GYNECOLOGIC CANCER INTERGROUP

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

SB Working group

- General Assembly

DRAFT

GYNECOLOGIC CANCER INTERGROUP (GCIG)

SYMPTOM BENEFIT COMMITTEE

FRIDAY, JUNE 3, 2016, 8:00AM – 10:00AM
LASALLE I ROOM, DOUBLE TREE HOTEL, CHICAGO

Chair : Florence Joly **co-Chair: Felix Hilpert**
Harmonization liaisons: S.Polleis (Ops), V.Gebski (Stats)

PLEASE SIGN IN ON ATTENDANCE FORMS

AGENDA

Welcome & Introductions *F Joly*

COI declarations

Minutes/Report: Nov 2015 (posted on GCIG website)

Discussion: PROs & CTCAE [30] *L. Minasian*

Summary of Tokyo SB lecture [20'] *F Joly*

New studies/concepts:
- Atalante - QoL Substudy (20') *E Pujade-Lauraine*

Update: ongoing studies [30']
- Elderly (5')
  . EWOC study GOG 273 *F Joly for G Freyer and G Fleming*
-AGO OVAR 19/TRUST QoL substudy (5') *F Hilpert*
- Survivorship
  - OvQuest , MOST OPAL, ECHO, Systematic Review (10') ** for *M Friedlander*
  - Expression V and VI(5') *D Sehouli*
  - Vivrovaire I , Survivorship in endometrial cancer (5') *F Joly*
  - Long-term Ovarian Cancer Survivor Project (5') *M Birrer*

Results: closed studies [10']
- Symptom Benefit study ** for *M Friedlander*
- Penelope : QoL Sub-study *F Hilpert*

Next meetings: Lisbon, October 2016, Chicago 2017 [5]
-Best supportive care in clinical trials in Gynecology: discussion *F Hilpert*
- Others topics (patient preferences)

ADJOURN

PRO-CTCAE™:

PATIENT-REPORTED OUTCOMES VERSION OF CTCAE

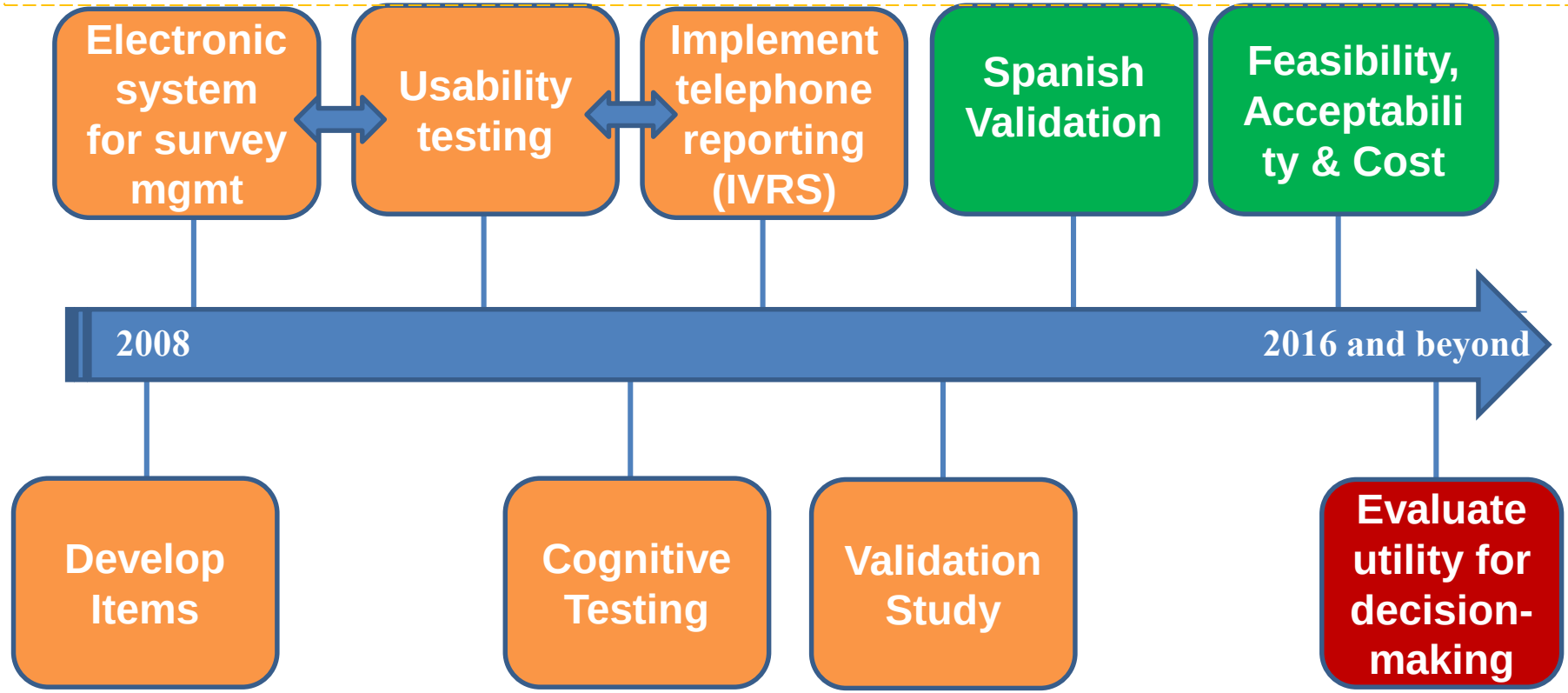
Lori Minasian, MD

Deputy Director, Division of Cancer Prevention, NCI

What is PRO-CTCAE™?

- PRO-CTCAE is designed for patient reporting of symptomatic adverse events
- PRO-CTCAE is an item bank of questions
  - Derived from the CTCAE adverse event items
  - Complimentary to CTCAE (and to be used with)
- PRO-CTCAE is ONLY for descriptive reporting
  - Not ready for clinical and protocol specific decision-making based upon individual PRO-CTCAE scores

