Carcinosarcoma

Trials in a rare malignancy

BACKGROUND

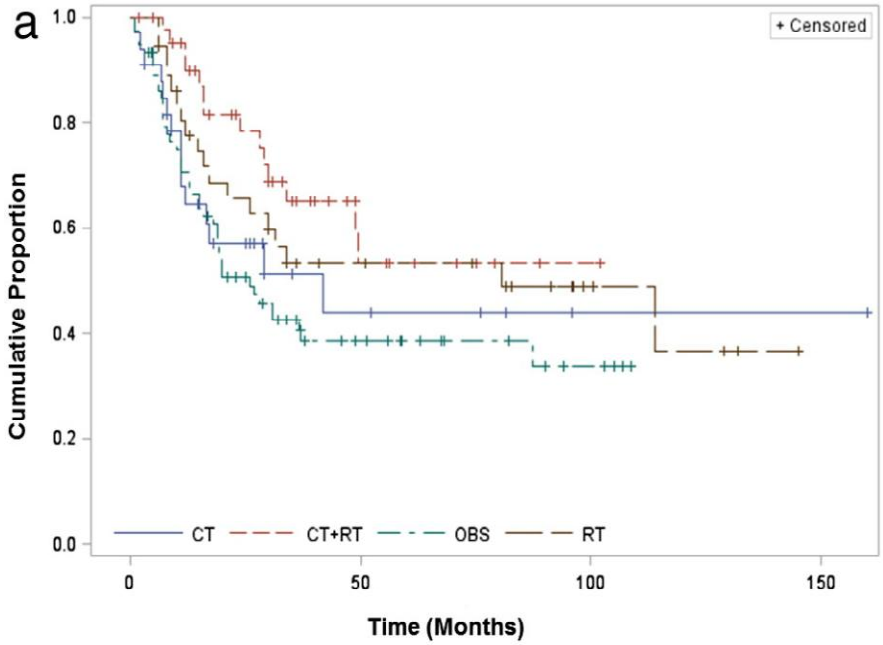
- Rare and highly aggressive epithelial malignancies
  - Biphasic tumors with epithelial and mesenchymal components
  - Uterine carcinomas (UCS) uncommon with >35% extra uterine disease at diagnosis
  - 90% of ovarian carcinomas (OCs) disease spread beyond ovary
- High recurrence rate (local or distant) 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

- Comprehensive approach
  - Complete surgical staging including lymphadenectomy
  - Systemic chemotherapy (early and advanced patients)
    - Combination of carboplatin-paclitaxel vs cisplatin-ifosfamide
- Adjuvant radiotherapy (external beam irradiation or vaginal brachytherapy) has not shown survival benefit
  - Contributes to reducing incidence of local pelvic recurrence

Progression free survival



Dickson et al. Gyne Onc 2015

CURRENT TREATMENT PARADIGM
FRONTLINE SETTING - Ovary

- Cytoreductive surgery
  - Improved survival with lymphadenectomy
- Platinum-based chemotherapy
  - Either carboplatin-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-ifosfamide
  - Lower RRs
- Inclusion in PII ROSIA trial

