2018

ICH GUIDELINE TRAINING

NIFDS

KoBIA & KRPIA

ICH S9 가이드라인 QnA 개요

PMDA Keiji Hirabayashi

An Overview of ICH S9 Guideline Questions and Answers

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Pharmaceuticals and Medical Devices Agency

Disclaimers

The views expressed in this presentation are those of the presenter and do not necessarily reflect the official views of Pharmaceuticals and Medical Devices Agency (PMDA).

Contents

Contents

ICH Safety Guidelines

S1: Carcinogenicity

S2(R1): Genotoxicity

S3: Toxicokinetics and pharmacokinetics

S4: General toxicity

S5(R2): Developmental and reproductive toxicity

S6(R1): Preclinical safety evaluation of biopharmaceuticals

S7: Safety pharmacology

S8: Immunotoxicity

S9: Nonclinical evaluation of anticancer pharmaceuticals / Q&As

S10: Photosafety evaluation

M3(R2): Nonclinical safety studies for human clinical trials and marketing authorization / Q&As

M7(R1): Assessment and control of genotoxic impurities

The Principle of Nonclinical Evaluation for Anticancer Pharmaceuticals is Unique

Other diseases

ICH M3(R2) guidance

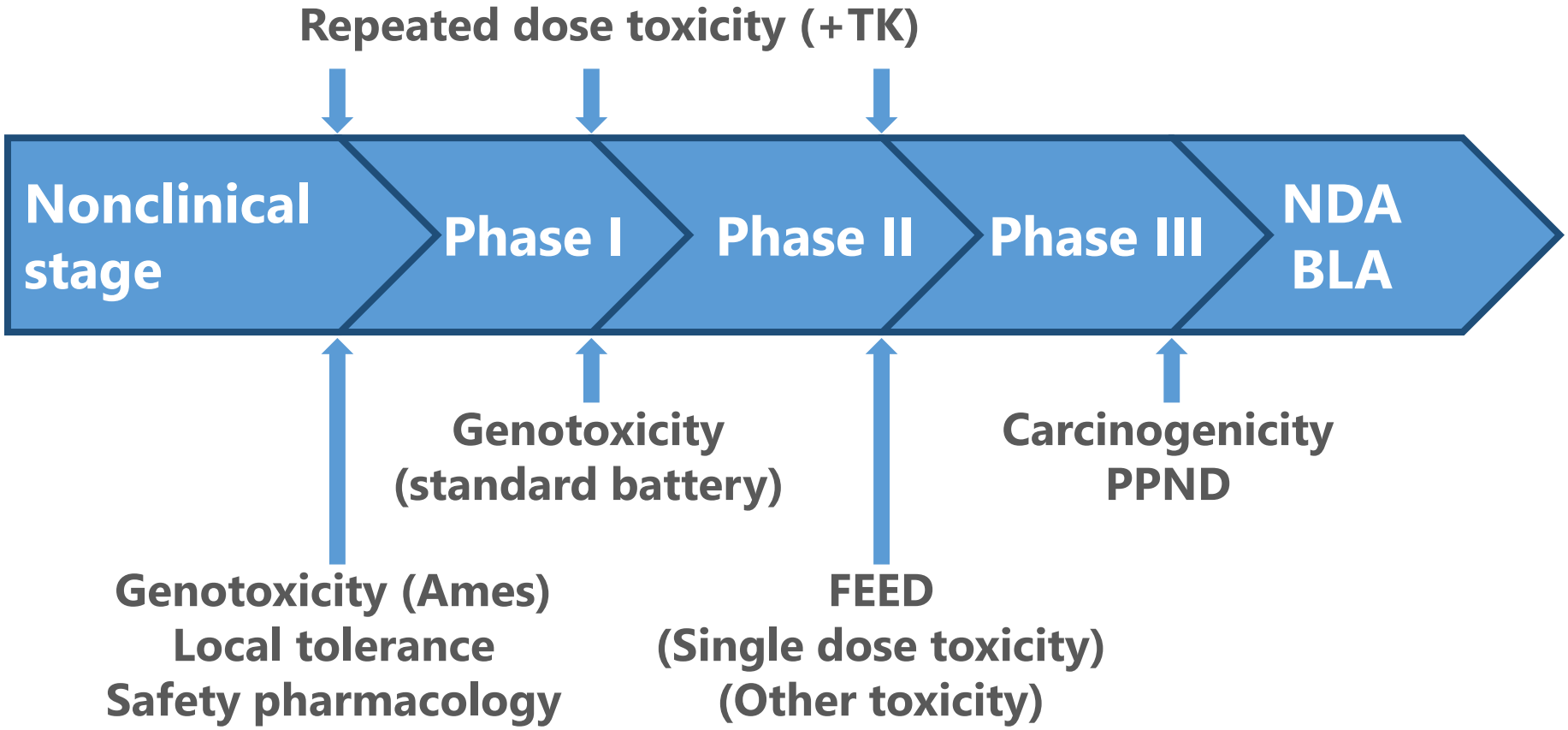
"Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals"

Cancers with serious and life-threatening malignancies

ICH S9 guideline

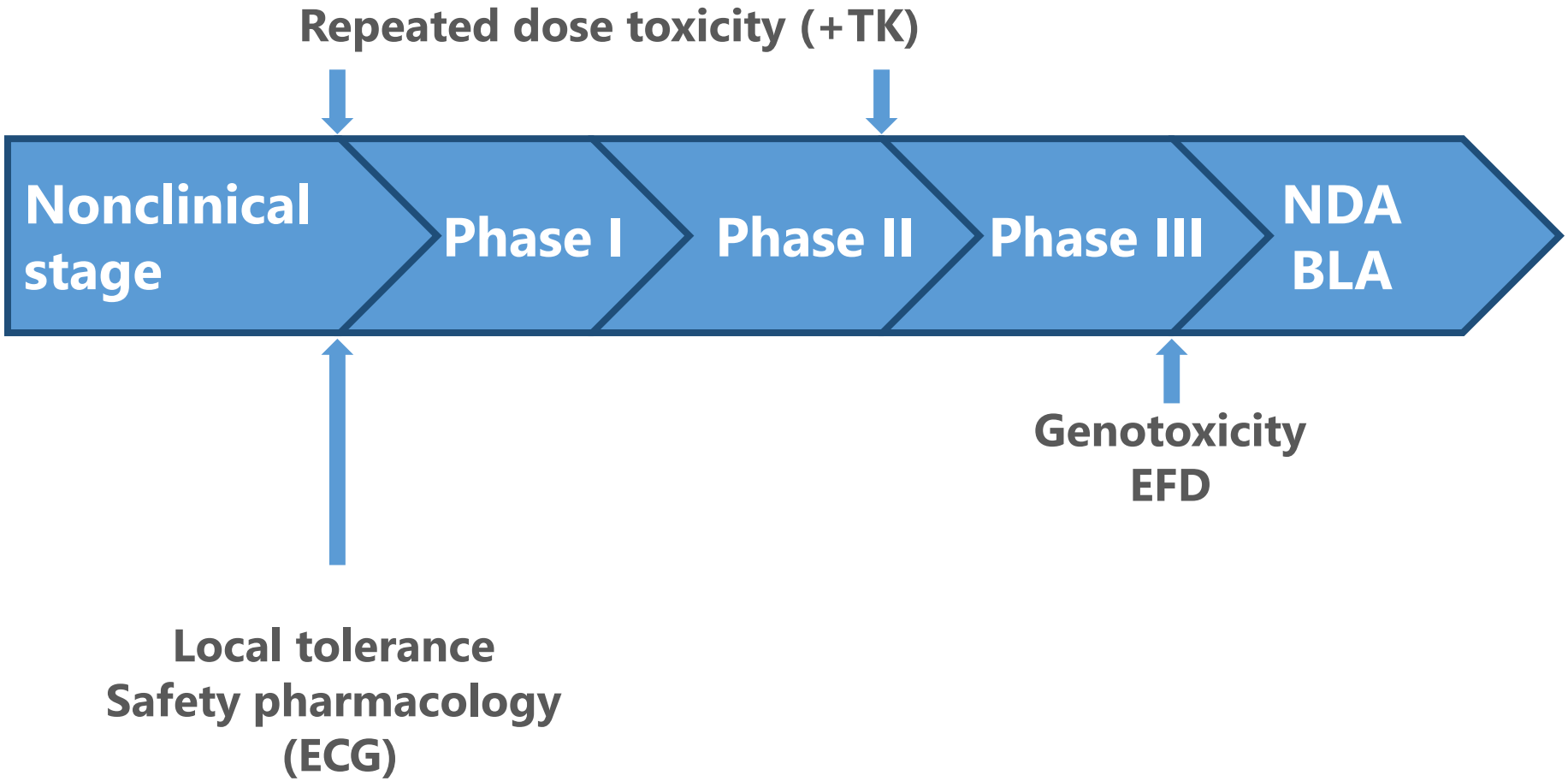
"Nonclinical evaluation for anticancer pharmaceuticals"

