



GCIG Early Phase Therapeutics Network Phase II Working Group

PI: Amit M. Oza

Proposed Research Plan

April 2013



Working Group Proposal

- Formalized plan at Endometrial Meeting, Leiden
- Identify groups/centres which have an interest in collaborative Phase II
- Collaborative Phase II trials:
 - Efficiency and innovation
 - Ability to conduct trials in rare populations
 - Control arm to add to Phase II: SOC/Rolling



Concept

- Network of international centres that can conduct clinical AND translational high impact clinical trials in a coordinated and complementary manner
- Profiling will make populations smaller
 - Molecular and genomic analysis
 - Pathology
 - Biomarker discovery
- Evidence based validation studies



PII Working Group

- Groups with Phase II interest
 - Tiered based on expertise
- Objectives: Work collaboratively and as a team to identified high risk/high reward translational/correlative studies projects that
- Consistency of design
 - control arm, correlatives
 - Patient populations:



Goal for first meeting

- Establish concept and framework
- Conceptual collaborative protocols
- Working group to develop protocols and liaise with Pharma, NCI solicitations, Grants, other groups
- Statistical models – innovative and practical
- Translational studies
 - Translational working Group



How should we accommodate sub-groups

- Ignore them?
- Treat them the same until we know they are different?
- Base on specific population and allow exploratory cohorts
 - Pathology
 - Molecular





Proposed Project 1

- **Rationale:** Randomized phase II setting with a rolling control group and several experimental agents.
- Eg: Platinum Resistant Ovarian Cancer, Recurrent Endometrial Cancer...
 - **Control Group:** standard treatments; assuming a RR of 10-15% and a 3-month overall median PFS.
 - **Aim:** Achieving at least an improvement in the RR to 25-30% and a doubling of the median PFS.
 - Randomization could be 2:1 or 3:1 or 4:1
 - *This approach allows several studies to be mounted concurrently and not sequentially.*



Rolling Randomized Phase II – multi centre design - GCIIG proposal.