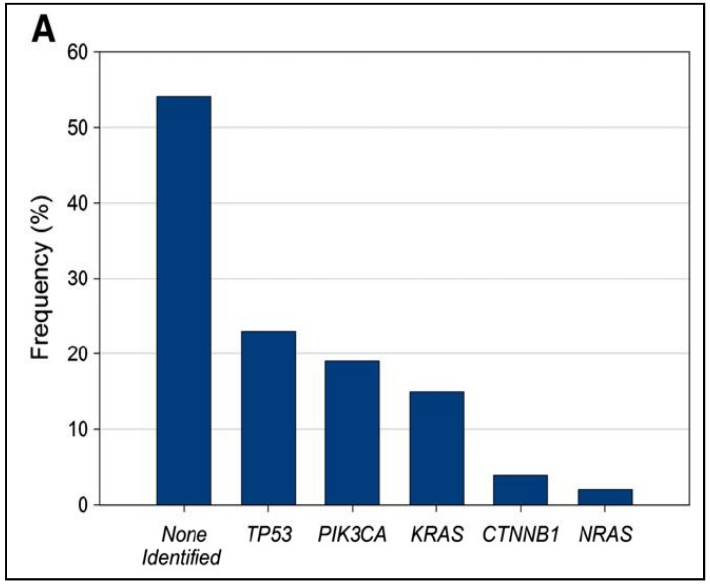
Optimal Treatment Remains Unknown

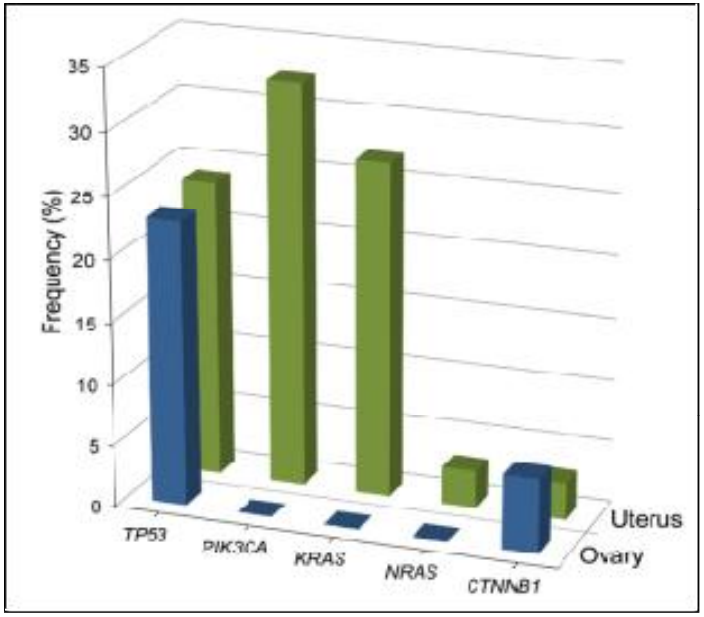
MOLECULAR CHARACTERISTICS

POTENTIAL TARGETS

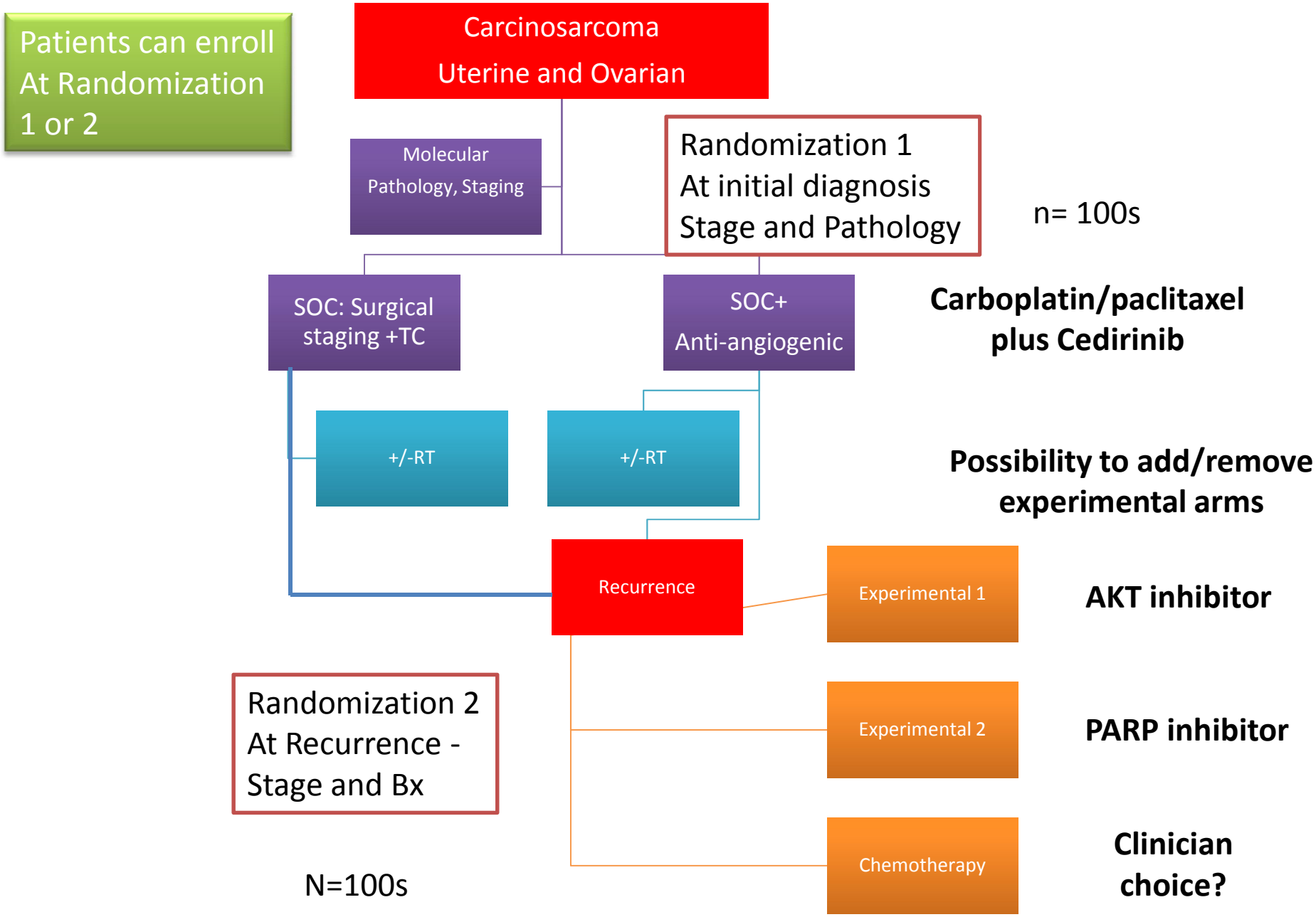
- p53 positivity in up to 60% of tumors;
- TP53 mutations in 23% of cases
- PI3KCA gene mutations (19%) in UCS cases
- KRAS - 24%
- PTEN mutations (0-14% -contradictory results)
- VEGF – 90-100%
- PARP1
- HER2 – 6% but variable rates up to 15%
- COX-2 – high expression better UCS
- EGFR – 30%
- c-KIT – rates from 0-100%

