Carcinogenicity Assessment of Biopharmaceuticals: A Review of Recent Practices with Case Studies

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Why do Carcinogenicity Testing?

- Provide a Science Based Risk Assessment for Cancer Potential in Patients
  - Genetic Toxicity is not of concern for most biopharmaceuticals
  - The 'concern' for some biopharmaceuticals is their potential mitogenicity or demonstrated immunosuppression
  - Does the pharmacology indicate some risk and the need for an assessment?

Looks easy, but it's very difficult !

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ICH S1A Guidance

- Carcinogenicity studies not needed for:
  - Pharmaceuticals with clinical dosing < 3/6 months
  - Life expectancy of the indication is < 2 - 3 years
- "Carcinogenicity studies not generally needed for *endogenous* substances given essentially as *replacement therapy*, particularly where there is *previous clinical experience* with similar products"
- "Although not usually necessary, carcinogenicity studies….should be considered for the other biotechnology products noted above…"

http://www.ich.org/MediaServer.jser?@_ID=489&@_MODE=GLB

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ICH S6 Guidance

- "Standard carcinogenicity bioassays are *generally inappropriate* for biopharmaceuticals"
- "Product-specific assessment of carcinogenic potential *may* still be needed depending on duration of clinical dosing, patient population, and/or biological activity (e.g., growth factors, immunosuppressive agents, etc.)"
- A standard carcinogenicity bioassay should be *considered* if "…the product is biologically active and non-immunogenic in rodents and other studies have not provided sufficient information to allow an assessment of carcinogenic potential…"

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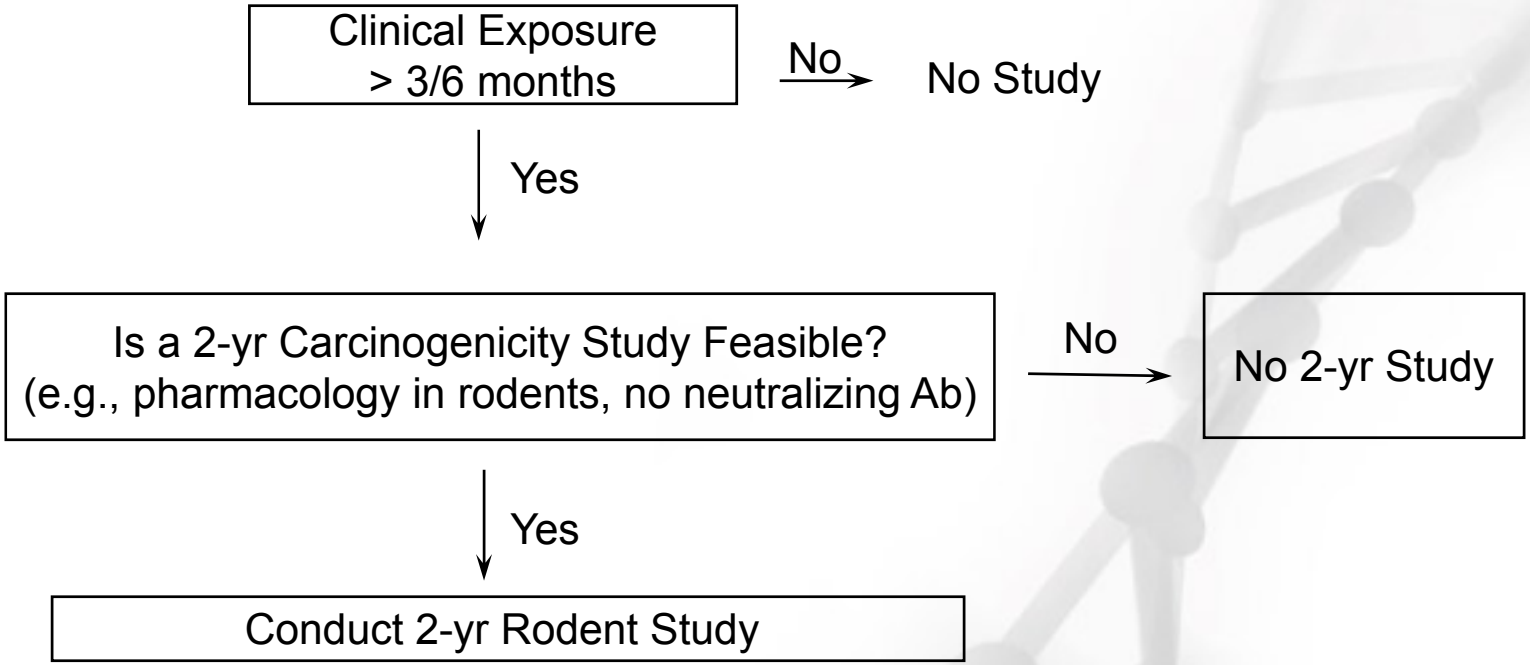
Historical Approach for Carcinogenic Assessment of Biopharmaceuticals (before 2008)



