Cancer Immunotherapy

For SWOG Translational Medicine Workshop
Based in part on trials and insights of the Cancer Immunotherapy Trials Network

Thanks to Mac Cheever
Thanks also to Dan Chen

Kim Margolin, M.D.
Stanford University
10/26/14
The cancer-immunity cycle

1. Release of cancer cell antigens (cancer cell death)
2. Tracking of T cells to tumors (CTLs)
3. Recognition of cancer cells by T cells (CTLs, cancer cells)
4. Infiltration of T cells into tumors (CTLs, endothelial cells)
5. Killing of cancer cells (immune & cancer cell)

Priming & activation (APCs & T cells)
Cancer antigen presentation (DC & APCs)
The objective of cancer immunotherapy should be the generation of durable responses

- Many human cancers may present as foreign, driven by their multitude of mutations
  This mutational complexity may help drive resistance to chemotherapy and targeted therapy, but make cancer more easily recognized by the human immune system

- Immune responses are dynamic, not fixed
  – Evolved to eradicate highly variable and mutagenic foreign pathogens such as viruses
  – The immune response can self-amplify and evolve due to epitope spreading
1. Focus on understanding of immune biology

- **Effective cancer immunotherapy requires a multitude of steps**
  - Outcomes for immune-combinations are likely not dichotomous “success” vs “neutral”
  - “synergy” “additive” “neutral” or “antagonistic” are reasonable outcomes that should be factored into study design

1. Focus on understanding of immune biology

- Understanding of immune biology can enable incorporation of early phase biomarkers to de-risk taking a neutral or antagonistic combination through P3

- Example: If a PDL1/PD1 inhibitor (drug X) is combined with a MDSC-depleting agent (drug Y), and if this combination is synergistic/additive one should be able to observe:
  - Depletion of appropriate myeloid cells
  - Enhanced PDL1 expression due to drug Y

Confirm the predicted biologic effect supporting the combination!

*In this hypothetical example, drug Y is sensitizing tumors to drug X*
2. Timing is important in cancer immunotherapy

- **Cancer immunotherapy relies on the function of a dynamic “living entity” to eradicate cancer cells (the host immune system)**
  - Recognition that the host immune system can fluctuate in its function, change over time, and be shaped by therapies

- **Understanding of immune states is important for immune-based combinations**
  - Prior therapies: did a patient receive prior HD IL-2?
  - Epigenetic modifiers?

Interpretation of results

2. Timing is important in cancer immunotherapy

- **Cancer immunotherapy relies on the function of a dynamic “living entity” to eradicate cancer cells (the host immune system)**
  - Recognition that the host immune system can fluctuate in its function, change over time, and be shaped by therapies

- **Understanding of immune states is important for immune-based combinations**
  - Prior therapies
  - Does a patient need to generate a new immune response or are we just releasing an existing immune response from inhibition? (irAEs vs anti-cancer immunity)

**Interpretation of results**

**Timing of efficacy, Toxicity, endpoints**

- “Tail” of survival curve?
  - Target:
    - Longer study
    - Slower enrollment
    - Delayed responses?
    - irRC?

- **Rapid response**
  - ORR
  - Duration of response
  - PFS
  - CR rate

- **Herbst et al. ASCO 2013**

- **Baseline**

- **Post-Cycle 2 (6wks)**
2. Timing is important in cancer immunotherapy

- **Use of Complete Response (CR) rate as an endpoint**

- **Example: If Drug X has a 5% CR rate**
  - And Drug Y has a 5% CR rate

- **CR rate can help establish an interesting combo CR rate in a very small study**

<table>
<thead>
<tr>
<th>Observed CR rate for Combo</th>
<th>95% CI for observed CR rate (N=20)</th>
<th>95% CI for observed CR rate (N=30)</th>
<th>95% CI for observed CR rate (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15%</td>
<td>4-39%</td>
<td>5-34%*</td>
<td>7-29%</td>
</tr>
<tr>
<td>20%</td>
<td>7-44%</td>
<td>8-39%</td>
<td>11-34%</td>
</tr>
<tr>
<td>25%</td>
<td>10-49%</td>
<td>12-44%</td>
<td>14-40%</td>
</tr>
</tbody>
</table>

