Clinical Development of Biologics

Expect the unexpected!

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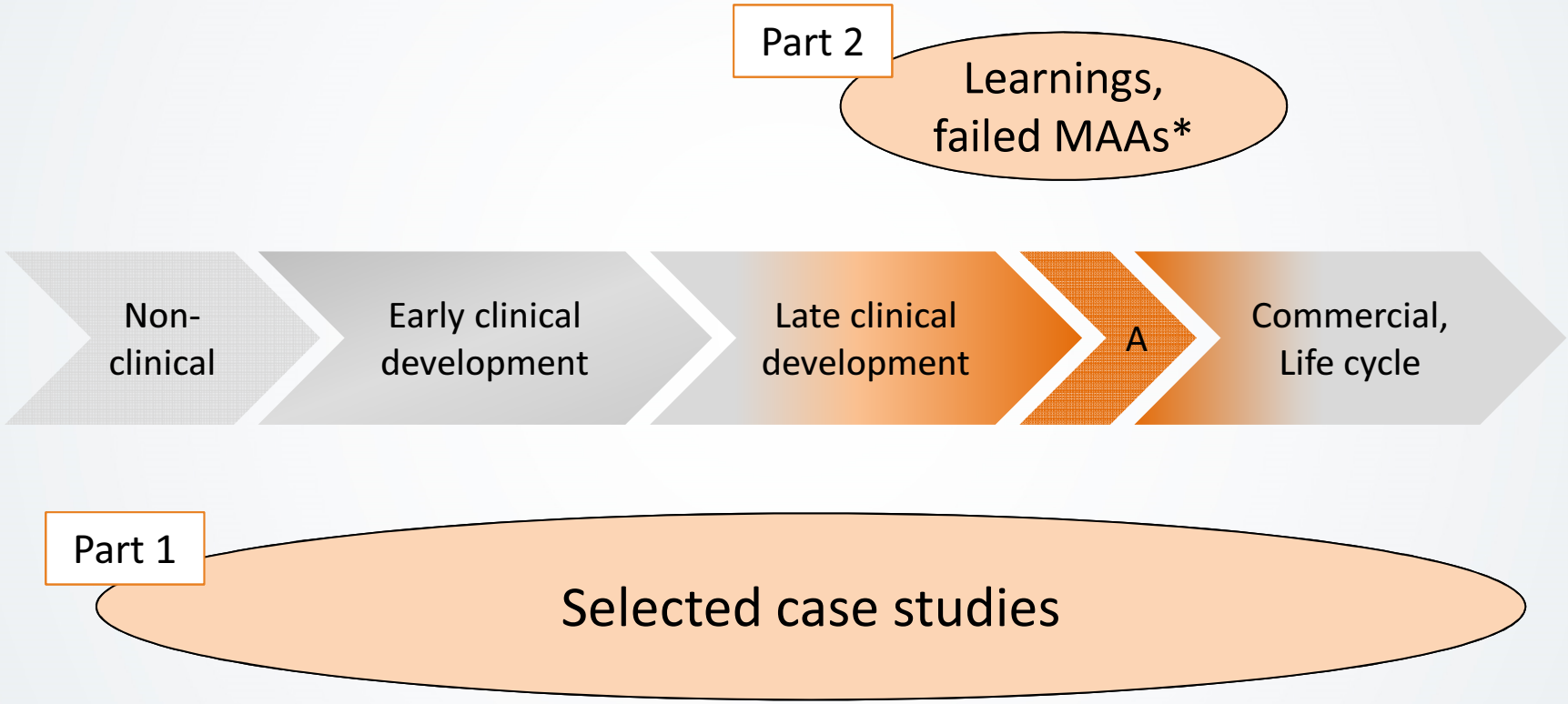
Expect challenges at every development stage



*Marketing Authorization Applications

Development Challenges Case Studies

Early stage development challenge

The case 1

- early stage antibody-drug conjugate
- intended for oncological indications
- at the transition stage to clinical studies
- toxicity studies completed
- mortalities and moribundy were observed
- key question: Should the development be discontinued?

Case 1 - the approach

- dose-response relationship?
- common pattern?
- relevance of the animal model?
- handling of animals?
- benchmark data with related ADCs?
- independent review by pathologist?

Case 1 - the recommendation

Discontinue program? – NO, would be premature!

