



19-21 October 2016
Innsbruck, Austria

SESSION 7: PRECLINICAL & TOXICOLOGY MODELS IN IMMUNO-ONCOLOGY

Challenges in the evaluation of preclinical toxicology in immuno-oncology

Belén Gracia Moneva
Spanish Medicines and Healthcare Products Agency
AEMPS
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Immunological treatment options

- **Monoclonal antibodies**
- **Proteins of immunological control**
- **Adoptive cellular therapy**
- **Cytokines**
- **Others**

Rituximab

Trastuzumab

Alemtuzumab

Cetuximab

Bevacizumab

Panitumumab

Catumaxomab

Ofatumumab

Ipilimumab

Brentuximab vedotin

Pertuzumab

Trastuzumab emtansine

Obinutuzumab

Ramucirumab

Nivolumab

Pembrolizumab

Dinutuximab

Blinatumomab

Elotuzumab

Daratumumab

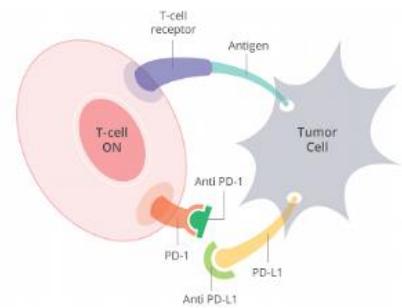
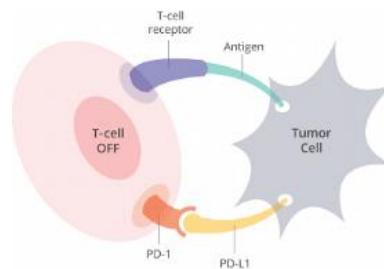


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Targets

PD-1

Nivolumab - monoclonal antibody anti-PD-1 metastatic melanoma, non-small cell lung cancer and advanced renal carcinoma



Pembrolizumab - monoclonal antibody-anti-PD-1 metastatic melanoma, lung cancer

Targets

Signaling lymphocytic activation molecule F7 (SLAMF7)

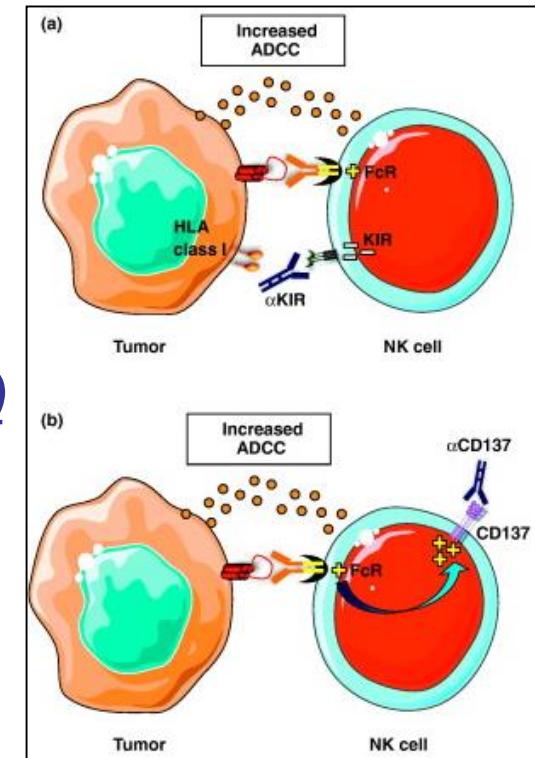
Anti-SLAMF7 antibody, **elotuzumab**, for multiple myeloma (MM). Receptor present on immune cells, including NK cells. It is also expressed on MM cells.

