

Carcinogenicity Assessment of Biologics

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Carcinogenicity Assessment of Biotechnology-derived Pharmaceuticals

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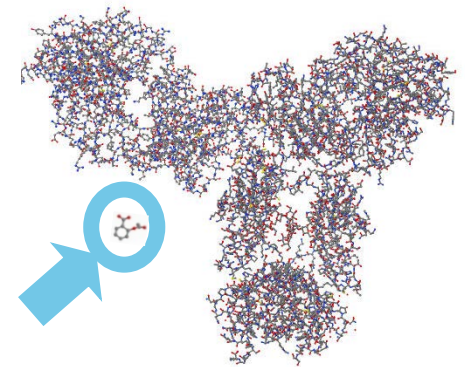
Small versus Large Molecules

◆ Small molecule pharmaceuticals

- Chemically-synthesized small molecules (up to 500 – 800 Da), which are capable of crossing cell membranes / entering the nucleus
- May be metabolized to active / genotoxic intermediates
- DNA interaction possible
- Toxicities are mostly due to off-target effects

◆ Biotechnology-derived pharmaceuticals

- Protein therapeutics manufactured in living cells
- Large molecules (around 3 KDa up to 150+ KDa) which require specific transport mechanisms to enter cells
- Direct interaction with DNA / other chromosomal material is highly unlikely and metabolic degradation pathway is of no concern
- Toxicities are primarily on-target effects (“exaggerated pharmacology”)



Carcinogenicity versus Genotoxicity



◆ Carcinogenicity

- The ability of a carcinogen to cause cancer
- A carcinogen is an agent whose administration to animals leads to a statistically significant increased incidence of neoplasms compared to untreated controls (*Casarett & Doull*)
- Neoplasm is a heritably altered, relatively autonomous growth of tissue (*Casarett & Doull*)

◆ Genotoxicity

- The ability of an agent to damage or alter the genetic information (DNA)

◆ Carcinogenicity can be a result of a genotoxic insult, but can also be induced by nongenotoxic mechanisms

Biologics and Carcinogenicity Assessment

“The assessment of a carcinogenic potential or the ability to promote tumor growth are among the most challenging areas in the nonclinical assessment of bio-therapeutics

In the initial development of these therapies, there appeared to be a perception that bio-therapeutics were exempt from carcinogenicity concerns

This perception was largely based on the fact that two-year rodent studies were often not possible and genotoxicity concerns typically do not exist for biologics

*With the rapid expansion of new bio-therapeutics and targets, increased attention has been directed toward carcinogenicity assessments” **

* Vahle JL et al. (2010) Toxicol Pathol 38: 522-33

Is There a Cause for Concern for Biologics?

- ◆ There is little to no concern that bio-therapeutics may induce a genotoxic insult or act as complete carcinogens
- ◆ But there is concern that bio-therapeutics may increase the incidence of existing neoplasms by secondary mechanisms related to their pharmacology, e.g.:
 - Promotion of growth / cell differentiation / proliferation
 - Enhanced cell proliferation can increase the probability of neoplastic progression
 - Immunomodulation
 - Chronic immune activation (inflammation) enhances the risk of neoplastic progression
 - Suppression of anti-tumor immune responses can foster carcinogenicity
 - Immune suppression may activate latent oncogenic viruses (e.g. HPV, EBV)