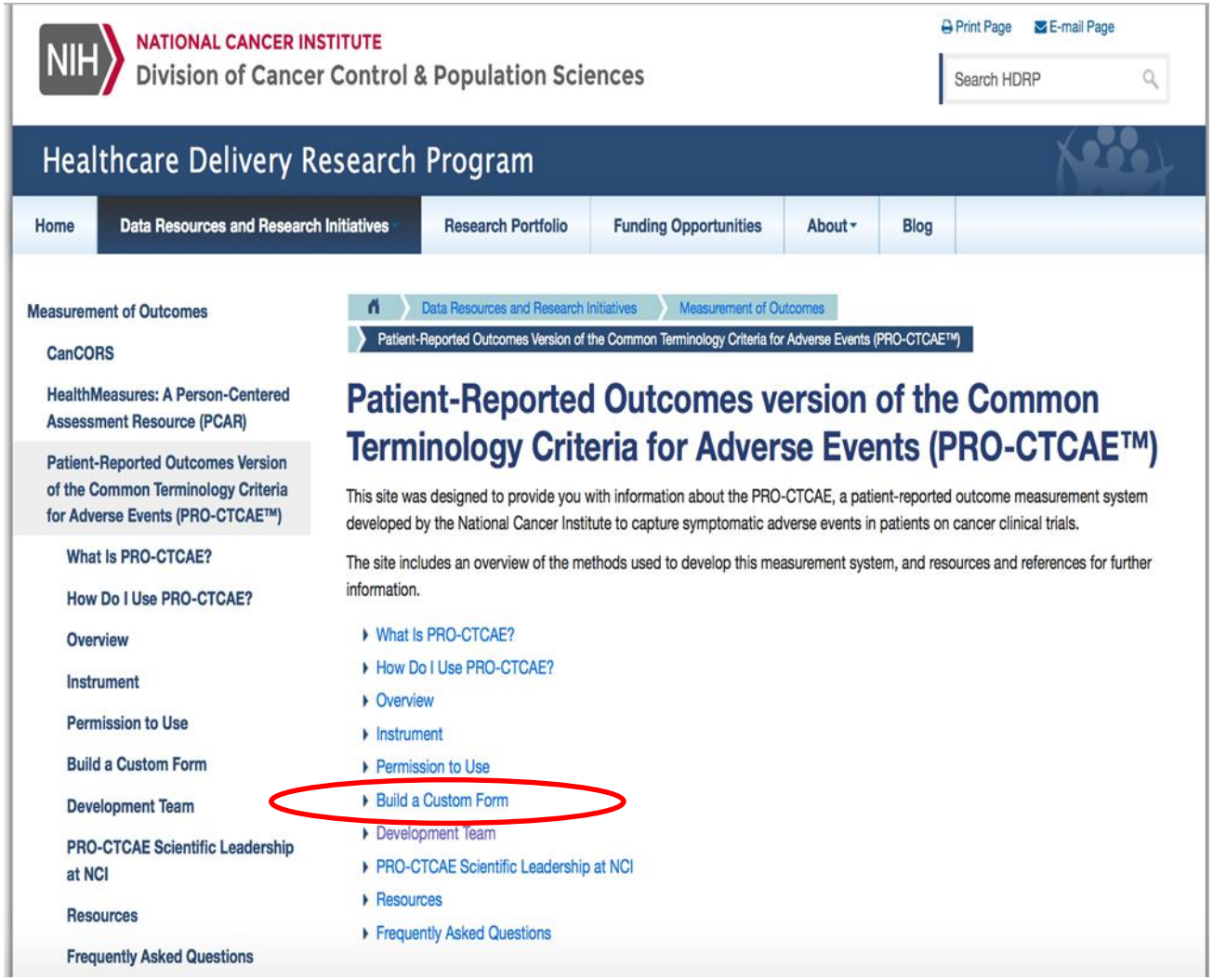
- Psychometrically robust library of items
- Electronic system fits data collection smoothly into trials workflow and offers favorable user-experience
- Accommodate patients with limited English proficiency/digital literacy
- Supply meaningful data to improve understanding of symptomatic AEs



Funded by NCI contracts HHSN261200800043C, HHSN261201000063C, and

PRO-CTCAE propreties

- Good content properties
- Favorable validity, reliability, and responsiveness



Key Points

- Different tools used for different purposes
- HRQOL provides an assessment for multiple different domains on how a patient experiences the combination of cancer, its treatment and related effects.
- Toxicity reporting is specific to safety and patients may not be aware of what is treatment related or cancer related.

Key Points

- PRO-CTCAE is a new tool:
- Derived from clinician rated CTCAE for the purpose of refining the understanding of adverse events as a consequence of treatment.
- Clinician graded CTCAE remains standard for protocol directed action specific individual adverse events
- PRO-CTCAE provides descriptive information to compliment clinician reporting
- Much more work is needed to understand how best to use PRO-CTCAE data.

Ongoing Work

- Responsiveness, minimal clinically important difference, cut-points, relationship among the attributes
- Several languages in development/validation, including Chinese, Korean, Italian, French, Swedish, Dutch, and Danish
- Evaluate different approaches to patient-investigator grade reconciliation and to analyzing and representing PRO-CTCAE data

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Incorporation of PROs in clinical trial

- Digest of the Tokyo OCC plenary session
- Recommandations for groups
- Publication (in process)

Florence Joly

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Plenary Presentation

Incorporating Patient Reported Outcomes in GCIG Ovarian Cancer Trials
Challenges and Opportunities

Florence Joly MD PhD (GINECO)
Michael Friedlander MD PhD (ANZGOG)



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Checklist for PRO's in GCIG phase 3 clinical trials

CONTEXT

- Patient population – what are the aims and objectives of treatment
- Are we measuring what patients consider important?
- Will the results impact on regulatory approval and/ clinical practice?

HYPOTHESES

- What is the PRO hypothesis?
- Will PRO's support the primary trial endpoint?
- What are the most important PRO endpoints?

METHODS

- Have we selected the right instrument/s?
- Criteria for what constitutes a clinical important difference
- Is the study adequately powered for the PRO/QOL endpoints?
- Do we have a SAP in place?
- Do we have a strategy to reduce missing data?
- How we will deal with missing data in the analyses?

Publications Adhere to the CONSORT-PRO extension guidelines

Challenges of GCIG for the future

Challenges
What are the most important PRO endpoints in GCIG clinical trials- can we reach consensus?
Are we ready to make PRO's the primary endpoint or co-primary endpoint in Platinum Resistant Ovarian Cancer?
Including PRO endpoints in trials with novel targeted therapies and immunotherapy- what's different – duration/new toxicites
Special settings e.g survivorship / surgical trials – what are the PRO endpoints
Are we ready to include patient reported adverse events and patient preferences in GCIG trials?

Tokyo consensus (QoL)

Most important PRO endpoints

First line :

- Overall survival (OS) is the ideal primary end point for first-line trials
- If PFS is utilized as primary end point, it should be supported by additional endpoints such as, time to first or second subsequent treatment, relevant patient reported outcomes (PRO), severity of adverse effects

Relapse

PFS is an acceptable primary endpoint in recurrent ovarian cancer trials only if supported by additional endpoints.

- Expected median OS > 12 months : PFS supported by TSST (defined as time to second subsequent therapy or death) and PROs are the preferred endpoints.
- Expected median OS ≤ 12 months: the preferable primary endpoint is OS. PFS is an acceptable primary endpoint only if supported by PROs or additional endpoints such as TUDD (time until definitive deterioration)

Challenges of GCIG for the future : After Tokyo

Challenges
What are the most important PRO endpoints in GCIG clinical trials- can we reach consensus? **partially**
Are we ready to make PRO's the primary endpoint or co-primary endpoint in Platinum Resistant Ovarian Cancer? **yes**
Including PRO endpoints in trials with novel targeted therapies and immunotherapy- what's different – duration/new toxicites **need to be worked**
Special settings e.g survivorship / surgical trials – what are the PRO endpoints **need to be worked**
Are we ready to include patient reported adverse events and patient preferences in GCIG trials? **yes**

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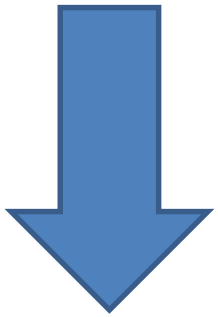
Questions for futures studies

Immunotherapy (ex:Atalante, AGO-OVAR 2.28)



Eric Pujade Lauraine , Felix Hilpert
and the SB Group

Special session in October 2016:
Maintenance with new drugs

ATALANTE
Atezolizumab and Avastin
in late recurrent disease

ATezolizumab and **A**vastin in **LA**te recurre**NT** diseas**E**
ENGOT-ov29

A randomized, double-blinded, phase III study of atezolizumab versus placebo in patients with late relapse of epithelial ovarian, fallopian tube, or peritoneal cancer treated by platinum-based chemotherapy and bevacizumab

Sponsor: ARCAGY-GINECO
ENGOT model A
Lead group: GINECO (PR JE Kurtz)
Co-lead group : ISGO (Pr J Korach)

ENGOT
European Network of Gynaecological Oncology Trial Groups

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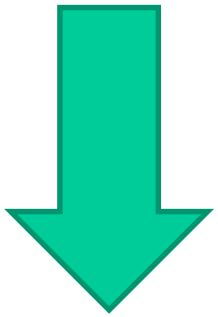
AGO-OVAR 2.28
ENGOT-ov28

Cediranib and Olaparib versus Platinum-based Chemotherapy in *Platinum-eligible* Recurrent Ovarian Cancer

Satellite Meeting
Chicago; June 3rd, 2016

In the late relapse setting (> 6 months), what would be the best QoL and PRO endpoints for OC patients treated with immunotherapy ?



