
Mmm... crack! Wait, stop thinking about crack! Its ruined my career! No one will ever take me seriously as a politician ever again. I am such a hoser. Mmm... crack!

Overview

- Background
- Questions – urgent and timely investigations?
- Proposed Approach
- Regulatory Solutions
- Output

Carcinosarcomas – Background

- Rare and highly aggressive epithelial malignancies
  - Malignant mixed Mullerian tumors (MMMT)
  - Uterine carcinomas (UCs) uncommon with >35% extra uterine disease at diagnosis
  - 90% of ovarian carcinomas (OCs) disease spread beyond ovary
- High recurrence rate (local or distant) within 1 year
- Overall survival 2yrs (8 to 26 months)
- ***Challenge***: No clear evidence to establish consensus guidelines for therapeutic management

Current Treatment Paradigm
Frontline Setting

Uterine Carcinosarcoma

- Comprehensive approach
  - Complete surgical staging
  - System chemotherapy (early and advance patients)
    - Combination of paraplatine-paclitaxel
- Active agents
  - Paraplatine
  - Cisplatin
  - Ifosfamide
  - Paclitaxel
- Adjuvant radiotherapy (external beam irradiation or vaginal brachytherapy) has not shown survival benefit
  - Contributes to reducing incidence of local pelvic recurrence

Ovarian Carcinomasarcoma

- Cytoreductive surgery
  - Improved survival with lymphadenectomy
- Platinum-based chemotherapy
  - Either paraplatine-paclitaxel or ifosfamide-cisplatin
- Little rationale using radiotherapy; role remains unknown.

Advanced/Metastatic Disease

Uterine Carcinosarcoma (UCs)

- Cytotoxic Agents
  - Ifosfamide 32% response rate (RR); Cisplatin 19%RR; and Paclitaxel 18% RR
  - Ifosfamide-Paclitaxel current SOC (USA)
- Biological Anticancer Treatments
  - Poor RR in unselected populations (0-5%)

Ovarian Carcinosarcoma (OCs)

- Chemo sensitivity equivalent to Ucs
- Common treatment combinations
  - Platinum-paclitaxel & Platinum-ifosfamine
  - Lower RRs
- Inclusion in PII ROSIA trial

