Design Issues in Clinical Trials of Ovarian Carcinoma

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Discussion Outline

- Brief overview of management of ovarian carcinoma
- Unique features of ovarian carcinoma which must be taken into account
- Goals of therapy
- Trial endpoints to reflect goals of therapy
- Settings to which these will be applied
- Recommendations

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Pathology

Celomic Epithelial Carcinomas	90%
Germ Cell Neoplasms	5%
Stromal Tumors	4%
Miscellaneous	1%

Ovarian Carcinoma

FIGO Stage

Stage	Description	Incidence	Survival
I	Confined to ovaries	20%	73%
II	Confined to pelvis	5%	45%
III	Spread IP or nodes	58%	21%
IV	Distant metastases	17%	<5%

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Standard of Care for Advanced Disease

- Maximum attempt at surgical cytoreduction
- Chemotherapy following surgery
- Regimen of choice

  Paclitaxel 175 mg/m2/3h
  Carboplatin AUC 6-7.5
  Repeat every 3 wks for 6 cycles

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Results of Treatment: Advanced Disease

Parameter	Small-Volume	Large-Volume
Response	95%	75%
Clinical CR	95%	50%
PFS (mos)	25	17
Survival (mos)	60	30

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Limited (Stage I-II) Disease: Risk Groups

Low Risk	Grade 1 disease Intracystic disease No extraovarian disease Negative peritoneal cytology No ascites
High Risk	Grade 2-3 disease Extracystic disease Extraovarian disease Positive peritoneal cytology Ascites

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Limited Disease: Recommendations

- TAH, BSO, careful surgical exploration
- Low-risk disease: no further therapy
- High-risk disease: platinum-based therapy

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Second-Line Therapy

- A majority will not achieve long-term control of disease.
  - Large-volume advanced disease: 80-85%
  - Small-volume advanced disease: 60-70%
  - High-risk limited disease: 20%
  - Low-risk limited disease: 10%
- An overall 62% will have either recurrent or persistent disease and be candidates for further therapy.

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Salvage Therapy

- Chemosensitive disease
  - Response to front-line therapy
  - Significant treatment-free interval
- Chemoresistant disease
  - Progressed on front-line therapy
  - Best response stable disease
  - Short treatment-free interval

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Salvage Therapy

- Chemosensitive disease
  - Retreat with platinum-based regimen
  - Expected response >60%, survival 30+ months
- Chemoresistant disease
  - Treat with alternative drug therapy
  - Expected response 12-32%, survival 8+ months

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Active Agents in Ovarian Carcinoma

- FDA approved

Cisplatin	Paclitaxel	Carboplatin
Topotecan	PLD	Melphalan
Altretamine		

- Active but not approved

Gemcitabine	Etoposide	Docetaxel
Navelbine	Ifosfamide	Cyclophosphamide
Bevacizumab	5-FU/LV	Tamoxifen
TLK 286		

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Summary of Current Management

- Advanced disease
  - Surgical cytoreduction
  - Paclitaxel/carboplatin
- Limited disease
  - Low-risk: no further therapy
  - High-risk: adjuvant paclitaxel/carboplatin
- Recurrent or persistent disease
  - Chemosensitive: paclitaxel/carboplatin
  - Chemoresistant: alternative active agents

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Research Directions of Immediate Interest

- Dose Intensity: IP therapy
- Addition of Cytotoxic Agents
- Role of Biologic Agents
- Maintenance/Consolidation Therapy

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Ovarian Cancer: Unique Features

- 90% arises from celomic epithelium on ovary and elsewhere in peritoneum
- Primary route of spread intraperitoneal seeding
- Accurate staging/assessment requires evaluation of peritoneal cavity
- No effective early diagnostic test – most patients have advanced disease

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Ovarian Cancer: Unique Features

- Multiple active systemic agents
- High response rates to standard front-line chemotherapy
- Significant impact of post-recurrence/ progression treatment on ultimate survival
- CA-125 widely used as marker of both progression and response