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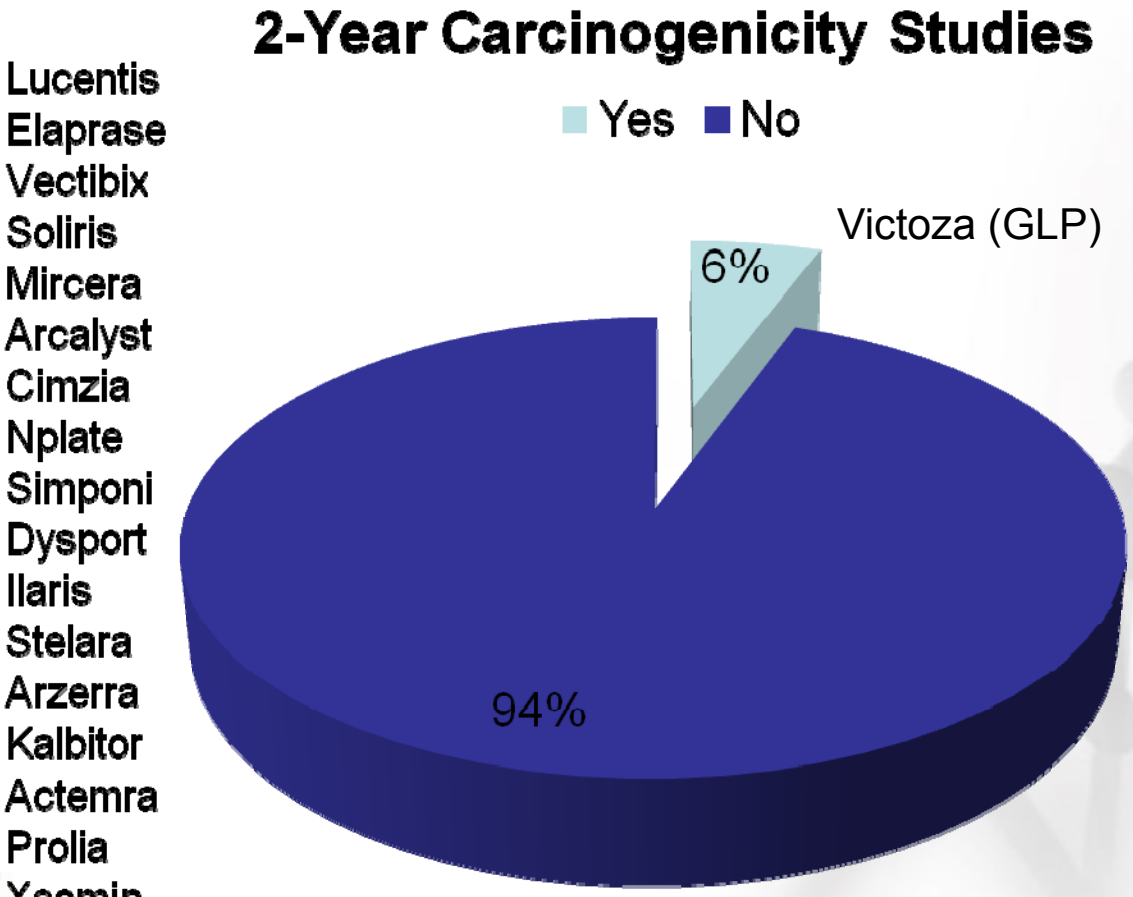
Recent Practice
CDER Approved BLAs Jan 2006-Aug 2010



