IMMUNOMODULATORY THERAPIES AND CANCER RISK

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OUTLINE

• Immunosurveillance of cancer – general concept
• Immunodeficiency and cancer
  – Experimental evidence
  – Clinical evidence
• Cancer risk assessment for immunomodulators
  – Regulatory considerations
  – Labeling examples
  – Weight of Evidence-based assessment
• Conclusions
CANCER AND IMMUNITY – GENERAL CONCEPTS

Gavin P. Dunn, Lloyd J. Old, and Robert D. Schreiber

Immunity, Vol. 21, 137–148, August, 2004,

Amgen Proprietary
Amgen Use Only
Immunosuppression increases tumors initiated by the chemical carcinogen methylcholanthrene (MCA) in the mouse.

Patient populations that inform cancer risk with immune alterations

Immunosuppressed populations

- Pharmacologically-induced
  - Organ transplant
- Acquired immunodeficiency
  - CD4+ T cell deficiency (HIV+ vs AIDS)
- Primary (genetic) immunodeficiencies
  - Various deficiencies in innate and adaptive immunity
  - Confounded by unresolved infection (chronic inflammation) and increased risk of autoimmunity with certain deficiencies

Populations with chronic immune activation

- Primary immunodeficient populations (with unresolved infections)
- Autoimmunity
Increased risk in kidney transplant recipients* over general population

<table>
<thead>
<tr>
<th>2-fold</th>
<th>3-fold</th>
<th>5-fold</th>
<th>15-fold</th>
<th>&gt;20-fold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common tumors (colon, breast, lung, stomach, breast, esophagus, pancreas, ovary)</td>
<td>Testicular Bladder</td>
<td>Melanoma Leukemia Hepatobiliary Cervical</td>
<td>Kidney</td>
<td>Kaposi’s sarcoma NHL Non-melanoma skin</td>
</tr>
</tbody>
</table>

- Both virally-associated and non-viral cancers are increased with immunosuppression
- With the exception of non-melanoma skin cancer, the greatest increase in relative risk for cancer following immunosuppression is highest for rare cancers (often virally associated)
- * immunosuppressive regimen included cyclosporine, tacrolimus, sirolimus, azathioprine, mycophenolate mofetil, anti-IL-2R antibodies

## HIV/AIDS AND CANCER RISK

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Incidence per 100,000 person-years</th>
<th>RR (AIDS vs pre-AIDS), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV+, Before AIDS</td>
<td>After AIDS</td>
</tr>
<tr>
<td>All</td>
<td>371</td>
<td>1201</td>
</tr>
<tr>
<td>Oral cavity/pharynx</td>
<td>11</td>
<td>42</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>16</td>
<td>53</td>
</tr>
<tr>
<td>NHL (all)</td>
<td>82</td>
<td>349</td>
</tr>
<tr>
<td>CNS NHL</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>Anus</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>Cervix</td>
<td>39</td>
<td>92</td>
</tr>
<tr>
<td>Liver</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>59</td>
<td>398</td>
</tr>
<tr>
<td>Lung</td>
<td>51</td>
<td>126</td>
</tr>
</tbody>
</table>

### HUMAN IMMUNODEFICIENCIES AND CANCER RISK

#### Table 1. Lymphoma risk in individuals with primary immunodeficiencies.

<table>
<thead>
<tr>
<th>Immunodeficiency class</th>
<th>Primary immunodeficiency</th>
<th>Cancer type</th>
<th>Relative risk or standardized incidence ratio (95% CI)*</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly antibody deficiencies</td>
<td>Common variable immune deficiency (CVID)</td>
<td>NHL/lymphoma</td>
<td>12.1 (6.03–21.6)</td>
<td>Vajdic et al. (2010)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12.1 (3.3–31.0)</td>
<td>Mellmekjaer et al. (2002)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>Kinlen et al. (1985)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>438 (females)</td>
<td>Cunningham-Rundles et al. (1987)</td>
</tr>
<tr>
<td>Combined T- and B-cell deficiencies</td>
<td>Severe combined immunodeficiency (SCID)</td>
<td>Lymphoma, leukemia</td>
<td>30</td>
<td>see Mueller &amp; Pizzo (1995)</td>
</tr>
<tr>
<td>Other well-defined immunodeficiency syndromes</td>
<td>Ataxia-telangiectasia</td>
<td>NHL/lymphoma</td>
<td>165 (4.19–922)</td>
<td>Vajdic et al. (2010)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leukemia</td>
<td>252–750 (whites–blacks)</td>
<td>Morrell et al. (1986)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>244 (27–880)</td>
<td>Olsen et al. (2001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>71–500 (whites–blacks)</td>
<td>Morrell et al. (1986)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>120 (36–241)</td>
<td>Olsen et al. (2001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>Perry et al. (1980)</td>
</tr>
<tr>
<td>Diseases of immune dysregulation</td>
<td>X-linked lymphoproliferative disease</td>
<td>Malignant neoplasms (predominantly lymphoma/lymphoreticular tumors, leukemias)</td>
<td>200</td>
<td>Nagy &amp; Klein (2010)</td>
</tr>
<tr>
<td>Diseases of immune dysregulation</td>
<td>X-linked lymphoproliferative disease</td>
<td>B-cell lymphomas</td>
<td>200</td>
<td>Nagy &amp; Klein (2010)</td>
</tr>
</tbody>
</table>