Special session in October 2016:

Maintenance with new drugs

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Studies updated - Elderly

EWOC

GOG 273

NRG-CC002

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EWOC-1

European Network of Gynaecological Oncology Trials groups ENGOT

Elderly Women Ovarian Cancer

Multicenter, randomized trial of carboplatin +/- paclitaxel in vulnerable elderly patients with stage IIB-IV advanced ovarian cancer

First ENGOT-GCIG international study of elderly patients in Ovarian Cancer

ENGOT OV-23

Participating Groups

GINECO, AGO, MITO, ANZGOG, Canada, ICORG, GOTIC, NSGO

GINECO

AGO Studiengruppe

Multicentre Italian Trials in Ovarian cancer MITO

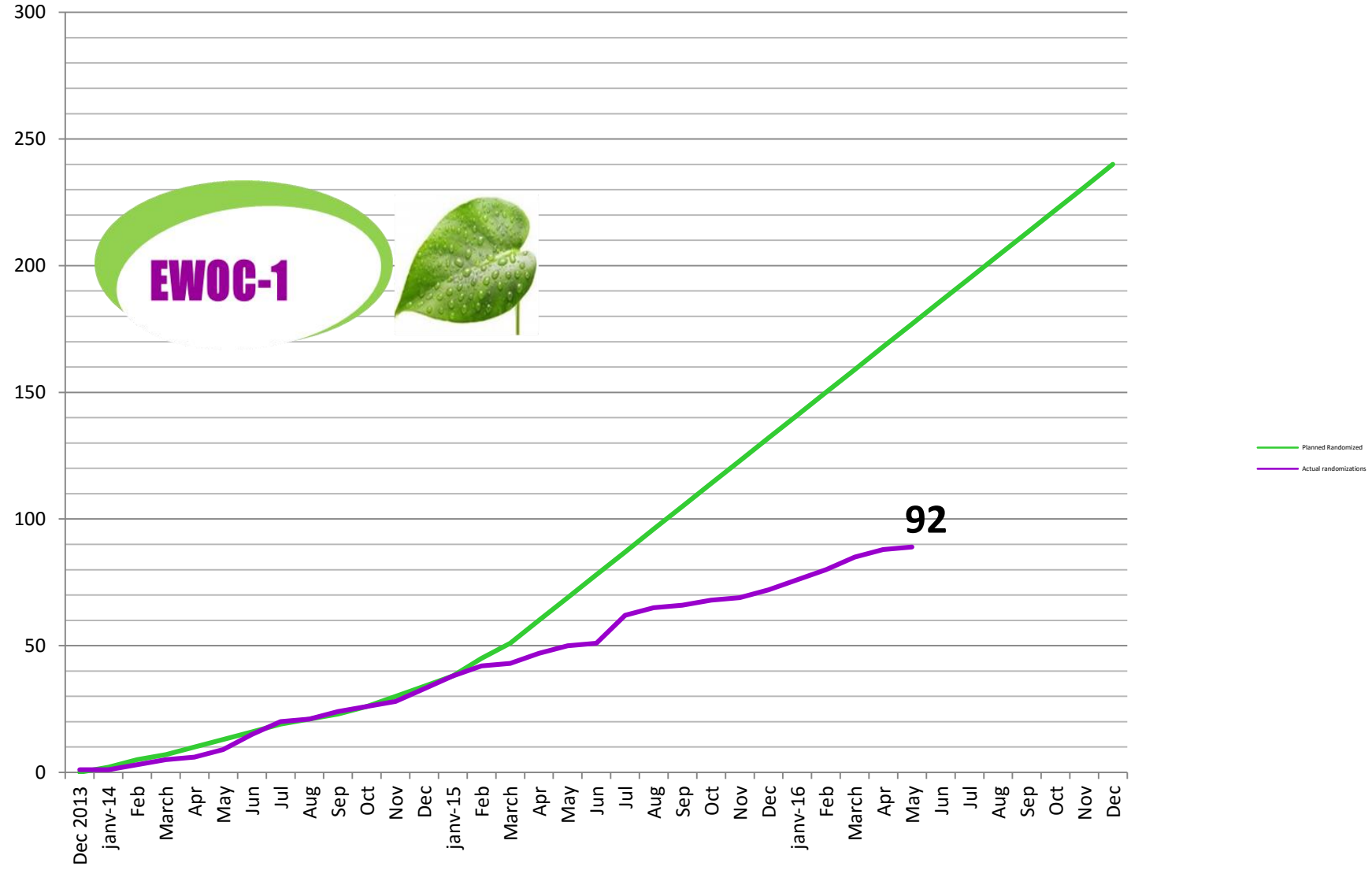
ANZGOG

CHUM

ICORG The All Ireland Cooperative Oncology Research Group

Gynecologic Oncology Trial and Investigation Consortium GOTIC

NSGO


EWOC-1
300
250
200
150
100
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92
Dec 2013
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janv-16
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Planned Randomized
Actual randomizations