Killer Cell Immunoglobulin Like Receptor (KIR)

Anti-KIR antibodies prevents a tolerogenic interaction and augments NK-cell spontaneous cytotoxicity

Tumor necrosis super family receptors (TNFRSF)

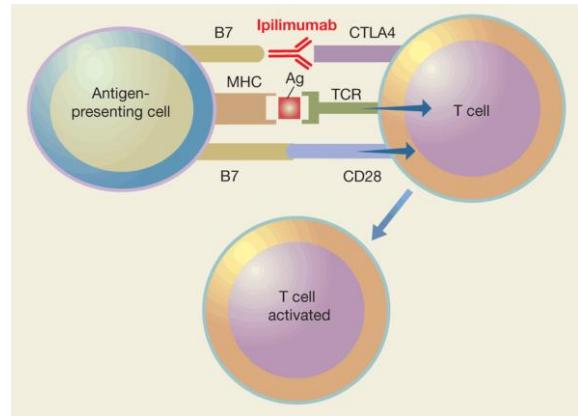
Agonistic antibodies of TNFRSF family of co-stimulatory receptors (CD134, CD137, etc) predominantly expressed by T-lymphocytes, NKT cells, NK cells and neutrophils that generates an anti-tumor response



Targets

T-lymphocyte associated antigen-4 (CTLA-4)

**Anti-CTLA-4-*Ipilimumab*- anti-
cytotoxic T-lymphocyte associated
antigen-4 (CTLA-4) mAb approved
for the treatment of metastatic
melanoma**





NON-CLINICAL SAFETY ASSESSMENT

Guideline S9 on Non-clinical evaluation for anticancer pharmaceuticals in man (EMA/CHMP/ICH/646107/2008) & Q/A doc EMA/CHMP/ICH/453684/2016

"This guideline aims to facilitate and accelerate the development of anticancer pharmaceuticals and to protect patients from unnecessary adverse effects, while avoiding unnecessary use of animals, in accordance with the 3R principles (reduce/refine/replace), and other resources."



But also,

Guideline S6 (R1) on Preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998)

intended to provide general principles for designing scientifically acceptable preclinical safety evaluation programs.

- 1) to identify **an initial safe dose** and subsequent dose escalation schemes in humans;
- 2) to identify **potential target organs** for toxicity and for the study of whether such toxicity is reversible; and
- 3) to identify **safety parameters** for clinical monitoring.



Monoclonal antibodies- the **immunological properties** of the antibody should be described in detail (antigenic specificity, toxicity towards human tissues distinct from the intended target...). Induction of antibody formation in animals is not predictive of a potential for antibody formation in humans.

Use of **relevant species** in safety evaluation programs



And, Non-Clinical Safety Studies For The Conduct Of Human Clinical Trials For Pharmaceuticals (ICH M3[R2])

International standards for, and promote harmonisation of, the nonclinical safety studies recommended to support human clinical trials of a given scope and duration as well as marketing authorization for pharmaceuticals.

This guidance should facilitate the timely conduct of clinical trials, reduce the use of animals in accordance with the 3R (reduce/refine/replace) principles and reduce the use of other drug development resources.

For biotech products, nc safety package in accordance with ICH S6, M3 only provides guidance with regard to timing of nc studies relative to clinical development.



And,

Strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07)

This document addresses non-clinical issues for consideration prior to the **first administration** of an investigational medicinal product in humans.

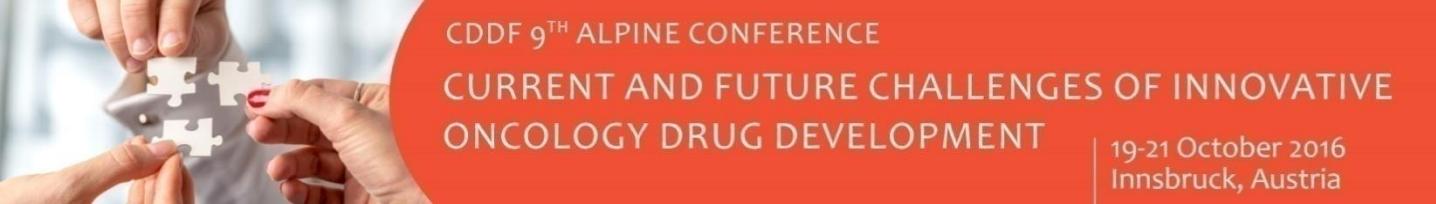


Others,

CHMP/SWP/169215/05 -Aug 2008 Need for Non-Clinical Testing in Juvenile Animals on Human Pharmaceuticals for Paediatric Indications

