Considerations for Immunogenicity Risk Assessment of Biotherapeutics

Status Update

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on behalf of the

EIP Immunogenicity Risk Assessment Working Group

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Disclaimer

This presentation represents the view of the EIP working group and is not necessarily reflective of the specific views of any member company.

Immunogenicity Risk Assessment Working Group Members

Team Leads:

Arno Kromminga – BioNTech

Joanna Grudzinska-Goebel – Bayer AG

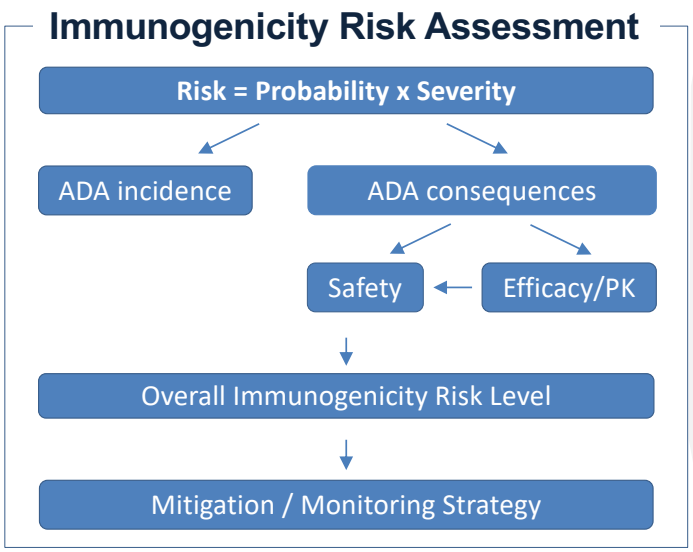
Veerle Snoeck – UCB

Team members:

- Andrea Kiessling – Novartis
- Åsa Marknell DeWitt – Thermofisher
- Bernd Potthoff - UCB
- Boris Gorovits - Sana
- Celine Marban-Doran – Roche
- Dan Mytch – Amgen
- Daniel Kramer – Sanofi
- Gregor Lotz – Roche
- Karin Benstein – Sanofi
- Karien Bloem, Sanquin
- Karin Weldingh– Novo Nordisk
- Kyra Cowan – Merck KGaA
- Linlin Luo – Merck & Co
- Mantas Malisauskas – Lundbeck
- Marcel van der Linden - Genmab
- Maria Jadhav – Novartis
- Marina Ichetovkin – Merck & Co
- Martin Ullmann - Fresenius-Kabi
- Melody Janssen – Scipotconsultancy
- Myrthe Rouwette - Byondis
- Sandra Ribes Miravet – Sandoz
- Sebastian Spindeldreher - iBiologix
- Stephanie Elm – Amgen
- Vibha Jawa – BMS

Meeting schedule: 1h, every two weeks

Integrated Approach for Immunogenicity Risk Assessment



Probability (low/(moderate)/high)

Risk factors:

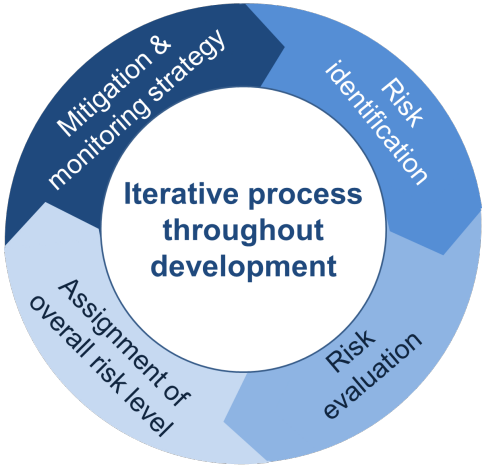
- **Product-related**
- **Process-related**
- **Patient-related**
- **Treatment-related**

Consequences

- **Cross-reactivity to endogenous counterpart with / without unique function**
- **Hypersensitivity** (infusion reaction, CRS)
- **Target/MoA** (immune complex formation, ADA-mediated immune activation, risk for ADA-mediated adverse clin. consequences))
- **Altered PK and/or PD** (neutralization/accelerated clearing of drug w/o alternative treatment options)
- **None**

Overall Risk Level (low/moderate/high)

- **Integrated analysis of probability & consequences of immunogenicity defines**
  - **Mitigation strategy**
  - **Bioanalytical monitoring (i.e. sampling and testing) strategy in nonclinical and clinical studies**



Our Mission and Tasks

Provide harmonized framework and practical guidance for Immunogenicity Risk Assessment of Biotherapeutics

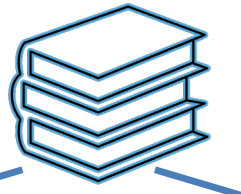
- **Exchange on IRA processes** established at different companies
- **Provide literature overview** on guidance available for IRA
- **Align on IRA** assessment with different focus during development

Exchange on IRA process

How is the IRA process established and performed at different companies?