*5.31%-33.6%
2. Timing is important in cancer immunotherapy

- Cancer immunotherapy relies on the function of a dynamic “living entity” to eradicate cancer cells (the host immune system)
  - Recognition that the host immune system can fluctuate in its function, change over time, and be shaped by therapies

- **Understanding of immune states is important for immune-based combinations**
  - Prior therapies
  - Does a patient need to generate a new immune response or are we just releasing an existing immune response from inhibition?
  - Can we modify or sensitize the host immune response?

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**Interpretation of results**

- Timing of efficacy, Toxicity, endpoints

- Optimize combination design

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*Robinson et al. Clin Pharm & Ther 2007*

*Prime-Boost*

*Combination: Concurrent, sequenced, phased, other?*

*D.S. Chen AACR Annual Meeting 2014*
3. Define a diagnostic paradigm

- There is great hope associated with immune-based combination therapy
  ...however, with the potential for greater efficacy comes the specter of greater toxicity

Hepatotoxicity with combination Ipilimumab+Vemurafenib

<table>
<thead>
<tr>
<th>Study Cohort and Patient No.</th>
<th>No. of Doses of Ipilimumab before ALT-AST Elevation</th>
<th>Time to Onset of ALT-AST Elevation after First Dose of Ipilimumab</th>
<th>Time to Resolution of ALT-AST Elevation</th>
<th>Treatment</th>
<th>Toxicity Related with Repeated Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>First cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>21 days</td>
<td>4 days</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>36 days</td>
<td>6 days</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>1</td>
<td>21 days</td>
<td>6 days</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>19 days</td>
<td>12 days</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Second cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>15 days</td>
<td>10 days</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>13 days</td>
<td>20 days</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

*The first cohort started with a run-in period of 1 month of single-agent vemurafenib (960 mg orally twice daily), followed by four infusions of ipilimumab (3 mg per kilogram of body weight every 3 weeks) and concurrent twice-daily doses of vemurafenib. The second cohort received a lower dose of vemurafenib (720 mg twice daily) together with the full dose of ipilimumab. NA denotes not available.

†This patient also had a grade 2 increase in the total bilirubin level.

‡This patient also had a grade 3 increase in the total bilirubin level.

Wolchok et al. NEJM 2013

“Immune-related” toxicity with combination Ipilimumab+Nivolumab

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Immune-related adverse events</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Skin rash</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Nervous system symptoms</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*Only the highest grade of event was counted for each patient. Adverse events that required dose reductions or interruptions were treated as grade 3 events. The median number of treatment cycles was 8 cycles in cohort 1, 5 cycles in cohort 2, 5 cycles in cohort 3, and 6 cycles in cohort 4. The number of patients with grade ≥3 immune-related adverse events was 14% in cohort 1, 12% in cohort 2, 21% in cohort 3, 13% in cohort 4, and 13% in cohort 5. The patients who had immune-related adverse events were counted only once for the adverse event. Only the highest grade of event was counted for each patient. Some immune-related adverse events were counted only once for each organ category because patients who had more than one adverse event were counted for each event but were counted only once for the organ category.
3. Define a diagnostic paradigm

Towards an immune-therapeutic paradigm for cancer immunotherapy

(a hypothetical example)

Is there immunologic ignorance?

- If yes:
  - CAR therapy combo
  - BiTE therapy combo

Are There activated anti-cancer T cells?

- If NO:
  - Vaccine combo
  - Anti-CTLA4 combo
  - Anti-CD40 combo
  - Anti-OX40 combo
  - HD-IL2 combo

Are activated anti-cancer T cells getting into the tumor?

- If NO:
  - Anti-VEGF combo
  - Intra-tumoral injection combo

Are activated anti-cancer T cells inhibited in the tumor?

- If YES:
  - Anti-PDL1/PD1 combo
  - IDOi combo

Are anti-cancer T cells inhibited by other cells?

