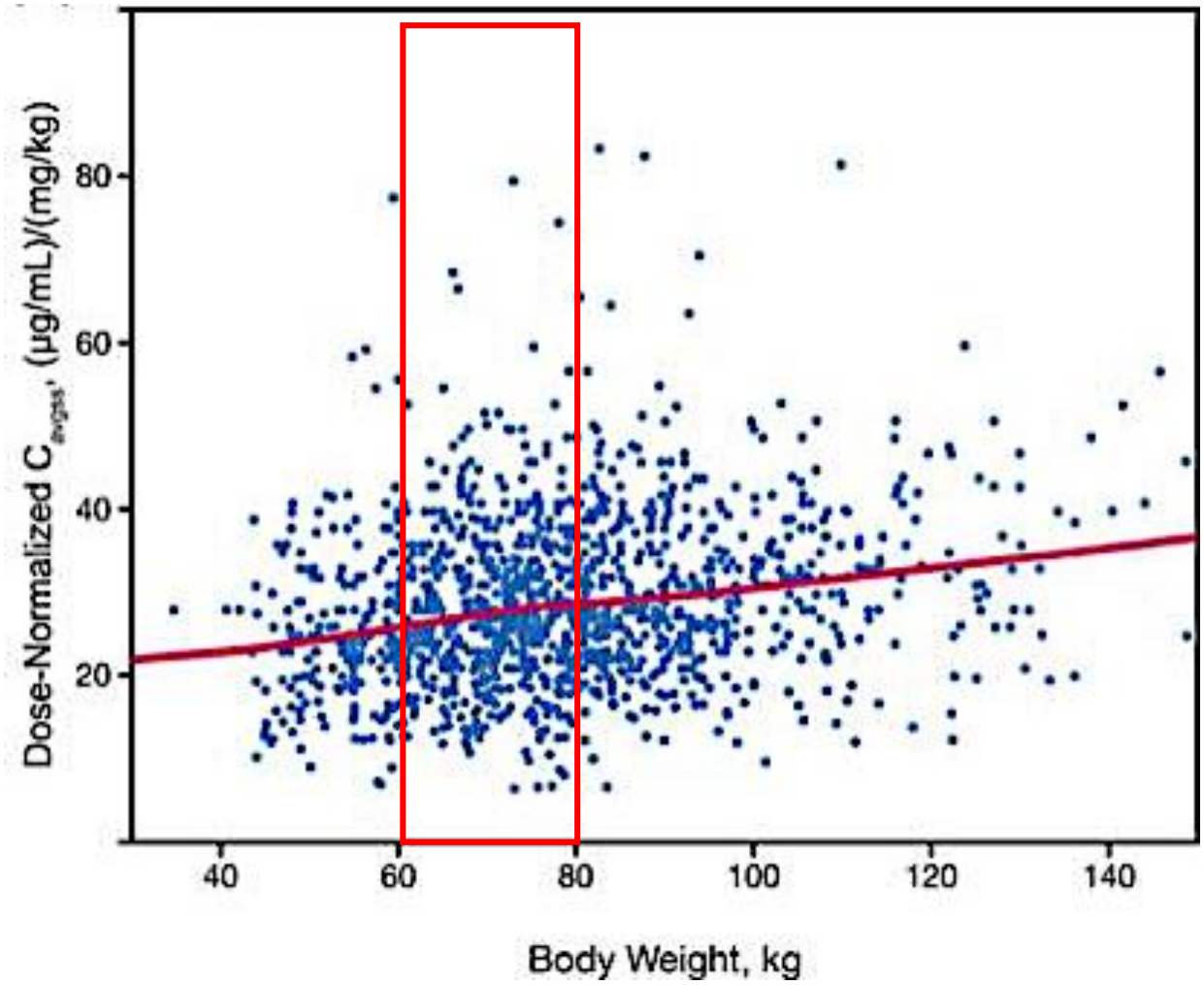


Comparison table of moAbs anti-PD-L1

	Atezolizumab	Durvalumab	Avelumab	BMS-936559
Humanized	✓	--	--	--
Fully human	--	✓	✓	✓
Ig subclass	IgG1 mod.	IgG1 mod.	IgG1	IgG4
ADCC/CDC	--	--	✓	--
PD-L1 affinity	+/++	++	+++	++
PD-L1 engagement	≥70% after 1 cycle	≥70% after 1 cycle of 10 or 20 mg/kg Q2W	1 µg/ml (95%)	NA
Half-life	27 days	12 days	6.1 days	/
Vd	6.9 L	5.6 L	4.72 L	/
Clearance	9.4 ml/h	8.24 ml/h	24.6 ml/h	/



Nivolumab dose-normalized C_{avgss} vs. body weight for body weight-based, Q2W dose regimens