Example of Timing of Toxicity Studies (ICH M3(R2))



EFD: before including women with child-bearing potential

Example of Timing of Toxicity Studies (ICH S9)



History of ICH S9 and the Q&As

ICH S9

Oct, 2009	ICH S9 reached to Step 4
Jun, 2010	ICH S9 was notified in Japan (Step 5)

ICH S9 Q&As

Oct, 2014	ICH S9 Q&As Implementation Working Group was formed
Apr, 2018	ICH S9 Q&As reached to Step 4

Objectives of ICH S9 Q&As

To clarify interpretation of the original guideline

The Number of Q&As for each Chapter

ICH S9 Chapter	No. of Q&As
1. INTRODUCTION	7
2. STUDIES TO SUPPORT NONCLINICAL EVALUATION	12
3. NONCLINICAL DATA TO SUPPORT CLINICAL TRIAL DESIGN AND MARKETING	7
4. OTHER CONSIDERATIONS	15
5. NOTES	

The Number of Q&As for each Chapter

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5. NOTES	

ICH S9
1. INTRODUCTION

1.1 Objective of the Guideline

1.2 Background

1.3 Scope

1.4 General Principles

Scope
(Patient Populations)

Question 1.3

In general, the guidance has been interpreted as applying when the patient's life expectancy is approximately 3 years. It would be useful to provide further clarity about the intended population.

Answer

The ICH S9 Guideline does not make a reference to years of life expectancy and the application of the guideline should not be based on an expectation of survival as measured in years. „

Scope
(the type and timing of tox. studies)

Question 1.6

In the case where a therapeutic increases survival, what further toxicology work is recommended, and what is the appropriate timing of any studies ?

Answer

When the anticancer pharmaceutical is shown to extend survival of patients, **no additional general toxicology studies are usually warranted.** The clinical safety data in the intended population is more relevant to assess human risks than those generated in additional animal studies. ,,,

Scope
(the type and timing of tox. studies)

Question 1.6 (continued)

In the case where a therapeutic increases survival, what further toxicology work is recommended, and what is the appropriate timing of any studies ?

Answer (continued)

„. If additional studies are deemed important, such studies **could be submitted post approval** of the anticancer pharmaceuticals. „

Scope
(the type and timing of tox. studies)

Question 1.7

Are additional nonclinical safety tests needed, when an anti-cancer pharmaceutical „„ is to be applied to another oncology indication that is not immediately life-threatening, but is serious ?

Answer

„„ **additional general toxicology studies e.g., chronic studies (6- or 9-month-studies) are generally not warranted.** „„ Toxicology studies **other** than general toxicology may be needed on **a case-by-case basis**.

Summary 1/2 (Patient Populations)

- Initial development programs in cancer that is **resistant and refractory** to available therapy
- Initial development programs in cancer that is **not resistant and refractory** (Q&A 1.1)
- Adjuvant or neo-adjuvant setting (Q&A 1.5)

ICH S9 should be used as a starting point.

Summary 2/2
(the type and timing of tox. studies)

- **No additional general tox. studies** are usually warranted.
- Other tox. studies (e.g., carcinogenicity or reproductive and developmental tox. studies) may be needed on a **case-by-case** basis.
- Additional studies could be submitted **post approval**.

Flexibility is accepted.

ICH S9
2. STUDIES TO SUPPORT NONCLINICAL EVALUATION

2.1 Pharmacology

2.2 Safety Pharmacology

2.3 Pharmacokinetics

2.4 General Toxicology

2.5 Reproduction Toxicology

2.6 Genotoxicology

2.7 Carcinogenicity

2.8 Immunotoxicity

2.9 Photosafety testing

General Toxicology (Recovery Groups)

Question 2.2 and 2.3

Should recovery groups be included:

- in toxicology studies to support FIH study ?
- in 3-month toxicology studies to support Phase III ?

Answer

A scientific assessment of the potential to recover from toxicity **should be provided** for general toxicology studies used to support clinical development, although recovery groups should not automatically be included in all general toxicology studies.

General Toxicology (Supportive Care)

Question 2.4

Is there a situation where adding supportive care drugs (e.g., antibiotics) to toxicology studies are appropriate ?

Answer

Treating affected animals with **supportive care** during toxicology studies **can be appropriate in some cases**, **e.g.,** when **secondary infection due to immunosuppression** is observed on the study. Giving supportive care prophylactically to all animals is generally not recommended.

Reproduction Toxicology (Need for a Definitive EFD Study)

Question 2.7

If clear evidence of embryofetal lethality or teratogenicity is observed in a dose-range finding study in one species, is a definitive study in that species recommended ?

Answer

A definitive study is generally **not warranted if** a dose-range finding study (including non-GLP) shows **clear evidence of embryofetal lethality or teratogenicity**. This dose-range finding study in a single species would be sufficient to support marketing.

Reproduction Toxicology (Non-human Primate Studies)

Question 2.9

- The only relevant species is a non-human primate (NHP).





- The mechanism of action is expected to yield a reproductive toxicity risk.
- Knockout animals or use of surrogate biologics in rodents have demonstrated a reproductive risk.

Should a study in pregnant NHPs be conducted ?

Reproduction Toxicology (Non-human Primate Studies)

Answer 2.9

- **A weight-of-evidence assessment** should be provided.
- An **NHP** study should **not** be **a default approach**.
- **If a clear risk** is indicated, an **NHP** study is **not warranted**.

Genotoxicity (*In vivo* Testing)

Question 2.11

Which and how many *in vitro* genotoxicity studies would need to be positive in order to make the *in vivo* genotoxicity assays unwarranted ?

