Spire Leeds Hospital

Systemic treatment for Ovarian Cancer

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Systemic treatment

- Primary treatment
  - Advanced disease
    - First-line
      - Neo-adjuvant chemotherapy
      - Chemotherapy scheduling
      - Bevacizumab
  - Early stage disease

- Relapsed disease

Pathology

- Subtypes
  - Epithelial (90%) → Grading
    - Serous
    - Endometrioid
    - Mucinous
    - Clear cell
  - Germ cell tumours (10%)
  - Sex-cord stromal cell tumours (rare)

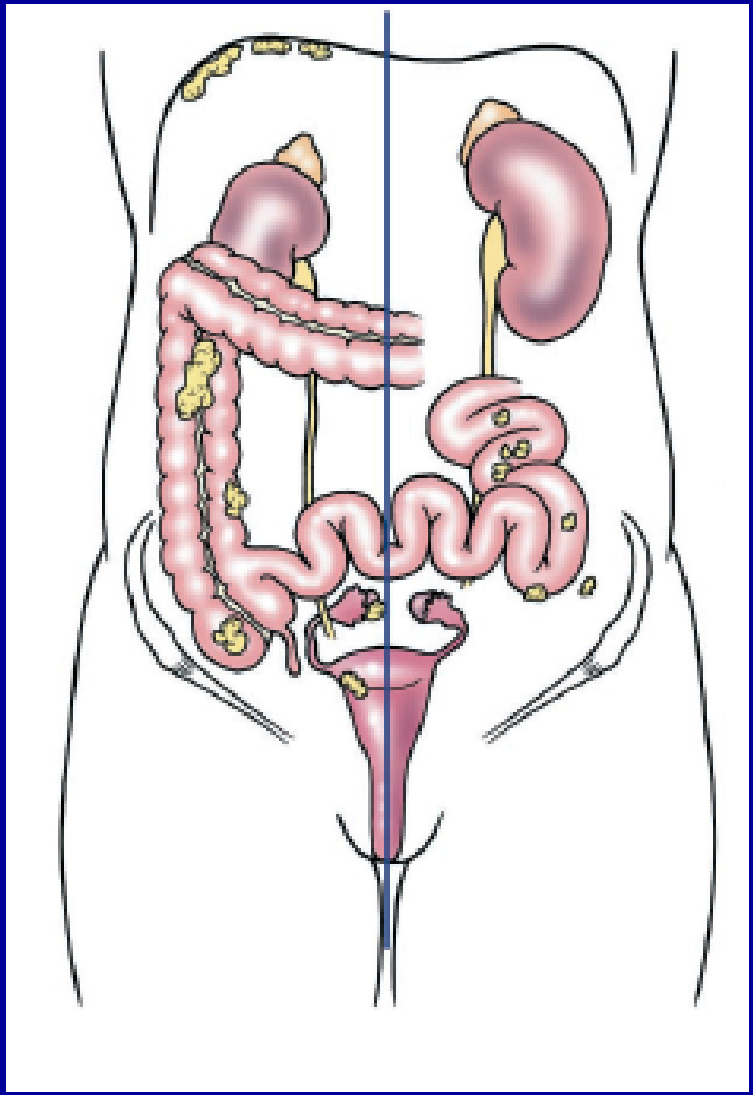
Grading
- Borderline
- Grade 1
  - well differentiated
- Grade 2
  - moderately differentiated
- Grade 3
  - poorly differentiated

Epithelial Ovarian Cancer

Including:

Primary peritoneal cancer

Fallopian tube cancer



What is the aim of systemic therapy?

- Primary treatment
  - Usually in combination with surgery

  – Depends on the stage of the disease
  - Advanced disease
  - Early stage disease

Importance of staging

- FIGO - staging system

Stage		5 yr survival
I	confined to ovary	90%
II	confined to pelvis	65%
III	abdominal extension or lymph nodes	35%
IV	distant metastases	10%

20% of patients

80% of patients

Primary treatment

Advanced disease

Chemotherapy

- Stage III & IV disease
  - Control cancer
  - Prolong life
  - Improve symptoms

} Palliative

  - First line
    - Highly effective
    - 70-80% response rate

    - Median Progression Free Survival 1-2 years
    - Median Overall Survival 3 years
    - 30% 5 year survival
    - Some long term survivors

Epithelial Ovarian Cancer

- Advanced disease
  - Platinum based chemotherapy
    - 1960s – alkylating agents
    - 1970s – discovery of cisplatin
    - AOCTG 1991- Meta-analysis
      - 45 trials; 8139 patients
      - Not conclusive, but suggested:
        - » Advantage of platinum based chemotherapy
        - » Platinum combination better than single agent
        - » Cisplatin and carboplatin equivalent
    - ICON 2 1998 **Carboplatin** vs CAP
      - No difference

Epithelial Ovarian Cancer

- Advanced disease
  - **Paclitaxel**

Study	No.	Agents	PFS (months)			OS (months)		
			Control	Pac	p	Control	Pac	p
GOG 111 McGuire 1996	386	Cisplatin/Paclitaxel vs Cisplatin/Cyclo	13	18	<0.001	24	38	<0.001
OV10 Piccart 2000	680	Cisplatin/Paclitaxel vs Cisplatin/Cyclo	12	16	<0.001	25	35	<0.001
GOG 132 Muggia 2000	424	Cisplatin/Paclitaxel vs Cisplatin	16.4	14.1	n.s.	30.2	26.0	n.s.
ICON 3 ICON 2002	2074	Carbo/Paclitaxel vs Carbo or CAP	16.1	17.3	n.s.	35.4	36.1	n.s.