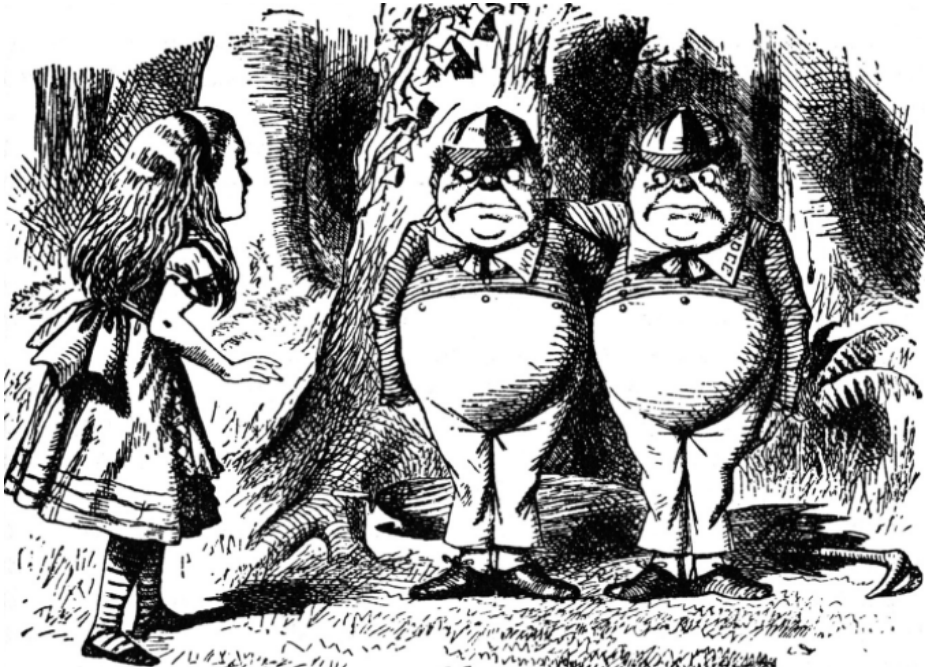
Optimal Treatment Remains Unknown

Molecular Characteristics

- MMMT akin to type II non endometriod
- Common Mutations
  - p53 positivity in up to 60% of tumors; TP53 mutations in 23% of cases
  - PI3KCA gene mutations (19%) in ECS cases
  - KRAS (24%)
  - PTEN mutations (0 to 14% - contradictory results)
- Rare Mutations
  - B-catenin (7%)
  - NRAS (2%)
  - CTNBB1 (4%)
- UCs
  - 45% express Abl
  - 19% express HER-2/neu,
  - 100% express PDGF-R β,
  - 32% express ER-β,
  - 23% express EP-B
- UCs over express
  - Cox2 (33%)
  - EGFR (30%)
  - Trop-2(35-57%)
  - c-KIT (16-25%)
  - PARP
  - VEGF is strongly expressed
  - High chromosomal instability

If we are going to ask a question internationally:

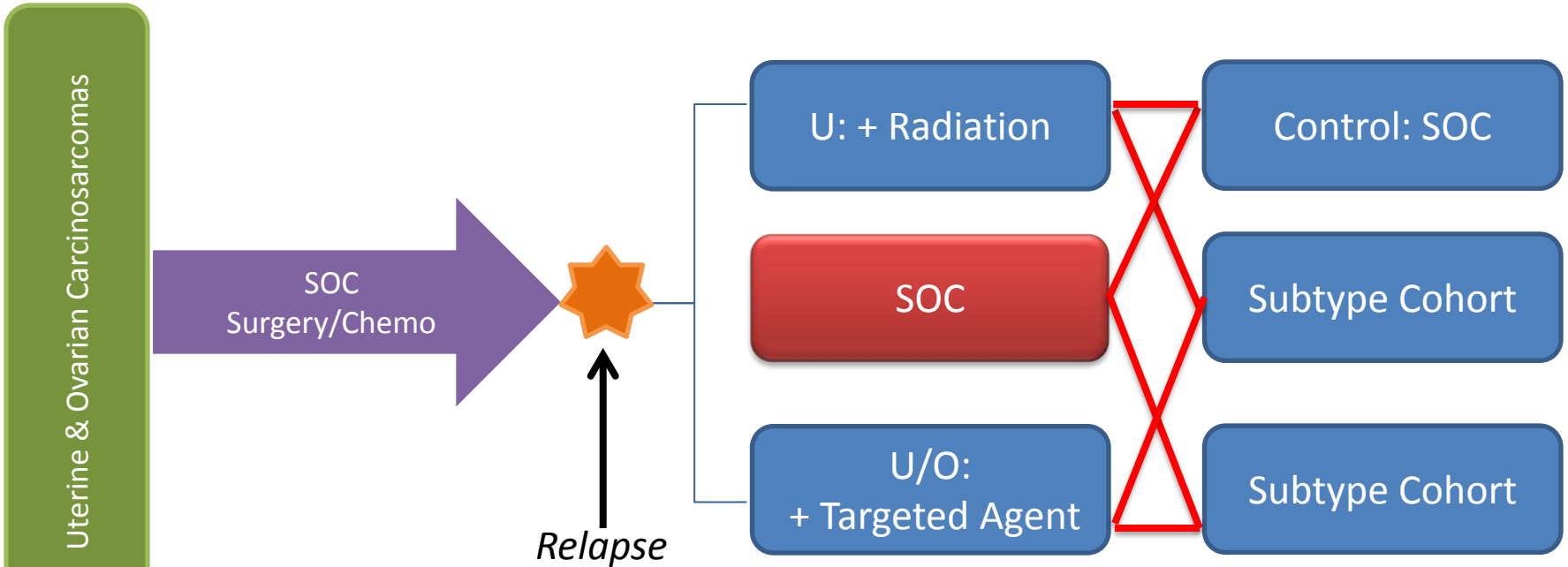
- What is it? Has to important and practice changing.
- Practical
- Max Parmar:
  - No Tweeldledum and Tweedledee studies



Questions – Urgent & Timely?