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ICHS6(R1): Draft Carcinogenicity

6. CARCINOGENICITY

- "In some cases, the available information can be sufficient to address carcinogenic potential and inform clinical risk without warranting additional nonclinical studies."
- "The mechanism of action of some biopharmaceuticals might raise concern regarding potential for neoplasm induction or tumour promotion (e.g. immunosuppressives and growth factors). If the weight of evidence (see above) support the concern regarding carcinogenic potential, rodent bioassays are not warranted. This potential hazard can be best addressed by product labeling and risk management practices. However, when the weight of evidence is unclear, the sponsor can propose additional studies that could mitigate the mechanism-based concern (see ICHS6 section 4.8)."

ICH Step 3: Not for Implementation

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ICHS6(R1): Draft Carcinogenicity

6. CARCINOGENICITY

- "Rodent bioassays or short-term carcinogenicity studies with homologous products are generally of limited value to assess carcinogenic potential of the clinical candidate."

ICH Step 3: Not for Implementation

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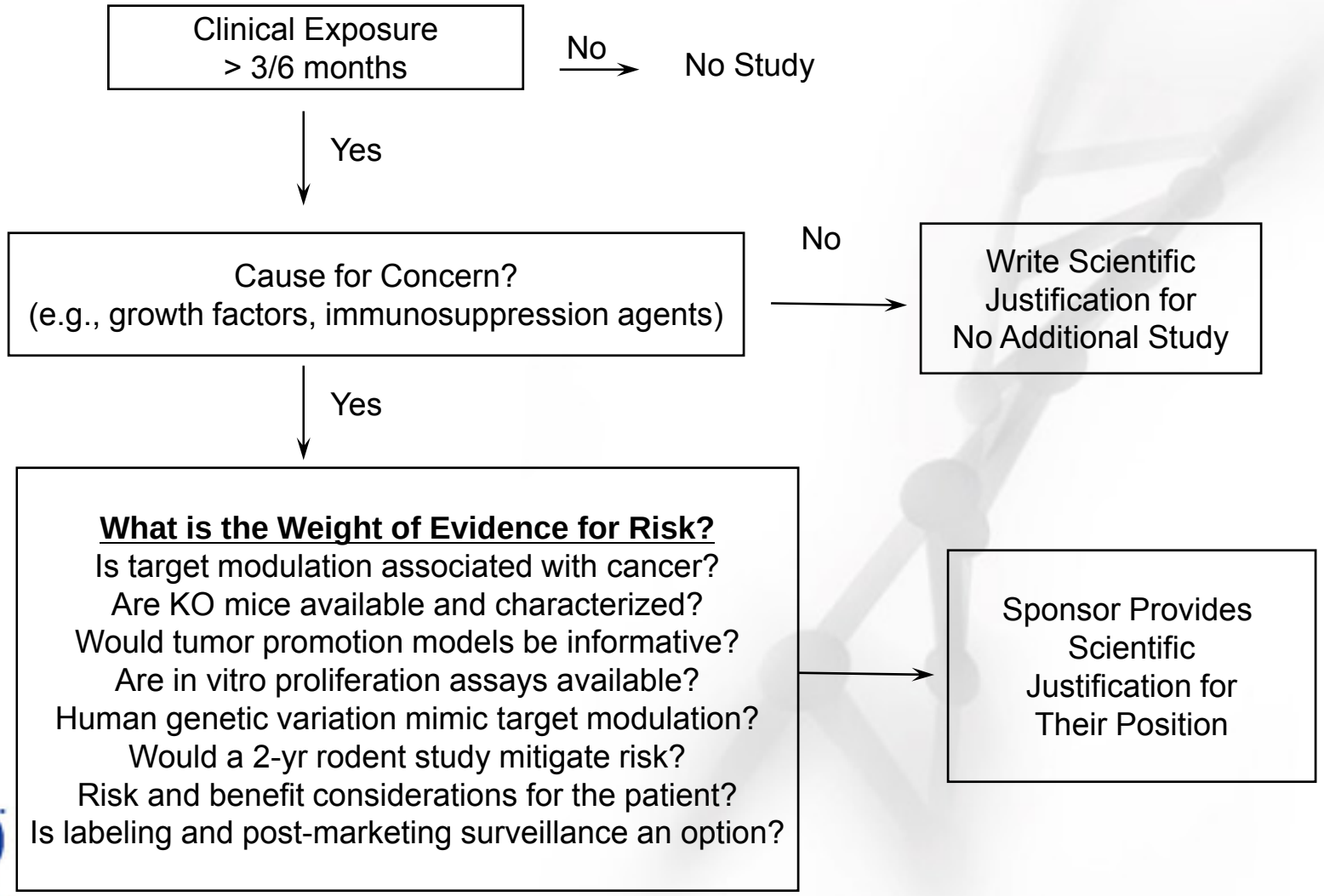
Current Approach for Carcinogenic Assessment of Biopharmaceuticals



