Session Title: “Radiation and Immunotherapy: How to Ignite Long Term Anti-Cancer Response”
Session Duration: 2 Hours
Number of Required Questions: 10
Number of Speakers: 4

Speaker 1: Elizabeth A. Repasky, Ph.D.
Presentation Title: Cancer and the Immune System: The Basics!

Outline/Synopsis example:
Recent and highly publicized demonstrations of the power of immunotherapy approaches for the treatment of cancer have resulted in a need for additional educational opportunities to learn how the immune system works, and to understand better why immunotherapy is rapidly becoming part of standard of care for several types of cancer. Many researchers, clinicians, medical physicists and other health care professionals wish to include an analysis of immune responses in their own experiments or as endpoints in clinical trials. This presentation will highlight basic principles of tumor immunology and summarize seminal discoveries which have catalyzed newly approved immunotherapies known as “checkpoint inhibitors” and “CAR T cells.” Additionally, I will discuss recent literature in which a role for the immune response has been shown to be critical in the outcome of experiments using radiation, chemotherapy ultrasound and several thermal therapies including ablation.

Question set 1:
1. CD8+ T cells are important for:
   a. Direct killing of tumor cells
   b. Helping B cells produce antibody
   c. Are part of the innate immune system
   d. Making antibodies

   Answer: (a)
   Reference: Irradiation and Immunotherapy: From Concept to the Clinic, April K. S. Salama, MD; Michael A. Postow, MD; and Joseph K. Salama, MD Cancer, Vol 122, Issue 11, pp 1659-1671, 2016

2. The primary function of Dendritic cells is to:
   a. Control blood pressure
   b. Conduct nerve impulses
   c. Make antibodies
   d. Present antigen

   Answer: (d)
   Reference: Irradiation and Immunotherapy: From Concept to the Clinic, April K. S. Salama, MD; Michael A. Postow, MD; and Joseph K. Salama, MD Cancer, Vol 122, Issue 11, pp 1659-1671, 2016
3. Cytokines are
   a. Antibodies
   b. Part of the granzyme B complex
   c. Circulating immune mediators
   d. Produced only by dendritic cells

Answer: (c)
Reference: Irradiation and Immunotherapy: From Concept to the Clinic, April K. S. Salama, MD; Michael A. Postow, MD; and Joseph K. Salama, MD Cancer, Vol 122, Issue 11, pp 1659-1671, 2016
**Speaker 2: Silvia Formenti**  
**Presentation Title:** “Radiation Therapy to Ignite an Anti-Cancer Immune Response”  
**Synopsis example:**  
Radiation therapy (RT) contributes both immunogenic and immunosuppressive signals to the tumor microenvironment. Preclinical strategies to enhance the formers and/or mitigate the latter have demonstrated the concrete possibility to shift this balancing act toward a therapeutic success (1). Results from preclinical experiments, in immunocompetent syngeneic models mimicking the setting of advanced cancer treated by radiation and immunotherapy have consistently found clinical confirmation. Particularly when combined with immune checkpoint blockade, radiotherapy has demonstrated to be a powerful adjuvant to immunotherapy. Clinical examples of synergy between RT and immune checkpoint inhibitors have been reported, and interim results in our prospective clinical trial confirm this finding (2-7).

Currently, multiple clinical trials are exploring optimal combinations and scheduling of RT and immunotherapy. While at least some early evidence from these trials confirms the hypothesis that radiation can enhances responses to immune checkpoint inhibitors, in the majority of patients tumors remain unresponsive, warranting investigation of markers that predict response. A recent study testing radiation with ipilimumab in melanoma (8) suggested that tumor expression of PDL-1 may predict lack of response to radiation and ipilimumab. However, in lung cancer patients treated with radiation and ipilimumab we found high PDL-1 expression among patients achieving durable complete and partial responses, without addition of PD-1 pathway inhibitors (9). In fact, higher expression of immune checkpoints has been hypothesized as a marker of more immunogenic tumors (10). In addition, pre-treatment mutational load has been found to be associated with responses to immune checkpoint inhibitors (11). It will be important to determine if radiation can compensate tumors with a low mutational load, by inducing de novo T cell priming to multiple tumor antigens (12) and could, therefore, achieve responses in the absence of pre-existing neoantigens (13).