Uterine and Ovarian carcinosarcomas are not the same

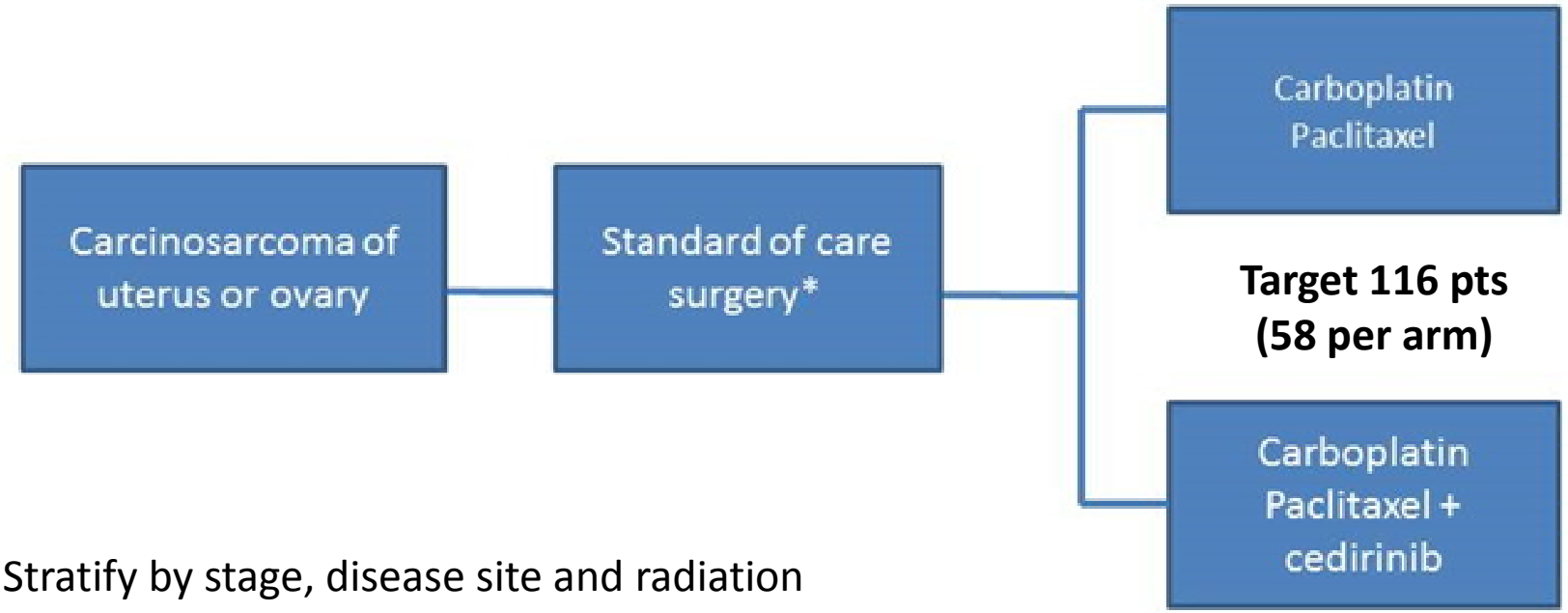




Be ambitious….


Patients can enroll
At Randomization
1 or 2
Carcinosarcoma
Uterine and Ovarian
Molecular
Pathology, Staging
Randomization 1
At initial diagnosis
Stage and Pathology
n= 100s
SOC: Surgical
staging +TC
SOC+
Anti-angiogenic
Carboplatin/paclitaxel
plus Cedirinib
+/-RT
+/-RT
Possibility to add/remove
experimental arms
Recurrence
Experimental 1
AKT inhibitor
Randomization 2
At Recurrence -
Stage and Bx
Experimental 2
PARP inhibitor
Chemotherapy
Clinician
choice?
N=100s

PROPOSED FIRST LINE TRIAL



* Stratify by stage, disease site and radiation

Primary Objectives

To evaluate the addition of targeted therapy as part of first-line therapy in carcinosarcomas of the uterus and ovary on PFS and OS.

Secondary Objectives

To explore potential biomarkers as predictors of response.

To explore the safety and tolerability of this regimen in carcinosarcomas of the ovary and uterus.

ENDPOINTS

Primary

- To compare progression free survival with the addition of cedirinib to carboplatin/paclitaxel in uterine and ovarian carcinosarcomas (evaluated according to the delay between randomization and the occurrence of disease progression according to RECIST v1.1 or death whatever the cause).

Secondary

- Assess response rate by RECIST 1.1 criteria between the different arms in patients with residual disease post surgery.
- Compare overall survival (defined by the time between randomization and the occurrence of death whatever the cause) with the addition of cedirinib with carboplatin and paclitaxel.
- Assess disease control rate (defined as either tumor response or stable disease) with the addition of cedirinib
- To assess the safety and tolerability of use of cedirinib in this population (toxicity profile will be evaluated according to the NCI CTC AE v.4.0)
- Assess impact on quality of Life (using EORTC QLQ-C30, QLQ-OV28, Hospital Anxiety Depression Scale (HADS), FACT/NCCN Ovarian Symptom Index (FOSI) and symptom questionnaires) with maintenance therapy with cedirinib.