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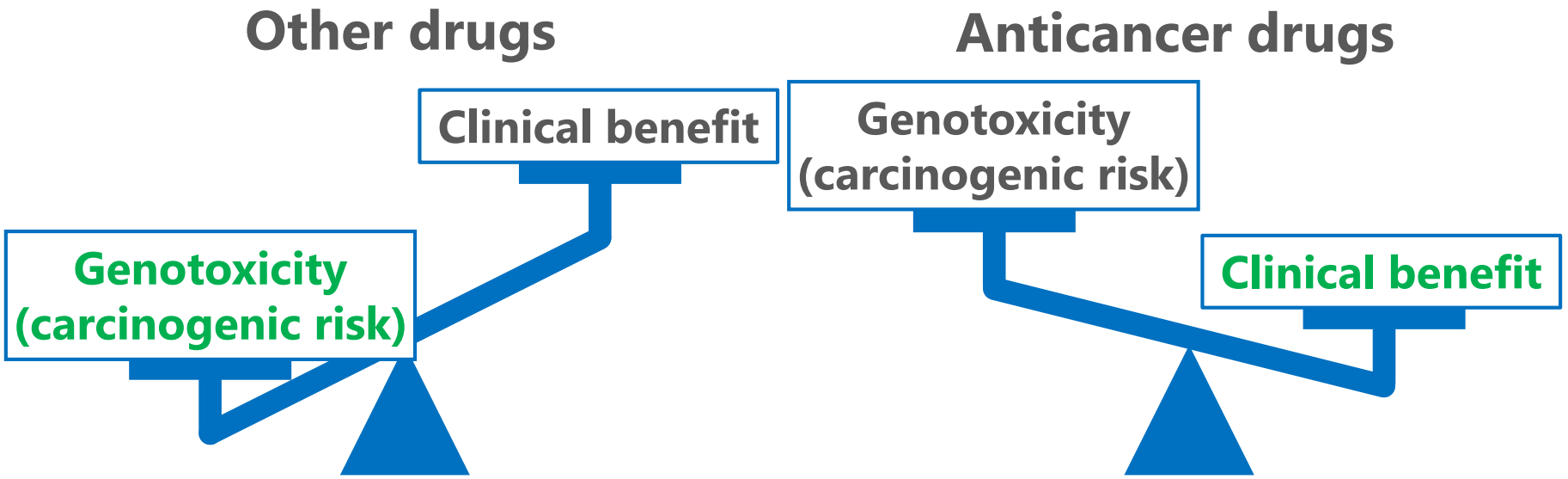


Genotoxicity (*In vivo* Testing)

Question 2.11

Which and how many *in vitro* genotoxicity studies would need to be positive in order to make the *in vivo* genotoxicity assays unwarranted ?

Answer

When the bacterial mutation (Ames) test is positive, then *in vivo* genotoxicity testing is not warranted. When the bacterial mutation assay is negative, but an *in vitro* chromosome damage test result is positive, *in vivo* genotoxicity testing should be considered.

Genotoxicity (*In vivo* Testing)

Bacterial mutation (Ames)	*In vitro* chromosome damage	*In vivo* genotoxicity
Positive	Negative or positive	Not needed
Negative	Positive	Needed

Answer

When the bacterial mutation (Ames) test is positive, then *in vivo* genotoxicity testing is not warranted. When the bacterial mutation assay is negative, but an *in vitro* chromosome damage test result is positive, *in vivo* genotoxicity testing should be considered.

Other Toxicities

Q&As 2.5, 2.6 and 2.10

- Abuse Liability
- Tissue Cross Reactivity
- Lactation and Placental transfer studies

generally not warranted.

Other Toxicities

Q&As 2.5, 2.6 and 2.10

- Abuse Liability
- **Tissue Cross Reactivity**
- Lactation and Placental transfer studies

generally not warranted.

In cases where there are no pharmacologically relevant species, **human tissue cross reactivity** or alternative methods **should be considered** for the first-in-human study.

3. NONCLINICAL DATA TO SUPPORT CLINICAL TRIAL DESIGN AND MARKETING

3.1 Start Dose for First Administration in Humans

3.2 Dose Escalation and the Highest Dose in a Clinical Trial

3.3 Duration and Schedule of Toxicology Studies to Support Initial Clinical Trials

3.4 Duration of Toxicology Studies to Support Continued Clinical Development and Marketing

3.5 Combination of Pharmaceuticals

3.6 Nonclinical Studies to Support Trials in Pediatric Populations

General Concept on Start Dose in First-in-Human (FIH) Study

Does a pharmaceutical indicate a clear risk ?

Yes ⬇

Pharmacological approach (e.g., MABEL)

⬇ **No**

Toxicological approach (e.g., NOAEL, STD_{10})

