Immunogenicity of immune checkpoint inhibitors: What are the implications for clinical practice?

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Expert panel

Prof. Peter Galle

University of Mainz,
Germany

Dr Victor Moreno

START Madrid-FJD,
Hospital Fundación Jiménez Díaz,
Madrid, Spain

Dr Vibeke Strand

Stanford University
School of Medicine,
Palo Alto, CA, USA

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Agenda

- Potential impact of ADAs in oncology patients: Lessons from rheumatology
- ADAs and immune checkpoint inhibitors: What do we know so far?
- Managing ADAs in the oncology clinic

ADA, anti-drug antibody.

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Potential impact of ADAs in oncology patients: Lessons from rheumatology

Prof. Peter Galle
University of Mainz,
Germany

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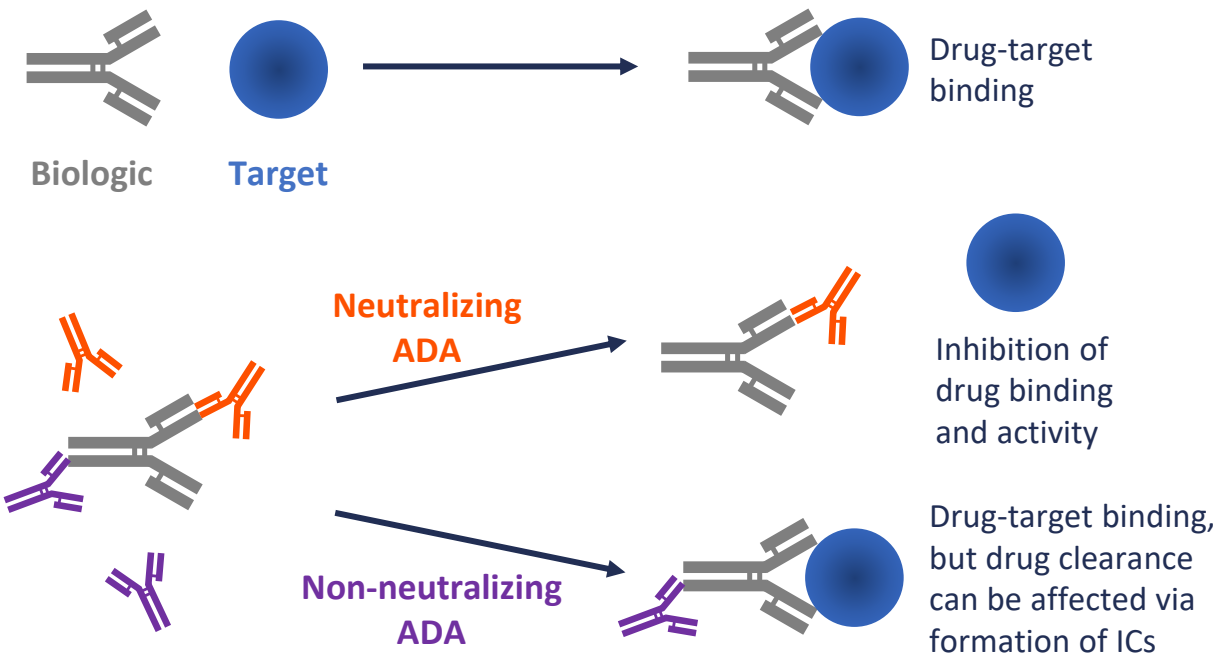
Biologic therapies and ADAs[1,2]



ADA, anti-drug antibody; IC, immune complex.

1. Gunn GR, et al. *Clin Exp Immunol*. 2016;184:137–46; 2. Strand V, et al. *Nat Rev Rheumatol*. 2021;17:81–97.

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Biologic therapies and ADAs

Factors that influence immunogenicity:

Drug-related
e.g. biologic sequence and structure

Treatment-related
e.g. dose, route of administration, concomitant medications

Patient-related
e.g. disease type and activity, genetics

ADA, anti-drug antibody.
Strand V, et al. *Nat Rev Rheumatol*. 2021;17:81–97.

