EIP&ABIRISK **Immunogenicity of Biopharmaceuticals**

Novel Aspects of the latest EMA immunogenicity guideline

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Disclaimer

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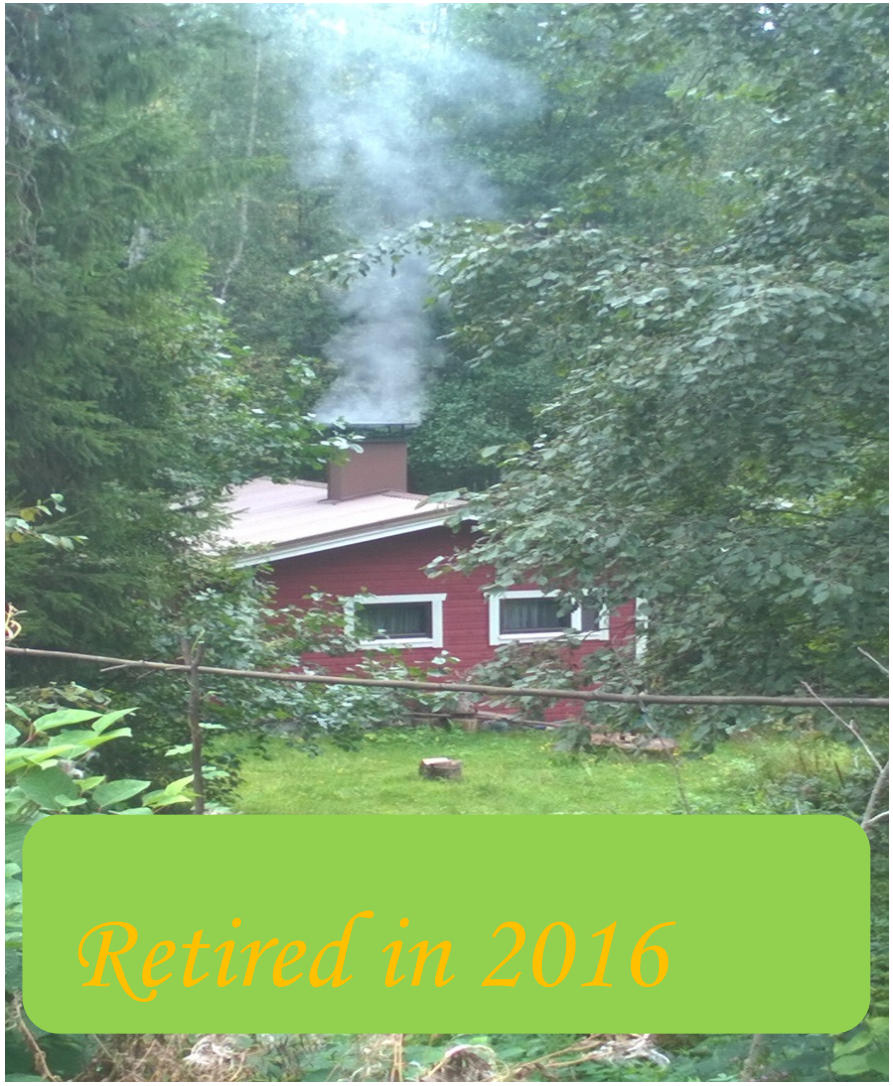

CHMP/EMA guidance on immunogenicity of therapeutic proteins

2007 Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins 2007

- **2012** Immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use 2012

2017 Guideline on Immunogenicity assessment of ~~biotechnology-derived~~ therapeutic proteins

Immunogenicity of therapeutic proteins
Novel aspects in the European approach

- General approach to immunogenicity
  - Search for harmful immunogenicity
  - Integrated analysis of the clinical impact
  - Risk-based approach

- Assays
  - Neutralizing ADAs
  - Drug/target interference

Guideline on Immunogenicity assessment of therapeutic proteins

- “The purpose of investigating immunogenicity of therapeutic proteins is to understand the clinical consequences; i.e. consequences to PK, PD, efficacy and safety.”

- Differences in immunogenicity will question the comparability of a biosimilar and its reference product as well as of new and old versions of a single product.
  - Minor differences in immunogenicity without a correlate at quality level and without negative impact on clinical efficacy and safety might be acceptable.