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Goals of Therapy

- Cure
- Clinical benefit
  - Prolong survival
  - Delay progression of disease
  - Reduce tumor burden
  - Alleviate symptoms
  - Minimize toxicity of therapy

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Current Endpoints

- Survival
- Progression-free survival
- Objective response (RECIST)
- Objective response (CA-125)
- Pathologic complete response
- Quality of life
  - FACT-O
  - QLQ-C30 and QLQ-OV28

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Disease Settings

- First-line therapy for new disease
  - Advanced (stage III-IV) disease
  - Limited (stage I-II) disease
- Maintenance therapy
- Recurrent/persistent disease
  - Chemosensitive disease
  - Chemoresistant disease

Disease Settings

- First-line therapy for new disease
  - Advanced (stage III-IV) disease
  - Limited (stage I-II) disease
- Maintenance therapy
- Recurrent/persistent disease
  - Chemosensitive disease
  - Chemoresistant disease

Advanced Disease

- Survival improvement generally required for approval
- Recent GCIG Consensus Conference concluded:
  - "There is an impact of post-recurrence/ progression therapy on overall survival."
  - "It is not possible to standardize post-recurrence/progression therapy at present."
  - "Although overall survival is an important end point, progression-free survival may be the preferred primary end point for trials assessing the impact of first-line therapy because of the confounding effect of the post-recurrence/progression therapy on overall survival."
  - "There should be clear definition of how to determine progression-free survival."

Advanced Disease

- Reasons to consider PFS as the primary end point for trials of advanced disease
  - PFS avoids confounding effect of additional therapy.
  - PFS provides a measure of clinical benefit: increased time off therapy without progression.
  - PFS improvement predicts survival improvement.

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Study	PFS (mos) Control	PFS (mos) Exper	Survival (mos) Control	Survival (mos) Exper
GOG 97 (n=458)	12	13	24	21
GOG 111 (n=386)*	13	18	24	38
GOG 152 (n=550)	11	11	33	32
GOG 52 (n=349)	24	22	42	32
GOG 158 (n=792)	19	21	49	57
GOG 114 (n=462)*	22	28	52	63
GOG 172 (n=416)*	22	28	50	66

*Trials with significant differences between arms

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Study	PFS (mos)		Survival (mos)	
	Control	Exper	Control	Exper
ICON 2 (n=1526)	17	16	33	33
ICON 3 (n=2074)	16	17	35	36
AGO/GINECO (n=1282)	18	18	41	46
AGO OVAR 3 (n=798)	19	17	44	43
OV 10 (n=680)*	12	16	26	36
EORTC Surg (n=278)*	13	18	20	26

*Trials with significant differences between arms

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Study	PFS (mos) Control	PFS (mos) Exper	Survival (mos) Control	Survival (mos) Exper
GOG 47 (n=440)	8	13	16	19
GOG 132 (n=614)	14	11	26	26

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Advanced Disease

- Reasons to consider PFS as the primary end point for trials of advanced disease
  - PFS avoids confounding effect of additional therapy.
  - PFS provides a measure of clinical benefit: increased time off therapy without progression.
  - PFS improvement predicts survival improvement.
- Caveats
  - Follow-up to determine progression must be uniform and of sufficient frequency.
  - Follow-up must account for CA-125.

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Disease Settings

- First-line therapy for new disease
  - Advanced (stage III-IV) disease
  - Limited (stage I-II) disease
- Maintenance therapy
- Recurrent/persistent disease
  - Chemosensitive disease
  - Chemoresistant disease

Limited Disease

- There have been no approvals specifically for the limited disease population
- Recent GCIG Consensus Conference concluded:
  - “There is an impact of post-recurrence/ progression therapy on overall survival.”
  - “It is not possible to standardize post-recurrence/progression therapy at present.”
  - “Early ovarian cancer: recurrence-free survival”