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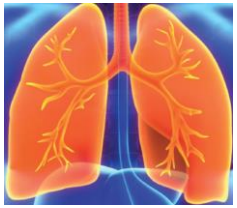
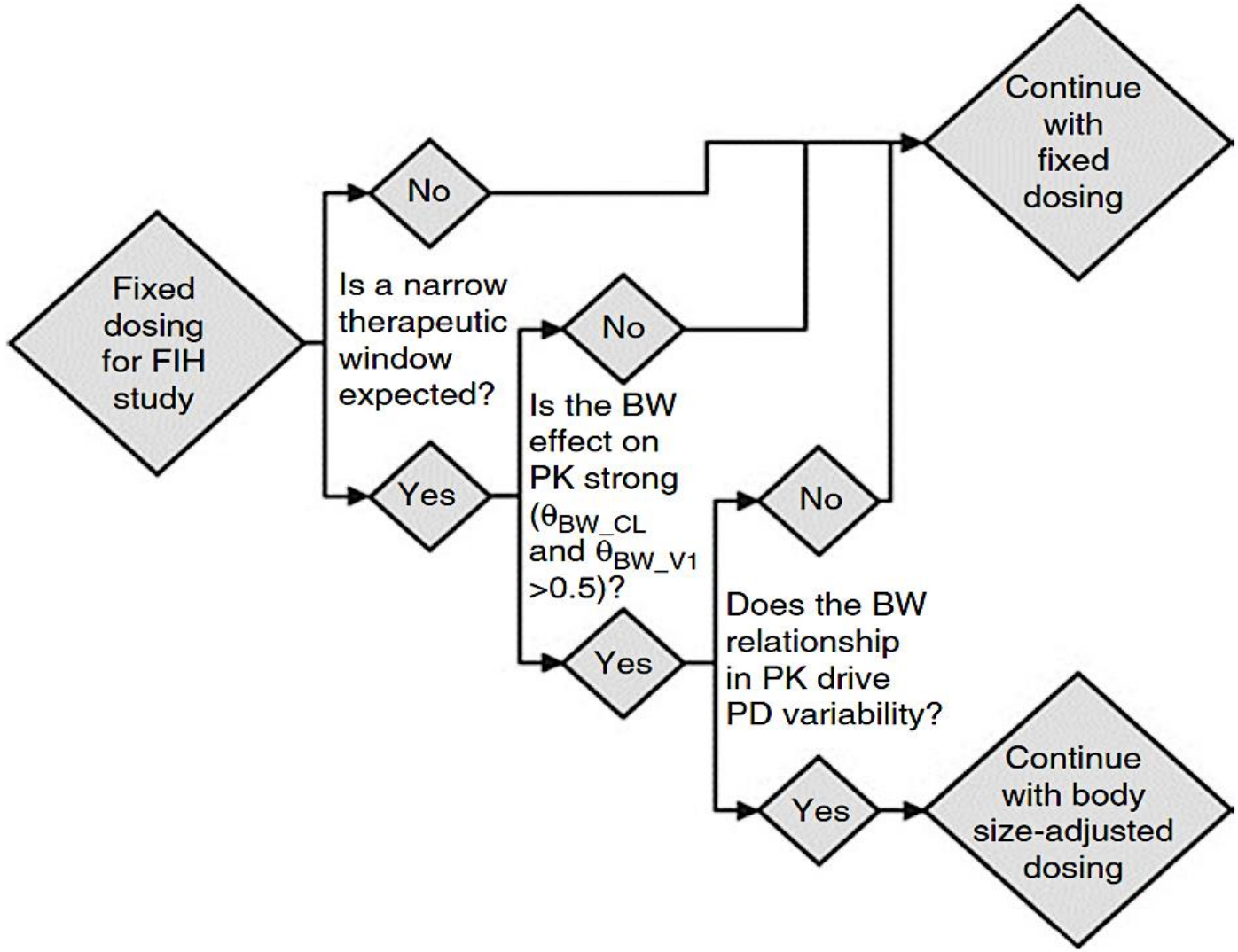


Decision tree for dosing monoclonal antibodies in adult patients: fixed dosing is a rational approach



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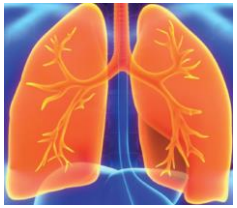
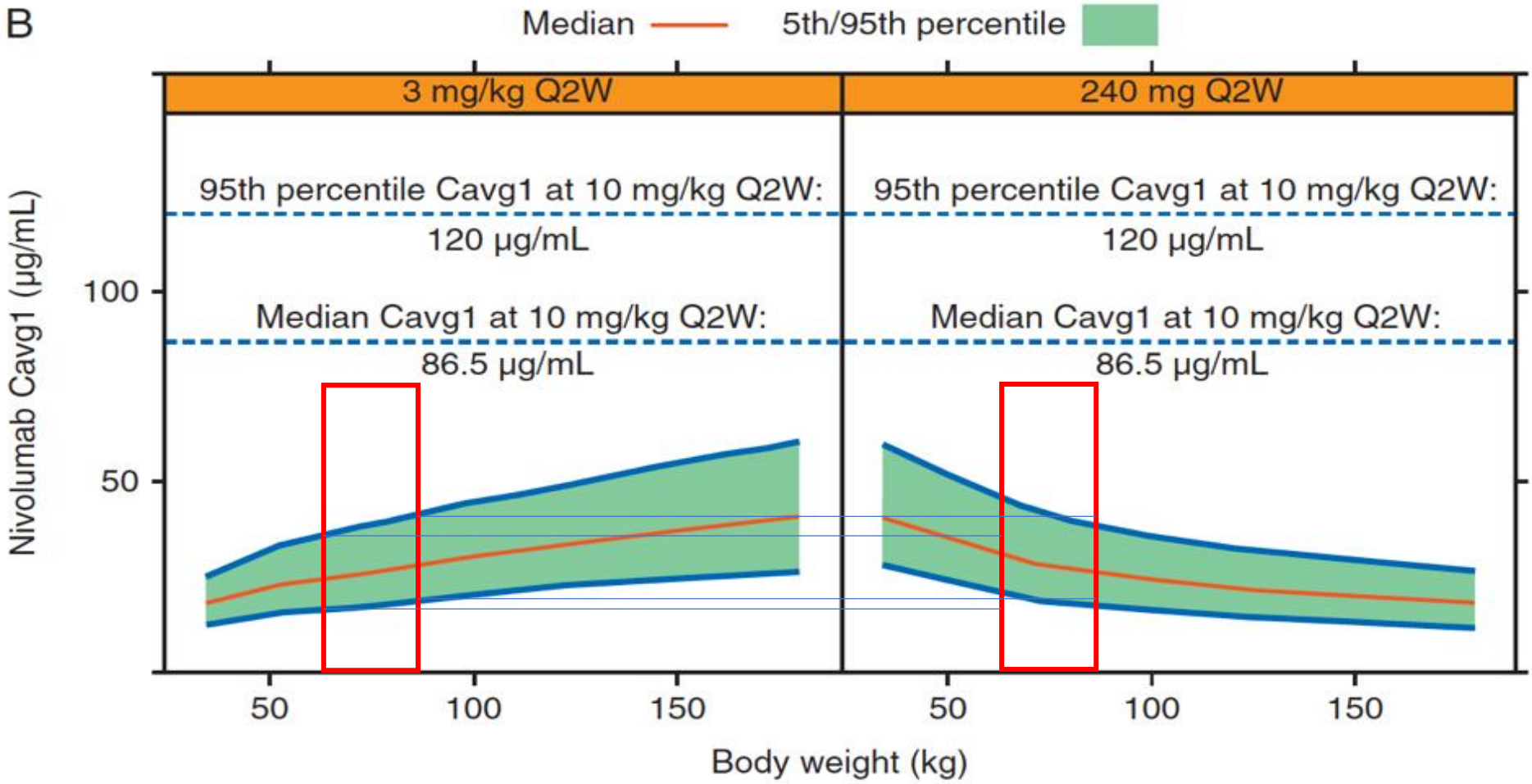