Immunogenicity of Flixabi[1]

Single dose study SB2-G11-NHV

Parameter	Time point	Result	SB2 N=53 n/n' (%)	EU sourced Remicade® N=53 n/n' (%)	US sourced Remicade® N=53 n/n' (%)	Total N=159 n/n' (%)
Anti-drug antibodies (ADA)	Day 1 pre-dose	Positive	0/53 (0.0)	0/53 (0.0)	0/53 (0.0)	0/159 (0.0)
		Negative	53/53 (100.0)	53/53 (100.0)	53/53 (100.0)	159/159 (100.0)
	Day 29	Positive	2/53 (3.8)	0/53 (0.0)	1/53 (1.9)	3/159 (1.9)
		Negative	51/53 (96.2)	53/53 (100.0)	52/53 (98.1)	156/159 (98.1)
	Day 71	Positive	25/53 (47.2)	20/53 (37.7)	20/53 (37.7)	65/159 (40.9)
		Negative	28/53 (52.8)	33/53 (62.3)	33/53 (62.3)	94/159 (59.1)
	Post-dose	Positive	25/53 (47.2)	20/53 (37.7)	20/53 (37.7)	65/159 (40.9)

[1]Bridging ECL assay with SB-2 as the antigen

Immunogenicity of Flixabi

Repeat dose study SB2-G31-RA

		SB2 N=290			Remicade® N=293		
Timepoint	Parameter	n'	n	(%)	n'	n	(%)
Week 0	ADA	290	5	(1.7)	293	7	(2.4)
	Nab	5	0	(0.0)	7	0	(0.0)
Week 2	ADA	286	10	(3.5)	291	14	(4.8)
	Nab	10	4	(40.0)	14	4	(28.6)
Week 6	ADA	282	21	(7.4)	286	16	(5.6)
	Nab	21	11	(52.4)	16	7	(43.8)
Week 14	ADA	274	73	(26.6)	280	63	(22.5)
	Nab	73	70	(95.9)	63	60	(95.2)
Week 22	ADA	268	121	(45.1)	273	108	(39.6)
	Nab	121	113	(93.4)	108	96	(88.9)
Week 30	ADA	251	133	(53.0)	264	116	(43.9)
	Nab	133	129	(97.0)	116	109	(94.0)
Week 30 overall	ADA	287	158	(55.1)	292	145	(49.7)
	Nab	158	146	(92.4)	145	130	(89.7)
Week 38	ADA	243	123	(50.6)	255	115	(45.1)
	Nab	123	114	(92.7)	115	103	(89.6)
Week 46	ADA	237	121	(51.1)	231	99	(42.9)
	Nab	121	113	(93.4)	99	87	(87.9)
Week 54	ADA	223	118	(52.9)	222	89	(40.1)
	Nab	118	99	(83.9)	89	78	(87.6)
Week 54 overall	ADA	287	179	(62.4)	292	168	(57.5)
	Nab	179	166	(92.7)	168	147	(87.5)

Immunogenicity of SB2 infliximab (Flixabi)

Assessment by two assays (SB2 and Remicade)

Time Points	Treatment	SB2 Assay				Remicade® Assay			
		No. of Patients		Positive Rate (%)	ADA Difference between Treatments (%)	No. of Patients		Positive Rate (%)	ADA Difference between Treatments (%)
		Total	Positive			Total	Positive		
Week 30	SB2	251	133	53.0	9.1	251	154	61.4	6.5
	Remicade®	264	116	43.9		264	145	54.9	
	Overall	515	249	48.3	N/A	515	299	58.1	N/A
Week 38	SB2	243	123	50.6	5.5	243	151	62.1	6.0
	Remicade®	255	115	45.1		143	143	56.1	
	Overall	498	238	47.8	N/A	498	294	59.0	N/A

Immunogenicity of infliximab (Flixabi)

Regulatory conclusions

- There was no obvious root cause for increased ADAs
  - Observed quality differences were not associated with functional differences
- No difference in trough levels over time
- There was no signs of inferior efficacy over 52 weeks
- Dose increases were similar in treatment arms
- Treatment-emergent adverse events or serious adverse events were not increased
- Immune-related adverse effects were not increased in the Flixabi-treated patients

Immunogenicity of therapeutic proteins
Novel aspects in the European approach

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  - Integrated analysis of the clinical impact
  - Risk-based approach

