Mmm... crack! Wait, stop thinking about crack! It's 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**

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**Optimal Treatment Remains Unknown**
Molecular Characteristics

• MMT akin to type II non endometrioid

• 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)

‘Watch Phase’

Because early stage, can compare outcomes to base data.

U: + Radiation
U/O: + Targeted Agent
SOC
Control: SOC
Subtype Cohort
Subtype Cohort

n= 50-60
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
Carcinosarcoma
Uterine and Ovarian

SOC: Surgical staging + TC
SOC+ Anti-angiogenic

 +/- RT

Recurrence

Randomization 1
At initial diagnosis
Stage and Pathology

n= 100s

Patients can enrol
At Randomization 1 or 2

Randomization 2
At Recurrence
Stage and Bx

Experimental 1
Experimental 2
Chemotherapy

N=100s
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
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)
Output

• Small Working Group Nominations to:
  – Develop trial concept and write protocol
    • Statistical Expertise
    • Harmonization/Regulatory Expertise
Questions?