IDMC meeting

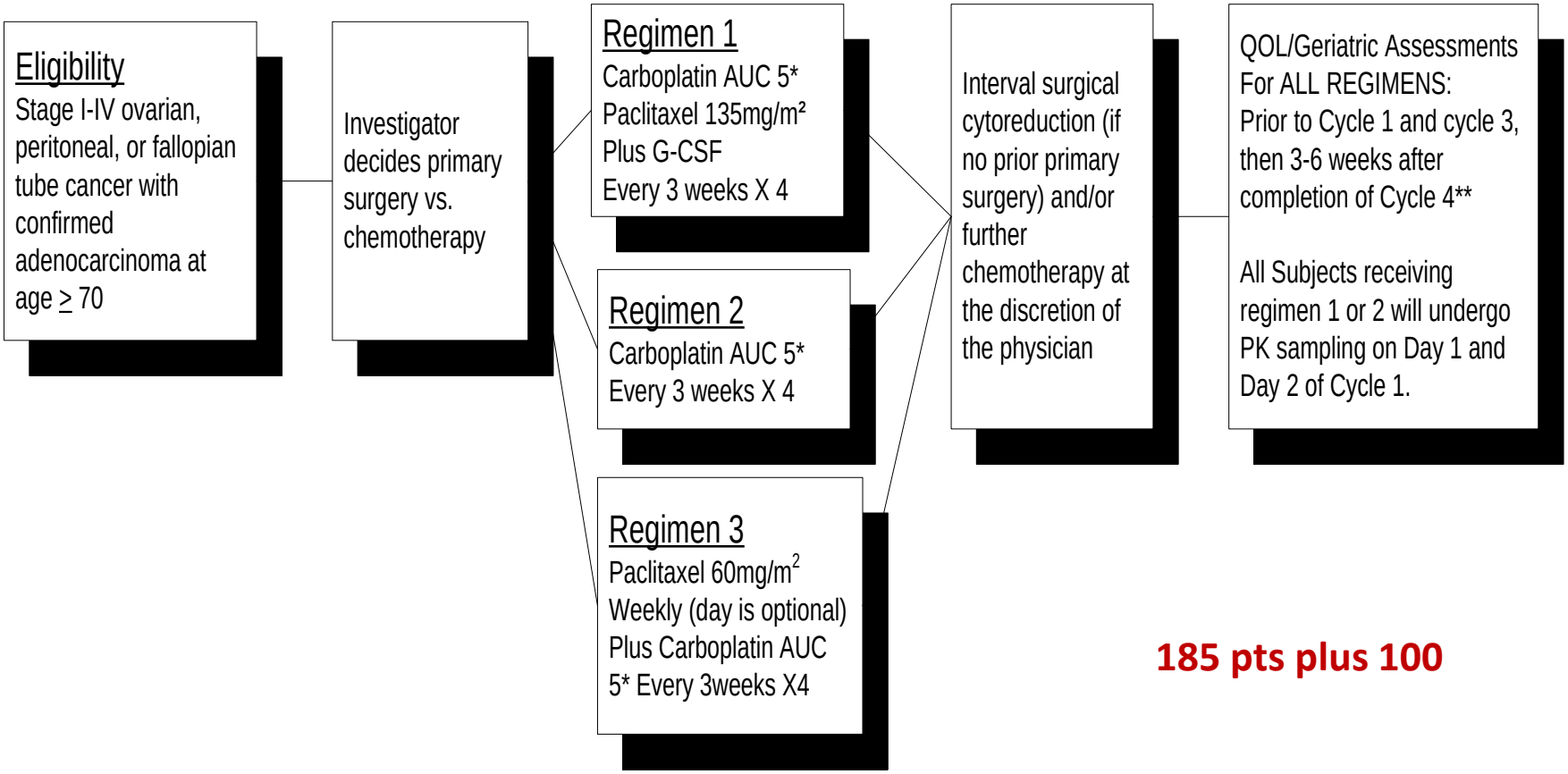
- The independent monitoring committee (IDMC) of the EWOC-1 trial was held 30 November 2015 to review the safety data of the first 65 patients

- IDMC recommendations :
  - *The Committee does not recommend stopping any of the treatment arms be stopped at this point in time.*
  - *However, the Committee needs to review the study again after 30 patients have been accrued to each arm and have had at least 6-cycles of therapy or experienced an event prior to receiving 6-cycles.*

CONCLUSION : **No treatment arm stopping at this stage**

GOG 273

This is a prospective observational study, not a comparison of treatment regimens.
All patients entered after 8/12/2013 will receive Regiment 3 treatment.



185 pts plus 100

Once Regimen I and 2 complete accrual, these two treatments arms will be closed. Regimen 3 will open as a single arm study

*Patients for whom the physician deems a carboplatin dose of AUC 5 to be unsafe, may be given an AUC of 4.

**For patients unable to complete 4 cycles, perform QOL/geriatric assessments at 12-15 weeks after initiating study treatment.

NRG-CC002

PRE-OPERATIVE ASSESSMENT AND POST-OPERATIVE OUTCOMES OF ELDERLY WOMEN WITH GYNECOLOGIC CANCERS

To determine whether the preoperative GA-GYN score will be associated with major post-operative complications in elderly patients (age ≥ 70) undergoing *open primary cytoreduction surgery*

N= 100 patients getting open primary

On going

Chair: Amina Ahmed

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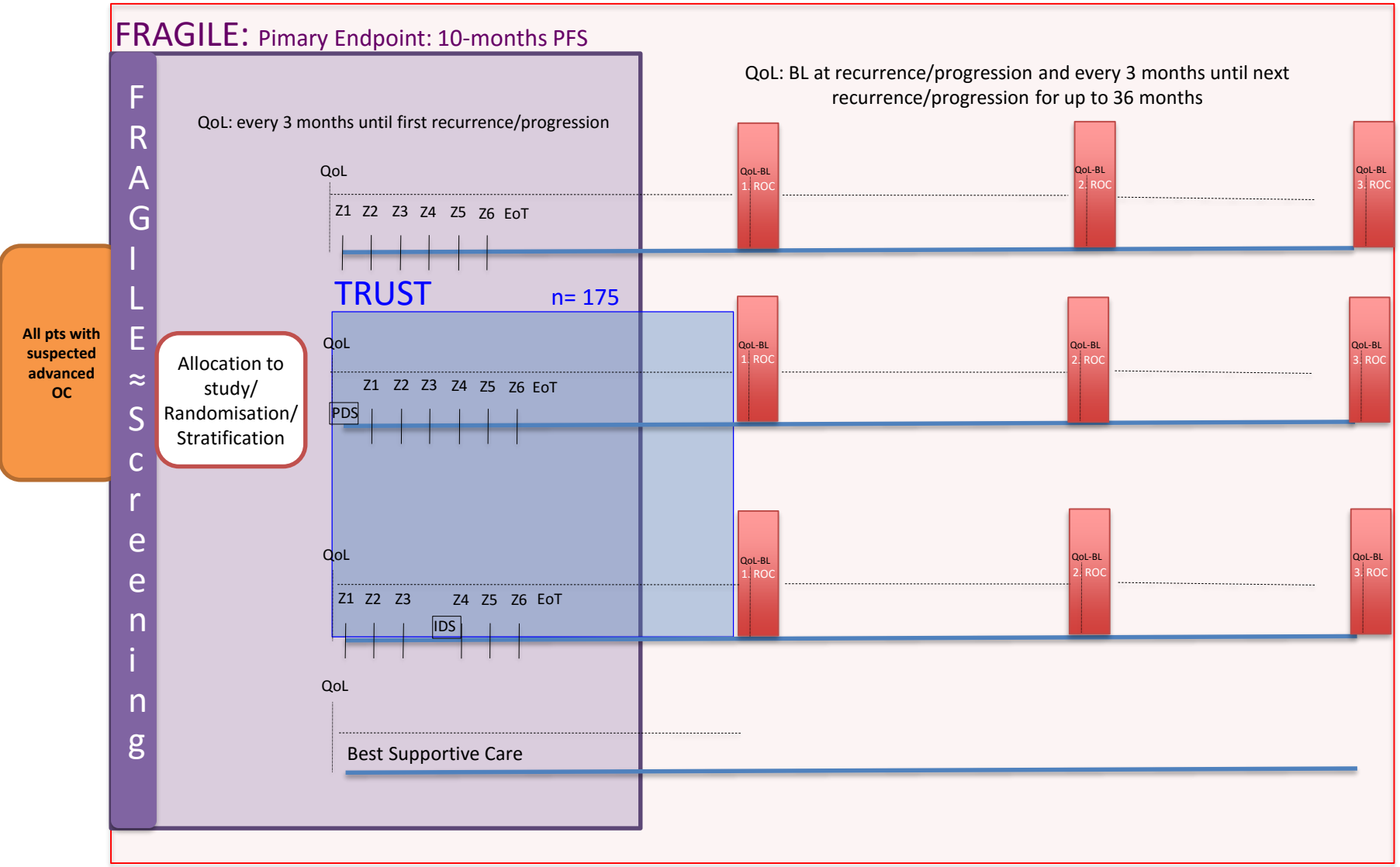
QoL and fragility substudy AGO-OVAR19-TRUST

TRIAL ON RADICAL UPFRONT SURGERY IN ADVANCED OVARIAN CANCER INCLUDING EVALUATION OF FRAGILITY AND LONG TERM QUALITY OF LIFE

AGO-OVAR 19 – QoL longitudinal n=440

(TRUST/extended cohort)