Proposed measures

- assessment by independed pathologist accross studies
- conduct mechanistical studies to better understand the MoA
- implement a risk minimization plan
- first in human study
  - low starting dose
  - cautious escalation scheme
  - sequential enrollment

Early clinical development challenge

The case 2

- novel monoclonal antibody
- targeting an immune cytokine
- intended for use in inflammatory diseases
- safety signal in Phase 1 healthy volunteer (HV) study
- Key question: How should we proceed?

Case 2 - the approach

- is the signal real?
- frequency (compared to avarage population)?
- predisposition?
- dose-response relationship?
- mechanistic link between MoA and signal?
- additional data from animal model?
- additional risks associated with the signal?

Case 2 - the recommendation

How to proceed? – Stop and continue!

- undue risk for healty volunteers, stop of Phase 1 study
- benefit-risk assessment for patients (pts)
- marked difference in cytokine levels between HV and pts
- reasonable target-disease-link
- high unmet medical need, potentially acceptable risk
- implement a risk minimization plan
- set-up dose escalation study in pts
  - inclusion/exclusion criteria reflect findings
  - algorithm for safety signal assessment

Late stage development challenge

The case 3

- late stage novel monoclonal antibody
- intended for use in metabolic diseases
- clinical trial application for phase III rejected because of
- potential risks with the manufacturing process
- What can we do?

Case 3 - the approach

- production in line with guidance documents?
- are the concerns potential or real?
- available data for this product?
- available data for related products?
- measures applied for risk minimization sufficient?
- advantages arising form the production process?
- consistency of evaluations across EU?

Case 3 - the result

- convincing strategy was developed
- risk minimization incorporated
- presented and discussed with the agency
- technology was finally accepted by the agency
- way paved for future CTAs
- way paved for MAA

From challenge to opportunity

The case catumaxomab

- first approved bispecific mab, approved since 2009
- for intraperitoneal treatment of malignant ascites
- rat/mouse hybrid antibody

Seimetz D, Lindhofer H, Bokemeyer C, Cancer Treatment Reviews, 2010

Case catumaxomab – important questions

- Is the drug immunogenic?

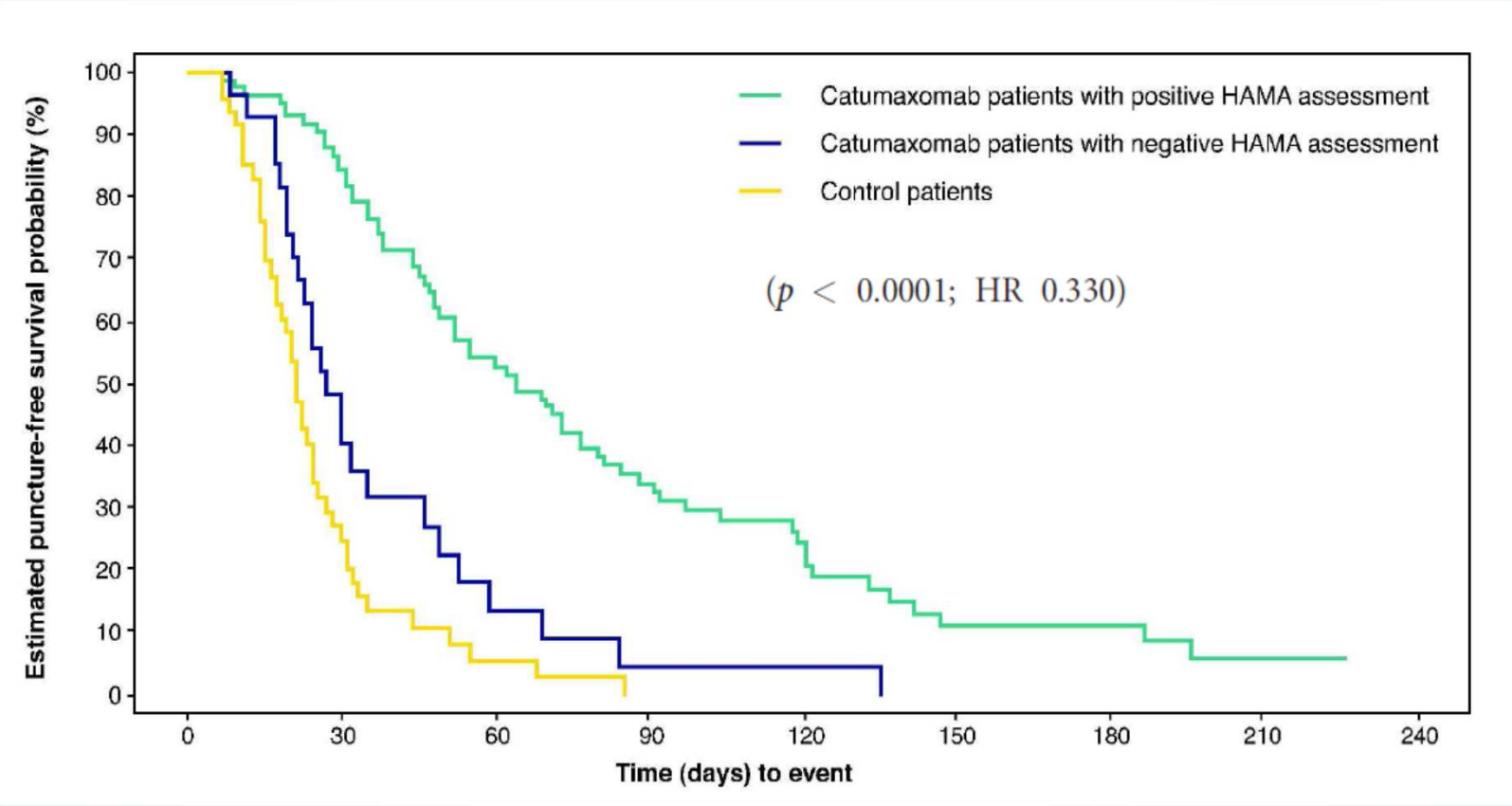
  YES
- Was this a concern for approval?

