Optimal Testosterone Levels for Androgen Deprivation Therapy

- Did we resolve the T <50 ng/dL vs. T <20 ng/dL debate?
- The data in mCRPC and mHSPC with abiraterone acetate lend further support to the idea that lower is better
- However, there is no definitive data that proves that these differences result in clinical significance

DNA Repair Alterations

- Occurs in 23% of mCRPC prostate cancers
- 12% of metastatic prostate cancer patients have germline alterations
- Much lower frequency of germline alterations (NCCN guidelines mention considering testing and that rate is ~6%)
- Carefully consider your NGS results, as most platforms will not provide information on somatic vs. germline alterations or mono-allelic vs. bi-allelic alterations
- TOPARP trial offers some clinical data with 88% response rate in those with DNA repair alterations and only 6% in those that don't
  - Multiple PARP inhibitors are now being studied in enriched randomized phase 3 trials e.g. olaparib, rucaparib, and niraparib
- Any agent that induces dsDNA breaks e.g. platinum and radium-223 may also have efficacy
- There are potentially other ways to induce BRCAness and trials evaluating hypoxia induction and next generation AR pathway inhibitors are underway
  - Olaparib may offer rPFS benefit when added to abiraterone in unselected mCRPC patients

Immunotherapy

- Sipuleucel-T should be used early in patients with asymptomatic mCRPC with lower PSA levels
  - Newest trial attempts to move into active surveillance
- Microsatellite instability (MSI) may be a good biomarker for potential response to PD-1/PD-L1 therapy (incidence ~2.7% from SU2C)
- PD-1/PD-L1 antibodies have shown early efficacy in patients with MSI, progression on enzalutamide and potentially in combination with PARP inhibitors
- Many combination therapy trials are ongoing with PD-1/PD-L1 antibodies to convert the non-inflamed to an inflamed phenotype
- We need additional and better markers for selection of patients for immunotherapies

Novel AR Targeted Agents

- Sequencing novel AR targeted agents back to back has low response rates
- Abiraterone acetate offers survival benefit when added to ADT for mHSPC
  - May be preferred over docetaxel for low volume disease
- Apalutamide and Enzalutamide are now FDA approved for M0 CRPC patients with MFS benefit
- Many trials of various combinations are ongoing