Nivolumab exposure (Cavg) in patients given 240 mg Q2W and 3 mg/kg Q2W



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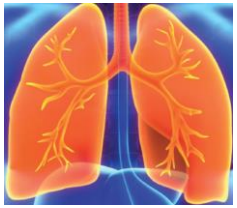
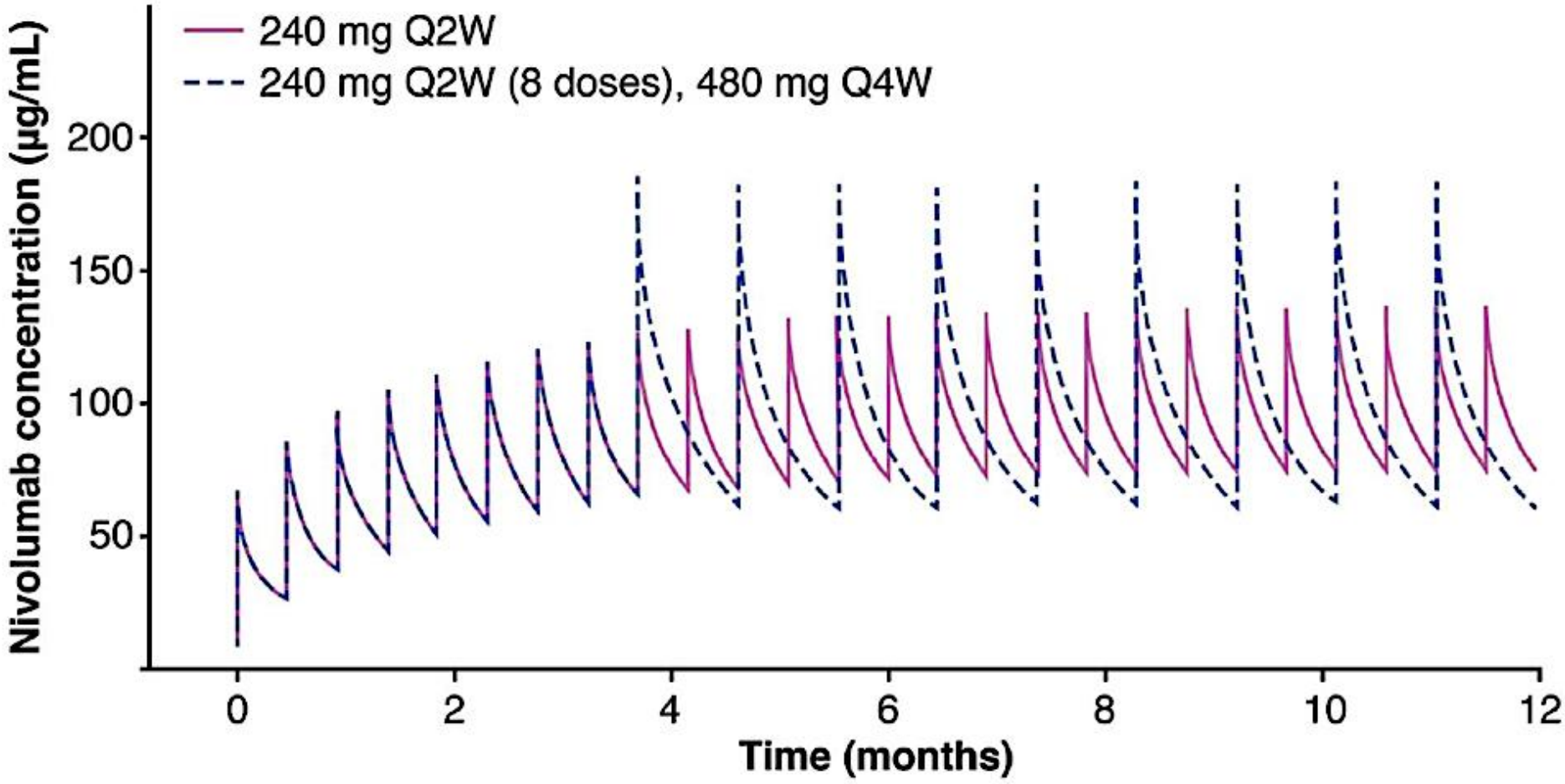