  NO
- What is the frequency of immunogenicity?

  ~ 80%
- Is there a difference between patients who do develop an immune response against catumaxomab and those who don‘t?

  YES

Immunogenicity positively correlates with clinical response



Ott MG et al, International Journal of Cancer, 2011

What can we learn from this?

- Immunogenicity may not always be a bad guy, see also*
- Immunogenicity as part of the mechanism of action?
- Immunogenicity as biomarker?

  but post-treatment …
- Immunogenicity as guide for biomarker identification?

  pre-treatment

*Have we overestimated the benefit of human(ized) antibodies?

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mAbs 2:6, 682-694; November/December 2010; © 2010 Landes Bioscience

Hypothesis generation work

- for a potential pre-treatment biomarker
- 34 catumaxomab treated pts, accross studies
- various (immunological) parameters were checked
- result: relative lymphocyte count (RLC) before treatment significantly correlates with outcome (cut-off value)

Med Hypotheses. 2014 Mar;82(3):295-9. doi: 10.1016/j.mehy.2013.12.014. Epub 2013 Dec 27.

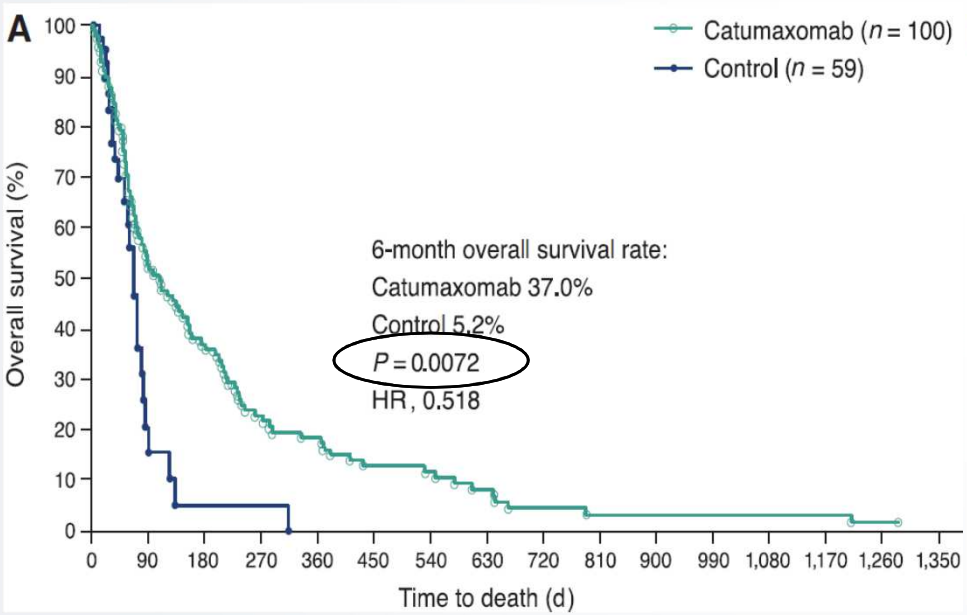
Relative lymphocyte count is a prognostic parameter in cancer patients with catumaxomab immunotherapy.