A pharmaceutical with a Clear Risk: Immune Agonist

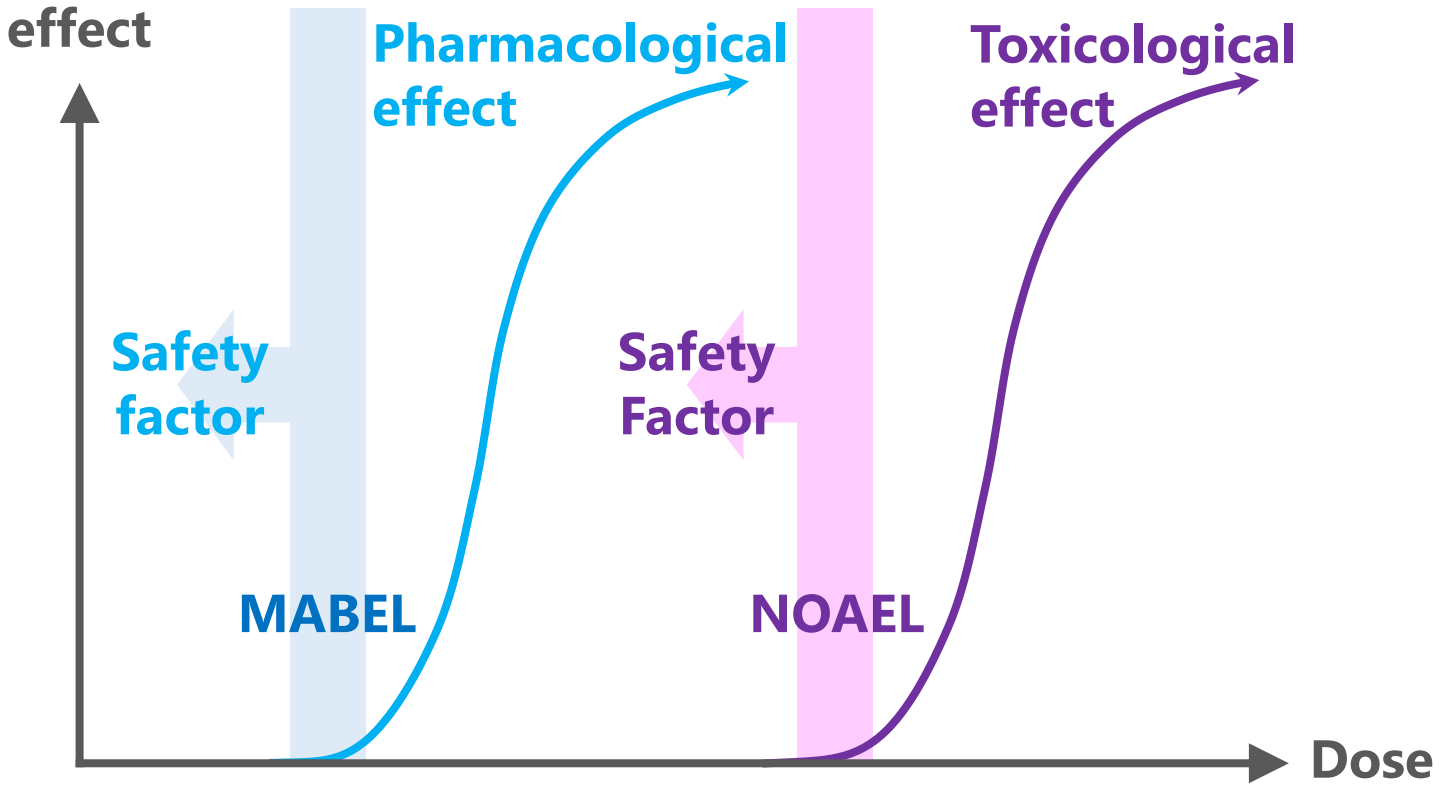
TGN1412

- 2006, UK
- TeGenero Immuno Therapeutics AG
- Autoimmune Disease, Chronic Lymphocytic Leukemia
- **Anti-CD28 superagonist antibody**
- Headache, fever, pain, vomiting, multiple organ dysfunction, etc. due to cytokine release syndrome


WRITHING PATIENTS SCREAMED THAT THEIR HEADS 'WOULD EXPLODE'

The living hell of guinea pig drug victims

MABEL approach and NOAEL approach



Start Dose (MABEL Approach)

Question 3.1

Small molecule drugs can also be immune agonists. Can a Minimally Anticipated Biological Effect Level (MABEL) approach also be used for small molecules ?

Answer

If appropriate, a MABEL could be used for small molecules using *in vivo* or *in vitro* data. This approach should be considered if risk factors are derived from knowledge of (1) the mode of action, (2) the nature of the target, and/or (3) the relevance of animal or *in vitro* models.

Start Dose (HNSTD)

Question 3.2

Is use of the highest non-severely toxic dose (HNSTD) to select an appropriate starting dose applicable to biopharmaceuticals ?

Answer

The HNSTD may be appropriate in determining a starting dose of a biopharmaceutical (e.g., when drug is **not an immune agonist**) taking into consideration differences in binding affinity between animals and humans and pharmacological properties of the biopharmaceutical (incl. ADCs).

Toxicology Studies to Support Clinical Trials

Question 3.3

In cases where the available toxicology information does not support a change in clinical schedules, what additional toxicology studies should be conducted, i.e., 1-month or 3-month toxicology study, if the 3-month studies with the original schedule have already been conducted ?

Answer

If needed, a study of **up to 1-month** duration should generally be sufficient to support a change in schedule and to support marketing.

Toxicology Studies to Support Clinical Trials

Initial clinical schedule/ 3-month toxicology study

A change in clinical schedule

Additional toxicology study

4. OTHER CONSIDERATIONS

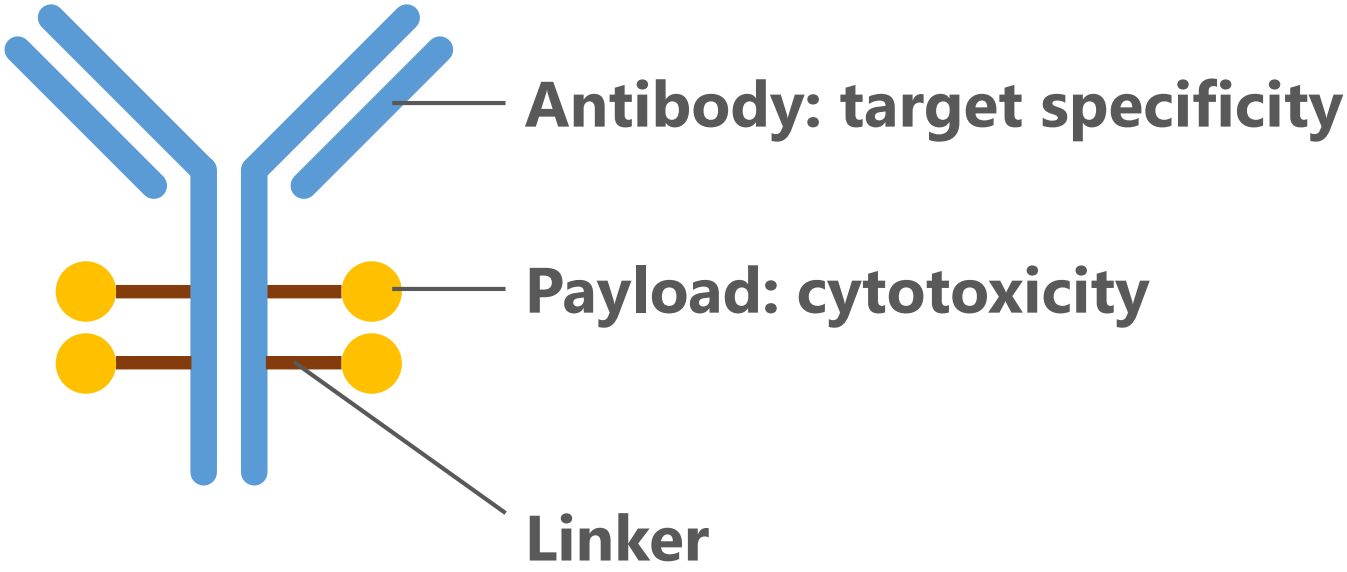
4.1 Conjugated Products

4.2 Liposomal Products

4.3 Evaluation of Drug Metabolites

4.4 Evaluation of Impurities

Antibody-Drug Conjugate



10 Q&As for ADC !!

Conjugated Products (Evaluation of Component)

Q&As 4.1~4.3

- **The whole ADC** molecule should be tested in **at least one species**.
- In general, studies of **the mAb alone** are **not** warranted.
- Evaluation of **the linker alone** is **not usually** warranted.

Conjugated Products (Evaluation of Payload)

Q&A 4.3

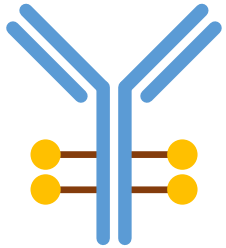
The pilot studies and the nature of the payload or payload with linker will determine what additional studies are appropriate.

If the toxicity of **the payload (+linker) is** „

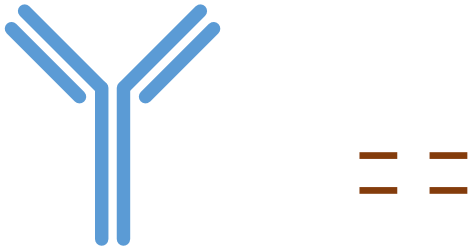
characterized:
GLP study may not be warranted or could be abbreviated.

not characterized:
The payload (+linker) could be **evaluated in one species**.

Antibody-Drug Conjugate



➡ **Should be tested at least one species.**



➡ **(In general) not warranted.**

➡ **Study with one species may be needed.**

Conjugated Products (First-in-human (FIH) Dose)

Question 4.6

Is there a recommended approach to setting a FIH starting dose for an ADC ?

Answer

- 1/10th the Severely Toxic Dose (STD) in 10% animals (**STD10**) **in rodents**
- 1/6th the Highest Non-Severely Toxic Dose (**HNSTD**) **in non-rodents**
- Other approaches are possible for new class of ADC.

