Breakout 3 Report:

Apoptosis Induction and Immunotherapy
Conclusions

1. Several new agents which target Bcl-2 family are becoming available.

2. Key drugs appeared to be:
   (1) ABT-737 Currently not effective against tumors with high levels of Mcl-1 but Mcl-1 may be downregulated by using other agents such as sorafenib or GSK-3b inhibitors.
   (2) TW37 targets all the antiapoptotic proteins. Studies in NOD/SCID s have not shown major toxicity to normal tissue.
   (3) Selectivity of Obatoclax (GX015-070) not certain. Mode of action of Genasense also not clear.
   (4) New agents against IAP 1 and 2 showing promise. Release of TNFα in cells causes death.
3. General concerns about the effect of signaling pathway inhibitors on immune responses should be the focus of future studies.
   - In animal models
   - In vitro on immune cells (sorafenib known to inhibit DC function)
   - In clinical trials- (velcade- proteosomal inhibitor- In inhibits T cells

4. Futures studies should be to obtain information on the effect of these agents on the immune response.
5. **Timing of administration of signaling pathway inhibitors maybe critical. Different forms of immunotherapy may be more effective after use of antiapoptotic drugs or signal pathway inhibitors.**

6. **Mode of death of cancer cells may be important in the generation of subsequent immune responses or in providing growth factors for tumor growth.**

No strong consensus reached on this point.
7. It was not always clear what the mode of tumor death was by immunotherapy and could be made a subject of future studies.

8. It was suggested that treating patients with antibodies to high mobility group protein 1 after chemotherapy may reduce inflammation and inhibit tumor growth.

9. An effective form of treatment may be immunotherapy combined with a MEK inhibitor plus a broad spectrum anti-apoptotic inhibitor such as TW37, or ABT737 combined with an inhibitor of mcl-1.