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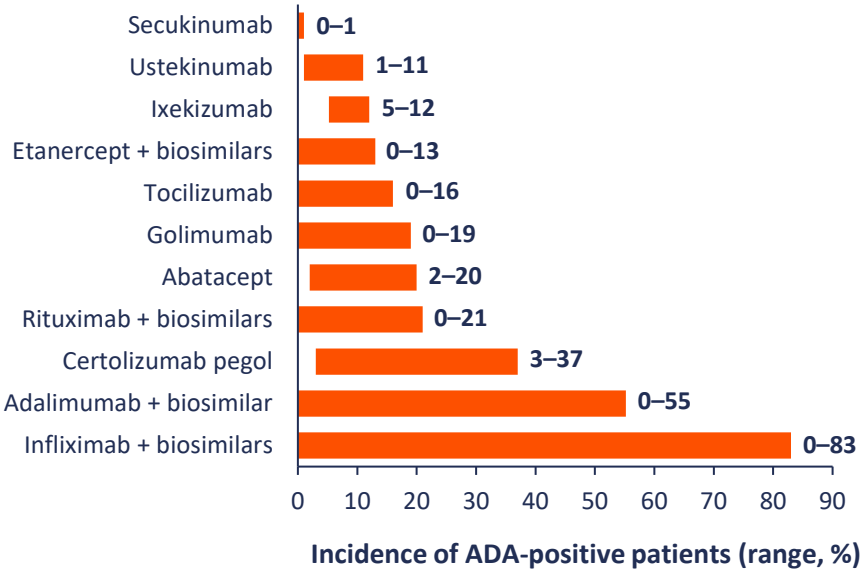
Experience with ADAs in inflammatory diseases

Immunogenicity of biologics for rheumatic diseases[1]



Adverse reactions related to ADAs[1,2]

- Infusion and injection-site reactions
- Delayed-type hypersensitivity (e.g. arthralgia and serum sickness)
- Rarely, anaphylaxis and thromboembolic events

Management of ADAs[1]

- Concomitant administration of MTX, AZA, MMF and LEF can decrease ADA formation

Therapeutic drug monitoring

- Reactive TDM is considered SoC for optimizing anti-TNF therapy in patients with IBD[3]
- TDM could be used for other inflammatory diseases such as rheumatoid arthritis[1]

ADA, anti-drug antibody; AZA, azathioprine; IBD, inflammatory bowel disease; LEF, leflunomide; MMF, mycophenolate mofetil; MTX, methotrexate; SoC, standard of care; TDM, therapeutic drug monitoring; TNF, tumour necrosis factor.

1. Strand V, et al. *Nat Rev Rheumatol*. 2021;17:81–97; 2. Krishna M, Nadler SG. *Front Immunol*. 2016;7:21; 3. Papamichael K, Cheifetz AS. *Curr Opin Rheumatol*. 2020;32:371–9.

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ADAs and immune checkpoint inhibitors: What do we know so far?

Prof. Peter Galle
University of Mainz,
Germany

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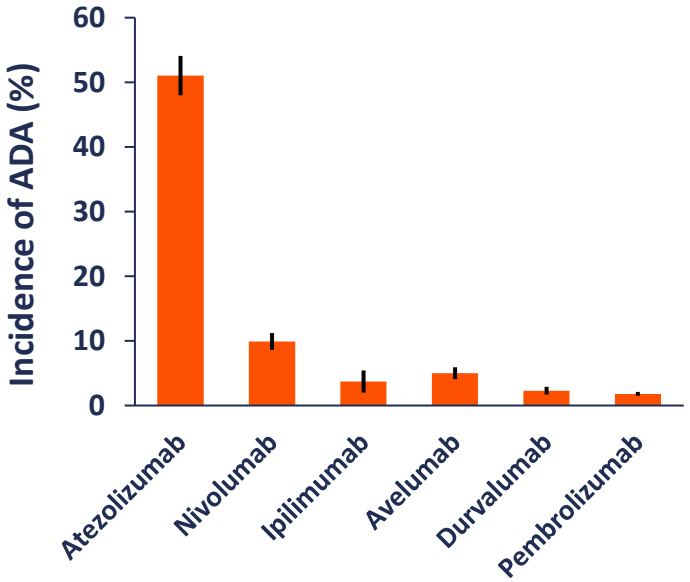
ADAs in patients treated with ICIs

Highest reported incidences of ADAs against ICIs (FDA and EMA data)[1]*



Atezolizumab[2]

Meta-analysis of 11 trials (N=7,303) in solid tumours, including lung, breast, renal, liver and urothelial cancers

- OS and PFS were higher in the atezolizumab arm versus control arm in ADA+ patients
- Atezolizumab efficacy was similar in ADA+ and ADA– patients
- Atezolizumab benefit was observed in ADA+ patients irrespective of the presence of neutralizing ADAs
- Data suggest some attenuation of OS benefit in ADA+ compared with ADA– patients

  (RHR 1.24; 95% CI 1.013–1.247)

*Data are averages of highest published incidences from FDA and EMA.