FIH Dose of Antibody-Drug Conjugate (Saber and Leighton, 2015)

Approach	Species	Median number for doublings to reach human MTD/RP2D/AD
STD10 / 10 *	Rodent	3
HNSTD / 6 *	Monkey	2.5

* Human Equivalent Dose (HED) converted from dose in animals based on body surface area (BSA)

STD10

(1/10, HED conversion)

FIH Dose

x2

x2

x2

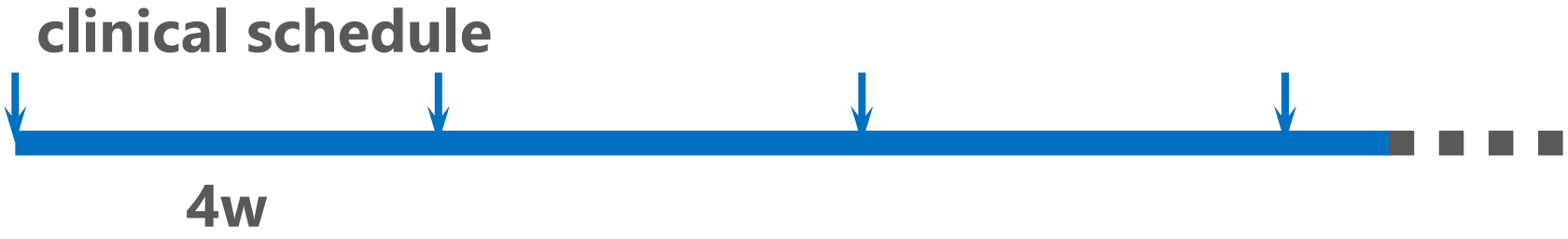
MTD

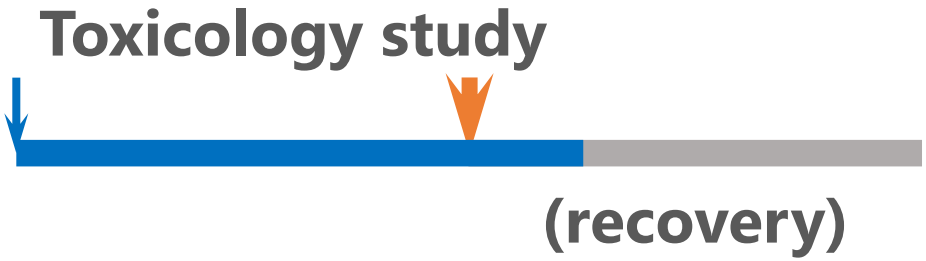
Acceptable !

Conjugated Products (Study Design)

Q&As 4.7

- **At least two doses** of the ADC should be administered for the initial **clinical trials of once every 3 or 4 weeks**.





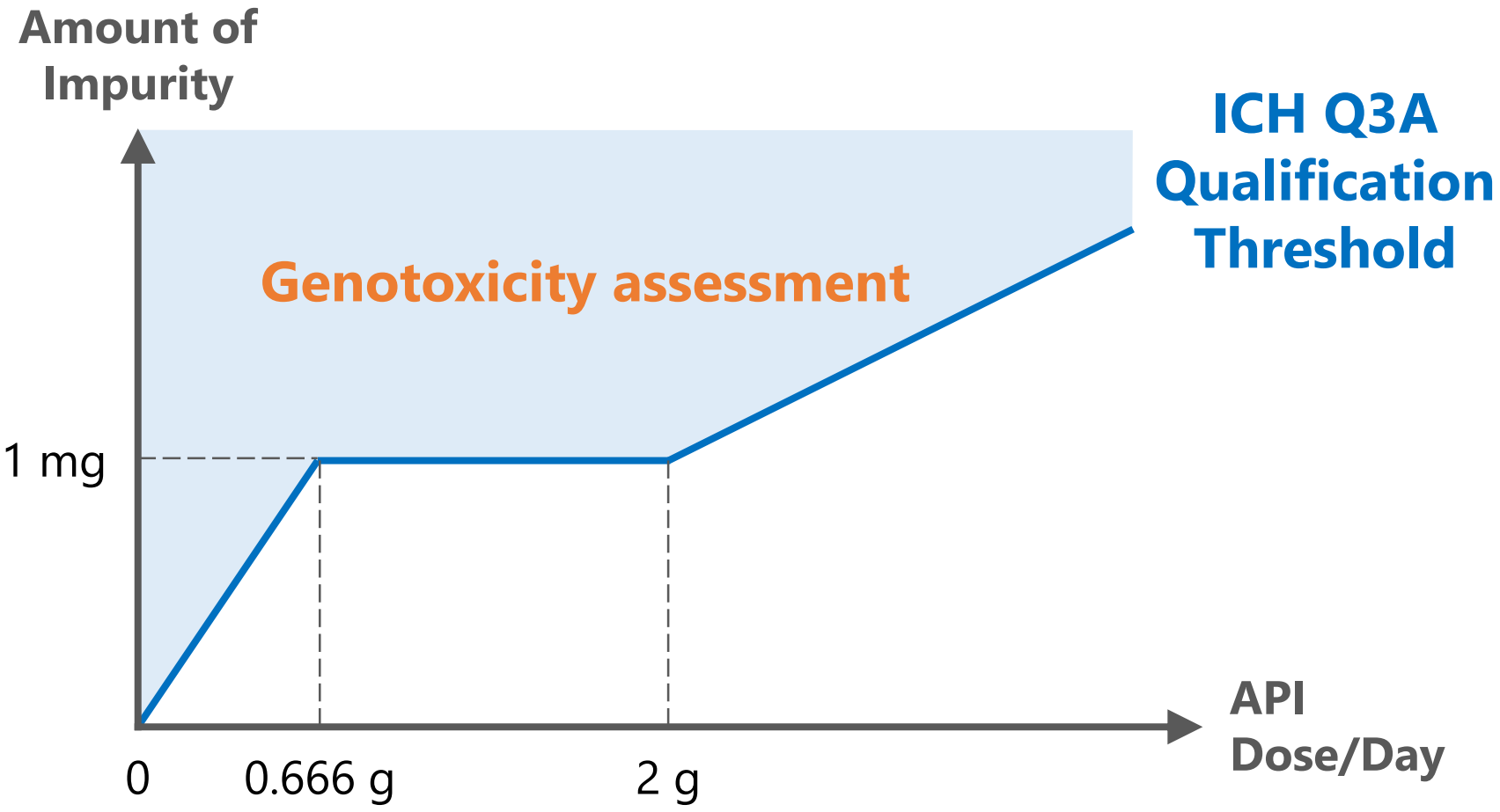
Conjugated Products (Study Design)

Q&As 4.8, 4.10

- If the epitope is **not present in nonclinical test species**, a tox. study in **one species** should be sufficient.

- When the antibody portion of an ADC binds **only** to human and **NHP** antigens, a tox. study in **only the NHP** would be appropriate.