- Assays
  - Neutralizing ADAs
  - Drug/target interference

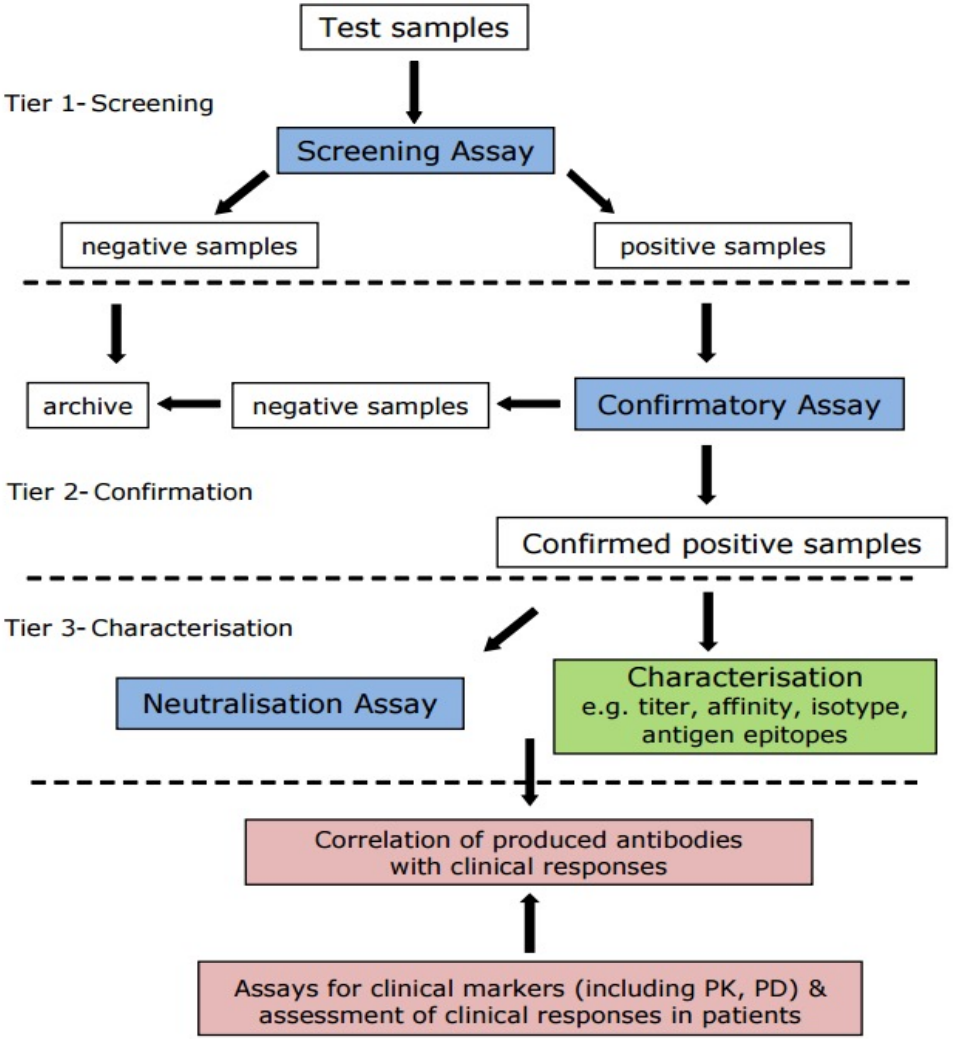
“Developing an integrated analysis strategy relevant for the intended treatment plan is critical for elucidating the clinical relevance of immunogenicity data.”

Immunogenicity guideline 2017

Integrated planning, analysis and assessment

→ Summary of Immunogenicity studies

- Analysis of risk factors
- The risk-based immunogenicity program
- Immunogenicity results
- Conclusions on the risk(s) of immunogenicity



Immunogenicity of therapeutic proteins
Novel aspects in the European approach

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  - Summary of immunogenicity program
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  - **Neutralizing ADAs**
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Comparative immunogenicity
CHMP assessment reports of ten biosimilars[1]

Immunogenicity-related questions to Applicants		
	Major	**Other concerns**
Clinical	1 (efficacy)	4 (safety)
Quality/Non-clinical	1	
ADA assays	(1)	**8**

[1]Biosimilars to new classes of therapeutic proteins since 2013, Tiina Reinivuori unpublished

Assays for immunogenicity

- The standard immunogenicity package:
  - Incidence, titer, persistence, **neutralizing capacity** and clinical correlations of ADAs

Assays for neutralizing ADAs

- NAbs need to be evaluated as part of the immunogenicity assessment since this often *correlates with diminished efficacy*
- Deviation from this concept needs a ***strong justification***. In such cases, it is advisable to seek regulatory advice.
- Two types of nAb assays are used - cell-based assays and binding, non-cell-based assays.