- Molecular alterations really involved as genetic drivers of the disease
- Impact of lymph node dissection (pelvic and/or lumboaortic) on overall survival
- Uterine: impact of pelvic RTE on OS
- Impact of adjuvant chemotherapy on survival for early stages.
  - Do all UCs, even stage IA, and all OCs need chemotherapy?
  - Impact of adjuvant multimodality therapy on PFS and OS?
- Is paraplatine-paclitaxel or paclitaxel- ifosfamide the best regimen?
- Place of other drugs (liposomal doxorubicin, trabectedin…) and targeted therapy (VEGF inhibitors, mTOR inhibitors, parp inhibitors, in selected subgroups?) alone or in combination.

Umbrella Study



Data Collected:
* Outcomes
* Baselines
* Tissue (molecular Characterization)

n= 50-60

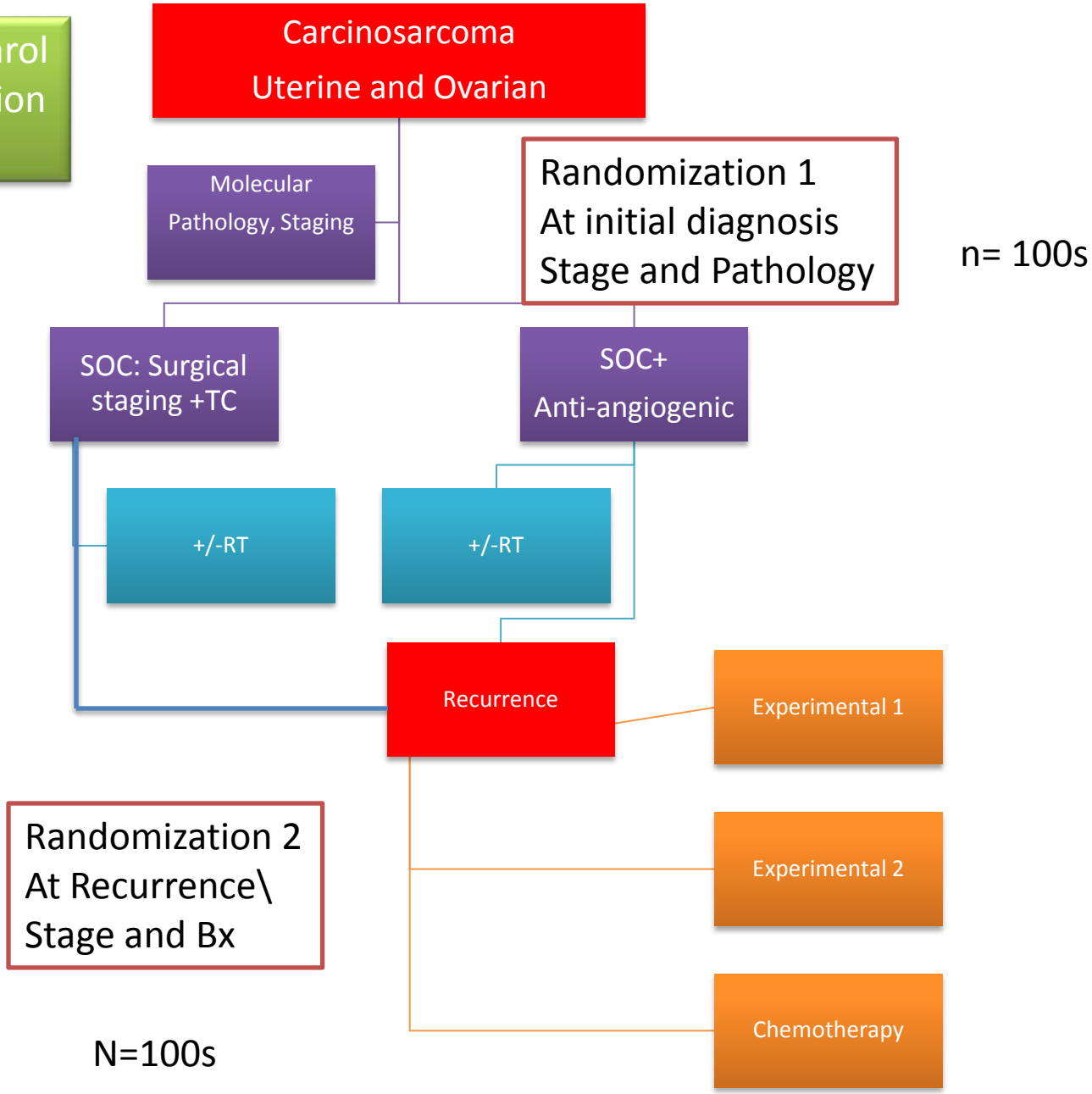
Because early stage, can compare outcomes to base data.