- If YES:
  - Treg inhibitor combo
  - MDSC inhibitor combo
Study Design Considerations

• The objective of cancer immunotherapy combinations should be the generation of durable responses
  – Few cancer therapy approaches can achieve this due to mutational complexity of human cancers
  – Ultimate success should be defined by “CURES.”

• Understand human immune biology
  – Biology and biomarkers can help prioritize immune-based combos, evaluate early efficacy and determine how to best combine therapies

• Timing is important
  – Human immune-responses are not static
  – Evaluation of efficacy and safety and design of combination studies must take this into account

• Right combination therapy for the right patient
  – Understand which patients are most likely to benefit most (efficacy-toxicity ratio) from monotherapy vs combination cancer immune therapy
The immune synapse as target

Lung cancer immunotherapy has been transformed by immune checkpoint blockade.
Will immunotherapy render chemotherapy obsolete? NO

- Strong endogenous anti-tumor immune response
- Weak endogenous anti-tumor immune response

1. Inducer of anti-tumor immunity (vaccine, TKI, epigenetic modulator)

   - Endogenous anti-tumor immune response
   - PD-L1 up-regulation in tumor

2. Anti-PD-1

   - PD-L1 up-regulation in tumor

RESPONSE

Anti-PD-1 mono-Rx

RESPONSE
TIPPING POINT FOR CANCER THERAPY

Prediction:

• Every cancer patient with T cell infiltration and PD-L1 expression will be treated with anti-PD1 regardless of tissue origin

• Focus of therapy for all cancers for the foreseeable future will be how best to convert anti-PD1 non-responders into responders, i.e., converting T cell poor tumors into T cell rich tumors
“Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer” [NSCLC: Partial Responses in 5 of 49]

[Brahmer et al (NEJM June 4 2012)]

Anti-PD1
NSCLC: PR 14 of 76 (18%)
All patients: Objective Responses:
  9 of 25 (36%) with PD-L1–positive tumors (P = 0.006)
  0 of 17 (0%) with PD-L1–negative tumors
[Topalian et al NEJM June 4 2012]
Agents that convert T cell poor to inflamed tumor

- Standard therapy: Radiation, chemotherapy, targeted agents, epigenetic modifiers

- Immunotherapy
  - Dendritic cell activators
  - Dendritic cell growth factors
  - Vaccines
  - Vaccine adjuvants
  - T-cell stimulators
  - T-cell growth factors
  - Genetically modified T cells
  - Immune checkpoint inhibitors
  - Agents to inhibit suppressive cells, cytokines, enzymes
Two basic tenets of T cell immunity

• **Recognition of *new* pathogens/antigens**
  – Randomly generated T cell receptors (TCR) have an almost infinite repertoire
    • ~ 1-5 billion separate TCR in each human
  – T cells recognize mutated & aberrant proteins on cancer cells

• **T cell responses require continuous control**
  – Multiple overlapping and redundant mechanisms
  – Virus and cancer usurp some of the same mechanisms to avoid destruction by the immune system, e.g. PD-1
[Tumors with increased mutations are more immunogenic/inflammatory, more T cell infiltrated, likely to respond to anti-PD1]

[Lawrence et al, Nature 499: July 2013]
Therapy of T cell-poor & T cell-inflamed tumors will differ substantially

<table>
<thead>
<tr>
<th>T cell-poor tumor</th>
<th>T cell-inflamed tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Must bring T cells into tumor. Then Rx with anti-PD1</td>
<td>Rx with anti-PD1 in combination with agents to inhibit or eliminate suppressive cells and Inhibitory cytokines</td>
</tr>
</tbody>
</table>

**Reasons for immune evasion**

<table>
<thead>
<tr>
<th>T cell-poor tumor</th>
<th>T cell-inflamed tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of innate immune activation</td>
<td>Expression of inhibitory factors</td>
</tr>
<tr>
<td>Lack of chemokines</td>
<td>T cell anergy</td>
</tr>
<tr>
<td>Dense stroma</td>
<td>Presence of regulatory immune cells</td>
</tr>
<tr>
<td>Immunosuppressive oncogene expression</td>
<td></td>
</tr>
</tbody>
</table>