Cell-based or ligand-binding assay?

- Cell-based assays for agonistic therapeutics
  - For example, monoclonal antibodies with important effector functions
- Non-cell-based competitive ligand binding assays (CLB) assays for antagonistic molecules with humoral targets.
  - E.g. etanercept

What could be the “strong justification” of not developing/performing an assay for neutralising antibodies?

(an absolutely personal view)

Neutralizing ADAs

Case infliximab (Remsima/Inflectra)[1]

	CT-P13 5mg/kg (N=128) n (%)	Remicade® 5mg/kg (N=122) n (%)
Screening		
ADA Positive	1 (0.8)	1 (0.8)
NAb Positive (%)	0	0
Week 30		
ADA Positive	30 (23.4)	25 (20.5)
NAb Positive (%)	29 (22.7)	25 (20.5)
ADA Negative	79 (61.7)	80 (65.6)

[1] Remsima EPAR

Impact of ADAs on efficacy

Case biosimilar infliximab[1]

		At Week 54		Up to Week 54
Seroconversion Subgroups	**Treatment**	**ASAS20 in Study CT-P13 1.1 (All randomized pop.) n/N (%)**	**ACR20 in Study CT-P13 3.1 (All randomized pop.) n/N (%)**	**Hypersensitivity/Infusion-related reactions in Studies CT-P13 1.1 and CT-P13 3.1 (Safety pop.) n/N (%)**
Seroconverted	CT-P13	14/29 (48.3)	82/167 (49.1)	23/212 (10.8)
	Remicade®	21/32 (65.6)	73/164 (44.5)	34/202 (16.8)
Non-Seroconverted	CT-P13	57/77 (74.0)	90/135 (66.7)	4/218 (1.8)
	Remicade®	54/76 (71.1)	85/139 (61.2)	8/219 (3.7)

[1]Remsima EPAR; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002576/WC500151486.pdf

Clinical correlations of ADAs

Case biosimilar infliximab (Remsima/Inflectra)[1]