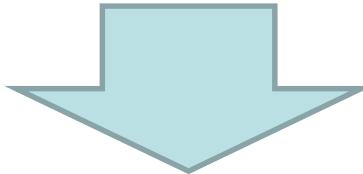
"Medicinal products under development for specific paediatric indications or in life-threatening or serious diseases without current effective therapies warrant a case-by-case approach. In some cases, some studies may then be adapted, deferred or omitted"

ICH S10-Photosafety evaluation of pharmaceuticals-Concept paper Jan 2008



Guideline S9 on non-clinical evaluation for anticancer pharmaceuticals in man (EMA/CHMP/ICH/646107/2008)

- 1) Identify the pharmacologic properties of a pharmaceutical
- 2) Establish a safe initial dose level for the first human exposure and,
- 3) understand the toxicological profile of a pharmaceutical (identification of target organs, exposure-response relationship, and reversibility).



Acceptable safety in humans





1) Identify the pharmacologic properties of a pharmaceutical and **safety pharmacology**

Assessment of the pharmaceutical's effect on vital organ functions including cardiovascular, respiratory and central nervous systems available before the initiation of clinical studies. Could be **included** in general toxicology studies. In the absence of a specific risk, such studies **will not** be called for to support clinical trials or for marketing.

2) Dose selection- LDT and MTD (CLASSIC)

The recommended human starting dose is determined by considering all available nonclinical toxicology and pharmacology data. Two approaches:

- 1 HNSTD-highest non-severely toxic dose from 1-month repeat-dose toxicity study in animal species. --- 1/6 HNSTD---FIH
STD10-1/10 the severely toxic dose in 10% animals (STD10) -small molecules
NOAEL not essential
- 2 Pharmacology data---percentage of tumour regression plateau mg/kg, Cmax and AUC.

Biopharmaceuticals with immune agonistic properties-minimally anticipated biologic effect level (MABEL) should be considered

No MAJOR CONCERN IN CALCULATION SAFE STARTING DOSE

Dose levels in these clinical studies often are close to or at the
adverse effect dose levels



Type, timing and flexibility called for in the design of nonclinical studies of anticancer pharmaceuticals can differ from those elements in nonclinical studies for other pharmaceuticals.



3) Understand the **toxicological profile** of a pharmaceutical (identification of target organs, exposure-response relationship, and reversibility).

Primary objective of a Phase I clinical trial in patients with advanced cancer is to assess the safety: MTD and DLT.

Duration of non-clin studies: 28 days (Phase I,II), 3 months (Phase III)

In case of biopharmaceuticals, ---S6

Assessment of the potential to recover from toxicity should be provided to understand the reversibility/irreversibility (1sp)

Relevant animal species

Immunotoxicological evaluation-immunostimulation, suppression, autoimmunity...



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In general, the non-clinical data to support Phase I and the clinical Phase I data would normally be sufficient for moving to Phase II and into a second or first line therapy in patients with advanced cancer.



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Other non-clinical data:

-Pharmacokinetics -in the animal species used for non-clin studies

-Reproduction toxicology

*Embryofetal toxicity studies of anticancer pharmaceuticals should be available when the marketing application is submitted but **not essential** to support clinical trials in advanced cancer or when are genotoxic or known to cause developmental toxicity. Effects on embryogenesis --Efforts to prevent pregnancy during treatment.*

Fertility and early embryonic development and pre and postnatal toxicology studies are not warranted in case patients with advanced cancer.