*SIIR is a reasonable estimate for relative risk when population prevalence is low (Chaturvedi et al., 2008).
ADAPTIVE IMMUNITY AND CANCER: THERAPEUTIC EVIDENCE

• Immunotherapies impacting T-cell mediated immunity indirectly demonstrate the importance of T cells in natural control of human cancer
  – CTLA-4 CPI: ipilimumab, Yervoy®
  – PD-1 CPIs: nivolumab, Opdivo®; pembrolizumab, Keytruda®
  – PDL-1 CPI: atezolizumab, Tecentriq®
  – Bi-specific T cell engager: blinatumomab, Blincyto®
  – CARTs: axicabtagene ciloleucel, Yescarta®; tisagenleucel, Kymriah®
IARC convened an international Working Group of experts to identify key characteristics exhibited by established human carcinogens.

The Key Characteristics:
- Provide a basis for systematically identifying, organizing, and summarizing mechanistic information as part of the IARC carcinogen evaluation process
- Guide assay development to assess cancer risk of novel/untested compounds

### Table 1. Key characteristics of carcinogens.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Examples of relevant evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is electrophilic or can be metabolically activated</td>
<td>Parent compound or metabolite with an electrophilic structure (e.g., epoxide, quinone), formation of DNA and protein adducts</td>
</tr>
<tr>
<td>2. Is genotoxic</td>
<td>DNA damage (DNA strand breaks; DNA–protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g., chromosome aberrations, micronuclei)</td>
</tr>
<tr>
<td>3. Alters DNA repair or causes genomic instability</td>
<td>Alterations of DNA replication or repair (e.g., topoisomerase II, base-excision or double-strand break repair)</td>
</tr>
<tr>
<td>4. Induces epigenetic alterations</td>
<td>DNA methylation, histone modification, microRNA expression</td>
</tr>
<tr>
<td>5. Induces oxidative stress</td>
<td>Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g., DNA, lipids)</td>
</tr>
<tr>
<td>6. Induces chronic inflammation</td>
<td>Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production</td>
</tr>
<tr>
<td>7. Is immunosuppressive</td>
<td>Decreased immunosurveillance, immune system dysfunction</td>
</tr>
<tr>
<td>8. Modulates receptor-mediated effects</td>
<td>Receptor in/activation (e.g., ER, PPAR, AhR) or modulation of endogenous ligands (including hormones)</td>
</tr>
<tr>
<td>9. Causes immortalization</td>
<td>Inhibition of senescence, cell transformation</td>
</tr>
<tr>
<td>10. Alters cell proliferation, cell death or nutrient supply</td>
<td>Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle control, angiogenesis</td>
</tr>
</tbody>
</table>

Abbreviations: AhR, aryl hydrocarbon receptor; ER, estrogen receptor; PPAR, peroxisome proliferator–activated receptor. Any of the 10 characteristics in this table could interact with any other (e.g., oxidative stress, DNA damage, and chronic inflammation), which when combined provides stronger evidence for a cancer mechanism than would oxidative stress alone.
CANCER RISK ASSESSMENT FOR T-CELL IMMUNOMODULATORS

REGULATORY CONSIDERATIONS
REGULATORY GUIDANCE DOCUMENTS

• ICH S1A Guideline on the need for carcinogenicity studies of pharmaceuticals, Nov 1995
  – Needed for pharmaceuticals with expected clinical use ≥ 6 months
  – Mechanistic studies part of risk assessment and important in considering whether to perform carcinogenicity studies and for their interpretation
  – Immunomodulation not specifically mentioned

• ICH S1B Testing for carcinogenicity of Pharmaceuticals, July 1997
  – Main focus = one carcinogenicity bioassay + another study (e.g., 2nd bioassay, TgHras2)
  – Introduction of the concept of “weight of evidence”

• ICH S1 2012 Concept Paper
  – Formation of an EWG to assess ways to improve risk assessment, value of rodent bioassays
  – Conceptually, knowledge of pharmacology enough for risk assessment (e.g., immunosuppressants)
  – Concept of a prospective analysis to inform EWG agreed upon - ongoing
REGULATORY GUIDANCE DOCUMENTS, CONT.