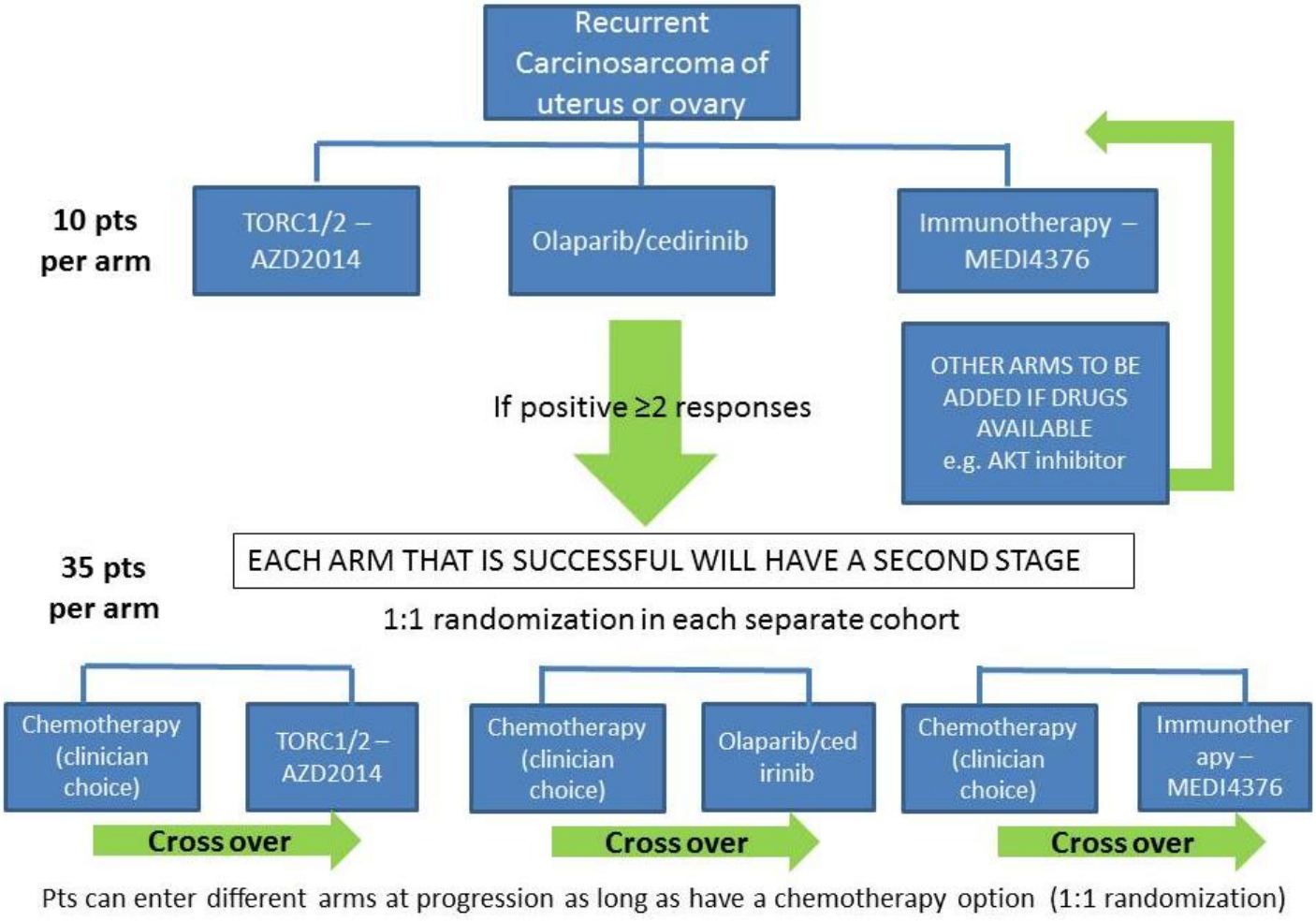
Exploratory

- Explore the role of circulating angiogenic factors as markers of response in patients treated with cedirinib.
- Assess the expression of VEGF as a marker of response.
- Perform next generation sequencing to explore mutations profiles in patients with ovarian and uterine carcinosarcoma to identify predictive markers.
- Explore the expression of PDL1 in this patient population.
- Explore the role of ctDNA as a marker of response.

STATISTICAL DESIGN

- A multicenter, two-arm, two-stage design:
- Patients will be randomized in a **2:1 ratio** to cediranib vs placebo treatment to assess meaningful difference in PFS.
- A one-sided log rank test with an overall sample size of **105** subjects (35 in the control group and 70 in the treatment group) achieves 80 % power at a 0.10% significance level to detect a hazard ratio of 0.6 when the control group median progression free survival time is **8 months.**
- The study will take approximately 3 years of which subject accrual (entry) occurs in the first 2 years.
- Target **116** patients to account for 10% drop-out rate.

A randomized phase II trial MUlti-arm Study comparing targeted therapy with chemotherapy at recurrence in Carcinosarcoma of the ovary and uterus (MUSiC).



ENDPOINTS

Primary

- Response rate by RECIST will be compared between chemotherapy and individual targeted treatments.