OVAR 19/FRAGILE

All pts with suspected advanced ovarian cancer

PROSPECTIVE COLLECTION OF VARIABLES

- Charlson-Comorbidity-Index (age adjusted)
- Time 'up and go' test
- HADS-Score
- Laboratory:
  - Albumine, creatinine
  - Hemoglobine, leucocytes, thrombocytes
  - CA 125
- ASA
- Symptoms y/n:
  - Abdominal pain requiring treatment y/n
  - Abdominal bloating y/n
  - Dyspnea y/n
- Suspected FIGO IV y/n
- ECOG
- Age
- Weight / Height / BMI
- Estimated ascites
- Palliative puncture required before planned surgery (ascites, pleural effusions) y/n

Treatment to the investigators decision (TRUST trial optional, NACT optional)

Documentation of:
surgical outcome, FIGO stage, histology, complications, revision surgery, systemic treatment, cycle number,
ECOG after 6 months

Follow-Up for months after 6th cycle

Primary end point: Evaluation of factors which describe frail pts who do not benefit from standard therapy sequence "surgery → CTX" (→ progression or death within 10 months after registration)

Secondary end-points: 3-months-survival, feasibility (time from surgery until 1st cycle 6 weeks, cycle number), residual tumor, FIGO-stage, TNM-stage, ECOG after 6 months, 6-months PFS, revision surgery

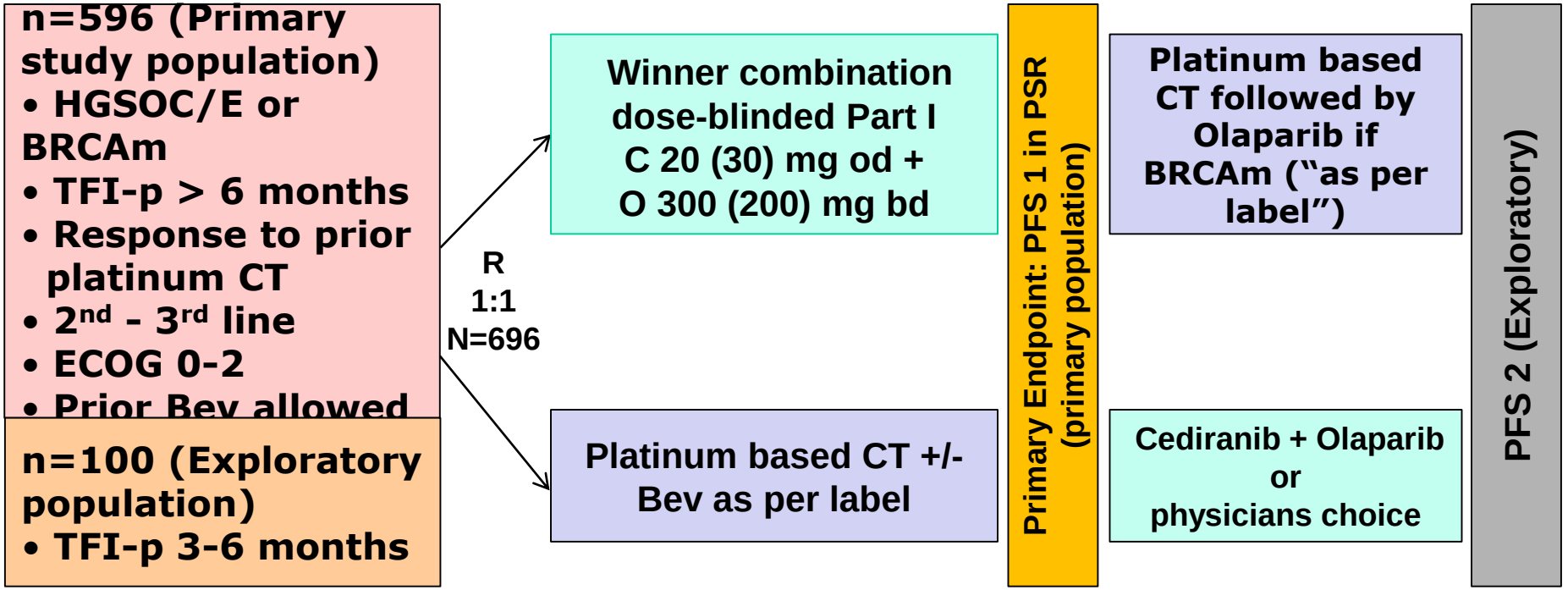
AGO-OVAR 2.28
ENGOT-ov28

Cediranib and Olaparib versus Platinum-based Chemotherapy in *Platinum-eligible* Recurrent Ovarian Cancer

Satellite Meeting
Chicago; June 3rd, 2016

AGO-OVAR 2.28
ENGOT-ov28

Study Design open-label, randomized, two-arm phase III



Study medication provided:

- Cediranib and Olaparib in both arms
- Olaparib in experimental arm as re-treatment with Olaparib is not covered by the label

AGO-OVAR 2.28
ENGOT-ov28

Quality of Life / PRO

- Secondary endpoint in the trial:
    - QoL/PROs including different subgroups (symptomatic vs. asymptomatic) and subdomains
- Quality of Life Subcommittee will be established

Lead: Felix Hilpert, MD, PhD (Hamburg)

AGO-OVAR 2.28
ENGOT-ov28

Quality of Life / PRO

- Open questions:
  - Use of PRO-CTCAE
  - Use of MOST, EQ-5D-3L
  - More frequent completion during treatment period

Open questions

Use of PRO-CTCAE
Use of MOST, EQ-5D-3L
More frequent completion
during treatment period

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Studies updated

Survivorship

Expression V/VI (J Sehouli)

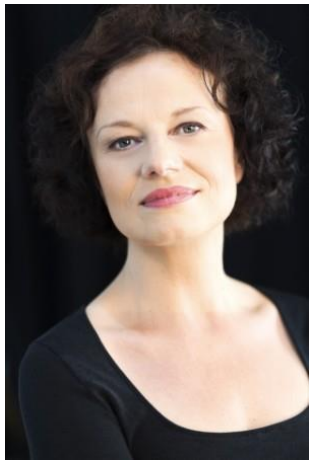
DOD Long term survivor project (M Birrer)

Vivrovaire (F Joly)

Most Opal, Echo, review (for M Friedlander)

Caroline meets HANNA – Holistic Analysis of loNgterm survivors with ovariaN cAncer”