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-Genotoxicity

Not essential for clinical trials in advanced cancer

-Carcinogenicity

Not essential for clinical trials and marketing in advanced cancer.

-Photosafety

Phase I (photochemical properties)-photosafety protective measures in CT

-Immunotoxicity

Specific studies

LIMITATIONS

-In species-specific cross-reactivity:



Lack of relevant animal species in which to conduct toxicological studies- toxicity not predictive for human situation. Non recognition of proteins from other different species than human. The nonclinical safety package consists primarily of in vitro safety and in vivo biological activity assessments. Valuable for non-target effects. Surrogate animal model

-Immunogenicity:



ADAs not predictive for human situation

-Immune-related adverse events (irAEs):



Proliferation or cytokine release –novel exploratory in vitro cellular proliferation and cytokine release assays. Predictive models?



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Combination therapies

- Well-studied individually in toxicology evaluations.
- Rationale for the combination
- In general, toxicology studies investigating the safety of combinations of pharm in advanced cancer are not warranted but,
 - if at least one of these compound is in early stage development (human toxicity profile has not been characterised) a pharmacology study to support the rationale for the combination should be provided that evidence an increased activity in the absence of a substantial increase in toxicity on the basis of limited safety endpoints (mortality, clinical signs, weight gain).



Non-clinical studies to support CT in pediatric population

Juvenile animals are not usually conducted in order to support inclusion of pediatric populations for the treatment of cancer

Only when human safety data and previous animal studies are considered insufficient for safety evaluation in the intended pediatric age group.



Ipilimumab

- *In vitro, ipilimumab binds to human CTLA-4 with high affinity. Ipilimumab did not show cross-reactivity with or binding to CTLA-4 from rats, mice or rabbits, but showed specific binding to cynomolgus monkey recombinant CTLA-4 and activated T-cells . Pharmacological activity only in primates*
- *Safety pharmacology programme (CVS, NS, RS) : in pivotal toxicity studies in monkeys for up to 6 months. No major findings involving safety pharmacology endpoints*



Ipilimumab

- Toxicology:

The cynomolgus monkey was selected as the toxicology species in single and repeat dose studies for up to six months because ipilimumab binds specifically to macaque CTLA-4, but not to homologous CTLA-4 in other traditional toxicology species and has pharmacologic activity only in primates.

Well tolerated with different immune-related adverse events (irAEs) of low incidence linked with the intended pharmacologic basis of CTLA-4 blockade

Immunotoxicity assessed in repeat dose tox studies- expected effects due to pharmacological action. Antigenicity: Non significantly immunogenic in monkeys

-Genotoxicity, carcinogenicity, reproduction toxicity : not conducted



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CURRENT AND FUTURE CHALLENGES OF INNOVATIVE
ONCOLOGY DRUG DEVELOPMENT

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Nivolumab

-Preclinical toxicity conducted in monkey- similarities in tissue binding profiles between cynomolgus monkeys and humans indicate that is an appropriate animal model. Rat and rabbit- no-binding

-Specific safety pharmacology studies were limited to a single-dose CVS safety study in Cynomolgus monkeys. Supported by ICH guidelines S6(R1), S7A, and S9.



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Nivolumab

- Toxicology:

Repeat toxicity studies-1 and 3-month iv in monkeys. Well tolerated Changes in immune cell parameters were observed, demonstrating that nivolumab elicited pharmacological responses in healthy monkeys.

-Genotoxicity, carcinogenicity, fertility and early embryonic development not conducted-Supported according to Guidelines

Embryofoetal toxicity -in ePPND study

-No dedicated local tolerance studies conducted

-No general nonspecific immunostimulatory or autoimmune-related toxicities were observed.