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ICON 1/ACTION Trials

- Pooled analysis of two trials including 925 patients, the majority of whom were at high risk for recurrence
- With platinum-based adjuvant chemotherapy
  - 11% improvement in RFS (5Yr 76% vs 65%) (HR 0.64, p=0.001)
  - 8% improvement in OS (5Yr 82% vs 74%) (HR 0.67, p=0.008)

Limited Disease

- Reasons to consider RFS as the primary end point for trials of limited disease
  - RFS avoids confounding effect of additional therapy.
  - RFS provides a measure of clinical benefit: increased time off therapy without progression.
  - RFS improvement predicts survival improvement.
- Caveats
  - Follow-up to determine progression must be uniform and of sufficient frequency.
  - Follow-up must account for CA-125.

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Disease Settings

- First-line therapy for new disease
  - Advanced (stage III-IV) disease
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- Maintenance therapy
- Recurrent/persistent disease
  - Chemosensitive disease
  - Chemoresistant disease

Maintenance/Consolidation

- There have been no approvals specifically for maintenance/consolidation
- Recent GCIG Consensus Conference concluded (the only statement not approved unanimously):
  - "Maintenance following first-line: OS"
  - "Since trials involving maintenance by definition have longer treatment on the experimental arm as compared with the control, the real question is whether the prolonged therapy improves survival."

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Maintenance/Consolidation

- Only one positive study of maintenance/ consolidation therapy to date
  - Positive for PFS
  - Difference maintained well beyond cessation of maintenance
  - Survival data not yet available

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*GOG Protocol 178: Schema**

Regimen I	Paclitaxel 175 mg/m2/3h Every month for 3 cycles
Regimen II	Paclitaxel 175 mg/m2/3h Every month for 12 cycles

*Advanced disease in clinical CR after front-line therapy

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GOG 178: Results

Parameter	12 Cycles	3 Cycles
Patients	110	112
Recurrences	20	34
Progression-Free Survival	28 mos	21 mos
Significance	p<0.0023	

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Maintenance/Consolidation

- Only one positive study of maintenance/ consolidation therapy to date
  - Positive for PFS
  - Difference maintained well beyond cessation of maintenance
  - Survival data not yet available
  - Confirmatory trial uses survival as the primary end point and a no maintenance control arm

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GOG Protocol 212: Schema

Regimen I	No further therapy
Regimen II	Paclitaxel 175 mg/m2/3h qmo x 12
Regimen III	Xyotax 175 mg/m2/3h qmo x 12

*Stage III-IV patients

**Initial treatment paclitaxel/carboplatin q3wks x 5-8

***Eligible for randomization if CCR achieved

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Maintenance/Consolidation

- Only one positive study of maintenance/ consolidation therapy to date
  - Positive for PFS
  - Difference maintained well beyond cessation of maintenance
  - Survival data not yet available
  - Confirmatory trial uses survival as the primary end point and a no maintenance control arm
- Recently activated trial involving some of the groups voting that survival is the only valid end point uses PFS as primary end point.
- Insufficient data to advocate any alternative to survival as the appropriate end point at the present time

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Disease Settings

- First-line therapy for new disease
  - Advanced (stage III-IV) disease
  - Limited (stage I-II) disease
- Maintenance therapy
- Recurrent/persistent disease
  - Chemosensitive disease
  - Chemoresistant disease

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Recurrence/Persistence

- Approvals have been based on response rates, survival, and studies which missed their primary end point and have been refused for the positive primary end point of PFS.
- Recent GCIG Consensus Conference concluded:
  - "The choice of the primary end point needs to be fully justified with appropriate power calculations. Symptom control/quality of life (for early relapse) and OS (for late relapse) may be the preferred primary end point although PFS should still be used in the assessment of new treatments."

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Recurrence/Persistence

- Reasons to consider PFS as the primary end point for trials of recurrent/persistent disease
  - PFS avoids confounding effect of additional therapy.
  - PFS provides a measure of clinical benefit: more time without increasing tumor burden.
  - PFS appears to predict for survival improvement.
- Caveats
  - Follow-up to determine progression must be uniform and of sufficient frequency.
  - Follow-up must account for CA-125.