Ströhlein MA[1], Lefering R[2], Bulian DR[3], Heiss MM[3].

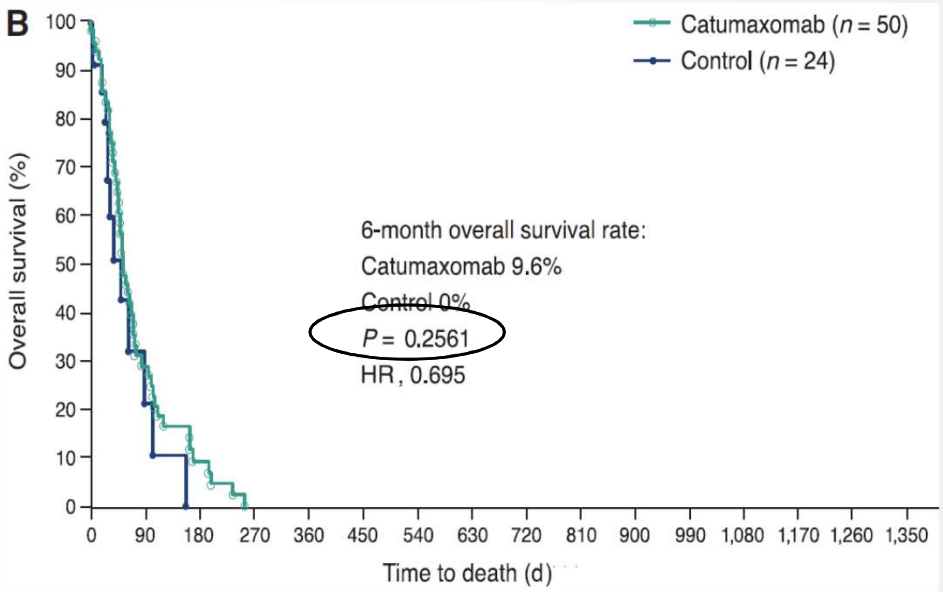
Hypothesis confirmed with pivotal trial data

Immunogenicitiy guided biomarker development …

A: OS in pts with an RLC >13%



B: OS in pts with an RLC ≤ 13%



Heiss MM et al, International Journal of Cancer, 2014

Challenges after approval

The case 5

- approved recombinant protein
- used to increase the level of endogenous protein
- development of new liquid formulation as portfolio extension
- bioequivalence study: bioequivalent, but immunogenicity observed
- Key question: what shall we do?

Case 5 - the approach

- immunogenicity to current or new formulation?

  the challenge: cross over design …
- neutralizing?
- changes in the manufacturing process of active substance?
- analytical data?
- available clinical data for this product?
- available data for related products?
- long term real-time stability data?

Case 5 - the result

- aggregate formation over time
- optimisation of pharmaceutical development required before line extension
- continue commercialization with current formulation