Importantly, the overall degree of immune impairment of the patients may be a critical predictor of response to RT + immunotherapy. For instance, we found that the pretreatment neutrophil/lymphocyte ratio may enable a priori selection of individuals with a propensity to respond to the combination of radiation and GM-CSF (14). In another study in metastatic breast cancer patients we found that the impaired ability of T cells to signal in response to TCR stimulation was associated with a shorter progression-free survival after treatment with radiation and fresolimumab (Formenti et al, manuscript in preparation). Overall, while RT has emerged as a promising partner for immunotherapy, the identification of tumor and patient characteristics that can predict which patients should receive upfront the combination of immunotherapy with radiotherapy instead of immunotherapy alone remains unclear.

**Question set 2:**

4. Targeting the tumor with local radiotherapy during immunotherapy can:
   a. enhance in field responses  
   b. enhance out of the field responses  
   c. enhance both in field and out of field responses  
   d. reduce toxicity of immune checkpoint blockade strategies
e. none of the above

Answer: (c)

5. Localized Ionizing Radiation has:
   a. Pro-immunogenic effects
   b. Immunosuppressive effects
   c. Both a and b
   d. Neither a not b

Answer: (c)

6. The Neutrophils/Lymphocytes ratio:
   a. Is measured within the tumor
   b. **Is measured in the blood**
   c. Predicts for toxicity to immune checkpoint blockade
   d. None of the above
   e. All of the above

Answer: (b)
Speaker 3: C. Norman Coleman, MD

Presentation Title: Clinical Trials Using Radiation and Immunomodulatory Agents

Outline example:

A. Provide data on the surge of interest in immuno-oncology, which is an emerging field. (graph)

B. Provide data on the number of clinical trials (at least in clinicaltrials.gov) so there is a sense of the volume of trials (graphs)
   - emphasize that most do not involve radiation

C. Provide data on the radiation trial design (table and possibly some schema illustrated)

D. Provide data, including some from my laboratory, on the impact of radiation fractionation on immune response (lab data and also “cartoons” of pathways)

E. Review questions that remain to be answered- dose, fractionation, volume, schedule (charts)

F. Present plans of NRG Immunotherapy Working Group (possibly chart, likely a list)

Question set 3:

7. The radiation fractionation scheme(s) proven to enhance the clinical immune response:
   a. 18 Gy single dose with the check point inhibitor 2 hr after start of radiation
   b. 6 Gy x 5 over 1 week, M-F with check-point inhibitor Sunday (day 0) and Sat (day 6)
   c. 8 Gy on M, Th week 1 and Wed, week 2 each Fx preceded by check-point inhibitor
   d. all of the above
   e. none of the above

Answer: (e)


8. Giving any radiation above 0.5 Gy to the draining lymph node has been shown to be detrimental so that IGRT and/or particle therapy are required for treating the sentinel lesion.
   a. True
   b. False

Answer: (b)

Synopsis example:
Medical physicists are uniquely positioned to help drive investigations in radiation and immunotherapy. Physicists bring expert skills underpinning the delivery of complex radiation treatments, and are able to innovate new approaches that may aid immunogenicity. Physicists have strong skill sets in experimentation, imaging, data analysis, mathematical modeling and simulation, radiomics, and statistics – all of which have relevance. A recent example includes the idea of using Cherenkov radiation (which is produced throughout tissue when irradiated by high energy clinical photon beams) to photo-activate compounds with immunogenic potential in situ. Another example involves using low energy x-rays to excite novel energy ‘down-converting’ phosphors which then emit UV light and photo-activate powerful anti-cancer therapeutics in-situ. A further example includes using modified implanted fiducial markers which include a payload of gold nanoparticles and immunoadjuvants. Once implanted, these drones are designed or programmed to start to release their content directly into the tumour. In these example, and others that will be covered, the unique skillset and perspective of the medical physicist makes an essential contribution to the collaborative team developing these fascinating and promising new treatment directions for the ultimate benefit of our patients.

Question set 4:

9. Which of the following best describes the abscopal effect?
   a. When tumor cells undergo cell-suicide
   b. When a local treatment causes tumor shrinkage at a distant site
   c. When un-treated cells neighboring treated cells die

   Answer: (b)

10. The major challenge to using Cherenkov light from a clinical MV photon beam to activate psoralen (a photo-therapeutic responding to UV light) is likely to be ...
   a. Generating Cherenkov light at all depths in tumor tissue
   b. Generating Cherenkov light at the activation wavelength
   c. Generating Cherenkov light of sufficient intensity in tissue
   d. Delivering a photo-therapeutic to the tissue to be treated

   Answer: (c)
   Reference: Axelsson et al., Cerenkov emission induced by external beam radiation stimulates molecular florescence, Medical Physics, 38(7), July 2011