Secondary

- Assess progression free survival (PFS) and PFS2 between the chemotherapy arm and individual targeted therapies.
- Compare overall survival between the chemotherapy arm and individual targeted therapies.
- Compare disease control rate (defined as either tumor response or stable disease) between the chemotherapy and different targeted drugs.
- Assess tolerability and safety of targeted therapies in this patient population.
- Determine the effect on quality of Life (EORTC QLQ-C30, QLQ-OV28, Hospital Anxiety Depression Scale (HADS), FACT/NCCN Ovarian Symptom Index (FOSI) and symptom questionnaires) with the use of targeted therapy.

Exploratory endpoints (will vary dependent on the arm the patient is on)

- Perform next generation sequencing to explore mutation profiles in patients with ovarian and uterine carcinosarcoma to identify predictive markers.
- Explore the expression of PDL1 in this patient population.
- Explore the role of ctDNA as a marker of response.
- Explore a multi-arm multi-centre study design in a rare tumor.

STATISTICAL DESIGN

The primary endpoint will be **response rate** for each cohort. We are aiming to increase the response rate from **10% to 30%.**

Stage I:

30 patients will receive 3 targeted therapies (10+10+10).

If **at least 2 responders** in one of the therapies, take the therapy to stage II. If not, drop the therapy.

Stage II:

For each individual cohort where the targeted therapy is selected after stage I, patients will be randomized at 1:1 with a control arm.

70 patients (35+35) will be required per cohort that advances to achieve 80% power at 0.1 significance level (one–sided).

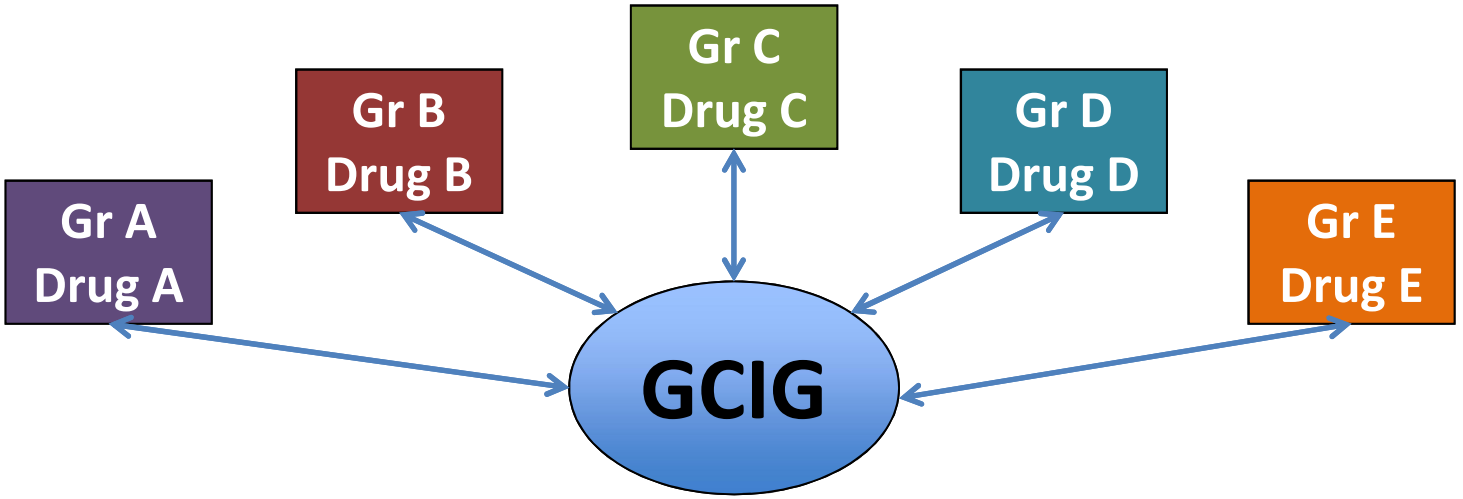
CORRELATIVES

- Archival tissue will be used for each patient and will be profiled with next generation sequencing.
- A central pathology review will be included.
- Tissue will be assessed for PD-L1 expression.

If had been in upfront study no need to repeat this

- A biopsy will be performed at enrollment and at progression (if feasible)
- Other correlative studies will include ctDNA.
- Response will be assessed by RECIST 1.1

CHALLENGES



- Can we group uterine and ovarian carcinosarcomas together?
- What are the appropriate arms for the trial?
  - SOC – is there one that can be agreed upon?
  - Experimental arm
  - Define PRO
  - Choice of endpoints and statistical design challenging
- Do we run this like the GTAC cervical trial? One drug per coop group?
- Funding - ***expensive***
- How do we centralize and maximize what we learn?