- Which factors are considered in the risk assessment and which tools are used?
- What is the focus of the overall risk assignment (safety / safety & efficacy)?
- How is the overall risk level defined (low/moderate/high) – are we aligned?
- When are what mitigation actions initiated?
- Which nonclinical/clinical bioanalytical strategies are employed for which biotherapeutic modality?
- How is the risk evaluation connected to the monitoring (i.e. sampling and testing) strategy?
- What are major learnings over past years (incl. health authority interactions)?

Literature overview



Guidance available for

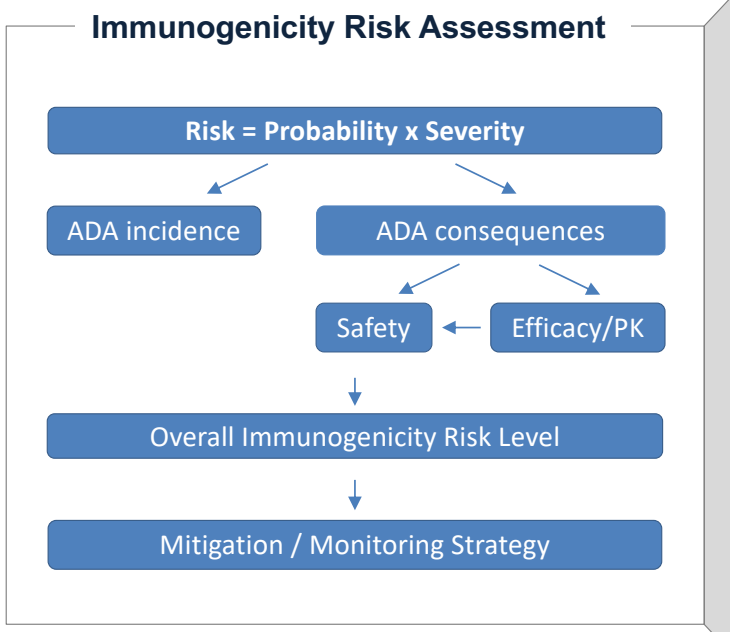
- IRA process in general vs. performed
  - early in development
  - at IND filing
  - assessment during late-stage clinical development and submission
- risk mitigation and bioanalytical monitoring

Case studies for

- risk factor evaluation with examples reflecting their impact
- low risk molecules where strong impact of immunogenicity on program success was observed
- high risk molecules with no impact of immunogenicity

Identify major guidances and gaps

Alignment on Immunogenicity Risk Assessment Process



Major Learnings

- IRA is performed with a focus on either safety or both safety and efficacy consequences
  - Business risk (e.g. reflected by non-safety-related loss of efficacy considered differently & less guidance available for its assessment
  - Focus depends on timing of analysis (candidate selection vs. nonclinical/clinical development)
- Analysis of product-, process-, patient- and treatment-related risk factors and ADA consequences run either consecutively or combined with 2 or 3 risk categories
- Harmonization on general bioanalytical strategies less in scope

Work in Progress

- Comprehensive overview of aligned risk factors and examples for higher risk findings (based on literature & experience)
- Linking of aspects / assessment to business risk potentially influencing
  - Competitive positioning
  - Development time & costs
  - Regulatory barriers
- Recommendations for risk mitigation measures

Next Steps

Provide a harmonized framework and practical guidance for Immunogenicity Risk Assessment of Biotherapeutics

- **Continue exchange on IRA established at different companies**
- **Finalize literature search on IRA and case studies**
- **Emphasize differences in risk evaluation during life-cycle management**
- **Elaborate on business risk considerations incl. mitigation measures**
- **Align on overall risk categorization with respective examples**

Thank you