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Potential Alternative Assessments

- Proliferation assays
  - In vitro cell based assays
  - Histopathology in chronic studies
  - Tumor implant models
- Transgenic models
  - Knock outs and knock ins
- Immunosuppression
  - No standardized test
  - Currently, the risk is reflected in the label
- Homologue/surrogate molecule studies
  - Difficult to translate into human risk when it's not the human medicine
    - Should only be done when alternative approaches to assess carcinogenic potential are not appropriate
    - Scientific justification should include the same biological response in rodents as in humans

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FDA: Generic DAARP PharmTox Comments to Sponsors

"We agree that standard carcinogenicity studies are not feasible for this product due to the lack of activity in a rodent species. However, your BLA should include a detailed discussion of why standard carcinogenicity studies are not possible and how you intend to conduct an alternative approach to carcinogenicity assessment. In addition, your BLA should discuss the available information you have collected via your own studies as well as those published in the literature regarding the potential impact of XXXXX on tumor surveillance and tumor development. You should also specifically state how you intend to address the carcinogenicity section of your product labeling." DAARP=Division of Anesthesia, Analgesia, and Rheumatoid Products.

Adapted from a presentation by Dr. Dan Mellon, FDA, 2009

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Amevive® (Alefacept)

- Historical example that identified the nonclinical risk in the cynomolgus monkey study
- Single post-marketing study in patients to further investigate clinical risk

Amevive® (Alefacept)

- CD-2:Fc fusion protein
- Recombinant production in mammalian cells
- Inhibits T-lymphocyte activation by inhibiting LFA-3 binding to CD2
- Indication: adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.
- FDA approved in 2003

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Amevive® (Alefacept)

- Pharmacologically active only in primates
- Studies up to 44-weeks in cynomolgus monkeys
  - Lymphomas observed
  - All animals were positive for lymphocryptovirus (LCV), which can lead to B-cell lymphomas when animals are immune suppressed.
- Carcinogenicity assessment: no 2-year studies
  - Lack of pharmacology in rodents

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Amevive® (Alefacept)

Post Marketing Requirements

- "To further evaluate the risk of infections and malignancies in patients treated with Alefacept in a single cohort of 5000 patients followed for 5 years"