- ICH S1 Regulatory Notice Document – 2013 – formalized prospective analysis of CADs vs bioassays
  - “Immunosuppression can be a causative factor for tumorigenesis in humans. Effects on the immune system can alter tumor surveillance or result in tumors secondary to recrudescence of oncogenic viruses. As such, an assessment of potential impact to the immune system should be evaluated according to ICH S8 guideline and factored into the CAD.”

- ICH S1 status report – through December 2017
  - Some DRA/Sponsors disagreements on Category 3a/b (highly likely or unlikely to be carcinogenic; rat bioassay would not add value)
    - “In a few cases, such as with immunomodulators where rodent carcinogenicity studies might not be informative, alternative assessments that characterized the extent of immunomodulation or suppression by the compound was not well addressed.”
    - “These types of deficiencies, when noted in the CADs, prompted DRAs to choose category 2” (i.e., rodent bioassays likely to add value)
• ICH S9, 2009
  – Carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer

• ICH S6, 1997 and S6(R1), 2011
  – Standard bioassays generally inappropriate for biopharmaceuticals
  – Product-specific assessment needed
  – Single rodent species bioassay to be considered
  – Strategy based on Weight-of-Evidence (e.g., genetics, class effects, MOA, etc)
  – MOA might raise concerns, e.g. “immunosuppressives”
    ➢ “Potential hazard can be best addressed by labeling”
CANCER RISK ASSESSMENT FOR T-CELL IMMUNOMODULATORS

LABELING EXAMPLES
LABELING EXAMPLE: PROGRAF® (tacrolimus, initial US approval 1994)

• **Box Warning**

  - Increased risk of development of lymphoma and other malignancies, particularly of the skin, due to immunosuppression (5.2)

• **5.2 Lymphoma and Other malignancies**

  Patients receiving immunosuppressants, including Prograf, are at increased risk of developing lymphomas and other malignancies, particularly of the skin [see Box Warning]. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

  As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

• **13 Nonclinical Toxicology**

  Carcinogenicity studies were conducted in male and female rats and mice. In the 80-week mouse study and in the 104-week rat study, no relationship of tumor incidence to tacrolimus dosage was found. The highest doses used in the mouse and rat studies were 1.2 to 3.3 times (mice) and 4.0 to 10.8 times (rats) the clinical dose range of 0.075 to 0.2 mg/kg/day when corrected for body surface area [see Warnings and Precautions (5.2)].
LABELING EXAMPLE: CELLCEPT® (mycophenolatymofetil, initial US approval 1995)

- Box Warning

Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma.

- Lymphoma and Malignancy

Patients receiving immunosuppressive regimens involving combinations of drugs, including CellCept, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see ADVERSE REACTIONS). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving CellCept (2 g or 3 g) with other immunosuppressive agents in controlled clinical trials of renal, cardiac, and hepatic transplant patients (see ADVERSE REACTIONS).

In pediatric patients, no other malignancies besides lymphoproliferative disorder (2/148 patients) have been observed (see ADVERSE REACTIONS).

- Nonclinical Toxicology

In a 104-week oral carcinogenicity study in mice, mycophenolate mofetil in daily doses up to 180 mg/kg was not tumorigenic. The highest dose tested was 0.5 times the recommended clinical dose (2 g/day) in renal transplant patients and 0.3 times the recommended clinical dose (3 g/day) in cardiac transplant patients when corrected for differences in body surface area (BSA). In a 104-week oral carcinogenicity study in rats, mycophenolate mofetil in daily doses up to 15 mg/kg was not tumorigenic. The highest dose was 0.08 times the recommended clinical dose in renal transplant patients and 0.05 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. While these animal doses were lower than those given to patients, they were maximal in those species and were considered adequate to evaluate the potential for human risk (see WARNINGS).
LABELING EXAMPLE: TYSABRI® (natalizumab, initial US approval 2004)

- Box Warning, no Warnings and Precautions regarding malignancy
- 5.6 Immunosuppression/Infections, no mention of malignancy
- 13 Nonclinical Toxicology