Nivolumab concentration-time profiles of 240 mg Q2W and 240 mg Q2W followed by 480 mg Q4W over 1 year



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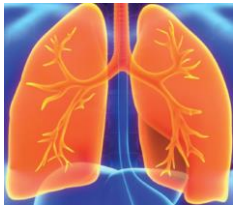
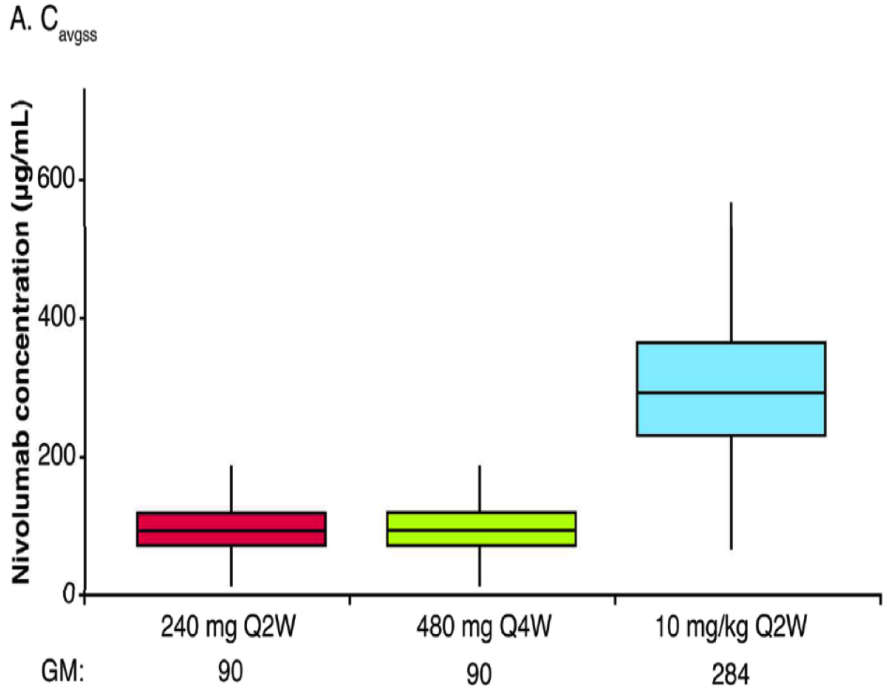
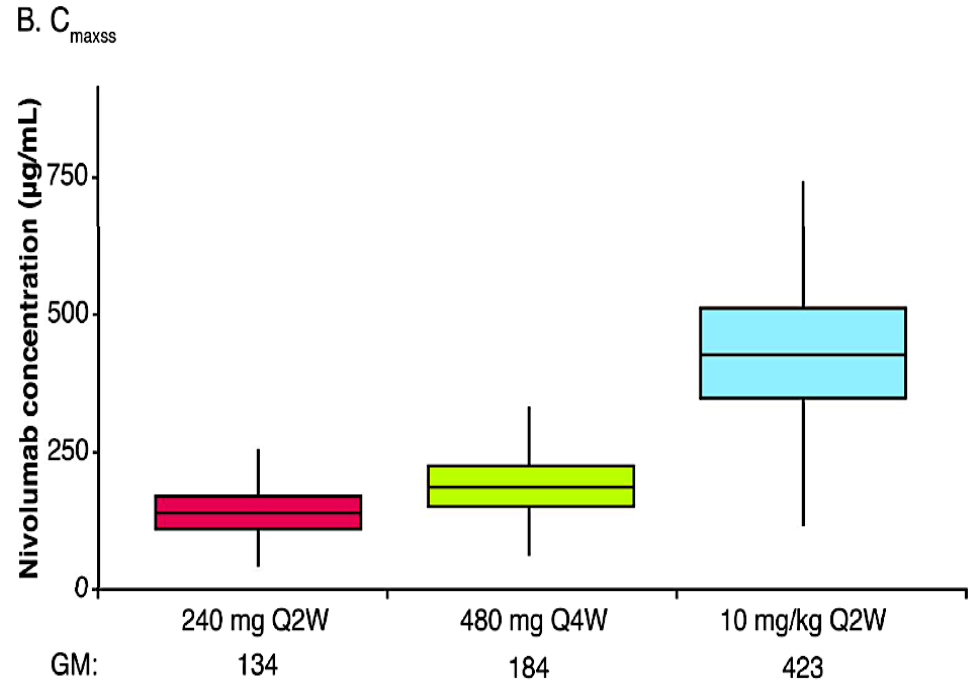


Exposure for nivolumab flat dosing at 240 mg Q2W and 480 mg Q4W compared with 10 mg/kg Q2W