-ADAs were detected in 67% monkeys receiving monthly doses of nivolumab



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Pembrolizumab

- The pharmacology of pembrolizumab was evaluated in Cynomolgus monkey as the similarities in binding affinities with human PD-1 were observed in in vitro experiments compared to mouse, rat and dog, where no binding was observed.
- Stand-alone studies evaluating safety pharmacology of pembrolizumab were not submitted (assessed in tox studies)
- No non-clinical dedicated pharmacodynamic drug-drug interactions studies with pembrolizumab were submitted.
- The toxicity of pembrolizumab was evaluated in a 1-month and a 6-month repeat-dose study in cynomolgus monkeys. Well tolerated and the NOAEL in both studies was the highest dose tested.
- No submitted studies for genotoxicity, carcinogenicity as well as fertility and early embryonic development.



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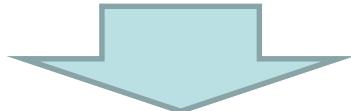
Elotuzumab

- Elotuzumab only recognizes human SLAMF7 protein.
- Because elotuzumab does not recognize non-human forms of SLAMF7 protein, in vivo safety data from animal studies are irrelevant. In the same line, no carcinogenicity data are available for elotuzumab in animals, nor were fertility and embryo foetal toxicity studies performed. Non clinical safety information primarily consists of limited in vitro human cell/tissue studies where no safety findings were identified.
- Clinical trials data were therefore an important source of information to support the safety in patients.



CONCLUSIONS

- Relevant animal model- poor predictive toxicology-limited data
- Immunogenicity non-predictive data
- Immune-related adverse events (irAEs) assessment non-predictive data
- New complex combinations -limited data



Risk mitigation strategies should be adopted for CT





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CURRENT AND FUTURE CHALLENGES OF INNOVATIVE
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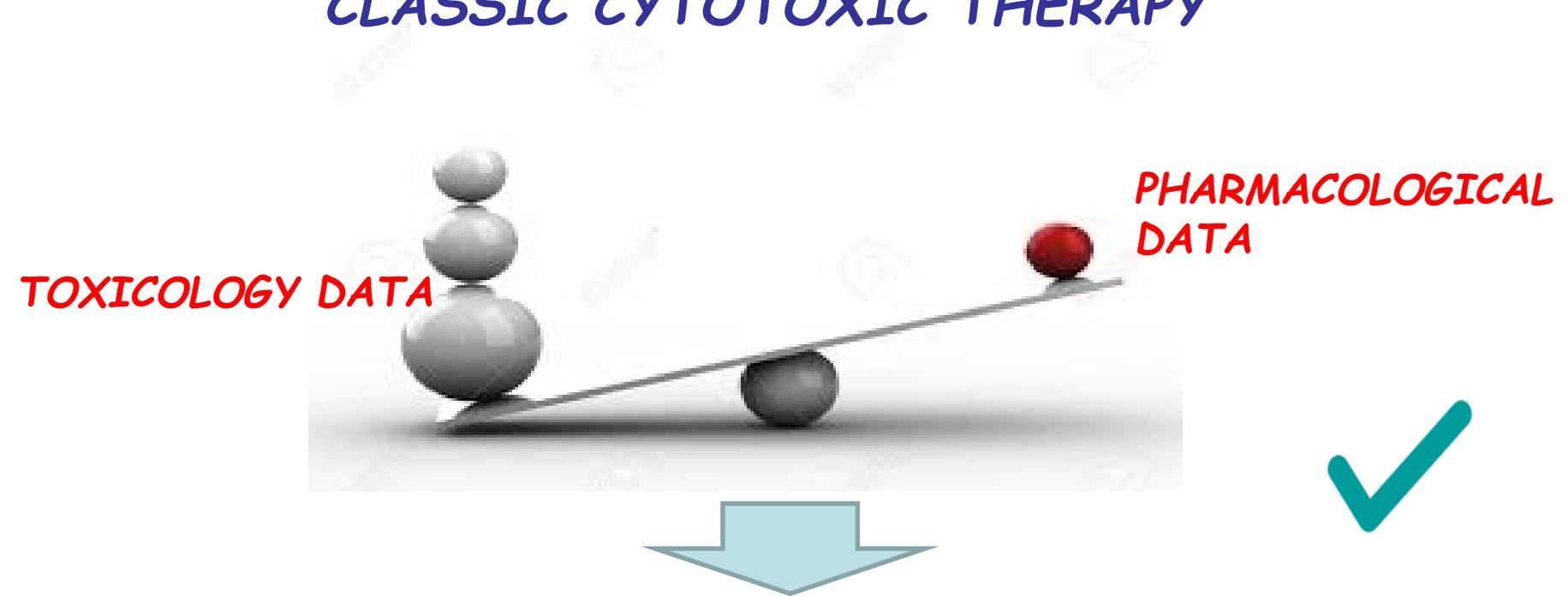
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ENOUGH??