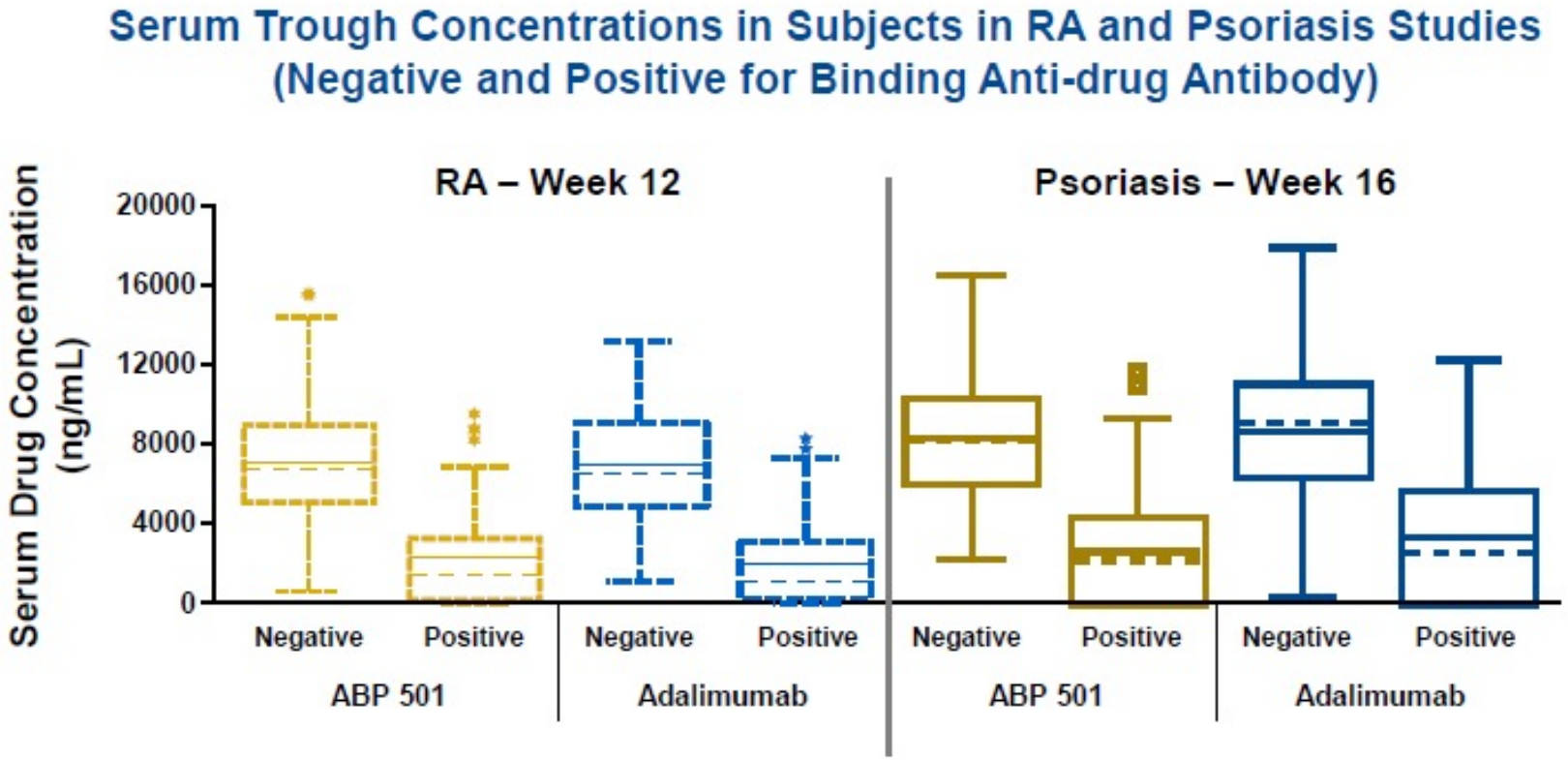
- ADA incidence: No difference between the reference and biosimilar
- For both products:
  - ADA-positive patients had a lower exposure (troughs)
  - ADA-positive patients had inferior efficacy
  - ADA-positive patients had more hypersensitivity/infusion reactions

→ Is there a need for nAb assay?

[1]Remsima EPAR; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002576/WC500151486.pdf