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Regulatory Guidance

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

**PRECLINICAL SAFETY EVALUATION OF
BIOTECHNOLOGY-DERIVED PHARMACEUTICALS
S6(R1)**

Parent Guideline dated 16 July 1997

Current *Step 4* version

Addendum dated 12 June 2011 incorporated at the end of June 2011

Primarily focused on small
molecules



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

**GUIDELINE ON THE NEED FOR CARCINOGENICITY STUDIES
OF PHARMACEUTICALS
S1A**

Current *Step 4* version

dated 29 November 1995

Exclusively focused on bio-
therapeutics



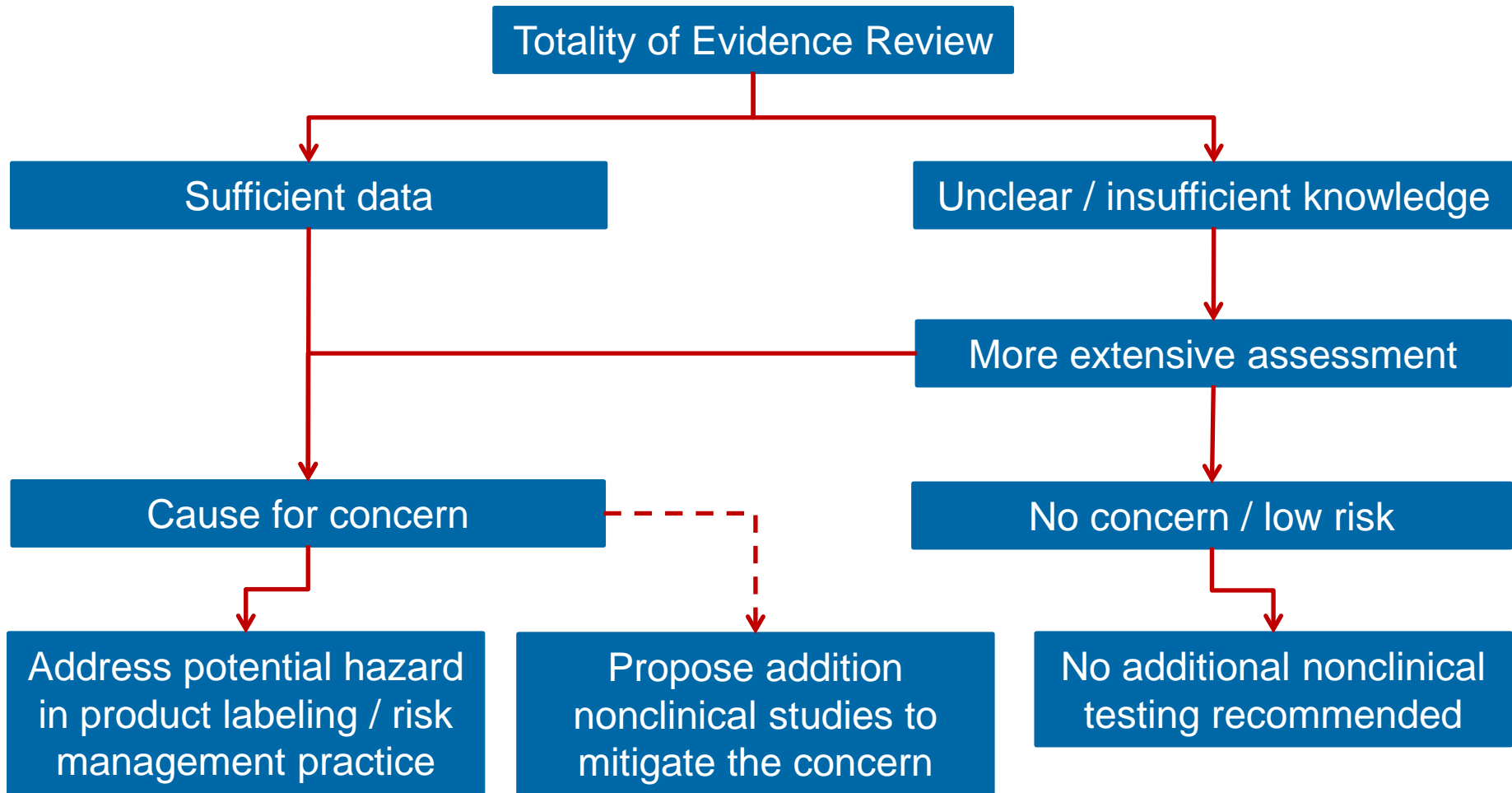
ICH S6 – General Approach

- ◆ *The need for a **product-specific assessment** of the carcinogenic potential for biopharmaceutical should be determined with regard to the intended **clinical population and treatment duration***
 - Expected clinical use is continuous for at least 6 month or frequently intermittent to treat chronic / recurrent conditions (ICH S1A)
 - “Case-by-case approach” based on scientific justifications guided by the specific product characteristics (ICH S6R1)
 - Consider target biology, clinical indication / medical need / life-expectancy and special risk factors in the target population (ICH S1A)

ICH S6 – Totality of Evidence Review

- ◆ *When an assessment is warranted, the sponsor should design a strategy to address the potential hazard...This strategy could be based on a **weight of evidence approach***
 - Review of data from various sources
 - Published data, e.g.; tg / KO models, animal disease models, human genetic diseases, epidemiology data
 - Information on class effects
 - Data on target biology / mode of action including down-stream signaling
 - Available *in vitro* / *in vivo* (especially chronic toxicity) and clinical data

ICH S6 – Totality of Evidence Review



ICH S6 – Risk Communication

- ◆ *The product-specific assessment of carcinogenic potential is used to **communicate risk** and provide input to the risk management plan along with **labeling proposals**, clinical monitoring, post-marketing surveillance, or a combination of these approaches*
 - Localization of carcinogenicity information in the label

US Label (21 CFR 201.56 /57)	EU SmPC (EMA Guideline on Summary of Product Characteristics)
Boxed Warning	4.4 Special Warnings and Precautions for Use
5 Warnings and Precautions	4.8 Undesirable Effects
6 Adverse Events	5.3 Preclinical Safety Data
13 Nonclinical Toxicology	Annex II C Other Conditions and Requirements of the Marketing Authorization