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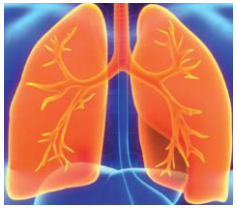
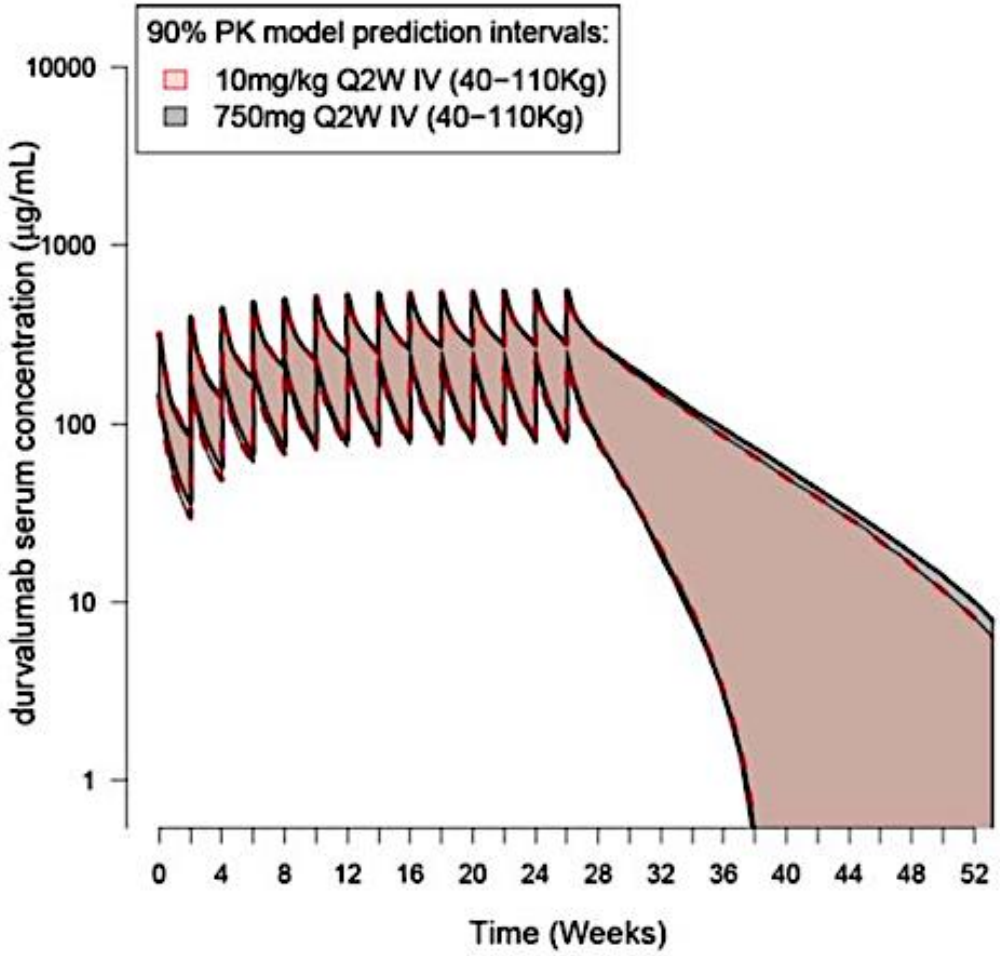
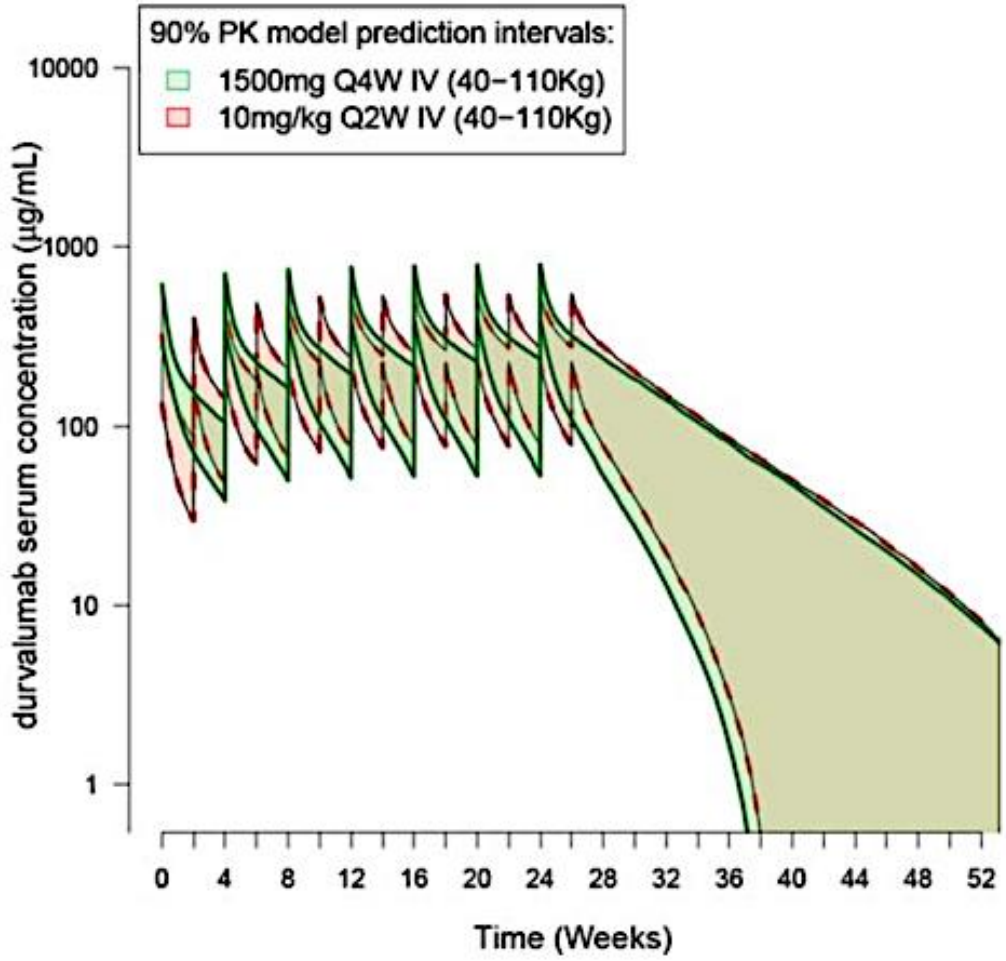