Expression VI



Jalid Sehouli, Hannah Woopen and Ioana Braicu

Expression VI

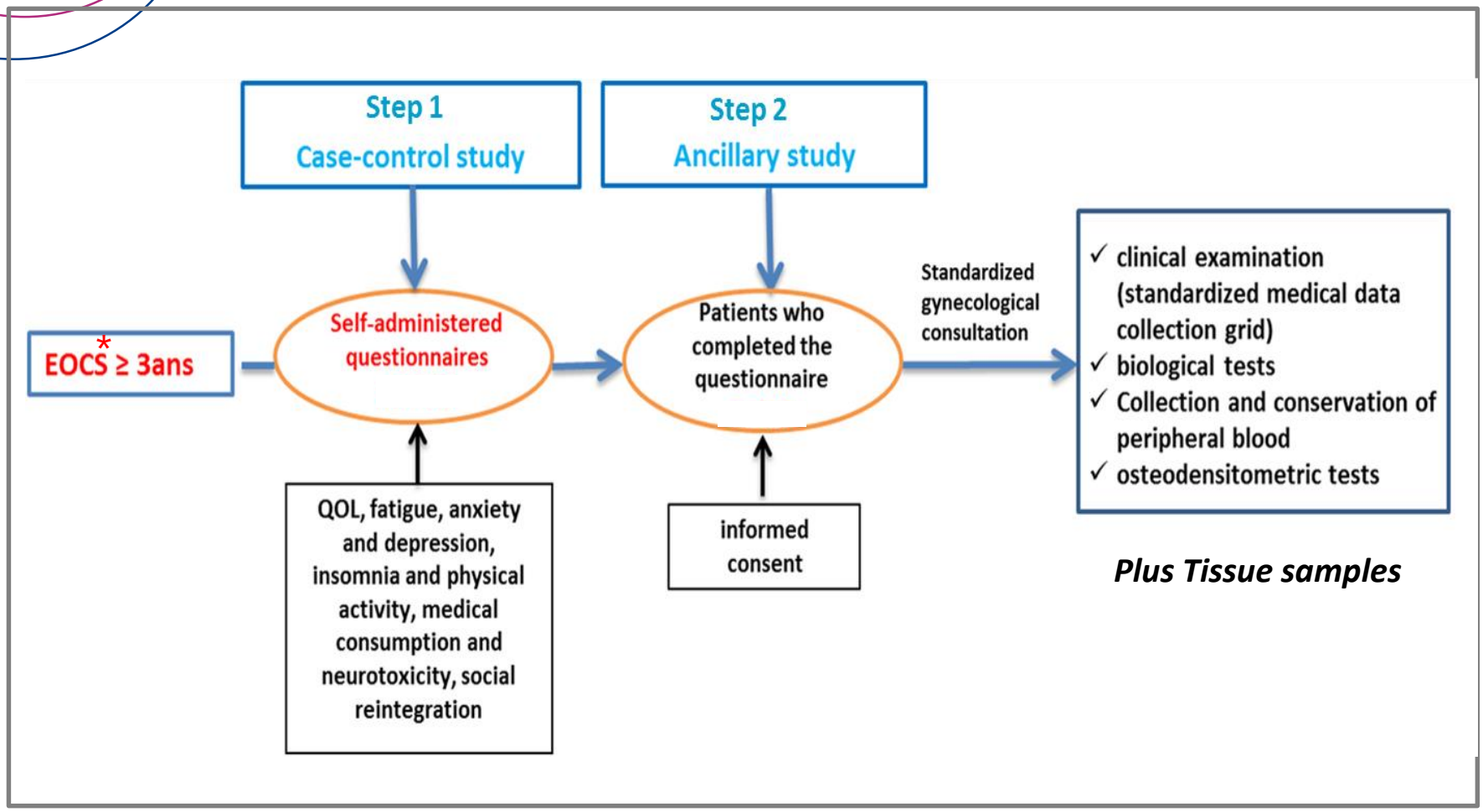
- International Survey of Longterm-Survivors
  - Paper-based and internet/app version
- Inclusion criteria:
  - Diagnosis of epithelial ovarian cancer ≥ 8 years
  - With/without recurrent disease
  - Any stage and grading

VIVROVAIRE-1

Living after epithelial ovarian cancer treatment: Assessment of fatigue, quality of life and gynecological sequelae among long-term Epithelial Ovarian Cancer Survivors

Pr Florence JOLY
Oncology department
Center François Baclesse – Caen – France

Study design



*** EOCS :** Epithelial Ovarian Cancer Survivors

Step 1- Case control study

✓ **27 active french centers**

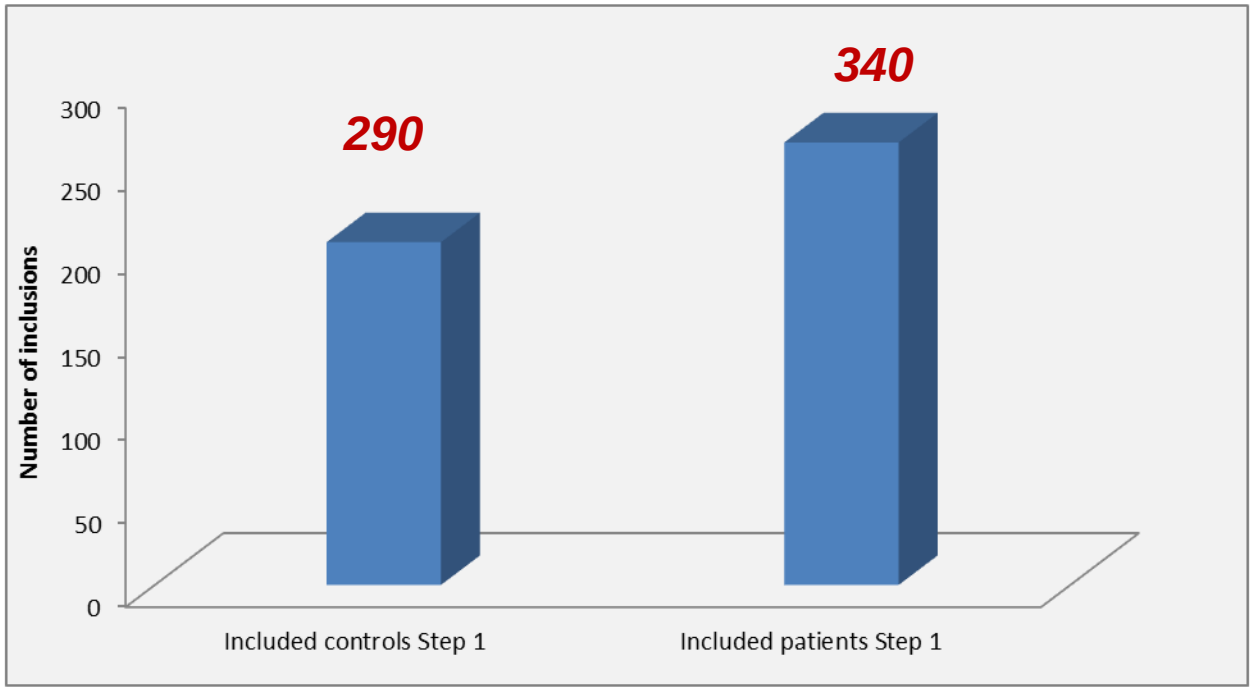


Figure1: The number of included patients and controls in Step 1

We decided to continue the inclusions to July 2016

Step 2

- ✓ **18 active centers participate in the Step 2**
  (gynecological evaluation, blood test and tissue samples)