'Watch Phase'

Discussion

- Be ambitious
- Randomized study easier to fund than observational
- More likely to make progress – asking a question
- Aggressive disease and short time to enrol if study is recurrence only
- Molecular characterization at presentation and recurrence is key – define biomarkers
- Build on uterine and ovarian carcinoma trials
  - Anti-angiogenics
- If not Carcinosarcoma studies – allow these patients on other ovarian and uterine studies
  - Define minimal dataset

Patients can enrol
At Randomization
1 or 2



Standard of Care

- Surgical staging
  - Uterine: LND
  - Ovarian: Ovarian surgical staging
- Radiation
  - Ovarian : No
  - Uterine:
    - Brachytherapy: Acceptable
    - Pelvic?? – question remains for Stage I/II
      - If enough patients: bifactorial randomization
      - If not enough, comfortable to define no RT
- Chemotherapy
  - Carboplatin and paclitaxel - community standard
    - (GOG261 – will complete in 6m)
- Embed PROs - define

Design Characteristics

- Single protocol
- Nested randomized clinical trials
- Good for patients – all patients
- Good for centres
  - Multiple cohorts can participate within a single protocol
- More likely to make progress – as asking multiple questions
- Model for other rare tumour types

Tissue Issues

- National/International Path review
  - Panel
- Tissue essential
  - Also at recurrence
- Some centres – can collect fresh frozen as well

Challenges

- Agree on research arms
  - SOC
  - Experimental
  - Define PRO
- Funding agency
- Regulatory Authorities

Rare Tumors
Harmonization issues

- Challenges:
  - High start up efforts, limited budget and very few patients
  - Risk of regulatory non acceptance of umbrella or other adaptive design
- Considerations:
  - Conduct feasibility within groups/countries that also addresses regulatory and financing obstacles
  - Form Steering Committee representative of participating regions
  - Provide clear rationale for study design in protocol
  - Discuss /seek advice with regulatory prior to submission

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Rare Tumors
Harmonization issues

- Challenges:
  - Biologic specimen collection and shipping
  - Need for histologic confirmation of diagnosis
- Considerations
  - Address upfront privacy laws, consent issues, and limitations for biologic sampling (Participating Group)
  - Share costs of supplies and shipping
  - Virtual or regional banking
  - Determine logistics of central pathology review (remote web-based, country, regional, single institute)

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specimen collection and shipping

Output

- Small Working Group Nominations to:
  - Develop trial concept and write protocol
    - Statistical Expertise
    - Harmonization/Regulatory Expertise

Questions?