EBF ADA focus group: Drug Tolerance: Can do / Must do

Case study: Regulatory interaction with regards to DT on a mAb

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Introduction to Case Study

Humanized mAb for oncology indication

Low immunogenicity risk profile

Fully validated state-of-the-art ADA assays used for clinical sample testing

Different Feedback from interactions with HA (EMA & FDA) on DT

Immunogenicity Assessment – Company Position

Focus on Drug Tolerance

mAb with low immunogenicity risk profile

- Overall low immunogenicity risk profile according to IRA
- Underlined and confirmed with data from clinical trials showing:
  - No TE ADA
  - Low ADA incidences
  - No impact on PK/safety/efficacy

DT assessed in ADA assay validation with polyclonal (pAb) and monoclonal idiotypic antibodies

- pAb added for historic reasons in each assay validation run
- mAb used for plate acceptance during sample analysis
- Assay was optimized for high DT with mAb and pAb
- Higher DT achieved with mAb than with pAb (>1.000 µg/mL drug at 100 ng/mL mAb and ~100 µg/mL drug at 100 ng/mL pAb)

DT needed for clinical samples analysis

- Drug concentrations of all clinical samples were below DT assessed for mAb
- Drug concentrations of ~15% of all clinical samples were above DT assessed for pAb

➔ Company Position: Validated DT is sufficient for clinical sample testing

Authority (EMA/FDA) interaction - FDA

Focus on Drug Tolerance

FDA accepted approach – No comments about DT

Authority (EMA/FDA) interaction - EMA

Focus on Drug Tolerance

EMA initial and follow-up request

- EMA had several questions on DT and questioned DT as 15% of clinical samples had concentrations above DT limit for **pAb**

Company pushback(s)

- Detailed response referring to presented integrated summary of immunogenicity (ISI)
  - Sufficient DT using mAb as ADA positive control
  - Acknowledgement that pAb PC shows different (lower) DT than mAb PC
  - Overall low immunogenicity of mAb
    - Low ADA incidences
    - No TE ADA
    - No clinical impact (PK, efficacy, safety)

EMA response

- EMA requested to validate sufficient DT with pAb incl reanalysis of clinical samples with concentrations >DT for pAb

Company decision

- After unsuccessful first and second push-back company decided to accept late request due to strategic considerations although technically the company still disagrees

Summary thoughts and Questions to Auditory

FDA

- Seems to be at the pulse for immunogenicity testing
- Seems to be open for scientific conclusive approaches and arguments

EMA

- At least during this interaction, EMA (or the particular reviewer) had a quite conservative view on DT values in ADA assays and it felt like concept of ISI was not fully understood
- Scientific explanations were not accepted (although EMA guideline specifically allows use of mAb as PC)

➔ Strategic decision to accept EMA request led to substantial workload for company
➔ As EMA review is visible to other health authorities, their assessment can have additional big impact on subsequent interactions with other HAs (e.g. Swiss Medic)
➔ Conservative HA feedback contradicts the current state-of-the-art integrated immunogenicity assessment and may delay introduction of fit-for-purpose immunogenicity testing in industry
➔Wish for full implementation of ISI concept at EMA

Questions to auditory:

- Have you experienced similar issues? Is this a single event or representative for EMA immunogenicity reviews?
- How could we tackle this from an industry perspective? Need for education of EMA on meaning/impact of such data?