No clastogenic or mutagenic effects of natalizumab were observed in the Ames test or *in vitro* chromosomal aberration assay in human lymphocytes. Natalizumab showed no effects in *in vitro* assays of α4-integrin positive human tumor line proliferation/cytotoxicity. Xenograft transplantation models in SCID and nude mice with two α4-integrin positive human tumor lines (leukemia, melanoma) demonstrated no increase in tumor growth rates or metastasis resulting from natalizumab treatment.
LABELING EXAMPLE: ORENCIA® (abatacept, initial US approval 2005)

- No Box Warning, no Warnings and Precautions regarding malignancy

- **5.6 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 [see Adverse Reactions (6.1)]. In clinical trials in patients with adult RA, a higher rate of infections was seen in ORENCIA-treated patients compared to placebo [see Adverse Reactions (6.1)].
LABELING EXAMPLE: ORENCIA® (abatacept, initial US approval 2005), cont.

- **13 Nonclinical toxicology**

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 a one-year toxicity study in cynomolgus monkeys, abatacept was administered intravenously once weekly at doses up to 50 mg/kg (producing 9 times the MRHD exposure based on AUC). Abatacept was not associated with any significant drug-related toxicity. Reversible pharmacological effects consisted of minimal transient decreases in serum IgG and minimal to severe lymphoid depletion of germinal centers in the spleen and/or lymph nodes. No evidence of lymphomas or preneoplastic morphologic changes was observed, despite the presence of a virus (lymphocryptovirus) known to cause these lesions in immunosuppressed monkeys within the time frame of this study. The relevance of these findings to the clinical use of ORENCIA is unknown.
LABELING EXAMPLE: XELJANZ® (tofacitinib, initial US approval 2012)

• **Box Warning**

Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus–associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications. (5.2)

• **5.2 Lymphoma and Lymphoproliferative Disorder**

Consider the risks and benefits of XELJANZ treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ in patients who develop a malignancy. Malignancies were observed in clinical studies of XELJANZ [see Adverse Reactions (6.1)].

• **13 Nonclinical Toxicology**

In a 39-week toxicology study in monkeys, tofacitinib at exposure levels approximately 6 times the MRHD (on an AUC basis at oral doses of 5 mg/kg twice daily) produced lymphomas. No lymphomas were observed in this study at exposure levels 1 times the MRHD (on an AUC basis at oral doses of 1 mg/kg twice daily).

The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib, at exposure levels approximately 34 times the MRHD (on an AUC basis at oral doses of 200 mg/kg/day) was not carcinogenic in mice.

In the 24-month oral carcinogenicity study in Sprague-Dawley rats, tofacitinib caused benign Leydig cell tumors, hibernomas (malignancy of brown adipose tissue), and benign thymomas at doses greater than or equal to 50 mg/kg/day (approximately 42 times the exposure levels at the MRHD on an AUC basis). The relevance of benign Leydig cell tumors to human risk is not known.
Table 2. Effects of Immunosuppressive Drugs on Mutagenesis and in 2-year Bioassays

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Genotoxic</th>
<th>Rat 2-year</th>
<th>Mouse 2-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>Fusion protein</td>
<td>Inhibits binding of CD28 to B7</td>
<td>No</td>
<td>ND</td>
<td>Lymphomas and mammary tumors in MVL/MMT virus + CD-1 mice&lt;sup&gt;25&lt;/sup&gt; ND&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Corticosteroid</td>
<td>Glucocorticoid-receptor agonist</td>
<td>Yes&lt;sup&gt;1&lt;/sup&gt;</td>
<td>M-Neg&lt;sup&gt;2&lt;/sup&gt;; F- ND</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>Corticosteroid</td>
<td>Glucocorticoid-receptor agonist</td>
<td>No</td>
<td>ND</td>
<td>Neg&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Busulfan</td>
<td>Cytotoxic</td>
<td>DNA alkylation</td>
<td>Yes</td>
<td>Inc&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Thymic and ovarian*&lt;sup&gt;2&lt;/sup&gt; Multiple tumor types&lt;sup&gt;2&lt;/sup&gt; Multiple tumor types&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Cytotoxic</td>
<td>DNA alkylation</td>
<td>Yes</td>
<td>Multiple tumor types&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Atazanerotide</td>
<td>Antimetabolite</td>
<td>Inosine monophosphate dehydrogenase inhibitor</td>
<td>Yes</td>
<td>Squamous cell and lymphoma&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Lymphoma and hematangiosarcoma in females&lt;sup&gt;2&lt;/sup&gt; M-Neg</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Antimetabolite</td>
<td>Dihydro-orotic acid dehydrogenase inhibitor</td>
<td>No</td>
<td>Neg&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Lymphoma and lung&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Antimetabolite</td>
<td>Dihydrofolate reductase inhibitor</td>
<td>Yes</td>
<td>Neg&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Neg&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>Antimetabolite</td>
<td>Inosine monophosphate dehydrogenase inhibitor</td>
<td>Yes</td>
<td>Neg&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Neg&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Calcineurin inhibitor</td>
<td>Binds cyclophilin and inhibits transcription of IL-2</td>
<td>Yes&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Neg&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Neg&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Calcineurin inhibitor</td>
<td>Binds cyclophilin and inhibits transcription of IL-2</td>
<td>Yes&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Neg&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Neg&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Mammalian target of rapamycin (mTOR) inhibitor</td>
<td>Binds FK-binding protein 12 (FRBP12)</td>
<td>Yes&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Neg&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Lymphoma and liver&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Everolimus</td>
<td>mTOR inhibitor</td>
<td>Binds FK-binding protein 12 (FRBP12)</td>
<td>No&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Neg&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Neg&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: ND, not done; IARC, IARC, International Agency for Research on Cancer.