Amevive® (Alefacept) Label

Warnings

Malignancies

- AMEVIVE® may increase the risk of malignancies. In the 24-week period constituting the first course of placebo-controlled studies, 13 malignancies were diagnosed in 11 AMEVIVE®-treated patients. The incidence of malignancies was 1.3% (11/876) for AMEVIVE®-treated patients compared to 0.5% (2/413) in the placebo group (see ADVERSE REACTIONS, Malignancies). In preclinical studies, animals developed B cell hyperplasia, and one animal developed a lymphoma (see PRECAUTIONS, Carcinogenesis, mutagenesis, and fertility). AMEVIVE® should not be administered to patients with a history of systemic malignancy. Caution should be exercised when considering the use of AMEVIVE® in patients at high risk for malignancy. If a patient develops a malignancy, AMEVIVE® should be discontinued.

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Amevive® (Alefacept) Label

Carcinogenesis, Mutagenesis, and Fertility

(Note: the bullets below are only a portion of this section of the label)

- The role of AMEVIVE® in the development of the lymphoid malignancy and the hyperplasia observed in non-human primates and the relevance to humans is unknown. Immunodeficiency-associated lymphocyte disorders (plasmacytic hyperplasia, polymorphic proliferation, and B-cell lymphomas) occur in patients who have congenital or acquired immunodeficiencies including those resulting from immunosuppressive therapy.
- No formal carcinogenicity or fertility studies were conducted.

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Arcalyst ® (Rilonacept)

- Recent example of using labeling to communicate risk
- No stated special post-marketing surveillance or REMS for carcinogenicity/malignancy in the FDA approval letter

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Arcalyst® (Rilonacept)

- IL-1 Trap fusion protein consisting of 2 cytokine receptor domains fused to an Fc from human IgG1
- Recombinant production in mammalian cells
- Neutralizes Interleukin 1α, 1β, and IL-1RA
- Indication: Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS)
- FDA Approved: February 2008

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Arcalyst® (Rilonacept)

- Notes from Pharmacology/Toxicology FDA Review of Approval Application
  - "….propose that the label include information indicating that the product has the potential to increase the risk of immunosuppression-related tumors, unless the Sponsor can provide data or scientific information to allow the division to conclude that such a risk is not present for this product."

Arcalyst® (Rilonacept)

FDA Risk Assessment and Risk Mitigation Review

- "Risks such as infection and malignancy are well-known risk associated with therapeutic biologics and are not unique to rilonacept or unexpected given its effect on the immune system"
- "The risk management proposal for rilonacept is consistent with those of routine risk minimization activities such as labeling and incorporates both routine and additional pharmacovigilance activities."
- Should rilonacept be considered…for additional indications…may need to re-considered based on risk benefit profile…"

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Arcalyst® (Rilonacept) Label

- 5.2 Immunosuppression
  - The impact of treatment with ARCALYST on active and/or chronic infections and the development of malignancies is not known [see Adverse Reactions (6.3)]. However, treatment with immunosuppressants, including ARCALYST, may result in an increase in the risk of malignancies.
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
  - Long-term animals studies have not been performed to evaluate the carcinogenic potential of rilonacept.

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Orencia ® (abatacept)

- An example where a mouse carcinogenicity study was conducted to determine potential human carcinogenicity risk, but the malignancy risk in the label reflects the clinical data

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails

Orencia ® (abatacept)

- CTLA4:Fc fusion protein
- Inhibits the proliferation of T cells and the production of cytokines: IL-2, TNF-α and IFN-γ
- Indication: Moderate to severe adult rheumatoid arthritis and juvenile idiopathic arthritis (>6 years)
- FDA approved in 2005

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Orencia ® (abatacept)

- General toxicology studies up to 1 year in duration
- Rat and rabbit reproductive toxicology package
- Mouse carcinogenicity study (up to 84 weeks and 88 weeks only in male and female mice respectively)