Assessment of Impurities (e.g., ICH Q3A)



Assessment of Impurities (ICH Q3A/B)

Question 4.12

Should impurities exceeding the established qualification limits in ICH A3A/B be assessed in genotoxicity studies „,

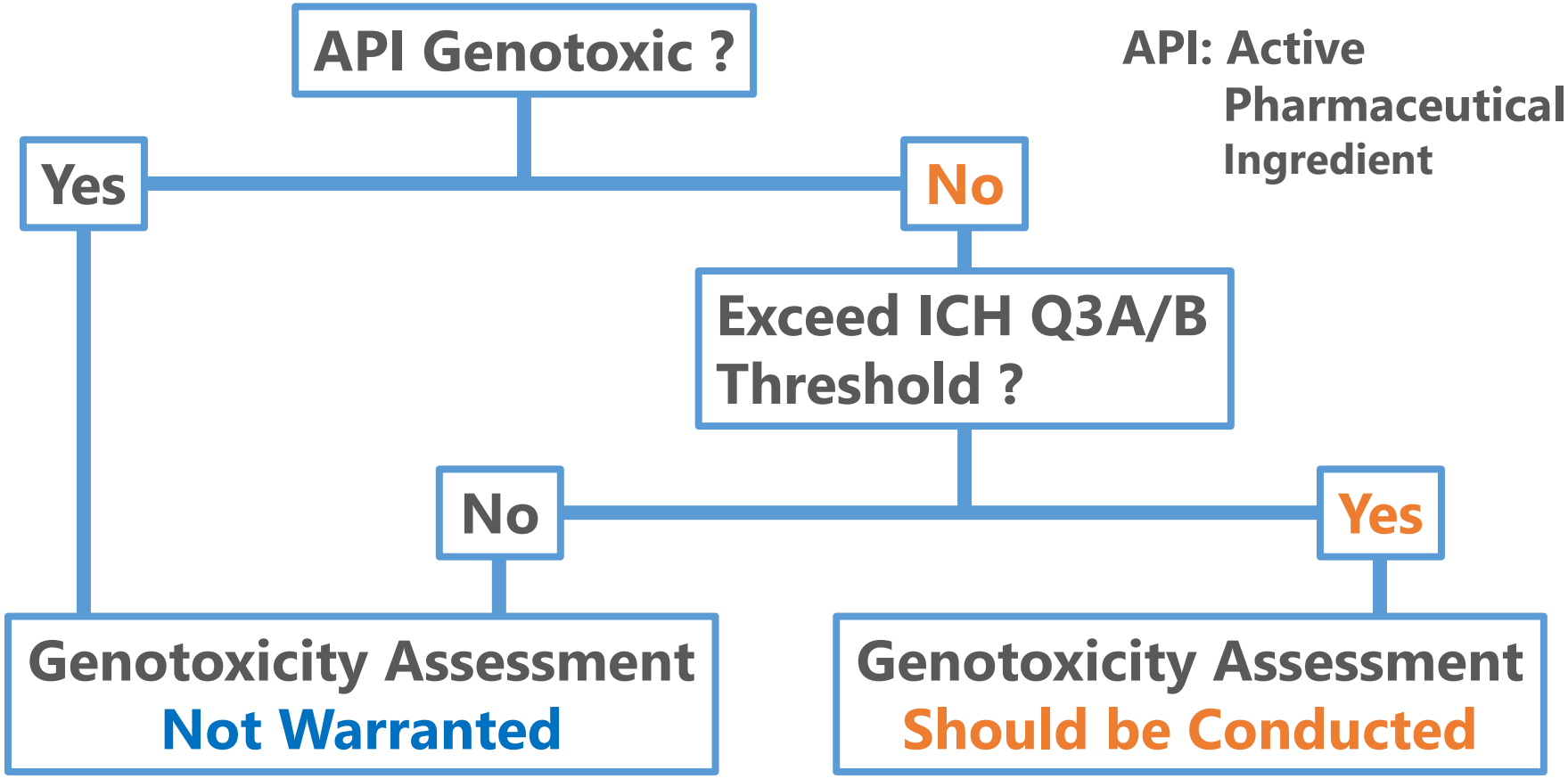
When the API is genotoxic ?

When the API is non-genotoxic ?

API: Active Pharmaceutical Ingredient

Assessment of Impurities (ICH Q3A/B)

Answer 4.12



API: Active Pharmaceutical Ingredient

Assessment of Impurities (ICH Q3A/B)

Question 4.14

If new impurities are observed above ICH Q3A/B qualification thresholds after the completion of registration toxicology studies, how should such circumstances be handled ?

Answer

A risk assessment should be conducted „

Assessment of Impurities (ICH Q3A/B)

Question 4.14

If new impurities are observed„

Factors to consider in risk assessment:

- **Structural similarity to the parent drug**
- **Toxicology alerts in the structure**
- **Presence of the impurity at lower levels in toxicology or clinical lots**
- **Metabolic status**
- **Patient group and dosing regimen** etc.

Assessment of Impurities (ICH M7)

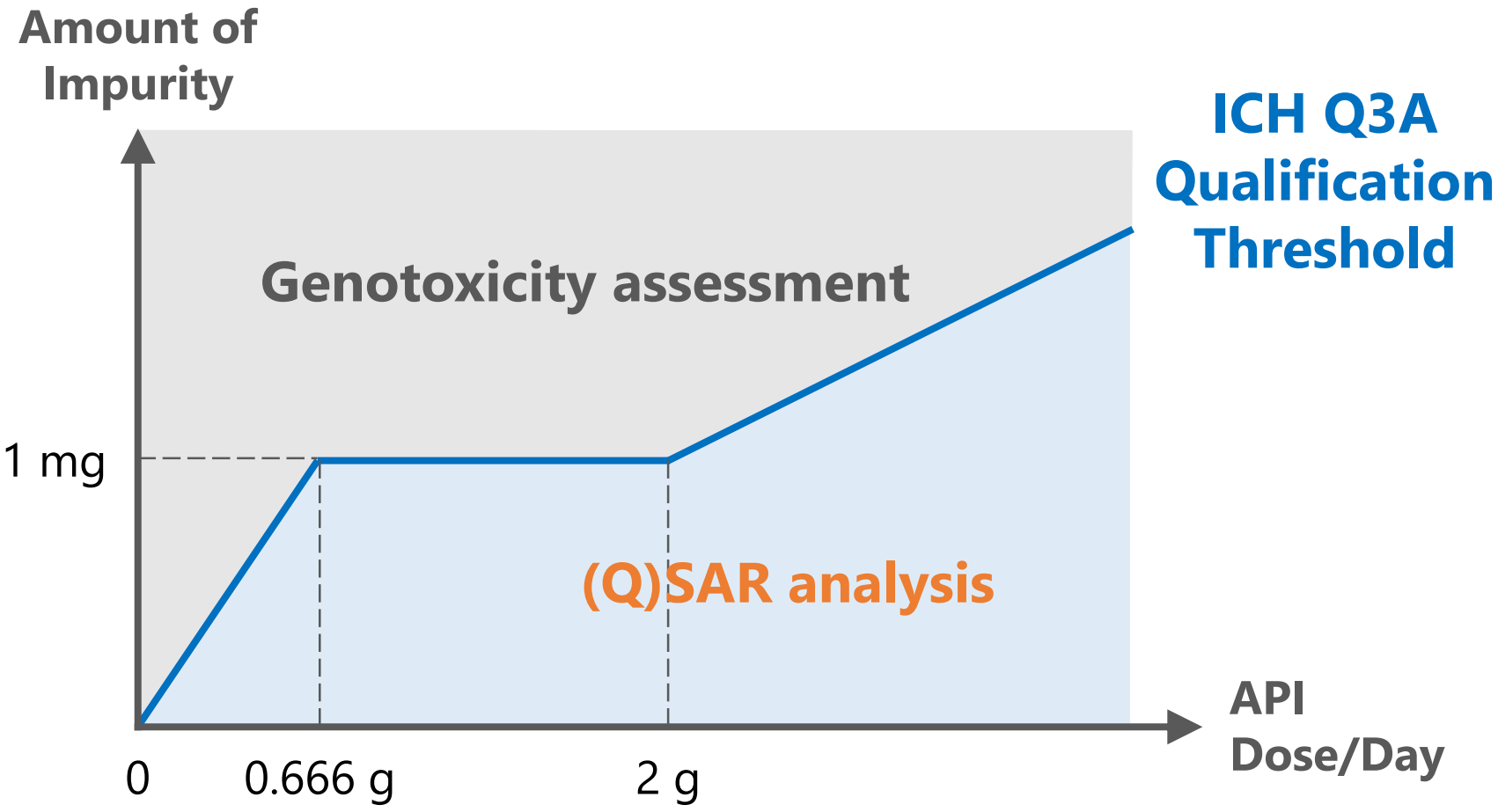
Question 4.13

Is ICH M7, giving guidance for the management of mutagenic impurities, applicable to the patient population covered in the scope of ICH S9 ?