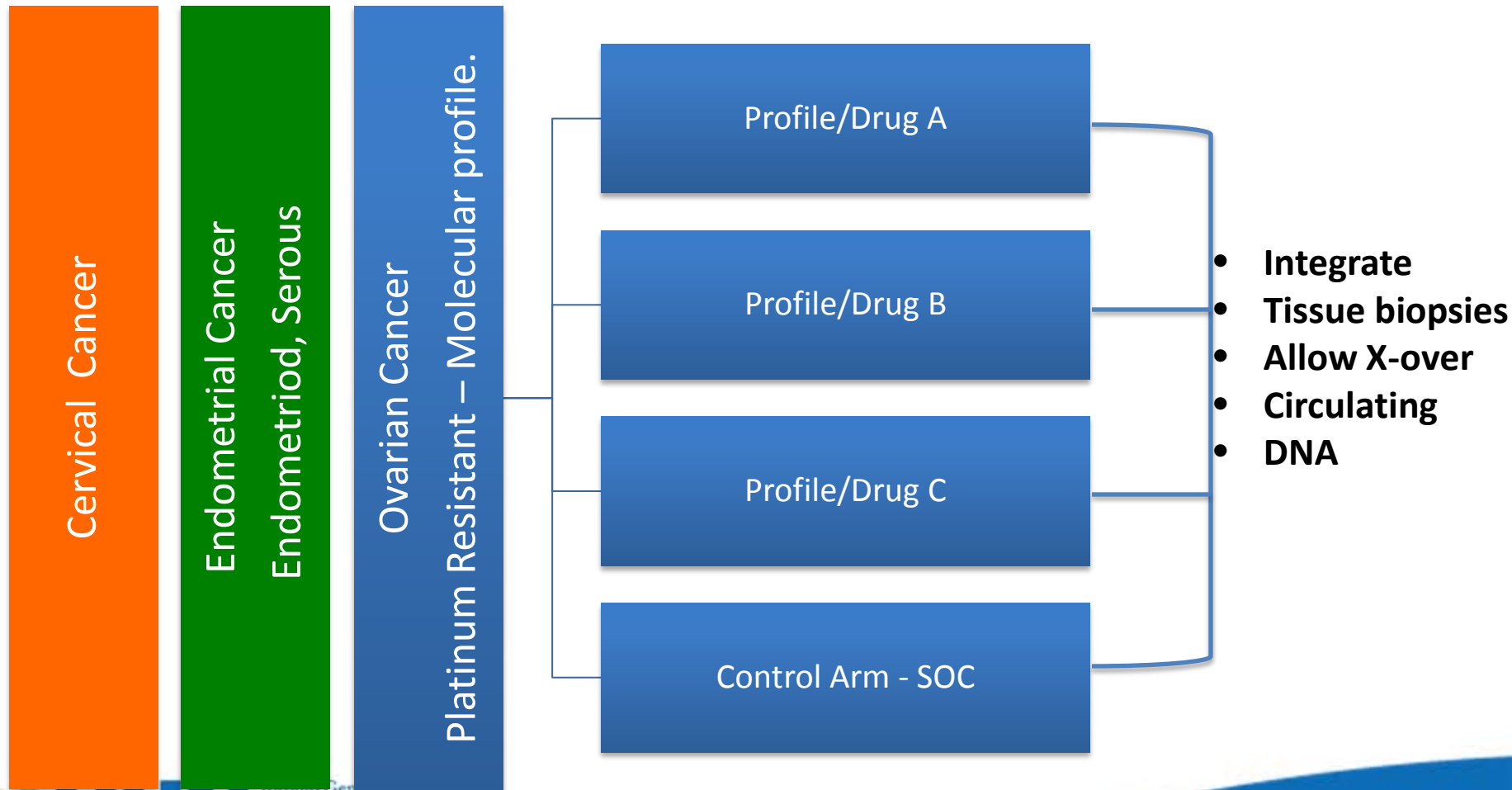
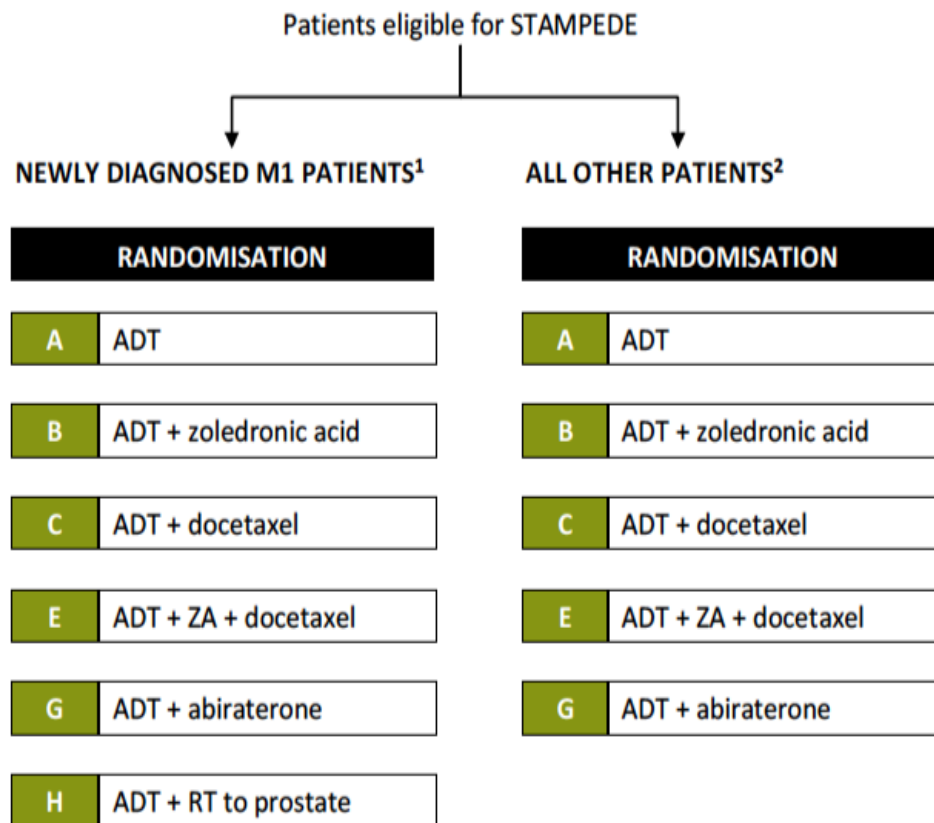




Figure 4: Recruiting arms of the STAMPEDE trial from protocol version 9.0 (Jan-2013 to Mar-2013)



¹ Except pts with a contra-indication to RT

² All suitable pts with newly diagnosed locally advanced disease should also have RT to the prostate

Accrual was initiated to the radiotherapy-to-the-prostate for metastatic disease arm, Arm H, in Jan-2013.



Proposed Project 2

- **Rationale:** Pathology and Molecular profiling are making smaller and smaller subgroups
 - Efficient study design for smaller subgroups/rare tumour
- **Methodology:**
 - ***Umbrella design:*** Combine rare histologies
 - seek out big effect sizes
 - ?use a patient as their own control
 - (PFS1, PFS2 would be both complete observations)
- **Aim:** Ability to detect a RR from 5% in the CONTROL to 40% in the STD (alternatively 10% to 50%) or a 30% improvement in PFS as suggested by Van Hoff et al.



