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