Answer

The scope of **M7** specifically states that the guidance **does not apply** to "drug substances and drug products intended **for advanced cancer indications** as defined in the scope of ICH S9."

Assessment of Impurities (ICH M7)



Assessment of Impurities (ICH Q3A/B and M7)

Question 4.15

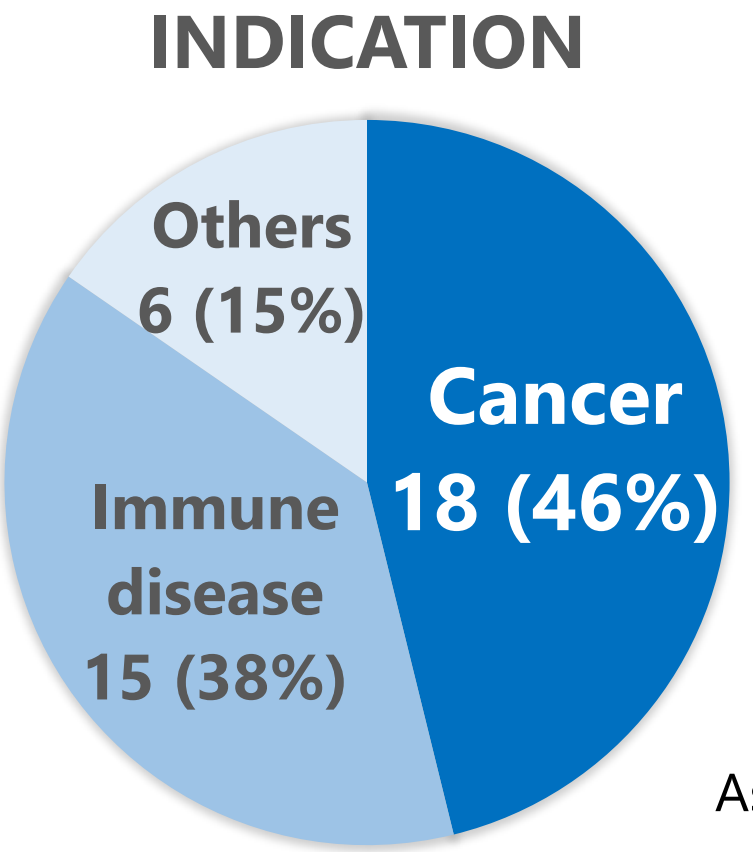
If a drug with an impurity is first developed in patients with late-stage disease, and later moves to a different population with long expected survival, how should the impurities in drug be managed ?

Answer

ICH Q3A/B and **ICH M7** should **both** be considered for the control of impurities.

Contents

Monoclonal Antibodies approved in Japan



As of May 9, 2017

Based on http://www.nihs.go.jp/dbcb/TEXT/Mab-T1-170509.pdf

Recent Trends in Development of Anticancer Biopharmaceuticals in Japan

Monoclonal antibody (mAb)

Immune checkpoint inhibitors (and combination therapy)

e.g., mAb against PD-1, PD-L1, CTLA-4, LAG-3, TIM-3, etc.

Antibody-drug conjugate (ADC)

4 Approved, **14 INDs** from 2014 to 2018 (as of Oct 31)

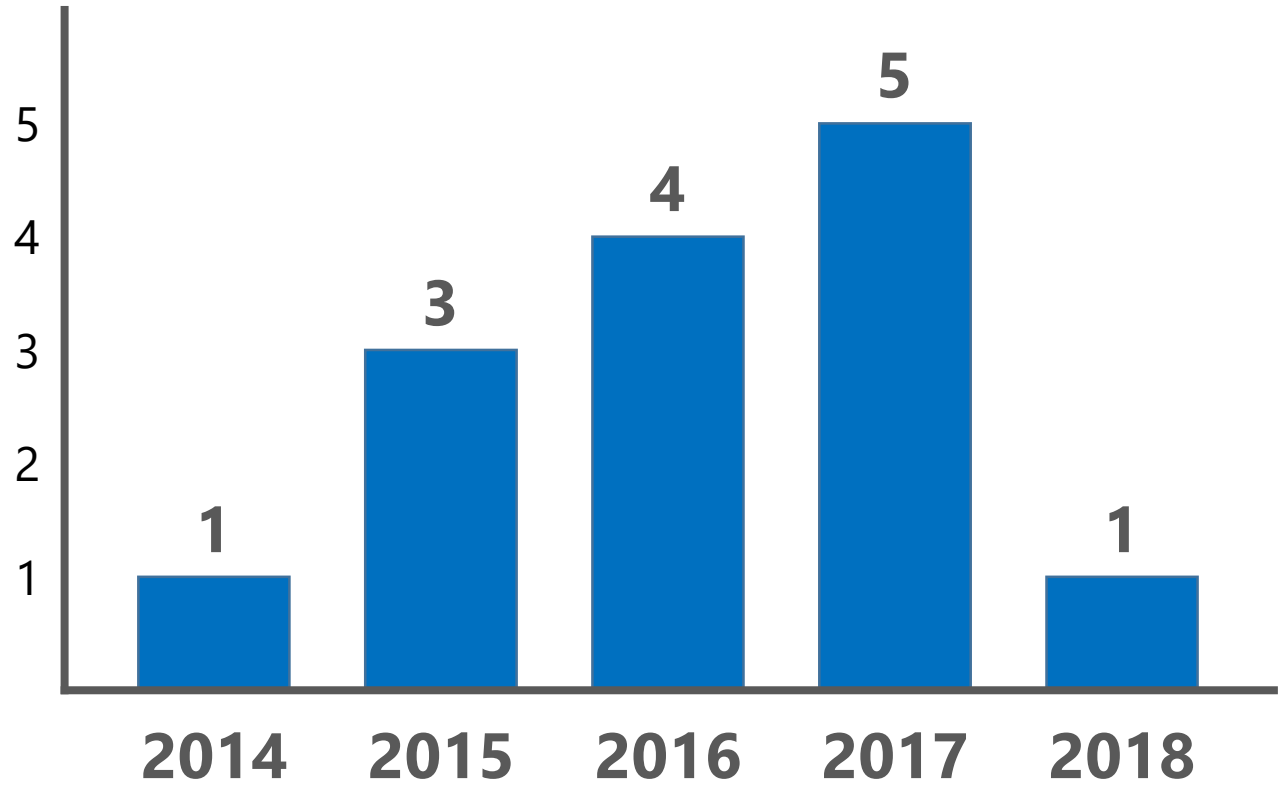
Bispecific antibody

6 INDs in 2018 (as of Oct 31)

ADCs approved in Japan

ADC	Approval	Indication	Target	Payload
Gemtuzumab ozogamicin (Mylotarg)	2000	AML	CD33	N-acetyl-γ-calicheamicin DMH (DNA cleavage)
Brentuximab vedotin (Adcetris)	2011	HL, ALCL	CD30	MMAE (Tubulin inhibition)
Trastuzumab emtansine (Kadcyla)	2013	Breast cancer	HER2	DM1 (Tubulin inhibition)
Inotuzumab ozogamicin (Besponsa)	2017	ALL	CD22	N-acetyl-γ-calicheamicin DMH (DNA cleavage)

ADC: The Number of IND submitted in Japan



A Case Study: ADC X

- **X** consists of an antibody against tumor antigen, linker and **a novel immune stimulatory agent**.
- It is expected to recruit immune stimulatory cells in the tumor microenvironment and enhance anti-tumor activity.
- In a FIH study, **X** is administered once or once every 3 weeks.
- The antibody portion of **X** binds **only** to human and **NHP** antigens.