CONCLUSIONS

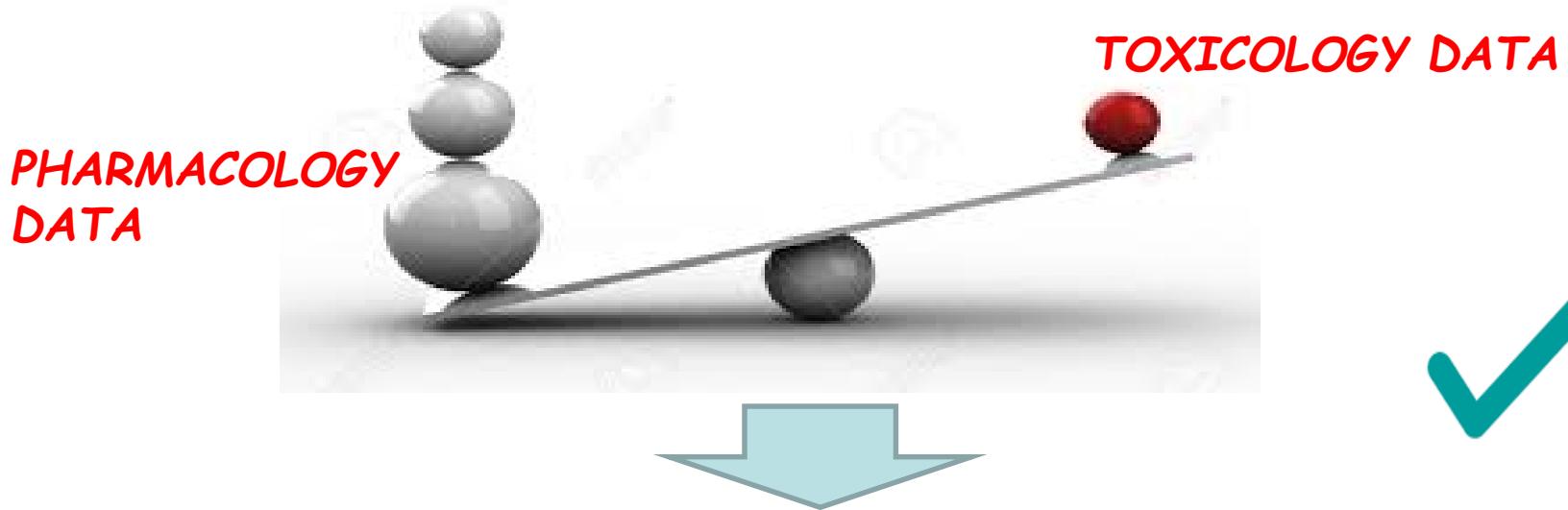
CLASSIC CYTOTOXIC THERAPY



Careful monitoring of patients adverse effects

CONCLUSIONS

IMMUNOTHERAPY PRODUCTS



Careful monitoring of patients' immune function



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Thank you very much for your attention !