17 Patient Counseling Information	

Infliximab (Remicade®) Label Information

- ◆ Monoclonal antibody against TNF- α for the chronic treatment of various auto-immune type diseases, e.g. Crohn's disease, RA, psoriasis

WARNING: SERIOUS INFECTIONS and MALIGNANCY

See full prescribing information for complete boxed warning
SERIOUS INFECTIONS

- Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis) and infections due to other opportunistic pathogens.
- Discontinue REMICADE if a patient develops a serious infection.
- Perform test for latent TB; if positive, start treatment for TB prior to starting REMICADE. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)

MALIGNANCY

- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor (TNF) blockers, including REMICADE.
- Postmarketing cases of fatal hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF blockers including REMICADE. All REMICADE cases were reported in patients with Crohn's disease or ulcerative colitis, the majority of whom were adolescent or young adult males. All had received azathioprine or 6-mercaptopurine concomitantly with REMICADE at or prior to diagnosis. (5.2)

5.2 Malignancies

Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF-blocking agents (initiation of therapy \leq 18 years of age), including REMICADE. Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports.

Lymphomas

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The significance of the results of nonclinical studies for human risk is unknown. A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNF α to evaluate tumorigenicity. CV1q is an analog antibody that inhibits the function of TNF α in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide)

17.1 Patient Counseling

Patients or their caregivers should be advised of the potential benefits and risks of REMICADE. Physicians should instruct their patients to read the Medication Guide before starting REMICADE therapy and to reread it each time they receive an infusion. It is important that the patient's overall health be assessed at each treatment visit and that any questions resulting from the patient's or their caregiver's reading of the Medication Guide be discussed.

- Immunosuppression

Inform patients that REMICADE may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctors if they develop any symptoms of an infection, including tuberculosis and reactivation of hepatitis B virus infections. Patients should be counseled about the risk of lymphoma and other malignancies while receiving REMICADE.