Critical Review of Preclinical Approaches to Evaluate the Potential of Immunosuppressive Drugs to Influence Human Neoplasia

Peter J. Bregeski<sup>1</sup>, Amy Volk<sup>1</sup>, Mindi R. Walker<sup>1</sup>, John H. Kray<sup>1</sup>, Pauline Martin<sup>1</sup>, and Jacques Descotes<sup>2</sup>
WEIGHT OF EVIDENCE BASED RISK ASSESSMENT

“Directed functional immune tests”

Fig. 2. Cancer risk assessment for immunomodulators. The need for an immunotoxicology centered assessment should be driven by the anticipated or unforeseen impact of an investigational therapy on the immune system and should be developed on a case-by-case basis and in alignment with current regulatory expectations. In some instances, rodent bioassays will be conducted (e.g., for small molecules). However, because rodent bioassays have limitations and are not necessarily informative for nongenotoxic immunomodulators, risk assessment needs to include an evaluation of the breadth and depth of the impact on the immune system in nonclinical and clinical studies with a focus on mechanisms relating cancer and immunity. Such elements should inform the need for further investigations or monitoring.
THE CANCER IMMUNITY CYCLE – MANY PLAYERS IN A BALANCING ACT

D Chen and I Mellman, Immunity, 2013
CURRENT FOCUS FOR RISK ASSESSMENT: NK AND CTL

Table 1. Standard Immunophenotyping Panels of Human and Nonclinical Species.

<table>
<thead>
<tr>
<th>Cell type/Species</th>
<th>Human</th>
<th>Rac</th>
<th>Dog</th>
<th>Macaque</th>
<th>Mini Pig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total T cell</td>
<td>CD3+</td>
<td>CD3+</td>
<td>CD3+</td>
<td>CD3+</td>
<td>CD3+</td>
</tr>
<tr>
<td>Helper T cell</td>
<td>CD3+CD4+</td>
<td>CD3+CD4+</td>
<td>CD3+CD4+</td>
<td>CD3+CD4+</td>
<td>CD4+CD8 low</td>
</tr>
<tr>
<td>Cytotoxic T cell</td>
<td>CD3+CD8+</td>
<td>CD3+CD8+</td>
<td>CD3+CD8+</td>
<td>CD3+CD8+</td>
<td>CD45+CD8 high</td>
</tr>
<tr>
<td>Total B cell</td>
<td>CD3–CD20+</td>
<td>CD3–CD45RA+</td>
<td>CD3–CD21+ (mature, nonactivated only)</td>
<td>CD3–CD20+</td>
<td>Ig+</td>
</tr>
</tbody>
</table>

Broere et al., 2011, Principles of Immunopharmacology
HESI-ITC COLLABORATION: OPTIMIZING EXISTING TOOLS TO MEASURE NK AND CTL FUNCTION

• Several sponsors engaged

• Sharing of information to help focus efforts

➢ 2019 state of the science paper in progress
CONCLUSIONS

• There is clear evidence that profound modulation of T-cell function can impact cancer risk
• All immunomodulators, including those impacting T cells, should not be viewed as being necessarily associated with the same risk
• Multiple examples illustrate how rodent studies are generally poorly predictive of cancer risk for such immunomodulators
• A weight of evidence based risk assessment is necessary
• Key challenges: selection of proper immune function tests and understanding of quantitative relationship between immunosuppression and increased cancer risk