Umbrella Designs- molecular or histologic types

Umbrella Ovarian Protocol

Umbrella Endometrial Phase II

Granulosa Cell

Carcinoma

Mucinous Cancer

Clear Cell

Mutation Profile

Plat Resistant

Carcinoma

Serous carcinoma

PIK3CA mutant

PTEN mutant

KRAS mutant

Recurrent

D

C

B

A

E

SOC

C

B

A

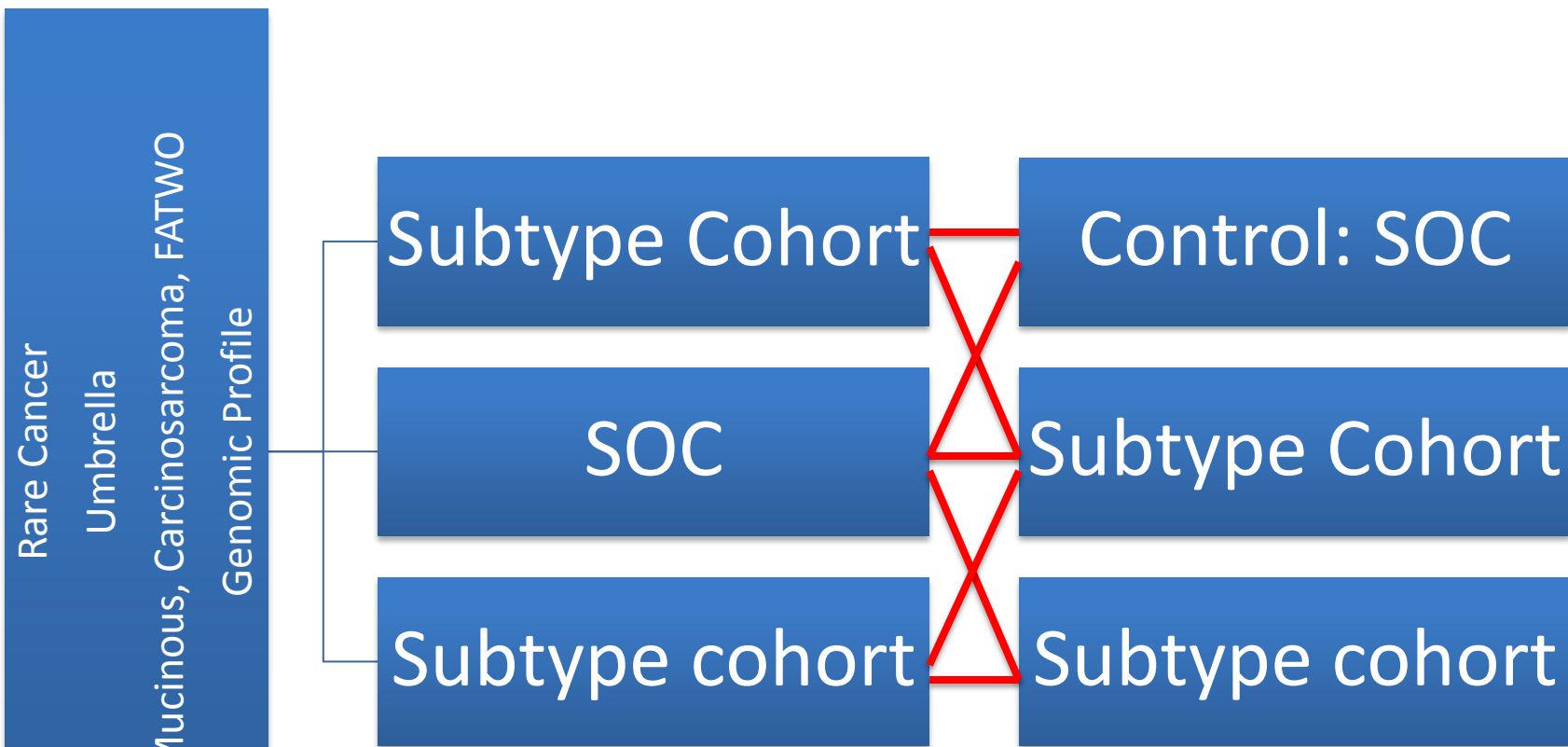
D

E

SOC



Rare Histology or Molecular profile



Comparators: Treatment A vs Control/SOC
Patient own data as control: PFS 1 vs 2. RR 1 vs 2
Look for Big differences: RR 5% vs 40%
?Bayesian



Has this been done
before?

Yes: Neo-Big

Trials: Stampede

- Centres can do trials as a network or independently
- Some trials may be run through one or more nodes
- Harmonize or set guidelines for issues of trial design, endpoints, molecular analyses so that combined analysis possible



Working group

- Agreed to form group to design/develop trials
- Membership:
 - Representation from groups
 - Statisticians
 - Translational Committee
 - Harmonization Committee
 - Pharma
- Funding –
 - Trial based funding
 - potential grant application
 - Pharma