Special Considerations Growth Hormones

- ◆ Theoretical concern of unwanted stimulation of growth / neoplastic progression of tumor cells
 - Growth factor receptors are constitutively expressed / up-regulated on tumor cells
 - Blockade of pathways important for tumor growth (e.g.: angiogenesis / bevacizumab: anti VEGF-A mAb) is used as anti-cancer therapy
- ◆ Potential risk mitigation strategies (staggered approach)
 - Analysis of target expression in various tumor tissues
 - *In vitro* mitogenicity assay (clinical relevance of in vitro cell proliferation to be determined)
 - *In vivo* analysis of cell proliferation (not warranted, if no finding suggestive of cell proliferation seen in repeat dose toxicity studies)
 - 2 year rodent bioassay (if feasible)

Special Considerations Immunomodulatory Drugs

- ◆ There is increasing epidemiologic evidence that chronic immunosuppressive therapy is associated with increasing incidences of certain tumor types
 - T cells, NK cells, dendritic cells and macrophages play a major role in tumor immunosurveillance
 - Several immunosuppressive biologics are associated with increased risk of lymphoma (and other malignancies), e.g.: anti-TNF- α mAb's, abatacept (CTLA-4-Ig fusion)
- ◆ Potential risk mitigation strategies (staggered approach)
 - Understand the immunological consequences of target engagement
 - Predictive value of rodent bioassay uncertain *
 - (Pre)neoplasia observed in NHP studies following reactivation of viral infection (difficult to standardize / interpret)

* Bugelski PJ et al (2010) Int J Toxicol 29(50): 435-66

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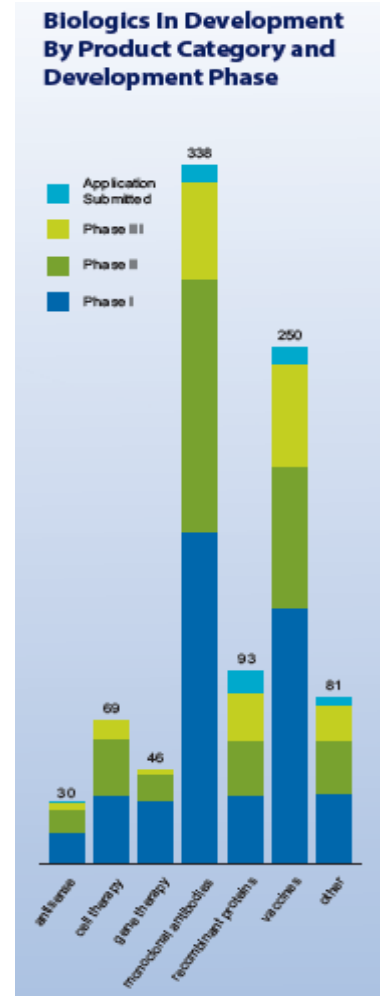
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Take Home Messages

Antibody Therapeutics

- ◆ Monoclonal antibodies are the major fraction of biologics in clinical development
 - 35 mAbs currently approved in EU / US and more than 300 in clinical development *
 - A broad variety of indications is targeted and a various administration paradigms / routes are employed



* US PhRMA Pipeline Report 2013

Antibody Therapeutics

◆ Genotoxicity and carcinogenicity data of approved mAb's

- No rodent bioassay data submitted
- All performed in vitro and / or in vivo genotoxicity assays negative
- 4 mAb's (all anti-TNF- α) have boxed warning for “lymphoma and other malignancies”