Recurrence/Persistence

- Large phase III trials of recurrent/persistent disease
  - ICON 4

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ICON 4: Trial Design

- Relapsed ovarian or primary peritoneal carcinoma
- Previous platinum-based chemotherapy
- TFI $\geq$ 6 months

RANDOMISE

Conventional platinum chemotherapy	Paclitaxel plus platinum chemotherapy

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	Plat (n = 128)	**Pac-Plat** (n = 119)
CR or PR	54%	66%

(Difference of 12%; 95% CI -0.1% to 24%; p=0.06)

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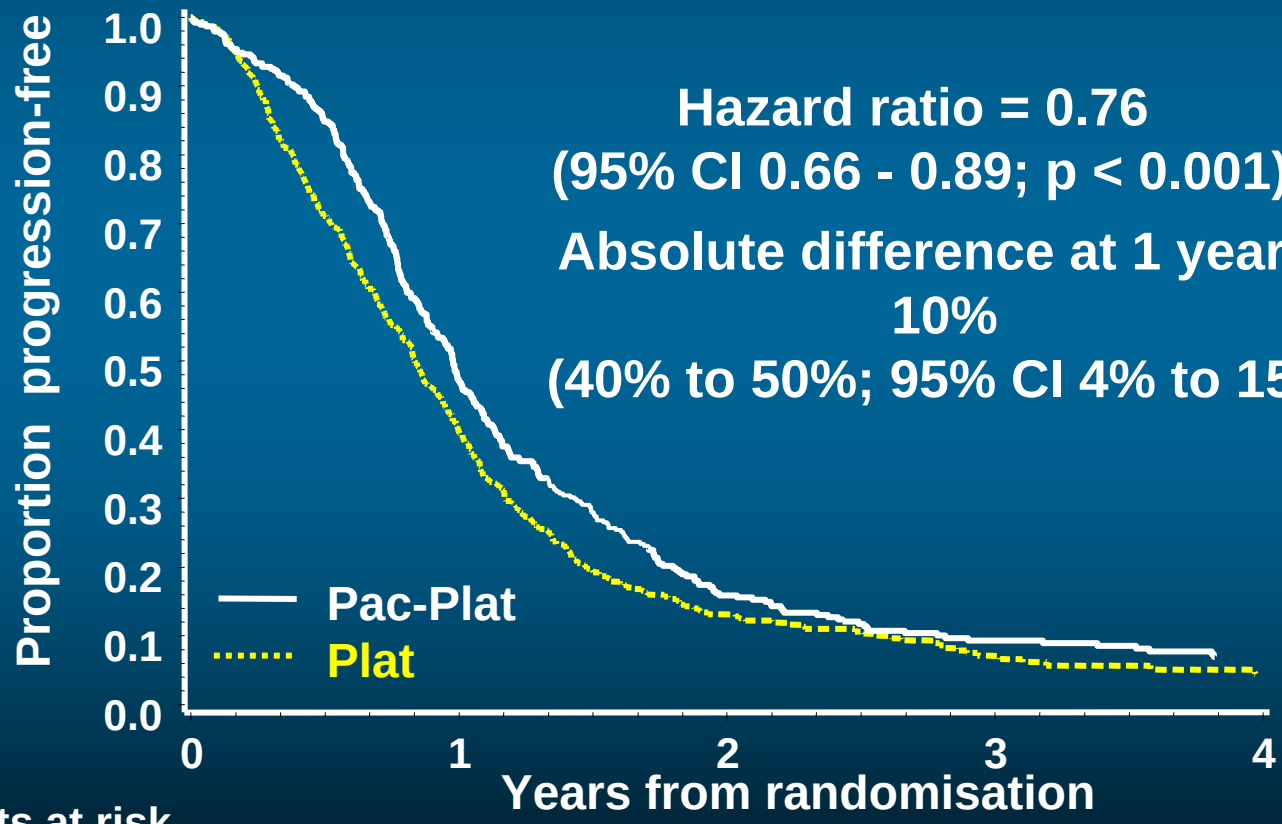
ICON 4: Progression-Free Survival