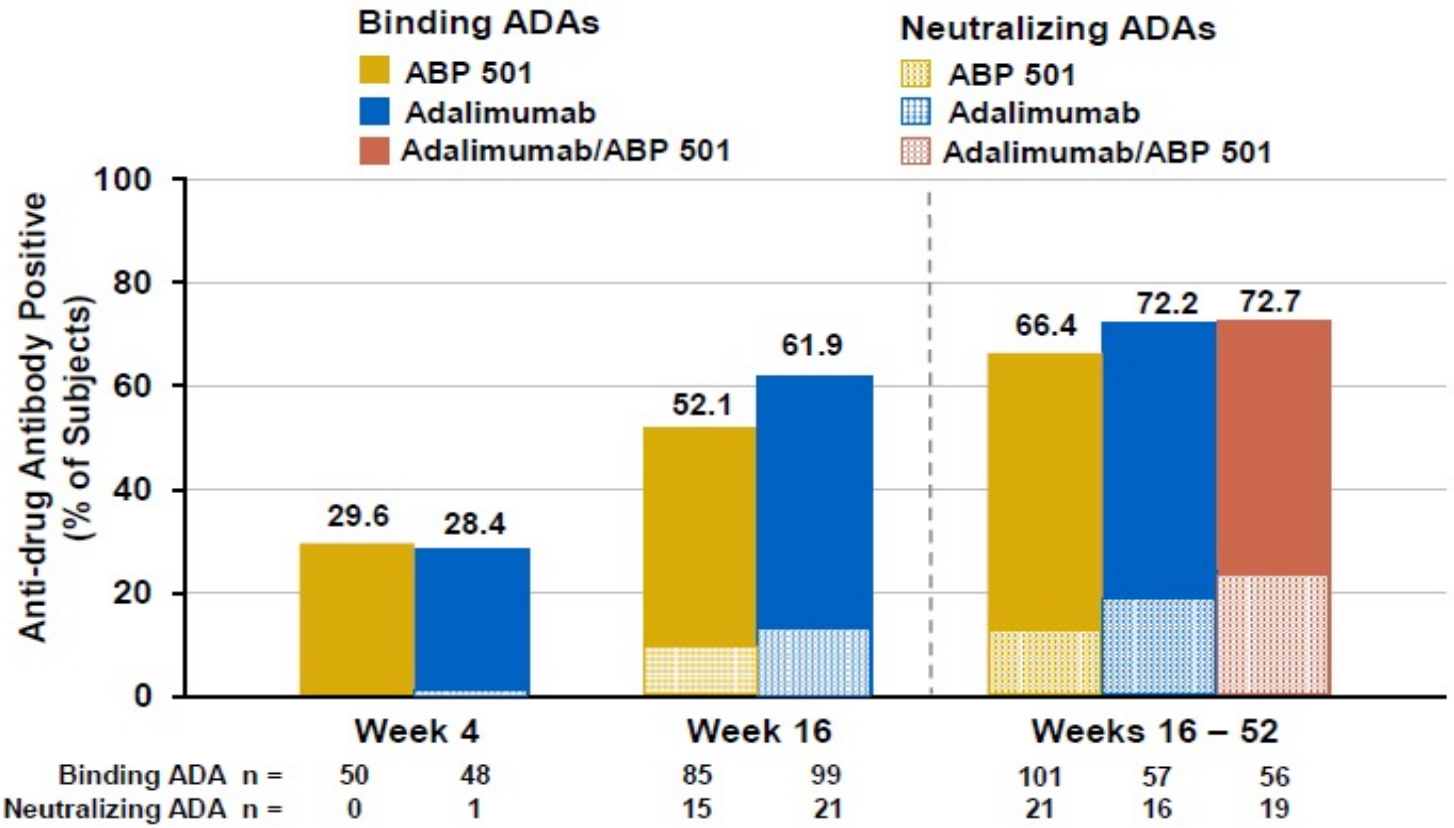
Impact of ADAs on exposure

Case adalimumab[1]



[1]FDA Arthritis Advisory Committee: Pfizer presentation 2016

Binding vs neutralising ADAs: Case adalimumab[1]



[1]FDA Arthritis Advisory Committee: Pfizer presentation 2016

Clinical impact of ADAs

Case biosimilar adalimumab (ABP 501)

- No difference between reference and biosimilar in ADA incidence

- For both products
  - Lower exposure in ADA-positive patients
  - Psoriasis: Lower PASI response in ADA-positive patients

→ Is there a need for nAb-assay?

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Drug/target interference

- “The Applicant has to demonstrate that the tolerance of the assay to the therapeutic exceeds the levels of the therapeutic protein in the samples for ADA testing.”
- “Due to technical limitations, it may not be always possible to develop fully tolerant assays. If this occurs, **the best possible assay** should be employed and the approach taken should be properly justified.”