**Therapeutic interventions**

<table>
<thead>
<tr>
<th>T cell-poor tumor</th>
<th>T cell-inflamed tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innate immune activation</td>
<td>α-PD-1/PD-L1</td>
</tr>
<tr>
<td>Stroma disruption</td>
<td>Treg depletion</td>
</tr>
<tr>
<td>Manipulation of oncogene singaling pathway</td>
<td>IDO inhibition</td>
</tr>
</tbody>
</table>

Gajewski et al Current Opinion in Immunology 2013, 25:268–276
The cancer-immunity cycle

1. Release of cancer cell antigens (cancer cell death)

Cancer antigen presentation (DC & APCs)

Tracking of T cells to tumors (CTLs)

Infiltration of T cells into tumors (CTLs, endothelial cells)

Recognition of cancer cells by T cells (CTLs, cancer cells)

Killing of cancer cells (immune & cancer cell)

Priming & activation (APCs & T cells)

The cancer-immunity cycle
**Stimulatory & Inhibitory Factors**

**Priming & activation**
- CD28/B7.1, CD137/CD137L
- OX40/OX40L, CD27/CD70, HVE M, GITR, IL-2, IL-12
- CTA4/B7.1, PD-L1/PD-1
- PD-L1/B7.1, prostaglandins

**Cancer antigen presentation**
- TNF-α, IL-1, INF-α
- CD40L/CD40
- CDN, ATP
- HMGB1, TLR
- IL-10, IL-4, IL-13

**Release of cancer cell antigens**
- Immunogenic cell death
- Tolerogenic cell death

**Tracking of T cells to tumors**
- Chemokines; CX3CL1, CXCL9, CXCL10, CCL5

**Infiltration of T cells into tumors**
- LFA1/ICAM1 Selections
- VEGF, Endothelin B-R
- Hyaluronin

**Recognition of cancer cells by T cells**
- TCR
- Reduced HLA

**Killing of cancer cells**
- INF-γ T cell granule content
- PD-L1/PD-1, PD-L1/B7.1
- IDO, TGF-β, BTLA, VISTA
- LAG-3, Arginase, MICA/MICB
- B7-H4, TIM-3/phospholipids
<table>
<thead>
<tr>
<th>Steps</th>
<th>(+) Stimulators</th>
<th>(-) Inhibitors</th>
<th>Other Considerations</th>
<th>Example References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Release of cancer antigens</td>
<td>Immunogenic or necrotic cell death</td>
<td>Tolerogenic or apoptotic cell death</td>
<td>Tumor-associated neoantigens and cancer testis antigens</td>
<td>Ferguson et al., 2011</td>
</tr>
</tbody>
</table>
| 2. Cancer antigen presentation | • Proinflammatory cytokines (e.g., TNF-α, IL1, IFN-α)  
• Immune cell factors: CD40L/CD40  
• Endogenous adjuvants released from dying tumors: CDN (STING ligand), ATP, HMGB1  
• Gut microbiome products: TLR ligands | IL-10, IL-4, IL-13 | Dendritic cell maturity | Lippitz, 2013; Mellman et al., 2011 |
| 3. Priming and activation | CD28:B7.1, CD137 (4-1BB)/CD137L, OX40:OX40L, CD27:CD70, HVEM, GITR, IL-2, IL-12 | CTLA4:B7.1, PD-L1:PD-1, PD-L1:B7.1, prostaglandins | Central tolerance, T cell repertoire, T regulatory cells | Franciszkiewicz et al., 2012; Lippitz, 2013; Riella et al., 2012; So et al., 2006 |
| 4. Trafficking of T cells to tumors | CX3CL1, CXCL9, CXCL10, CCL5 | | | Franciszkiewicz et al., 2012; Peng et al., 2012 |
| 5. Infiltration of T cells into tumors | LFA1:ICAM1, selectins | VEGF, endothelin B receptor | | Franciszkiewicz et al., 2013 |
| 6. Recognition of cancer cells by T cells | T cell receptor | Reduced peptide-MHC expression on cancer cells | | Mellman et al., 2011 |
Agents to convert T cell poor tumors into T cell inflamed tumors