Hazard ratio = 0.76
(95% CI 0.66 - 0.89; p < 0.001)

Absolute difference at 1 year = 10%
(40% to 50%; 95% CI 4% to 15%

Patients at risk

Pac-Plat	392	179	52	25	17
Plat	410	157	45	17	7

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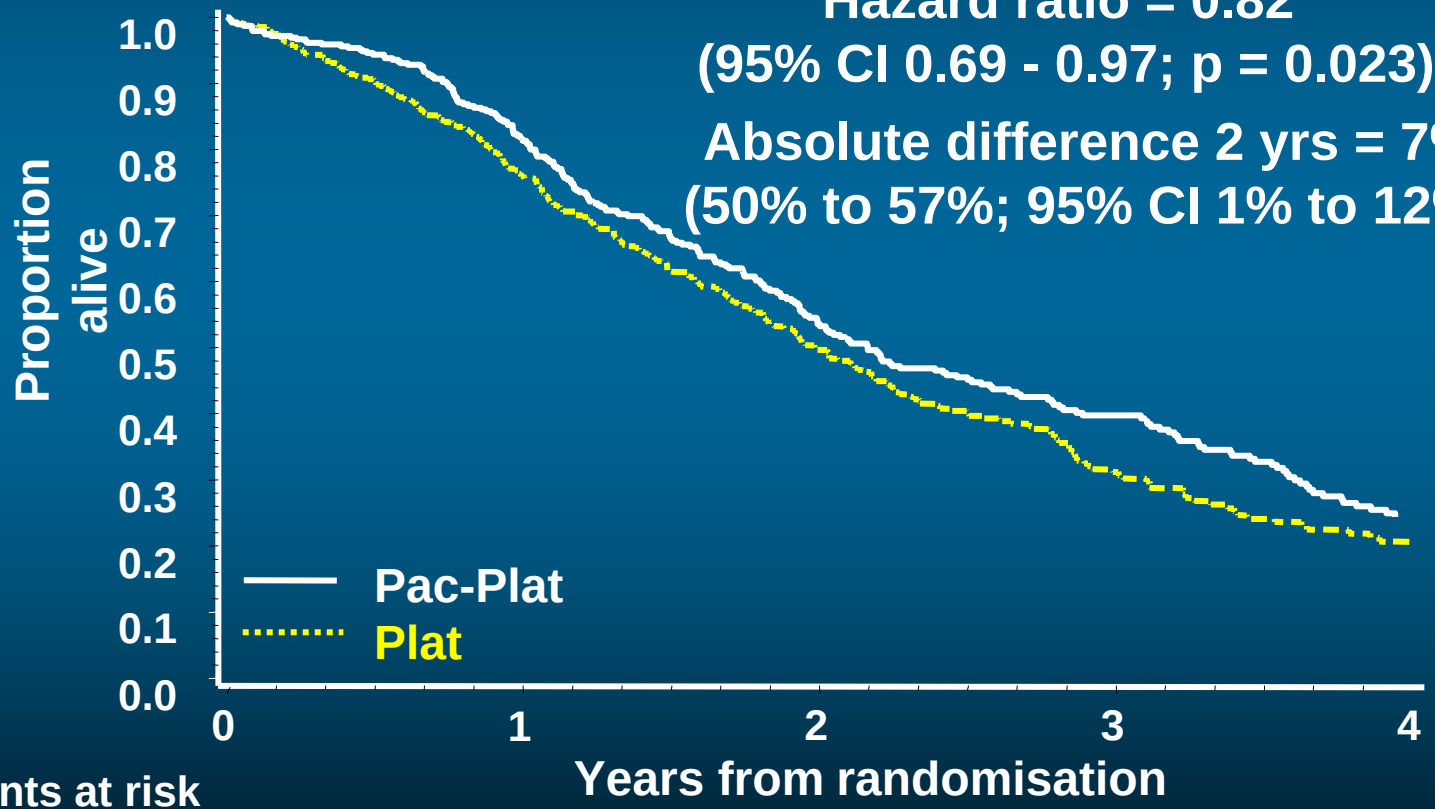
ICON 4: Overall Survival