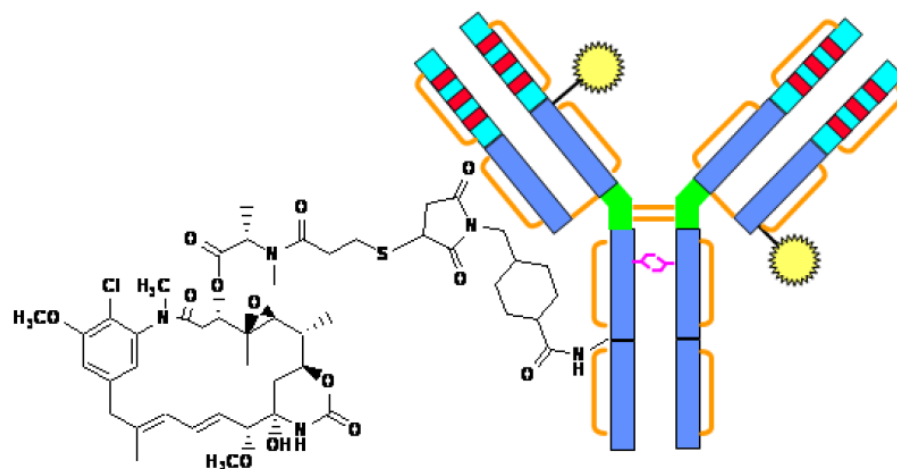
Genotoxicity	Carcinogenicity	Black Box	Warning & Precautions	Nonclin Toxicology
30% (9 / 30)	0% (0 / 30)	13% 4 /30	27% (8 / 30)	100% (30 /30)

◆ In general, impact of nonclinical data on labeling minimal

Natalizumab (Tysabri®)	Ustekinumab (Stelara®)	Ofatumumab (Arzerra®)
No effects in in vitro assays of α 4-integrin positive human tumor line proliferation/cytotoxicity. Xenograft transplantation models in SCID and nude mice with two α 4-integrin positive human tumor lines (leukemia, melanoma) demonstrated no increase in tumor growth rates or metastasis resulting from natalizumab treatment.	Published literature showed that administration of murine IL-12 caused an anti-tumor effect in mice that contained transplanted tumors and IL-12/IL-23p40 knockout mice or mice treated with anti-IL-12/IL-23p40 antibody had decreased host defense to tumors... The relevance of these experimental findings in mouse models for malignancy risk in humans is unknown.	In a repeat-dose toxicity study, no tumorigenic or unexpected mitogenic responses were noted in cynomolgus monkeys treated for 7 months

Antibody-Drug-Conjugates (ADC)

- ◆ ADC are developed for targeted tumor therapy in oncology indications
 - 2 ADC approved recently (Brentuximab vedotin / Adcetris®; T-DM1 / Kadcyra®) and 15+ molecules in clinical development
 - Consist of a small molecule (warhead) attached by a linker to an antibody
 - Small molecule is typically an anti-mitotic (MMAF, MMAE, DM1, DM4) or DNA breaking agent (calicheamicin)



Beck A et al. (2010) Discov Med 10(53): 329-39

Antibody-Drug-Conjugates (ADC)

- ◆ *In vitro* and *in vivo* genotoxicity studies were conducted with warhead
 - Both ADC were concluded as clastogenic / aneugenic

Test System	Adcetris® (MMAE) *	Kadcyla® (DM1) **
Ames Assay	Negative	Negative
Mouse Lymphoma Assay	Negative	NA
Rat Micronucleus Assay <i>in vivo</i>	Positive	Positive

- ◆ No carcinogenicity studies were conducted */**

- Consistent with ICHS1A

- ◆ No impact on label / prescribing information */**

- Results were summarized in nonclinical toxicology section

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with brentuximab vedotin or the small molecule (MMAE) have not been conducted.

MMAE was genotoxic in the rat bone marrow micronucleus study through an aneugenic mechanism. This effect is consistent with the pharmacological effect of MMAE as a microtubule disrupting agent. MMAE was not mutagenic in the bacterial reverse mutation assay (Ames test) or the L5178Y mouse lymphoma forward mutation assay.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ado-trastuzumab emtansine.

DM1 was aneugenic or clastogenic in an *in vivo* single-dose rat bone marrow micronucleus assay at exposures that were comparable to mean maximum concentrations of DM1 measured in humans administered KADCYLA. DM1 was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay.