PK profiles of durvalumab following weight-based dosing (10 mg/kg q2w i.v.) compared with flat-dosing





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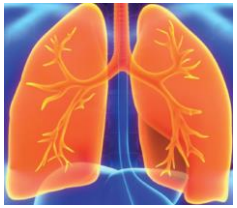
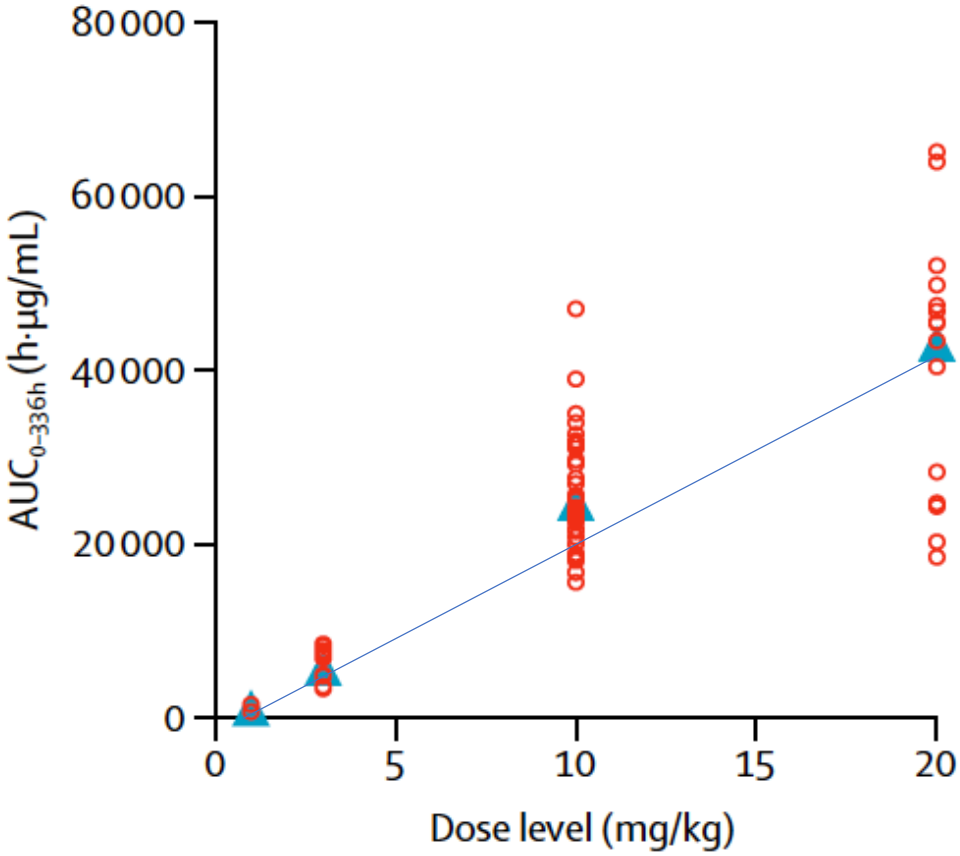
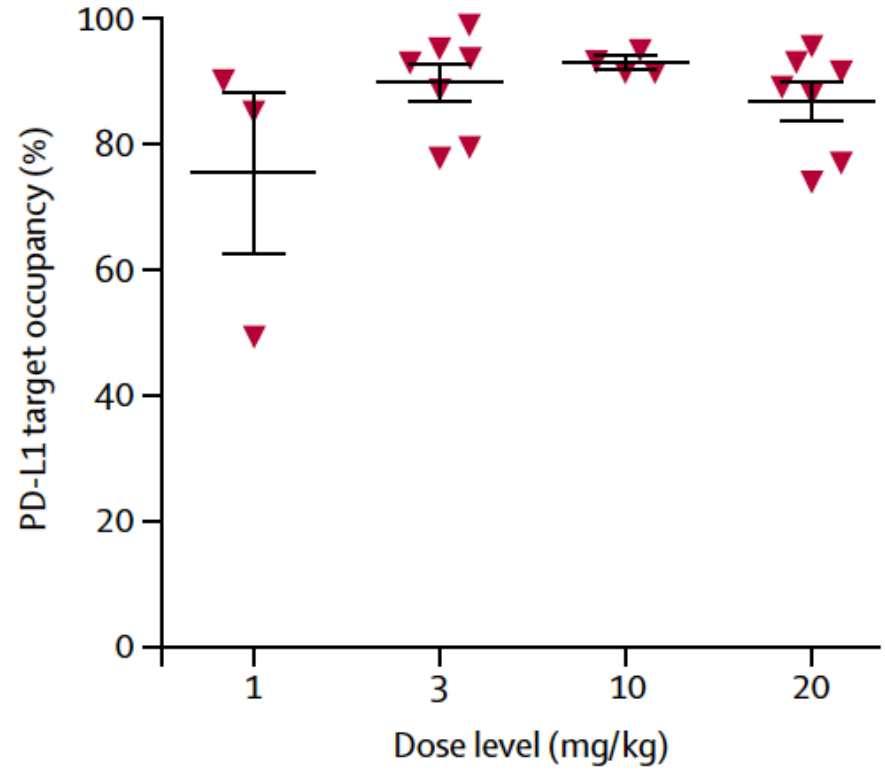