Patients at risk

Pac-Plat	392	306	167	96	43
Plat	410	295	150	68	33

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Recurrence/Persistence

- Large phase III trials of recurrent/persistent disease
  - ICON 4
  - AGO OVAR 2.5

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AGO Trial: Schema

Regimen I*	Carboplatin AUC 5
Regimen II*	Gemcitabine 1000 mg/m2 d1&8 Carboplatin AUC 4 d1

***Each regimen repeated every 3 weeks**

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AGO Trial: Results

Parameter	Gem/Carbo	Carbo
Response*	47%	31%
PFS**	8.6 mos	5.8 mos
OS	18.0 mos	17.3 mos

***p=0.0016**

****p=0.0031**

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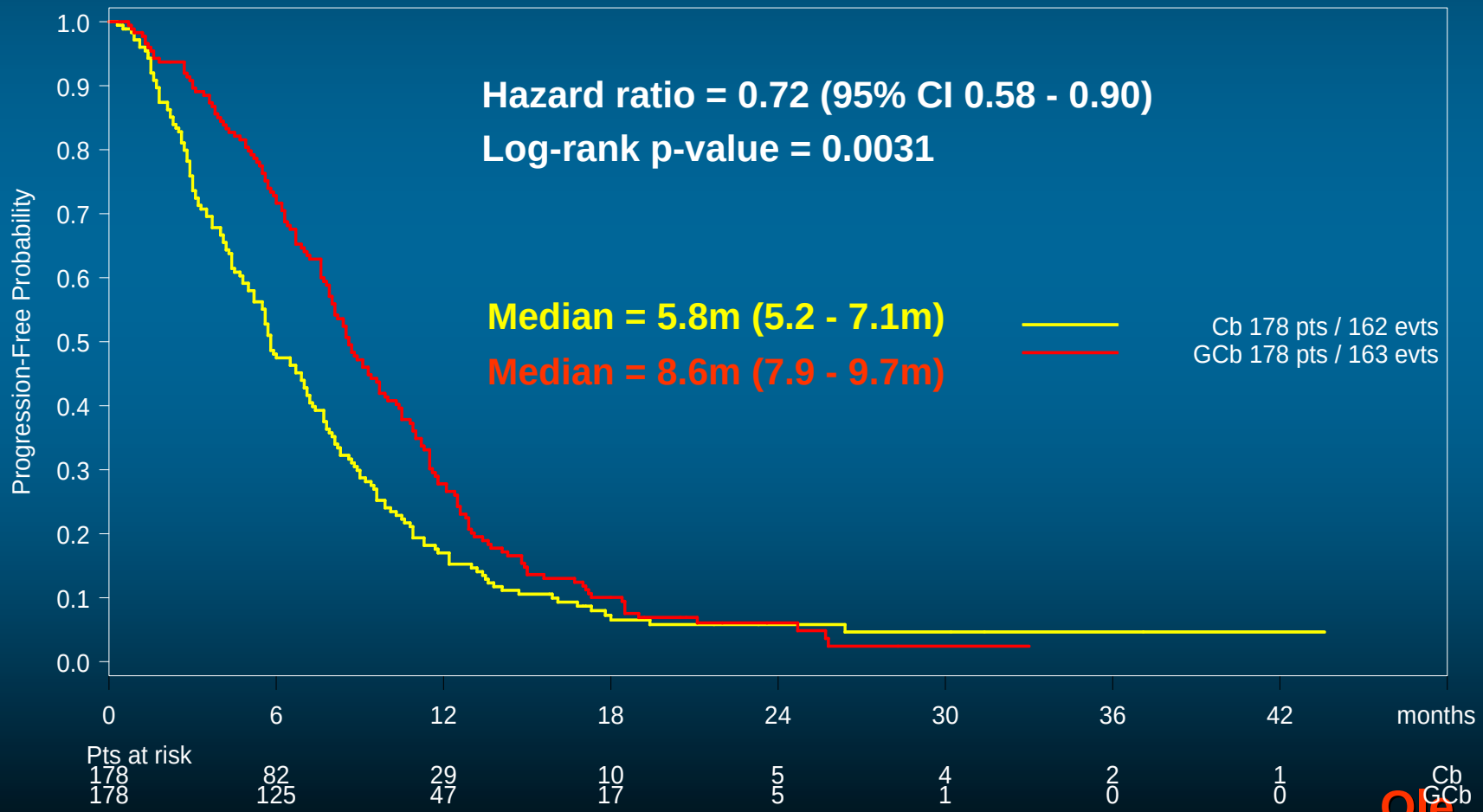
GCIG Gem/Carbo Trial: PFS by Therapy