**Primming & activation**
- Anti-CD137, Anti-OX40
- Anti-CD27, Anti-GITR
- IFN, IL-12
- Anti-CTLA4, Anti-TIM-1

**Cancer antigen presentation**
- Flt3L, GM-CSF
- Anti-CD40
- CpG, Imiquimod, MPL, Poly ICLC

**Release of cancer cell antigens**
- Chemotx, Radiation, Targeted Tx
- Chemoembolization, Cryo Tx, Oncolytic viruses, **OGX-427**

**Tracking of T cells to tumors**
- Chemokines; CCL21
- TCGFs (IL15, IL7, IL21, IL2)

**Infiltration of T cells into tumors**
- Anti-VEGF
- Hyaluronidase

**Recognition of cancer cells by T cells**
- TILs, CARs, Recombinant TCRs

**Killing of cancer cells**
- Anti-PD1/PD-L1
- Anti-LAG-3, Anti-VISTA
- IDO inhibitors
- Anti-IL10, Anti-TGFb

[Revised from: Chen & Mellman Immunity 39, July 25, 2013]
Cancer: Immunity Cycle: Agents in Development

1. **Release of cancer antigens**
   - Chemotherapy
   - Radiation
   - Targeted therapy
   - Chemoembolization
   - Oncolytic viruses
   - Cryotherapy

2. **Cancer antigen presentation**
   - DC activator
     - Anti-CD40
   - DC growth factor
     - Flt3L
   - Vaccines
   - Vaccine adjuvants
     - TLR agonists (systemic and intratumoral injection)
     - CpG
     - Imiquimod
     - MPL/ GLA
     - Poly ICLC
     - Venti (TLR 8 agonist)
     - BCG

3. **Priming & Activation**
   - T cell stimulators
     - Anti-CD137
     - Anti-OX40
     - Anti-CD27
   - Checkpoint inhibitors
     - Anti-TIM-1
     - Anti-CTLA4
     - Anti-GITR
Cancer Immunity Cycle: Agents in Development

(4) Trafficking of T cells to tumors
- Chemokines
  - CCL21
- T cell growth factors
  - IL7
  - IL15
  - IL21

(6) Recognition of cancer cells by T cells
- T cells
  - CARS
  - Recombinant TCR
  - Tumor Infiltrating T cells
- Increase HLA
  - IFN
  - Demethylation agents

(5) Infiltration of T cells into tumors
- Anti-VEGF
- Hyaluronidase

(7) Killing of cancer cells
- Checkpoint inhibitors
  - Anti-PD1
  - Anti-PD-L1
  - Anti-Vista
  - Anti-LAG3
- IDO inhibitor
- Cytokine neutralizers
  - Anti-IL10
  - Anti-TGF-beta
“IL-15 administered by continuous infusion to rhesus macaques induces massive expansion of CD8 T effector memory population in peripheral blood”

Continuous intravenous infusion for 10 days resulted in a massive (70-fold) expansion of CD8 TEM cells in the peripheral blood

Sneller et al BLOOD, DEC 2011  VOLUME 118, NUMBER 26
Continuous Infusion

Varied daily sub-Q doses

CD8+ T cells

Absolute lymphocyte count x 10^{-3}

Sneller et al BLOOD, DEC 2011  VOLUME 118, NUMBER 26
“CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice & humans”

Patients with surgically incurable pancreas cancer.
- Partial response - 4 of 21 patients
- Stable disease - 11 of 21 patients
- Progressive - 4 of 21 patients

[Beatty (Vonderheide) et al Science. 2011 331:1612-6]
Interleukin 7 (IL-7)