* Brentuximab vedotin EPAR 2012 / US Prescribing Information

** Ado-trastuzumab emtansine FDA Pharmacology Review 2013 / US Prescribing Information

Non-Antibody Bio-therapeutics

- ◆ Non-antibody protein therapeutics include recombinant (fusion) proteins / peptides of various sizes but also antisense / gene / cell therapy, and vaccines
 - Huge variety in nonclinical assessment strategies ranging from lack of rodent bioassay data (“mAb approach) over standard 2 year bioassays in one or two species (consistent with ICHS1B) up to addition of extensive mechanistic studies to mitigate a risk / finding (e.g. GLP-1 analogues)
 - For more “drug-like” molecules (e.g.: GLP-1 analogues), the nonclinical assessment strategy tend to follow the “standard” (small chemical) approach

GLP-1: Case Example for Risk Mitigation Strategy

- ◆ Exenatide (Byetta® / Bydureon®) and liraglutide (Victoza®) are approved for the treatment of type 2 diabetes
 - MoA: Mimicking the anti-hyperglycemic activity of endogenous GLP-1, mainly enhance glucose-dependent insulin secretion by pancreatic beta-cell
- ◆ A concern for a potential carcinogenic potential were raised by the FDA / EMA based on nonclinical data

	Exenatide	Liraglutide
Genotoxicity	Negative in standard package of in vitro and in vivo genotoxicity assays in bacteria, mammalian cells, and rodents	
Carcinogenicity (mouse / rat)	Increased incidence of benign thyroid C-cell adenomas at highest dose in female rats	C-cell adenoma / carcinoma in both species /sexes
Repeat-dose studies	No findings of concern	Reversible C-cell hyperplasia in mice but not rats or monkeys

GLP-1: Case Example for Risk Mitigation Strategy

- ◆ An extensive package of mechanistic studies was performed to investigate the human relevance
 - Analyses of GLP-1R on C-cells of human / toxicology species revealed a higher number of C-cells and GLP-1 expression in normal rat tissue compared to human tissue samples and a higher number of receptors per cell in rat cell lines compared to human suggest a greater sensitivity of rodents
 - Analyses of downstream signaling showed that liraglutide massively induced cAMP / calcitonin secretion in rat but only marginal in human cell lines
- ◆ Conclusion was that C-cell hyperplasia / tumors observed in the carcinogenicity studies are caused by a non-genotoxic mechanism for which rodents are particularly sensitive, i.e.: continuous release of calcitonin due to persistent activation of C-cell GLP-1 receptors and the accompanying increased demand for calcitonin synthesis.

GLP-1: Case Example for Risk Mitigation Strategy

- ◆ Nonclinical data did not impact exenatide (Byetta®) label
- ◆ Mechanistic studies ensured approvability but current label for liraglutide (Victoza®) contains boxed warning

WARNING: RISK OF THYROID C-CELL TUMORS

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors [see *Contraindications (4), Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)*].

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Carcinogenicity Assessment Strategy

- ◆ Identify potential / theoretical concerns early based on
 - Target biology, mode of action, published nonclinical evidence, prior clinical experience
 - Scrutinize relevance / validity of published data
- ◆ Adapt weight of evidence review as data emerge
 - Assess internal pharmacology / toxicology data for signals of concern
 - Monitor literature, external clinical data and regulatory interactions
- ◆ Agree Carcinogenicity assessment strategy with regulatory agencies
 - Pre-IND meeting (lack of chronic data problematic) or EoP2 meeting (may be too late in case additional investigations are recommended), CAC, EMA Scientific Advise
 - Carcinogenicity data usually required for BLA filing or even as PMC
 - Companies developing anti-PCSK9 mAb's received FDA guidance to submit a “thorough carcinogenicity assessment” early (EoP2) *