Unexpected opportunities after approval

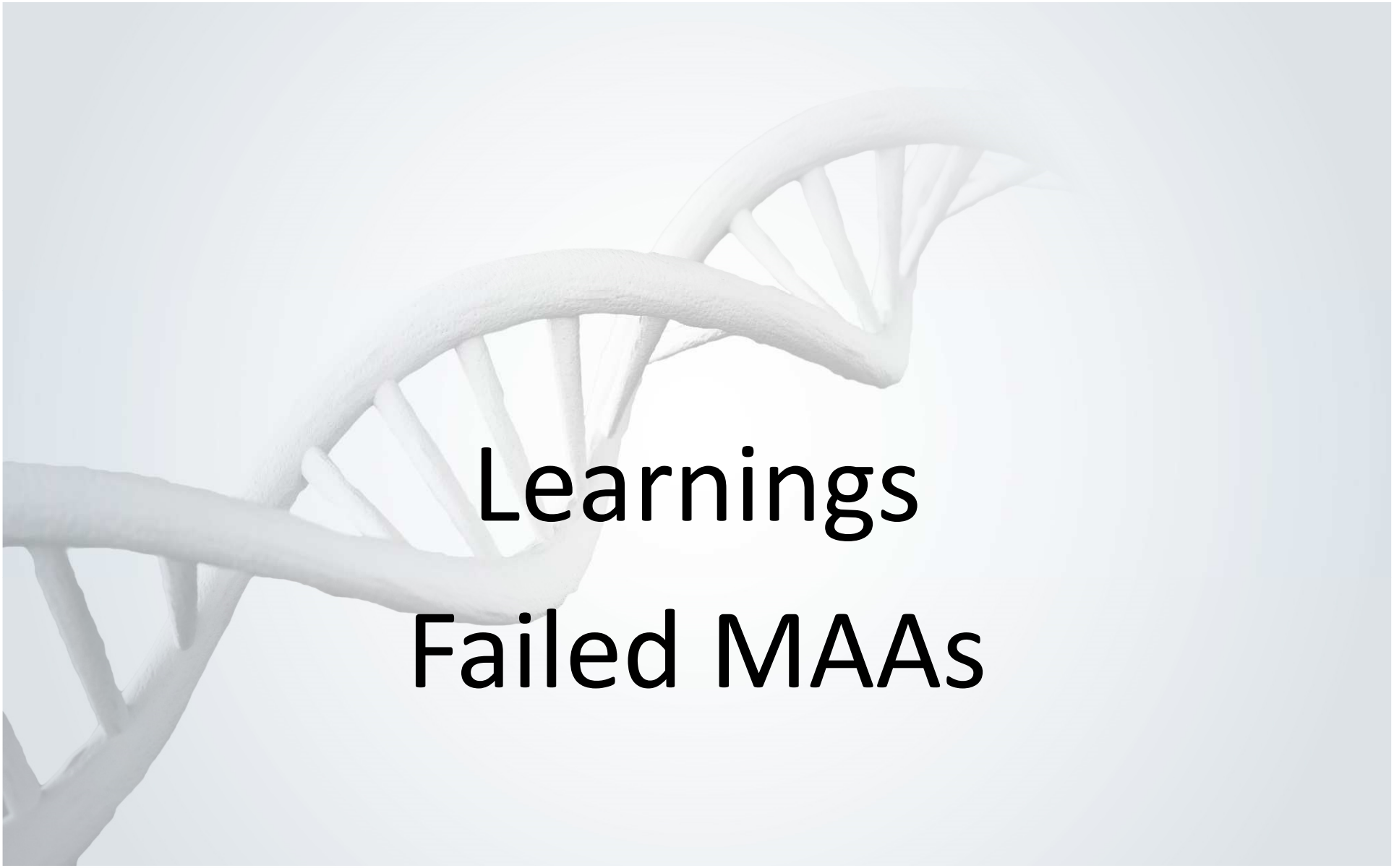
6

The opportunity case

- approved since 25 years
- therapeutic protein of 1296 AA, heterodimer
- originally used for treatment of strabismus, convulsion of eye lid
- *total sales estimate: 15.7 billion
- Question: which product is this?

The example:

Will be shown during the conference



Learnings Failed MAAs

Major clinical findings in failed MAAs*

- Proof of product rationale insufficient
- Magnitude of clinical effect insufficient
- Methodological flaws in the pivotal study design, e.g.
  - Lack of appropriate comparator
  - Heterogeneous study population
  - Weakness of endpoints, determination thereof
- Handling of safety findings inappropriate
- Lack of an integrated approach

*adapted from Schneider & Schäffner-Dallmann, Nature Reviews Drug Discovery, 2008