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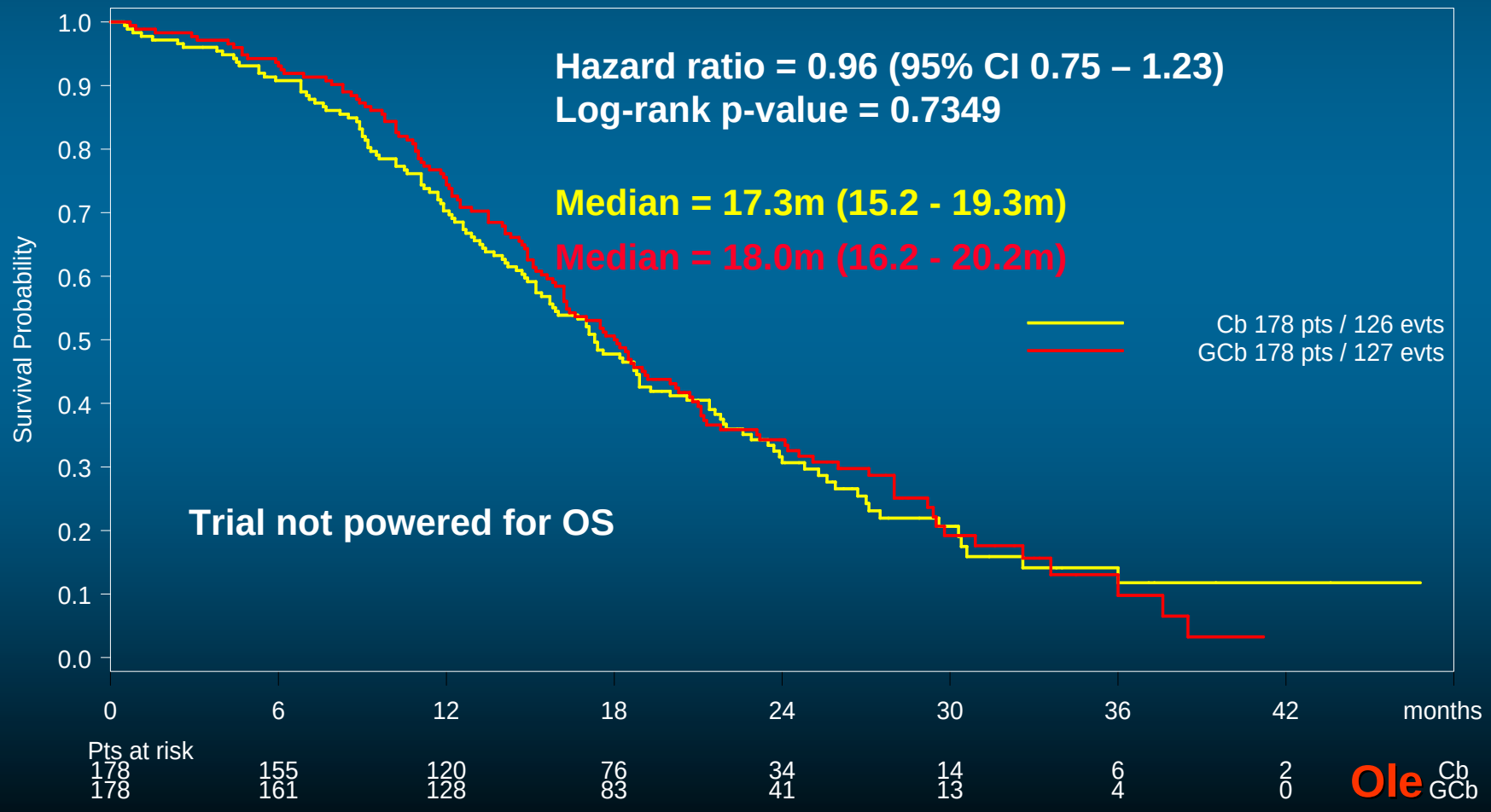
GCIG Gem/Carbo Trial: Survival by Therapy