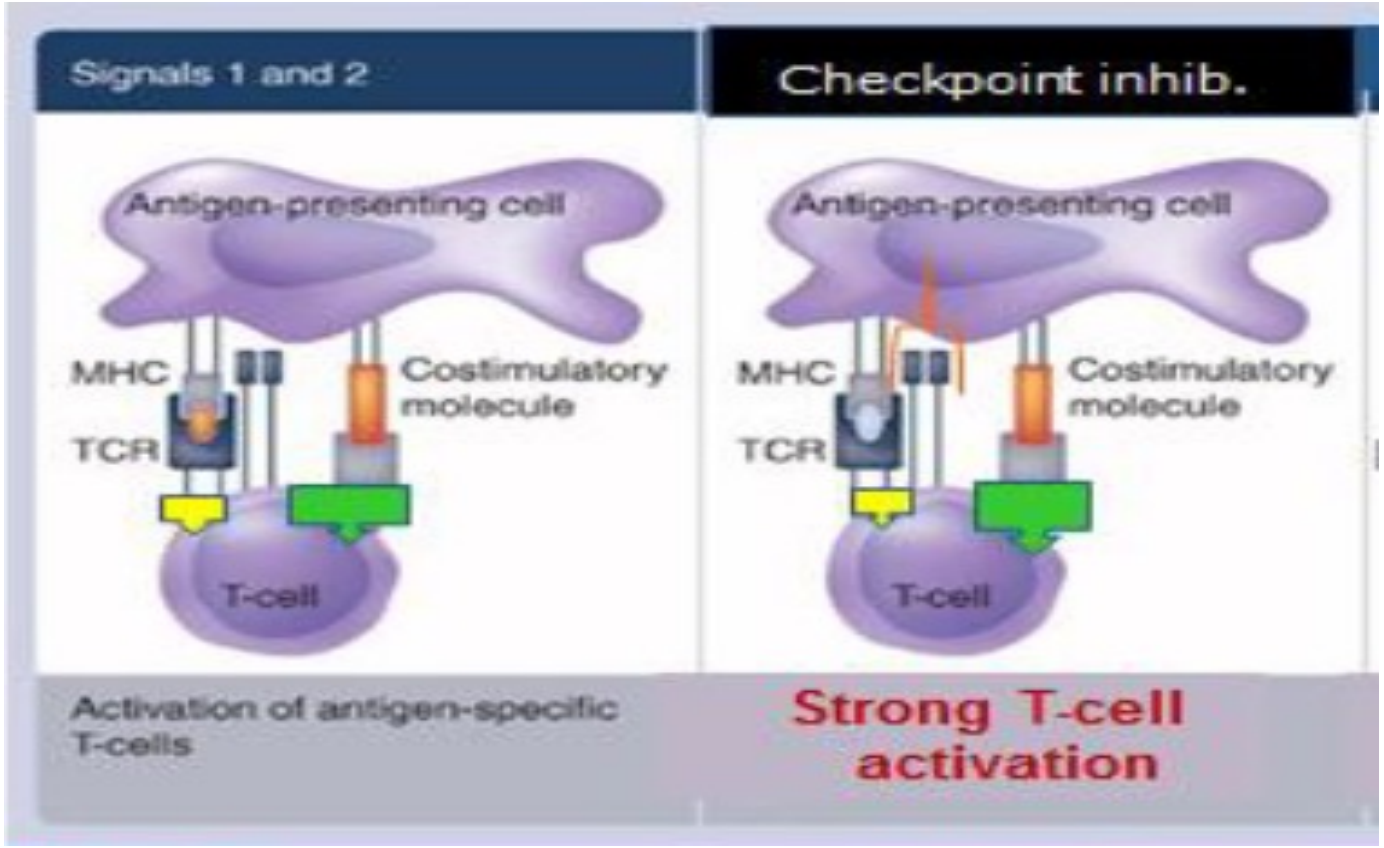
Sensitivity of ADA assays

“A low false positive rate is desirable (preferably 5%) but false negative results are unacceptable.”

ECL bridging ADA assays

- May require two antigen conjugates (indirect)
- Antigen labeling may alter antigen
- Susceptible to interference by therapeutic and the matrix
- May not detect IgG4
- Vendor-specific equipment & reagents

Check-point inhibitors



Immunogenicity of check point inhibitors[3]

- Nivolumab[1,4] 10% (pre-existing 5%)
- Pembrolizumab[1] 2%
- Ipilimumab[2] >2%

[1]mAb against PD-1
[2]mAb against CTLA-4
[3]bridging electrochemiluminescence (ECL) immunoassays
[4]"the immunogenic potential of nivolumab was minimal with relatively low titers, low persistent positive rates, low incidences of neutralising antibodies and no impact of immunogenicity on safety".

Pembrolizumab

Performance of the ADA assay

- The presence of anti-drug antibodies (ADA) was assessed in samples taken from **1094** subjects.
- ADA concentration results obtained in **729**, out of the 997 assessable patients were considered inconclusive, due to the circulating pembrolizumab above the estimated test tolerance level.
- ADA results were conclusive in **268** patients; four patients were declared ADA positive at screening and in the confirmatory assay; in one patient ADAs were seen as treatment emergent.

Check point inhibitors: ADAs in NSCLC

INN	pembrolizumab	atezolizumab
Drug target	PD-1	PD-L1
Structure	humanized	humanized
Immunogenicity assay format	bridging ECL	bridging ELISA
ADA response in NSCLC	**2,6%**	**54.1%**

Regulatory consequences

Nivolumab

- SmPC text

Pembrolizumab

- SmPC text

Ipilumab

- To improve the specificity and sensitivity of the serum ECL assay to detect antibodies, which will be used for ongoing and future Phase 3 clinical studies.

Thank you for your attention!