AUC vs. dose level and target occupancy of avelumab





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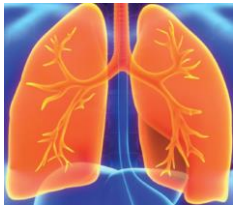
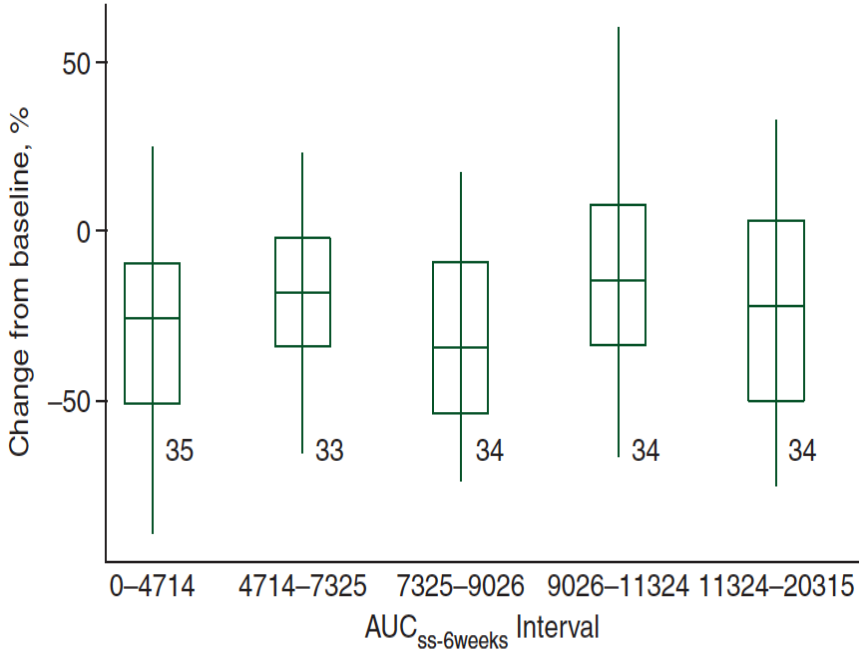
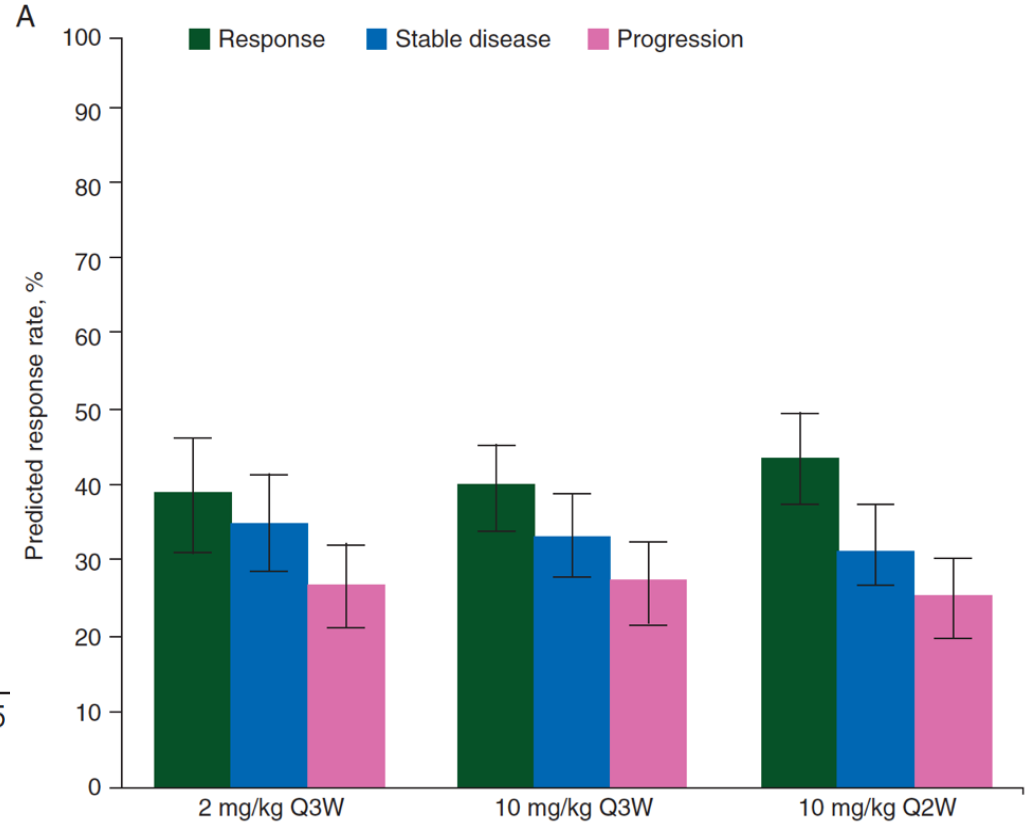


Observed percentage change from baseline in tumor size vs. AUCss-6wk (µg·day/mL) and response rates by pembrolizumab in NSCLC patients with PD-L1 expression in ≥50% of tumor cells





