Angiogenesis and immunotherapy combinations (1)

- **Basic scientific questions / potential obstacles**
  - **Preclinical assays are limited in their potential to predict toxicity and effects in patients. Mouse models have the advantage to be a high throughput approach that can filter a lot of information.**
  - **Companion animals with spontaneous tumors may represent a better model.**
  - **Mechanistic studies are elegant but dose and schedule must be found in early clinical trials.**

- **What additional information would be good to get?**
  - **Retrospective analysis of tumour samples may be very helpful.**

Angiogenesis and immunotherapy combinations (2)

- How to discern the relative effects of immunotherapy versus the anti-angiogenic effect - a potential dose issue?
  - Functional imaging may be helpful but not enough validated
  - No biomarkers available for angiogenesis inhibition; objective quantification to date impossible.
  - Go to the clinic!

- How define dose and schedule?
  - Go back to data from single agent(s)
  - When combination provides additive / synergistic expected side effects: start with lower dose
  - Phase 0?
  - Aim for randomized 3-arm phase II trials

Angiogenesis and immunotherapy combinations (3)

- How to set priorities for clinical development of drugs?
  - “market-oriented” approach.
  - Ideal if one drug has already been approved.
  - No priority between antibodies and STI
- Correlative studies for (predictive) biomarkers, serum / tissue sampling, PD studies (e.g. functional imaging)
  - Consider phase 0 trials

Angiogenesis and immunotherapy combinations (4)

- How to select patients (sub-) populations?
  - Late stage patients versus adjuvant setting
  - Adjuvant setting only if one drug had already been approved
  - Potential exceptions:
    - Relapse rate is extremely high e.g. GBM, after metastatectomy
    - In case bevacizumab is positive in CRC adjuvant: phase III in combination with immunotherapy?
    - Safety aspect must then be built in phase III
    - Historical controls are generally worthless.

Summary

- Preclinical science must create the rationale for early clinical trials but usually provides limited data on toxicity and dosage
- Early clinical research must incorporate translational research programs
  - Search for biomarkers (long way to go!)
  - PD data