Standard Rodent Bioassay

- ◆ 2 year rodent bioassays are generally conducted for small molecules, despite controversial discussion about predictive value
 - Most bio-therapeutics are not cross-reactive to rodent targets due to exclusive species specificity (especially mAb's)
 - Studies in non-relevant species generally not warranted (ICH S6)
 - Even in case of rodent cross-reactivity, technical feasibility of traditional rodent bio-assays can be challenging
 - Lack of relevant pharmacology in rodent species
 - Immunogenicity consequences during long-term exposure
 - Use of a surrogate (homologous) protein to the clinical candidate is discouraged
 - Translatability of results uncertain
 - The surrogate is a unique molecule and may differ in various attributes (e.g. sequence, binding affinity, manufacturing, PK)

Alternative Assessment in Standard Repeat Dose Studies

- ◆ Standard repeat dose toxicity studies can pick-up signals for a potential carcinogenicity risk, e.g.: preneoplasia (hyperplasia, cellular hypertrophy, and atypical cellular foci) or immune suppression *
- The NHP as model for carcinogenicity testing is considered impractical **
 - Long life-span (approx. 25 – 30 yrs compared to approx. 2 yrs in rats)
 - Chronic study duration usually 6 month for biologics (approx. 2% of overall life-span compared to almost 100% coverage in rodents (absence of evidence ≠ evidence for absence)
 - Statistical power of NHP studies (n = 3 – 4 animals / dose / sex) low
- Longer study duration in NHP to gain additional data on carcinogenicity?
 - Technical feasible extension period, e.g. 12 instead of 6 month would add only a few percent treatment duration relative to the overall life-span
 - Low background incidence of neoplastic lesions require treatment period of 5 – 10 yrs required to demonstrate detectable background tumor incidences ***/**

* Reddy MV et al. (2010) Vet Pathol 47(4): 614-29

** Gold LS et al. (1999) Environ Health Perspect 107(4): 527-33

*** Chamanza R et al. (2010) Toxicol Pathol 38(4): 642-57

**** Schoeffler DJ & Thorgeirsson UP (2000) In Vivo 14: 149-56

Case Example #1: Antibody X

◆ Human monoclonal antibody

- MoA: Antagonist of soluble target preventing target interaction with receptor
- Indication: Chronic inflammatory diseases

◆ Available data

- Internal data
 - NHP single toxicology species, no rodent cross-reactivity
 - No adverse findings or neoplastic/pre-neoplastic lesions in NHP repeat dose studies up to 6 months
- External data
 - Hodgkin's lymphoma associated with target blockade
 - However, there are also data to suggest blockade of target could have beneficial effects
 - Target may have anti-proliferative properties towards certain tumor cells and may also negatively impact anti-tumor immunity

Case Example #1: Antibody X

◆ Regulatory interaction at pre-IND meeting

- Company position: No genotoxicity / carcinogenicity studies required
- FDA position: Agreed on genotoxicity waiver but requested evaluation of carcinogenic potential in one species unless company is able to provide evidence that not possible; consider use of KO model or surrogate

◆ Options **considered and ruled out** for *in vivo* carcinogenicity assessment

- Rodent bioassay: Not possible because of lacking rodent cross-reactivity
- Target deficient mice: Literature suggests gene disruption may affect other nearby genes, so KO data may not be reflective of impact to only target
- Surrogate molecule: Available reagent had acceptable *in vitro* potency but lacked *in vivo* potency (i.e. unlikely to provide clinically meaningful data)
- Use of clinical product in humanized target tg mice: Species mismatch likely to result in immunogenicity, confounding data interpretation

Case Example #1: Antibody X

◆ Further regulatory interactions

- Final company position: Given the lack of suitable reagent/model options to provide clinically meaningful data, proposed to use results from the completed repeat dose studies in cynomolgus monkeys to provide nonclinical risk assessment information regarding carcinogenic potential following chronic administration
- Agency questioned that the absence of pre-neoplastic lesions in NHP after a 6 month treatment period ruled out carcinogenic potential and requested to robustly evaluate the target deficient (KO) mouse as potential model for *in vivo* assessment
- Detailed assessment of gene deficient mice concluding that this model is not suitable for *in vivo* assessment submitted to agency