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Recurrence/Persistence

- Large phase III trials of recurrent/persistent disease
  - ICON 4
  - AGO OVAR 2.5
  - PLD vs Topotecan

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PLD vs Topotecan: Schema (n=474)

Regimen I	PLD 50 mg/m2 every 4 weeks
Regimen II	Topotecan 1.5 mg/m2 days 1-5 every 3 weeks

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PLD vs Topotecan: Results

Parameter	PLD	Topotecan
Response	20%	17%
PFS	16 wks	17 wks
OS	60 wks	57 wks

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PLD vs Topotecan: Results

Parameter	PLD	Topotecan
Chemosensitive Disease		
Response	28%	29%
PFS*	29 wks	23 wks
Survival*	108 wks	71 wks
Chemoresistant Disease		
Response	12%	7%
PFS	9 wks	14 wks
Survival	36 wks	41 wks

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PLD vs Topotecan: Long-Term Results

Parameter	PLD	Topotecan
Survival	63 wks	60 wks
Chemosensitive	108 wks	70 wks
Chemoresistant	36 wks	41 wks

Recurrence/Persistence

- Large phase III trials of recurrent/persistent disease
  - ICON 4
  - AGO OVAR 2.5
  - PLD vs Topotecan
- Observations
  - PFS improvement predicts for survival improvement in two trials; 75% received further therapy in the third.
  - Effect of therapy greater in chemosensitive patients.
  - Role for CA-125 in end points must be defined.

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Recommendations

- First-line therapy, advanced disease
  - Primary end points
    - Survival
    - PFS (predicts survival, reflects clinical benefit, avoids confounding effect of further therapy)
  - Supporting end points
    - Response
    - Complete response
    - Quality of life

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Recommendations

- First-line therapy, limited disease
  - Survival
  - Disease-Free Survival (predicts survival, reflects clinical benefit, avoids confounding effect of further therapy)

Recommendations

- Maintenance/Consolidation
  - Survival
  - Case for an alternative end point not clear at the present time, but PFS would:
    - Avoid confounding effect of further therapy
    - Reflect clinical benefit in the form of greater time without progressing tumor burden

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Recommendations

- Recurrence/Persistence
  - Primary end points
    - Survival
    - PFS (predicts survival, reflects clinical benefit, avoids confounding effect of further therapy)
  - Supporting end points
    - Response
    - Complete response
    - Quality of life

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Recommendations

- Issues for further discussion
  - Role for CA-125 in determination of progression and response
  - Clinical trial endpoints for regulatory approval
    - First-line therapy for advanced ovarian cancer
    - Maintenance therapy
    - Subsequent therapy
    - Patient reported outcomes
  - Biomarker and endpoint research priorities

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