Key for success at the time of authorization

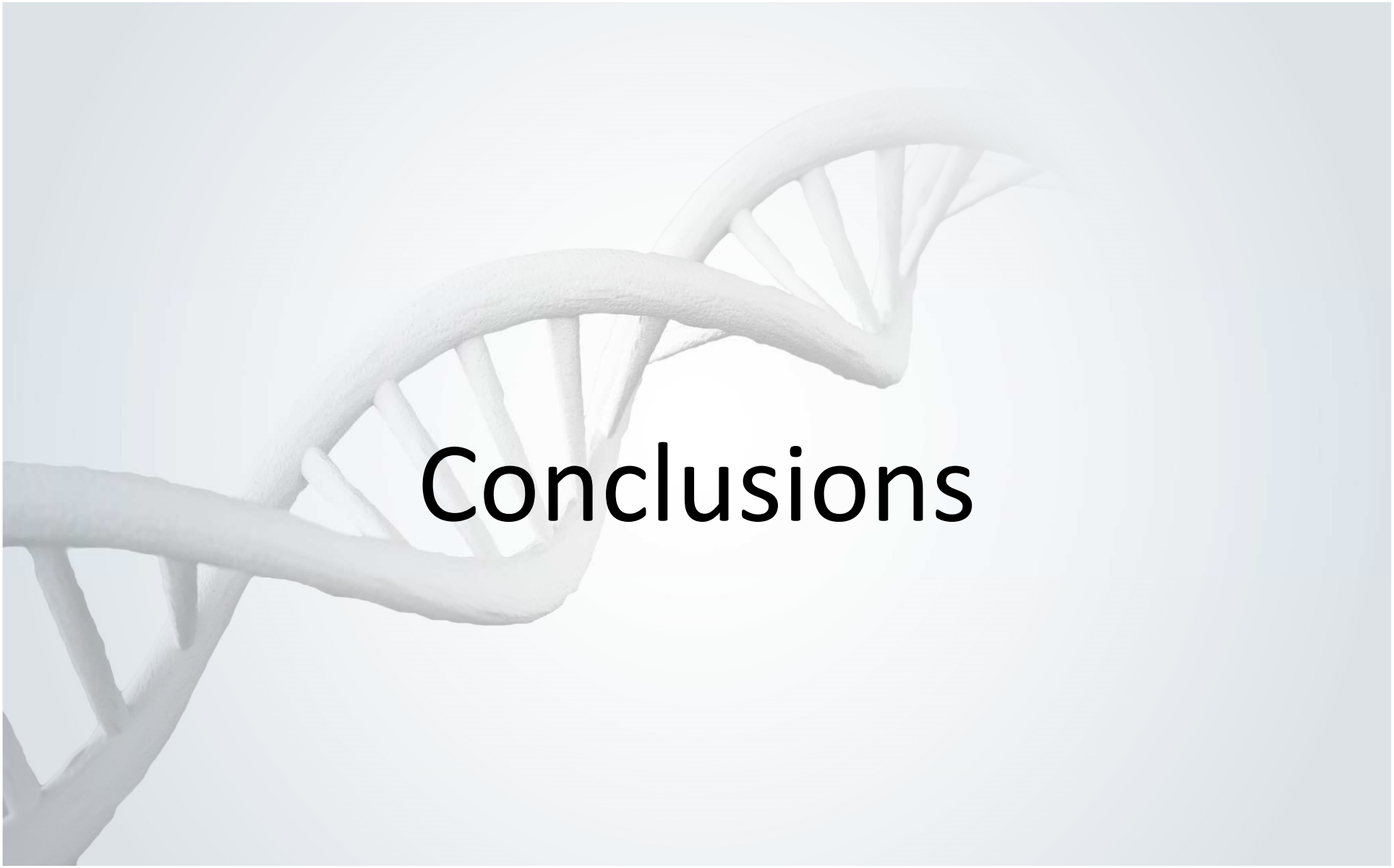
An integrated program to achieve a positive benefit-risk ratio

Key success criteria for clinical development (1)

- First of all, integrate your approach
  - Select your lead candidate wisely (consider immunogenicity, potency, patents)
  - Bridge non-clinical results incl. limitations to clinical trial design
  - Bridge clinical findings to post approval risk management plan
- Appropriate proof of product rationale
  - Demonstrate the anticipated mechanism of action
  - Link to pathogenesis of disease
  - Understand potential non-target effects
- Enhance magnitude of clinical effect
  - Sufficiently homogeneous target population, consider biomarker
  - Select your lead indication wisely (highest chance for success)
  - Consider combinations early on

Key success criteria for clinical development (2)

- Well-designed pivotal study/ies
  - appropriate comparator(s), anticipate changes in the landscape, pricing/reimbursement!
  - find balance between sufficiently homogeneous and relevant study population
  - choose appropriate endpoints and assessment schedules
  - consider appropriate timing of different studies (back-up strategy)
- Appropriate handling of safety findings
  - Thorough assessment algorithm: related?, predictable?, limited?, reversible?
  - Consider counter measures
  - Proactive risk management strategy and plan
  - Reflect findings in labeling
  - Post approval studies to fill in the gaps
  - Collection of long term data (consider early!)



Conclusions

Conclusions – general

- Expect the unexpeted! – This is reality in drug development and FUN
- Once expected, the challenges become smaller and better to handle
- You have strategic options

Conclusions – strategic options

Prevention

- Prevent predictable challenges by integrated, multidisciplinary planning

Treatment

- Handle remaining challenges as they occur

Transformation

- Consider to transform challenges into opportunities

Creation

- Be open for the unexpected and create new opportunities

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