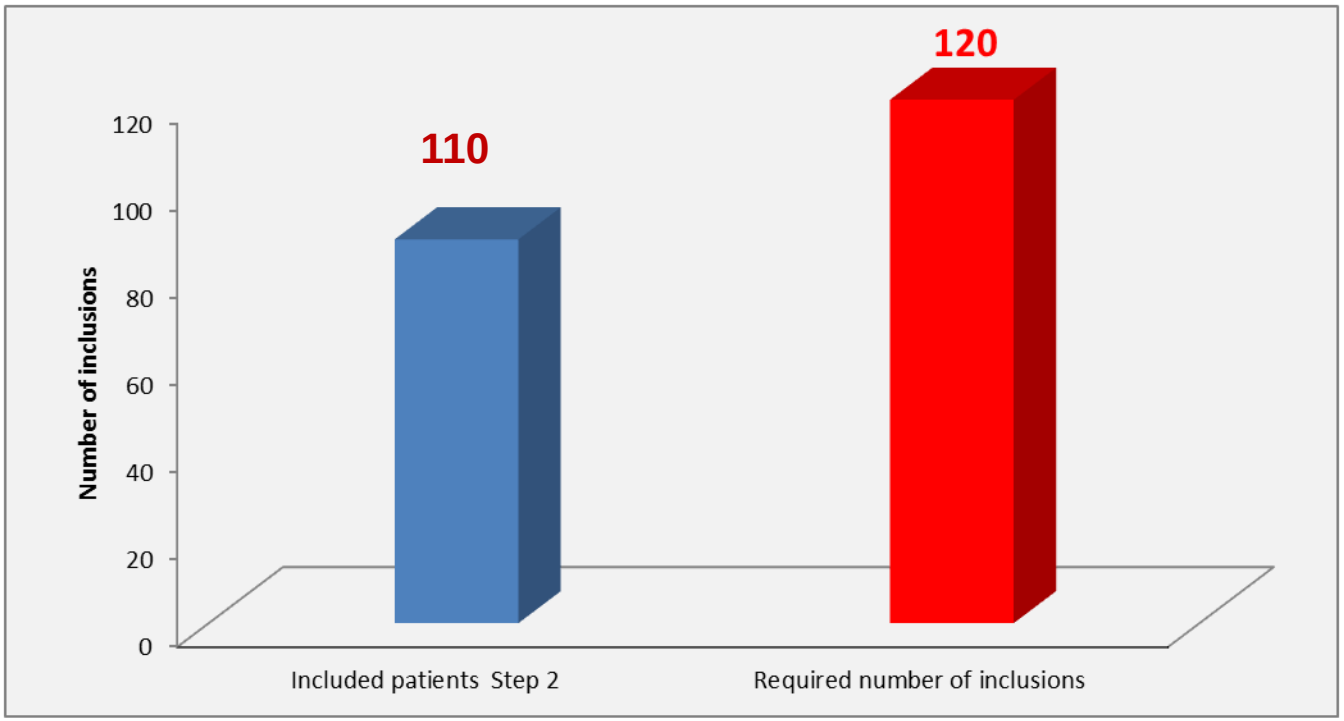
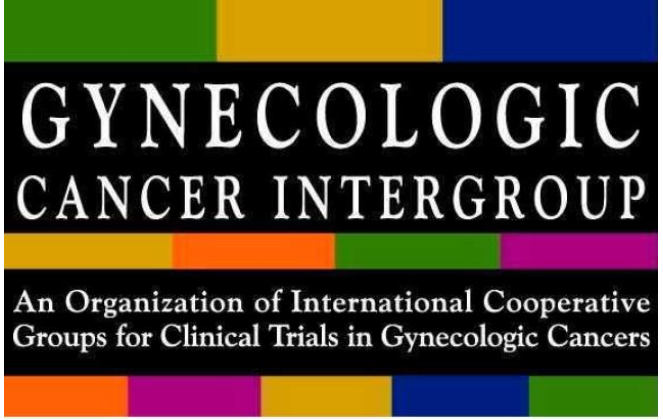


Figure 2: The number of included patients in Step 2



The Long-Term Ovarian Cancer Survivor Project

A Department of Defense Initiative

PI: Michael Birrer

Co-PI: Lari Wenzel

Scientific Advisory Board Chair: Philip DiSaia

International Scientific Advisory Board Chair: Eric Pujade-Lauraine

Advocate Advisory Board Chair: Mary Scroggins

Two-Phase Award

- **Phase I**
- 2 years grant
  - 3 teams awarded
- Build consortium
  - Establish function network
  - Demonstrate effective communication
  - Engage advocates
- Obtain initial data

- **Phase II**
- 2 + 2 years grant
  - 2 teams awarded
- Use consortium to obtain definitive data
- Mid-project oral presentation after 2 years for additional 2 years funding

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CANCER CENTER

Specific Aims

Aim 1: To determine the genomic (RNAseq miRNAseq, methylation patterns) **and proteomic** characteristics of LT versus ST survivors.

Aim 2: To characterize and quantitate immune infiltrates and **angiogenesis** in LT versus ST survivors.

Aim 3: To validate a genetic signature that predicts for recurrence of early-stage, high-grade EOC

Aim 4: To determine the impact of host factors including genomic SNP profiles and key measures of patient stress on long term survival

Aim 5: To understand the extent to which health-related QOL measures, additional PROs, and key CTCAE criteria predict LT OC survival

Aim 6: To examine, as an exploratory aim, the potential relationship between health-related QOL, PROs, and key CTCAE criteria and genomic features predicting disease recurrence

Phase I Proof of Concept Studies

- Project 1 Collect additional clinically annotated primary ovarian cancers
  - Group 1 FFPE from patients on GOG 172,182,218
  - Group 2 Clinical data from GOG136 cases
  - Group 3 FFPE and clinical data for LT survivors NOT on GOG trial

- Project 2 Genomic, epigenomic and biologic analysis of LT survivors
  - Demonstration study on 30 LT cases

- Project 3 Database development for QOL, PROs and Survivorship
  - Initiate database mergers and identify the LT survivor population
  - Recruit, consent and pilot a survey on LT survivorship

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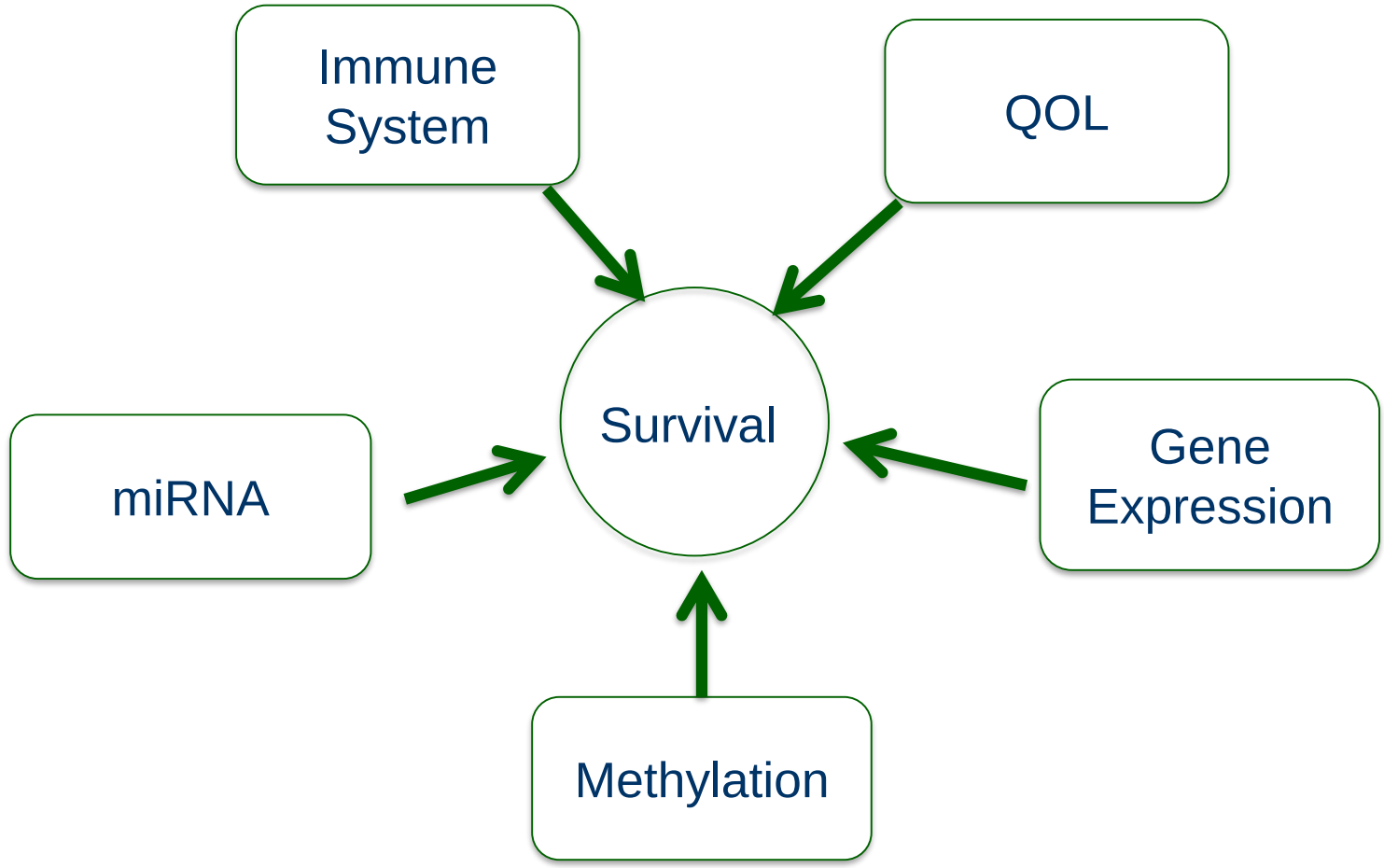
Integrated Analysis