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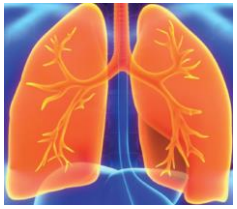
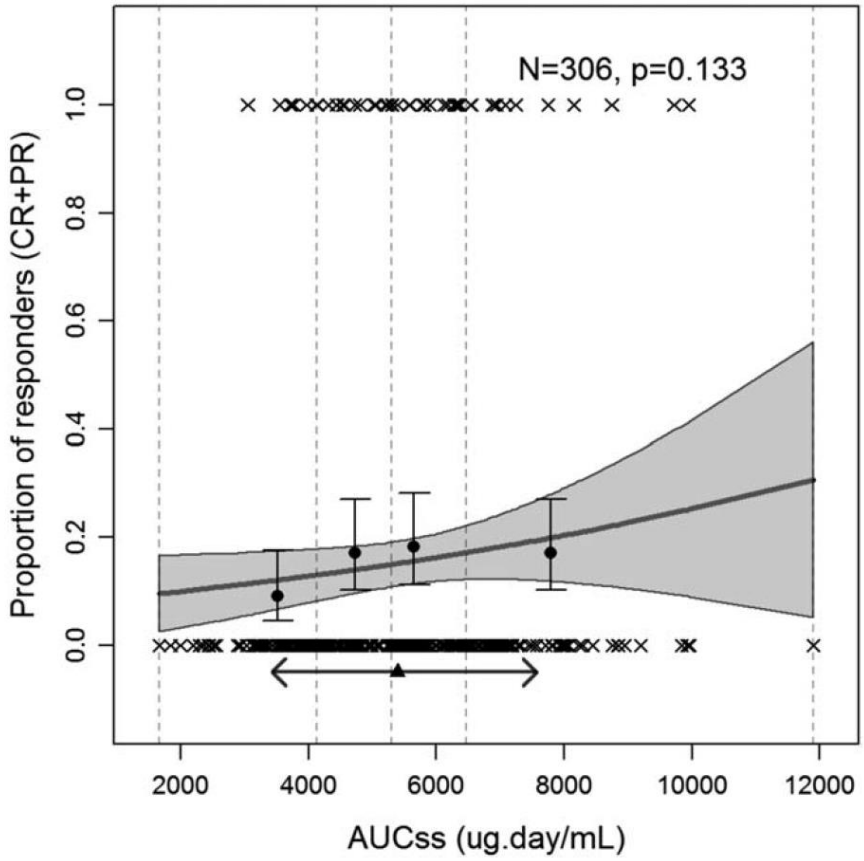
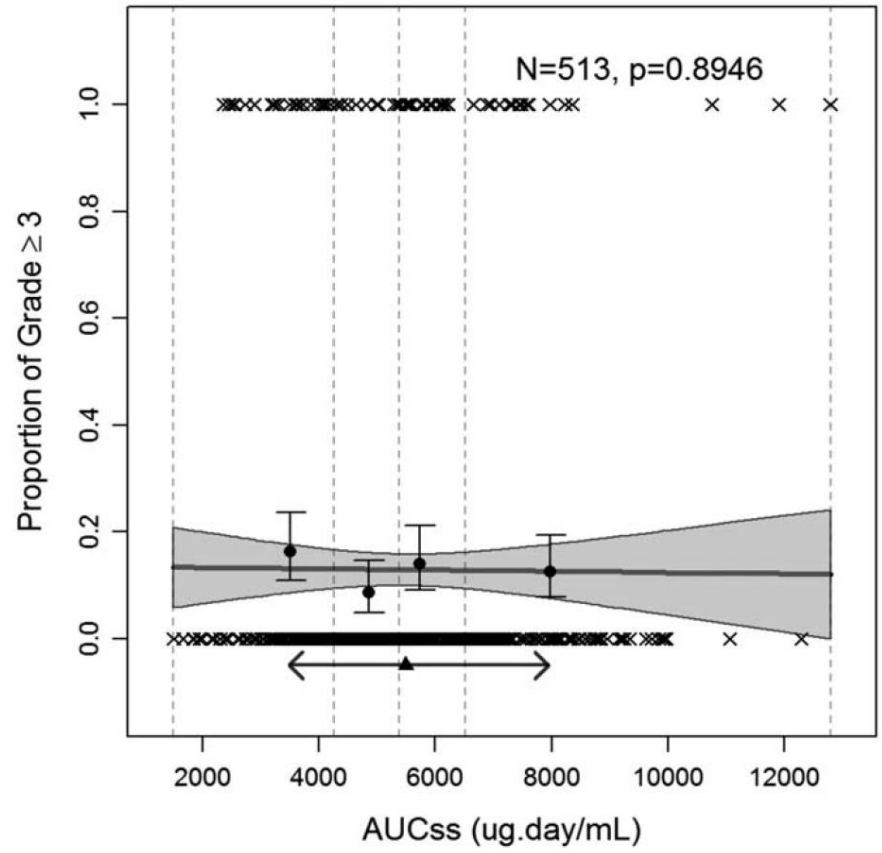


ORR and ADRs vs. atezolizumab steady state AUC in patients





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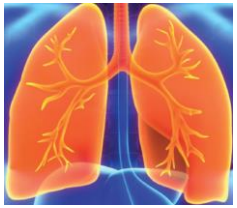

Conclusions

- Immune checkpoint inhibitors differ from a pharmacokinetic and target-engagement point of view
- Drug dose optimization should take into consideration the pharmacokinetics of immune-checkpoint inhibitors
- Flat-dose regimens are compatible with optimized exposure and target saturation (PD-L1 or PD-1)