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Orencia ® (abatacept) Label

13 Nonclinical Toxicology

13.1 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

'In a mouse carcinogenicity study, weekly subcutaneous injections of 20, 65, or 200 mg/kg of abatacept administered for up to 84 weeks in males and 88 weeks in females were associated with increases in the incidence of malignant lymphomas (all doses) and mammary gland tumors (intermediate- and high-dose in females). The mice from this study were infected with murine leukemia virus and mouse mammary tumor virus. These viruses are associated with an increased incidence of lymphomas and mammary gland tumors, respectively, in immunosuppressed mice. The doses used in these studies produced exposures 0.8, 2.0, and 3.0 times higher, respectively, than the exposure associated with the maximum recommended human dose (MRHD) of 10 mg/kg based on AUC (area under the time-concentration curve). The relevance of these findings to the clinical use of ORENCIA is unknown.'

'In the 1 year monkey study…….. no evidence of lymphoma or preneoplastic changes noted'

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Orencia ® (abatacept) Label

- Section 5.6: Information on immunosuppression

‘The possibility exists for drugs inhibiting T cell activation, including ORENCIA, to affect host defenses against infections and malignancies since T cells mediate cellular immune responses. The impact of treatment with ORENCIA on the development and course of malignancies is not fully understood’

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Orencia ® (abatacept) Label

Adverse reaction section – malignancies:

In the placebo-controlled portions of the clinical trials (1955 patients treated with ORENCIA for a median of 12 months), the overall frequencies of malignancies were similar in the ORENCIA- and placebo-treated patients (1.3% and 1.1%, respectively). However, more cases of lung cancer were observed in ORENCIA-treated patients (4, 0.2%) than placebo-treated patients (0). In the cumulative ORENCIA clinical trials (placebo-controlled and uncontrolled, open-label) a total of 8 cases of lung cancer (0.21 cases per 100 patient-years) and 4 lymphomas (0.10 cases per 100 patient-years) were observed in 2688 patients (3827 patient-years). The rate observed for lymphoma is approximately 3.5-fold higher than expected in an age- and gender-matched general population based on the Surveillance, Epidemiology, and End Results Database.1 Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma. Other malignancies included skin, breast, bile duct, bladder, cervical, endometrial, lymphoma, melanoma, myelodysplastic syndrome, ovarian, prostate, renal, thyroid, and uterine cancers

Clinical Data Only, No Mention of Tumors in Mice

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Stelara® (ustekinumab)

- An example of how literature, an advisory committee, post-marketing commitments, and REMS (Risk Evaluation and Mitigation Strategy) were used to communicate risk to patients and gather additional information on carcinogenicity/malignancy risk

Stelara® (ustekinumab)

- Human IgG1κ monoclonal antibody
- Recombinant production in mammalian cells
- Binds with high affinity and specificity to the p40 protein subunit used by both the interleukin (IL)-12 and IL-23 cytokines.
- Indication: adults with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
- FDA approved in September, 2009

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Stelara ® (ustekinumab)

- Repeated dose studies up to 26 weeks in cynomolgus monkeys
- Carcinogenicity studies not conducted

Stelara ® (ustekinumab)

From FDA Pharm/Tox Review of the Submission

- Results from the 6-month cynomolgus monkey study, "..no tumors or histopathological evidence of pre-neoplastic changes…"
- "…published literature reported that human subjects with genetic deficiencies in IL-12 signaling were susceptible to infections, presumably due to immunosuppression. Immunosuppressive agents have the potential to increase the risk of malignancy. Published literature further 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. Adequate labeling on nonclinical information and post-marketing patient monitoring of infection and malignancy are necessary."

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/125261s000_PharmR.pdf

Stelara® (ustekinumab)

Dermatologic and Opthalmologic Drugs Advisory Committee

- Advice and recommendations concerning: a.) dosing regimen b.) carcinogenicity c.) long-term safety and d.) self-administration. Committee voted majority 7:3 in approval of dosing regimen. The committee voted 11:0 that the potential malignancy risk and drug information should be voiced to physicians.