Already data (Biology and QoL from phase1, International collaboration , phase 2

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ANZGOG Update

Symptom Working Group

Presentation prepared by Michael Friedlander

GCIG Symptom Benefit Study

Baseline quality of life as a predictor of early cessation of chemotherapy and survival in platinum resistant/refractory recurrent ovarian cancer (PRR-ROC)

Felicia Roncolato, Rachel O'Connell, Luke Buizen, Florence Joly, Anne Lanceley, Felix Hilpert, Aikou Okamato, Eriko Aotani, Sandro Pignata, Paul P. Donnellan, Amit M. Oza, Elisabeth Avall-Lundqvist, Jonathan S. Berek, Katrin M. Sjoquist, Kim Gillies, Martin R. Stockler, Madeleine T. King and Michael Friedlander on behalf of GCIG Symptom Benefit group

Session: Gynecologic Cancer
Type: Oral Abstract Session
Time: Sunday June 5, 9:45 AM to 12:45 PM
Location: E450ab

Validation MOST done (papers in progress)

- MOST-OSI / ODDSI were more sensitive than majority of candidate scales, but this differed by clinical grouping.
- MOST- less responsive than some scales- depends on context
- Appears to be fit for purpose
- “Living instrument” that can be modified
- MOST designed to complement HRQOL instruments
- The detailed analyses will help inform choice of PROM’s in clinical trials depending on the context and specific questions being addressed

MOST User guide

In addition to scientific papers reporting the detailed methods and results of validation analyses, we will also prepare a User Guide.

This will include:

- instructions for scoring multi-item scales (such as symptom indexes)
- approaches to defining and analyzing endpoints based on data from the MOST
- approaches to presenting and reporting results from the MOST
- how to interpret results from the MOST, including the minimally important difference (MID).

- These three papers will provide validation of the MOST in the clinical context of measuring symptom benefit with chemotherapy in recurrent ovarian cancer.
- Further validation studies are planned for other contexts, including post chemotherapy follow up- MOST-OPAL

If we can't prevent it, can we at least improve outcomes?

Ovarian cancer prognosis and lifestyle study

Webb, Nagle, deFazio, Friedlander, Grant, Obermair
NHMRC 2012-2016

871 patients recruited to date – recruitment closed November 2015

Months post-diagnosis										
T=0 Diagnosis	T~3 Mid-chemo	T~6 Post-chemo	T~9	T~12	T~15,18, 21	T~24	T~27, 30, 33	T~36	T~39, 42, 45	T~48
OPAL Q	OPAL Q	OPAL Q	OPAL Q	OPAL Q	-	OPAL Q	-	OPAL Q	-	OPAL Q
-	-	MOST	MOST	MOST	MOST	MOST	MOST	MOST	MOST	MOST

MOST administered every 3 months after completion of chemotherapy for 2 years

OvQuest

- **Internet-based cross-sectional self-report questionnaire**
- **Eligibility: >18, ovarian cancer diagnosed at least 6 months ago, received chemo**
- **Content:**
  - Self-reported demographics, cancer, treatment and follow-up care
  - HRQOL - FACT-O
  - Symptoms - FACT-GOG-NTX, SPHERE, ISI,
  - Physical activity - IPAQ-SF
  - Supportive care needs - SCNS-SF34
  - Free text comments

AUSTRALIA NEW ZEALAND GYNAECOLOGICAL ONCOLOGY GROUP

OvQuest

Ovarian cancer survivorship survey

Living after the diagnosis and treatment of ovarian cancer

UNSW

Approval number HC13316

Participant selection and purpose of study

You are invited to take part in a study supported by the Australia New Zealand Gynaecological Oncology Group (ANZGOG) and Ovarian Cancer Australia, to better understand the concerns and challenges faced by women who have been treated for ovarian cancer.

AUSTRALIA NEW ZEALAND GYNAECOLOGICAL ONCOLOGY GROUP

OvQuest

YOUR ELIGIBILITY FOR THIS STUDY

The following questions are to confirm that you are eligible to participate in this study.

Please confirm that the following statements are true:

- [ ] I am 18 years of age or older
- [ ] I was first diagnosed with ovarian cancer at least 6 months ago
- [ ] I have received treatment with chemotherapy

<< BACK NEXT >>

Completed:

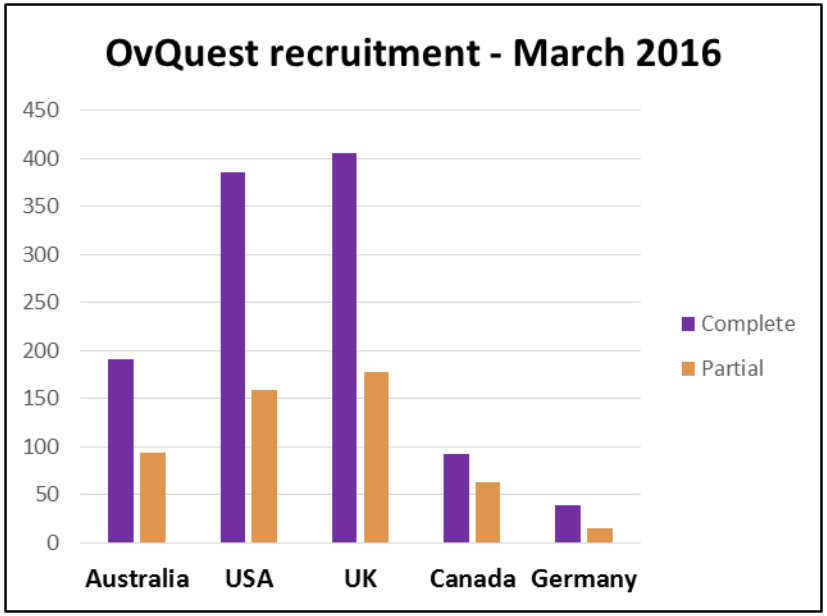
Ovarian Cancer Australia

Progress

Closed in Australia, USA, UK, Canada
Germany closing mid-2016

Recruitment:

1114 completed surveys
534 partial



- Australian data presented ANZGOG and IGCS 2014
- International data - oral presentation ESGO 2015

  Obesity, physical inactivity and symptoms after ovarian cancer treatment