Supplementary slides

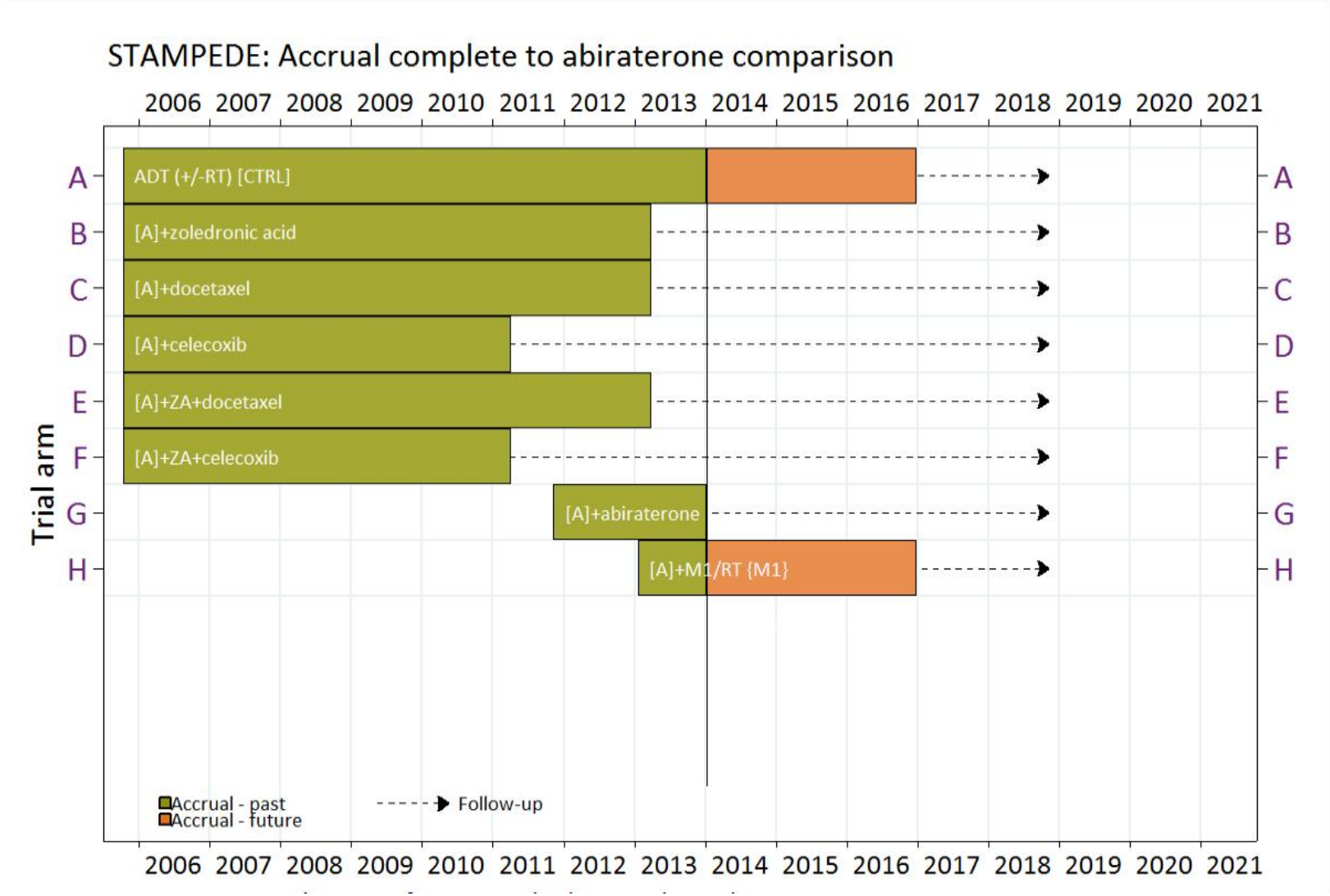
QUESTIONS – URGENT & TIMELY?

- 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 platinum-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.

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

MULTI-ARM MULTI-STAGE TRIALS



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