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Stelara ® (ustekinumab)

Post Marketing Requirements

2.) Enroll 4,000 Stelara™ (ustekinumab)-treated subjects into the Psoriasis Longitudinal Assessment and Registry, (PSOLAR) and follow for 8 years from the time of enrollment. Subjects will be followed for the occurrence of …malignancy...

3.) Provide data analyses from the Nordic Database Initiative regarding the occurrence of …malignancy…with exposure to ustekinumab.

4.) Complete the treatment and evaluation of subjects enrolled in the ongoing PHOENIX 1 (C0743T08) trial for a total of 5 years from initial enrollment …Subjects will be followed for the occurrence of …malignancy…

9.) Complete the treatment and evaluation of subjects enrolled in the ongoing PHOENIX 2 (C0743T09) trial for a total of 5 years from initial enrollment …Subjects will be followed for the occurrence of …malignancy…

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/125261s000_Approv.pdf

Stelara ® (ustekinumab)

Risk Evaluation and Mitigation Strategy (REMS) Requirements

1.) Evaluations of dermatologists/healthcare providers' understanding and patients' understanding of the risks of Stelara™ (ustekinumab), including evaluations of the following:

A.) Prescribers' understanding of the risks of Stelara™ (ustekinumab), including the risks of serious infection, RPLS, and malignancy and how to select patients who are appropriate for treatment.

B.) Patients' understanding of the risks of Stelara™ (ustekinumab), including the risks of serious infection, RPLS, and malignancy.

4.) A summary of all reported serious infections, RPLS, and malignancies with analysis of adverse event reporting by prescriber type (e.g., dermatologist, nurse, Internist, oncologist), when available.

Note: 2), 3) and 5) purposefully not included

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http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/125261s000_Approv.pdf

NeoRecormon® (Epoetin beta)

- An example of where pre-clinical studies have been performed but the relevance for clinical practice or risk assessment is questionable, since publications on findings in patients are most prominent in the label

www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp

NeoRecormon® (Epoetin beta)

- Erythopoietin is a gylcoprotein that stimulates the formation of erythrocytes from its committed progenitors
- EMEA approved July 1997
- Indication: Anemia
- 2 year bioassay with murine homologue conducted
- Effect of epoetin beta on proliferation and colony formation of human tumour cell lines (in vitro and in vivo)
- Rat study in which tumours were treated with cyclophosphamide and epoetin beta
  - Studies demonstrated that epoetin beta had no tumourigenic potential

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Recormon® (Epoetin beta)

- Following publication of two clinical studies showing an increased mortality in cancer patients who were administered epoetin alfa (Leland-Jones B, 2003) or epoetin beta (Henke M et al, 2003), the Pharmacovigilance Working Party (PhVWP) investigated this issue
- As a result, the several sections of the SPC (Summary of Product Characteristics) was amended

Recormon® (Epoetin beta)

- Under Section 4.4 Special warnings and special precautions for use a paragraph titled “Effect on tumour growth” was added
  - *Epoetins are growth factors that primarily stimulate red blood cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells. As with all growth factors, there is a concern that epoetins could stimulate the growth of any type of malignancy. Two controlled clinical studies in which epoetins were administered to patients with various cancers including head and neck cancer, and breast cancer, have shown an unexplained excess mortality.*

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Summary – Case Studies

- Current practice is to use the “weight of evidence” to determine the best plan for addressing carcinogenicity risk
  - Repeat dose toxicology data
  - Sponsor pharmacology data
  - Related products on the market
  - Literature
- Risk can be assessed and communicated using both non-clinical and clinical data
  - Additional toxicology studies
  - Post-marketing surveillance
  - REMS

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Summary - Carcinogenicity

- The default should not be “do nothing” for a chronic use biopharmaceutical
- The default should not be a 2-year rodent study
- If literature clearly indicates increased risk, this can be communicated without additional toxicology data
- If literature indicates no increased risk and there’s no proliferative signal in chronic study(ies), there may be adequate information to communicate risk without additional studies
- The “weight of evidence” should be assembled by the sponsor

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