MAJOR QUESTIONS DISCUSSED

- What are the most promising combination opportunities irrespective of logistical issues?
- What are the most appropriate clinical endpoints for immunotherapy trials?
- Should we focus on metastatic disease setting? MRD/adjuvant setting?
- Should we thinking about integrating non-immunologic agents that possess immunomodulatory properties?
- Will there be an immunologic cocktail for each patient? Each tumor type? Common themes?
- What non-scientific barriers are limiting progress (legal/IP, reagent availability, regulatory)?
SCIENTIFIC CONSIDERATIONS

• Consideration of mechanisms to engage non T cell components of immune system
  – Antibody/B Cells
  – NK cells
  – Macrophage subsets
  – Combinations of above

• Immunomodulatory effects of non-immunologic agents
  – VEGF modulation
  – Chemotherapy-induced loading of antigen onto APCs
TRANSLATIONAL CONSIDERATIONS

• Optimal use of mouse models as preclinical testing ground
  – Good models used the wrong way
  – Application of mouse model data to inappropriate clinical setting
  – Could we create better models that are more predictive?

• Minimal residual disease mouse models
  – Should use as such if planning MRD clinical trial

• Fundamental genetic differences between mouse and human
  – KIRs, TLR9 distribution
  – Concept of “humanized mice”
  – Kinetics of tumor growth in mouse versus man

• Expecting synergy in mouse model to cross threshold for clinical translation
  – What if model chosen is inadequate?
  – What if genetics are different?
CLINICAL CONSIDERATIONS

• Metastatic versus minimal residual disease setting
  – Metastatic
    • Pros: biopsiable tumor, tumor biology effects (Ag loading, necrosis/inflammation), better risk/benefit, measurable clinical response, faster time to clinical endpoint, smaller sample size
    • Cons: tumor bulk, poor PS, global immunosuppression
  – MRD
    • Pros: less immunosuppression, less tumor bulk
    • Cons: hard to study tumor microenvironment, difficult to assess response, longer clinical endpoints, larger sample size, less favorable risk/benefit
  – Possible compromise? Low volume metastatic disease

• Clinical endpoints for immunotherapy trials
  – Are standard response criteria adequate?
    • Time to response
    • Progression then regression
    • Prolonged stable disease
    • Risk of attributing response to downstream therapy
  – Is objective response the best endpoint?
    • TTP, OS
  – Is there need for a new response assessment tool?

• Biomarkers
  – Gather data early
  – Need favorable and unfavorable clinical outcome patients in order to validate biomarkers as surrogate or predictor
  – This requires resources, effort, patient cooperation—but the scientific need is great
  – Biomarker alone unlikely to gain approval—clinical activity trumps