ADA, anti-drug antibody; CI, confidence interval; EMA, European Medicines Agency; FDA, US Food and Drug Administration; ICI, immune checkpoint inhibitor; OS, overall survival; PFS, progression-free survival; RHR, ratio of Hazard ratios.

1. Enrico D, et al. *Clin Cancer Res*. 2020;26:787–92; 2. Peters S, et al. *Clin Transl Sci*. 2022;15:141–57.

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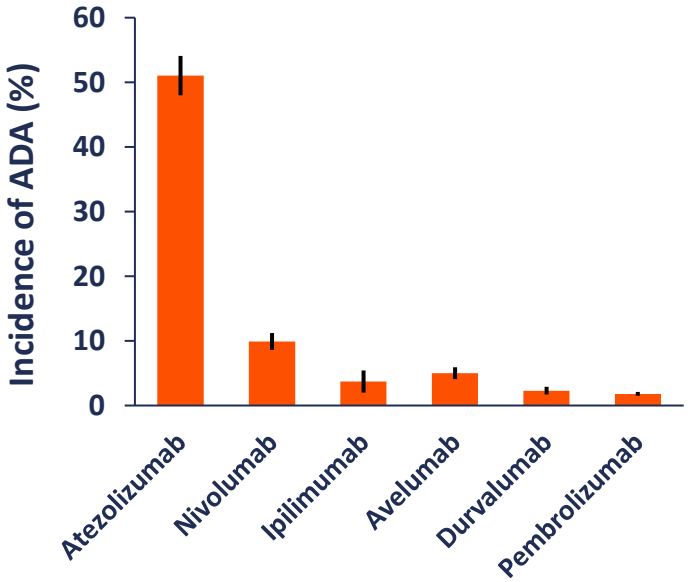

Pembrolizumab

- Meta-analysis of 12 studies (N=3,655) in patients with melanoma; Hodgkin lymphoma; lung, head and neck cancers; and colorectal and urothelial cancers[2]
  - 1.8% of evaluable patients were ADA+ and 0.5% had neutralizing ADAs
  - ADAs did not appear to have any effect on exposure, safety or efficacy of pembrolizumab
- Real-world study of 41 patients with melanoma[3]
  - 7% had reduction in drug levels and an increase in ADAs
  - No correlation between ADA-positivity and disease progression

*Data are averages of highest published incidences from FDA and EMA.

ADA, anti-drug antibody; EMA, European Medicines Agency; FDA, US Food and Drug Administration; ICI, immune checkpoint inhibitor.

1. Enrico D, et al. *Clin Cancer Res*. 2020;26:787–92; 2. van Vugt MJH, et al. *J Immunother Cancer*. 2019;7:212; 3. Sasson SC, et al. *Sci Rep*. 2021;11:19253.

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Managing ADAs in the oncology clinic

Prof. Peter Galle
University of Mainz,
Germany

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Guideline recommendations on immunogenicity

ACG 2019 guideline on Crohn's disease[1]

- Anti-TNF monotherapy is effective at maintaining anti-TNF-induced remission, but due to the potential for immunogenicity and loss of response, combination with AZA/6-MP or MTX should be considered

BSG 2019 guidelines on inflammatory bowel disease[2]

- MTX may be used in combination with infliximab to reduce immunogenicity in Crohn's disease
- Patients with IBD should be reviewed 2–4 weeks after completing loading doses of anti-TNF therapy to assess response and optimize maintenance dosing based on clinical response and measures such as serum drug and ADA levels
- Treatment options for failure of initial anti-TNF therapy may be informed by serum drug and ADA levels

ACR 2021 guideline on rheumatoid arthritis[3]

- Patients treated with mAbs may require ongoing MTX to prevent formation of ADAs

ADA measurement is not standardized nor routinely conducted in oncology clinical practice, but immunogenicity testing is mandatory during mAb clinical development (early phase clinical trials)[4]

6-MP, 6-mercaptopurine; ACG, American College of Gastroenterologists; ACR, American College of Rheumatology; ADA, anti-drug antibody; AZA, azathioprine; BSG, British Society of Gastroenterology; IBD, inflammatory bowel disease; mAb, monoclonal antibody; MTX, methotrexate; TNF, tumour necrosis factor.

1. Lichtenstein GR, et al. *Am J Gastroenterol*. 2018;113:481–517; 2. Lamb CA, et al. *Gut*. 2019;68:s1–106; 3. Fraenkel L, et al. *Arthritis Care Res*. 2021;73:924–39; 4. Borregón M, et al. *Cancer Chemother Pharmacol*. 2022;89:577–84.

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