- Homeostatic growth factor for T cells
  - Induces proliferation & maintains T-cell responsiveness
  - Prevents and reverses T-cell anergy
- Signals through the IL-7 receptor
  - IL-7R expression is maintained on resting T cells
  - IL-7 is continuously available in secondary lymphoid organs from stromal cell IL-7 production
- The effects of IL-7 are most potent on recent thymic emigrants
  - IL-7 continuous signaling induces anti-apoptotic and costimulatory responses essential for the survival of naïve T cells
Interleukin 7 (IL-7)

- IL-7R is down-regulated with T cell activation
  - Becomes re-expressed after several days

- IL-7R expression is low on FOXP3+ Treg cells
  - More potent on conventional CD8+ & CD4+ T cells
  - Versus CD4+ regulatory T cells (Tregs)

- IL-7R is selectively expressed on effector T cells that are destined to enter the central memory T-cell pool
  - By implication, IL-7 is a modulator of the effector to memory cell transition
Low CD4+ T Cell Counts as a Prognostic Factor for Overall Survival in Patients with High Grade Glioma

Median OS = 13.1 vs. 19.7 months
(p=0.002)

IL-7 potential for prevention: Rx of immune deficiency may reduce viral cancers

- **Human papilloma viruses (HPVs)**
  - Cervical, penis, anus, vagina, vulva, mouth & throat
- **Merkel cell polyomavirus (MCV)**
  - Merkel cell cancer
- **Human herpes virus 8 (HHV-8)**
  - Kaposi sarcoma (KS); multicentric Castleman disease
- **Epstein-Barr virus (EBV)**
  - Nasopharyngeal, Burkitt lymphoma, Hodgkin lymphoma & stomach cancer
- **Hepatitis (HBV) & (HCV)**
  - Liver cancer
- **Human T-lymphotrophic virus-1 (HTLV-1)**
  - Adult T-cell leukemia/lymphoma (ATL)
IL-7 to ↑ repertoire, # naïve T cells recognizing random mutations in carcinogen-induced CA

- Melanoma
- Lung
- Head & Neck
- Stomach/ Esophagus
- Bladder

- **Need therapy trials concurrently testing response of premalignant lesions**
Phase 1 Study of the Safety, Pharmacokinetics, & Pharmacodynamics of the Oral Inhibitor of IDO1 INCB024360 in Patients With Advanced Malignancies

Figure 1. IDO1-Mediated Catabolism of Tryptophan

[Beatty (Gajewski) et al ASCO Poster 2013]
Serum concentration of L-kynurenine predicts the clinical outcome of patients with diffuse large B-cell lymphoma treated with R-CHOP

Overall survival curves of patients with DLBCL according to serum levels of L-kynurenine. Three-yr overall survival rates for patients with L-kynurenine levels of <1.5 and ≥1.5 μM were 83% and 61%, respectively (P < 0.005).

Yoshikawa et al  EJH 84 (304–309)  2009
Phase 1 Study of the Safety, Pharmacokinetics, & Pharmacodynamics of the Oral Inhibitor of IDO1 INCB024360 in Patients With Advanced Malignancies

Figure 2. Patients With Longer Duration of INCB024360 Versus Last Prior Therapy

Dashed line represents 112 days (16 weeks) of therapy with INCB024360

[Beatty (Gajewski) et al ASCO Poster 2013]
Great expectation: (expanded) immunoprevention of cancer

- Advanced cancer: Multiple agents approved
- Prevention of recurrence: Multiple agents approved
- **Primary prevention: What studies are needed?**
  - Therapy trials concurrently testing response of premalignant lesions:
    - Metaplasia with dysplasia
    - Carcinoma in situ
    - Atypical adenomatous hyperplasia
    - HPV-related respiratory papillomatosis
    - Field cancerization
Assessment of benefit

- Slow, atypical responses from immunoRx
- Distinguish inflammatory infiltrate from tumor
- Traditional assessment e.g. RECIST and objective responses may not apply
- Relapse-free survival is the gold standard
The immune system is complicated!

• Probably more complex than understanding the molecular biology of tumors

• A worthwhile goal—to move away from the model of immunotherapy as the “non-MATCH” cohort and to funnel patients into immunotherapeutic buckets/barrels