Case Example #1: Antibody X

◆ Detailed assessment of gene deficient mice submitted to agency

- Lack of regulatory, logistical, and study design precedence with use of target gene deficient mice
- Gene deficiency represents an all or none and represents a life-time deficiency with adaptations and other phenomena not indicative of the clinical situation
- Various examples of unexpected deficiency phenotypes and examples of the impact of strain on gene deficient mouse phenotype were reviewed
- Differences in target pharmacology in mouse and man with potential to confound study interpretation were assessed
- Final conclusion: Propose not to conduct 2 year study in gene deficient mice

◆ Final FDA response

- 2 year study in gene deficient mice not required but monitor patients for potential development of tumors

Case Example #2: Antibody Y

◆ Humanized monoclonal antibody

- MoA: Depletion of (non-T non-B) immune cells expressing target receptor
- Indication: Chronic inflammatory diseases

◆ Available data

- Internal data
 - NHP single toxicology species, no rodent cross-reactivity
 - No adverse findings or neoplastic/pre-neoplastic lesions in NHP repeat dose studies up to 9 months
- External data
 - Target cells found in association with solid tumors (especially of epithelial origin but any role in tumor growth remains unclear
 - Some clinical studies suggest target cell presence may be a positive prognostic indicator of cancer patient survival
 - Nonclinical data are mixed

Case Example #2: Antibody Y

- ◆ Options considered and ruled out for *in vivo* carcinogenicity assessment
 - Rodent bioassay: Not possible because of lacking rodent cross-reactivity
 - Target deficient mice: KO mice have reduced levels of, but are not depleted of target cells – differs from product MOA so clinical relevance questionable
 - Alternative target deficient mice: Deficient for other genes that results in depletion of the target cells, but the absence of those genes also has other pharmacological effects inconsistent with the targeted MoA
 - Some other pharmacological differences in mice regarding target cell depletion are likely
 - MoA-based cell depletion in humans can not be completely replicated in rodents due to differences between species in MoA, therefore surrogate molecule unlikely to provide clinically meaningful data

Case Example #2: Antibody Y

◆ Regulatory interaction at EoP2 meeting

- Final company position: Given the lack of suitable reagent/model options to provide clinically meaningful data, proposed to use results from the completed repeat dose studies in cynomolgus monkeys to provide nonclinical risk assessment information regarding carcinogenic potential following chronic administration
- EMA endorsed proposal but asked to pay attention to available information of target on cellular instability, cell division processes, cellular communication, apoptosis, as well as any impact on immune function, with a weight of evidence approach advised
- FDA agreed that carcinogenicity risk assessments is sufficient to support initiation of the planned clinical trials but requested to monitor patients for potential development of tumors
- FDA concluded that it is unlikely that additional nonclinical studies would be required for the filing of a BLA

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Take Home Messages

Take Home Messages

- ◆ The expanding target diversity and increasing number biologics in development has focused attention toward carcinogenicity assessments
 - There is little to no concern that bio-therapeutics may induce a genotoxic insult or act as complete carcinogens but there is concern that bio-therapeutics may increase the incidence of existing neoplasms by secondary mechanisms, non-genotoxic mechanisms
- ◆ ICH S6(R1) require a weight of evidence approach to assess the carcinogenicity potential (if warranted)
- ◆ The product-specific assessment of carcinogenic potential is used to communicate risk and provide input to the risk management plan along with labeling proposals, clinical monitoring, post-marketing surveillance, or a combination of these approaches
- ◆ Develop the nonclinical assessment strategy early and align with regulatory expectations

Acknowledgement

- ◆ Scott Manetz, PhD DABT, Biologics Safety Assessment, MedImmune LLC Gaithersburg



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