What nonclinical safety assessment is needed to start FIH study ?

A Case Study: ADC X

- *In vitro* cytokine release assay
- Single dose tox. study with only the immune stimulatory agent in rats (including cytokine measurement)
- Single dose tox. study with ADC in rats (including cytokine measurement)
- Single dose tox. studies with ADC in NHPs (including CV and cytokine measurement)
- Repeat dose tox. studies with ADC in NHPs (including cytokine measurement)
- *In vitro* phototox. test

A Case Study: ADC X

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Antibody-Drug Conjugate

Question 4.6

Is there a recommended approach to setting a FIH starting dose for an ADC ?

Answer

- 1/10th the Severely Toxic Dose (STD) in 10% animals (STD10) in rodents
- 1/6th the Highest Non-Severely Toxic Dose (HNSTD) in non-rodents
- **Other approaches are possible for new class of ADC.**

A Case Study: ADC X

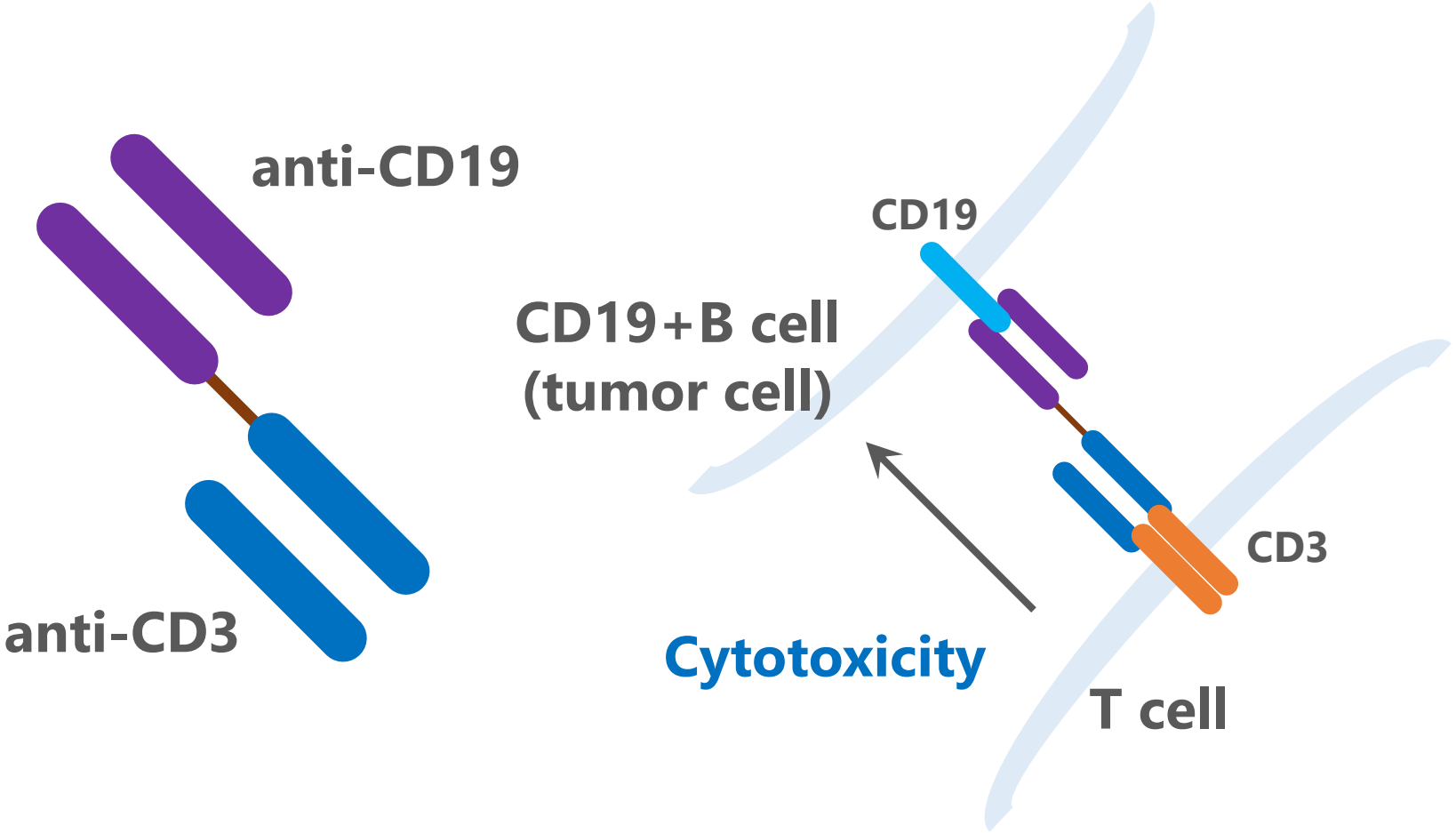
FIH starting dose

FIH starting dose was selected based not only on HNSTD, but also on **dose that showed no cytokine elevations** after the first dose of **X** in NHPs.

MABEL approach was adopted.

Bispecific Antibody: Blinatumomab

A bispecific antibody that binds to CD19 and CD3



Nonclinical package of Blinatumomab

- 14-Day repeat dose toxicity study in rats (*i.v.*)
- 4-Week repeat dose toxicity study in chimpanzees (*i.v.*)
- 4-Week repeat dose toxicity study with mouse surrogate (*i.v.*, *s.c.*)
- 13-Week repeat dose toxicity study with mouse surrogate (*s.c.*)
- Embryo-fetal developmental study with mouse surrogate
- Local tolerance study
- Tissue cross-reactivity study

Approach for FIH Dose Could Vary with Targets in Bispecific Antibody

IND	Target 1	Target 2	Approach for FIH dose
1	CD3	Tumor antigen	Pharmacological
2	CD3	Tumor antigen	unknown
3	CD3	Tumor antigen	Pharmacological
4	CD3	Tumor antigen	Pharmacological
5	CD3	Tumor antigen	Pharmacological
6	Tumor antigen	Tumor antigen	Pharmacological
7	Immune-related	Immune-related	Pharmacological
8	Tumor antigen	Tumor antigen	Toxicological

Conclusion

ICH S9 Q&As provides guidance for clarifying need and design of toxicology study for anticancer drugs.

It is necessary to take case-by-case approaches for nonclinical safety assessment of anticancer drugs.

Thank you for your time and kind attention !