Epithelial Ovarian Cancer

- First-line chemotherapy
  - Carboplatin
    - 6 cycles - 3-weekly
  - Carboplatin & Paclitaxel
    - 6 cycles - 3-weekly
  - Carboplatin & Paclitaxel
    - 18 weeks - weekly (low dose)

- Dependent on:
  - Performance status
  - Comorbidity
  - Patient choice

Chemotherapy

- Stage III & IV
  - Primary surgery (optimal debulking)
    - followed by chemotherapy

      or
  - Primary (Neoadjuvant) chemotherapy
    - Interval Debulking Surgery (IDS)
      - Not amenable to optimal debulking
      - Patient fitness
      - Effusions / Ascites
  - Palliative chemotherapy
    - Not fit for surgery

Primary treatment

Advanced disease

Neoadjuvant chemotherapy

Neoadjuvant chemotherapy

- Theoretical reasons for benefit
  - High response rates (70-80%)
  - Early exposure to systemic therapy
  - Assess chemosensitivity
    - Predictor of outcome
    - Avoid surgery if progressive disease
  - Medical cytoreduction
    - Increases resectability
    - Avoid aggressive surgery (stoma formation)
    - Improved fitness for surgery (metabolic effects of disease)

- Examples in other solid tumours
  - Established
    - » Breast; Gastric; Oesophageal
  - Investigation
    - » Lung; Colon

EORTC 55971

- Compare primary debulking surgery (PDS) followed by 6 courses platin-based chemotherapy (CT) (Arm A) with 3 courses neoadjuvant chemotherapy (NACT), interval debulking surgery (IDS) and another 3 courses of CT (Arm B) in Stage IIIc-IV OVCA.

- 718 patients - median follow-up was 4.8 years

	Primary Debulking Surgery	Primary chemotherapy
Optimal debulking (< 1cm)	48%	83%
Post-op mortality (≤ 28 days)	2.7%	0.6%
sepsis	8%	2%
Hameorrhage (G3/4)	7%	4%
OS (ITT)	29 mos	30 mos
PFS (ITT)	11 mos	11 mos

Vergote NEJM 2010

Primary treatment

Advanced disease

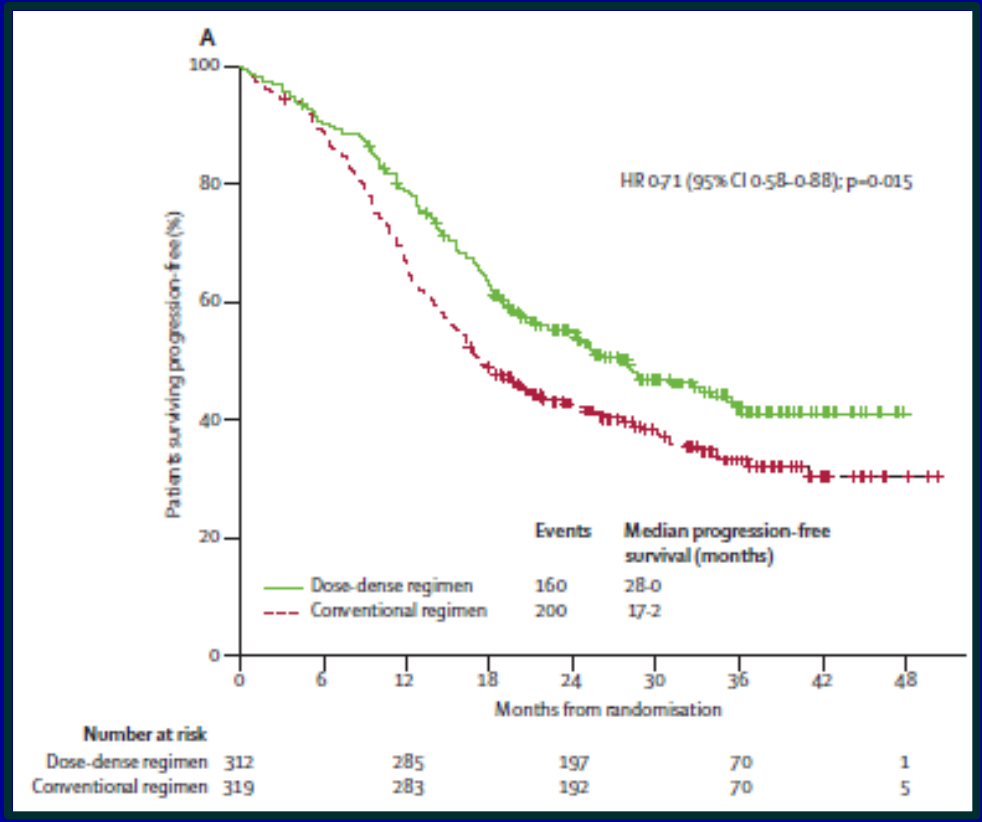
Chemotherapy scheduling

Chemotherapy scheduling

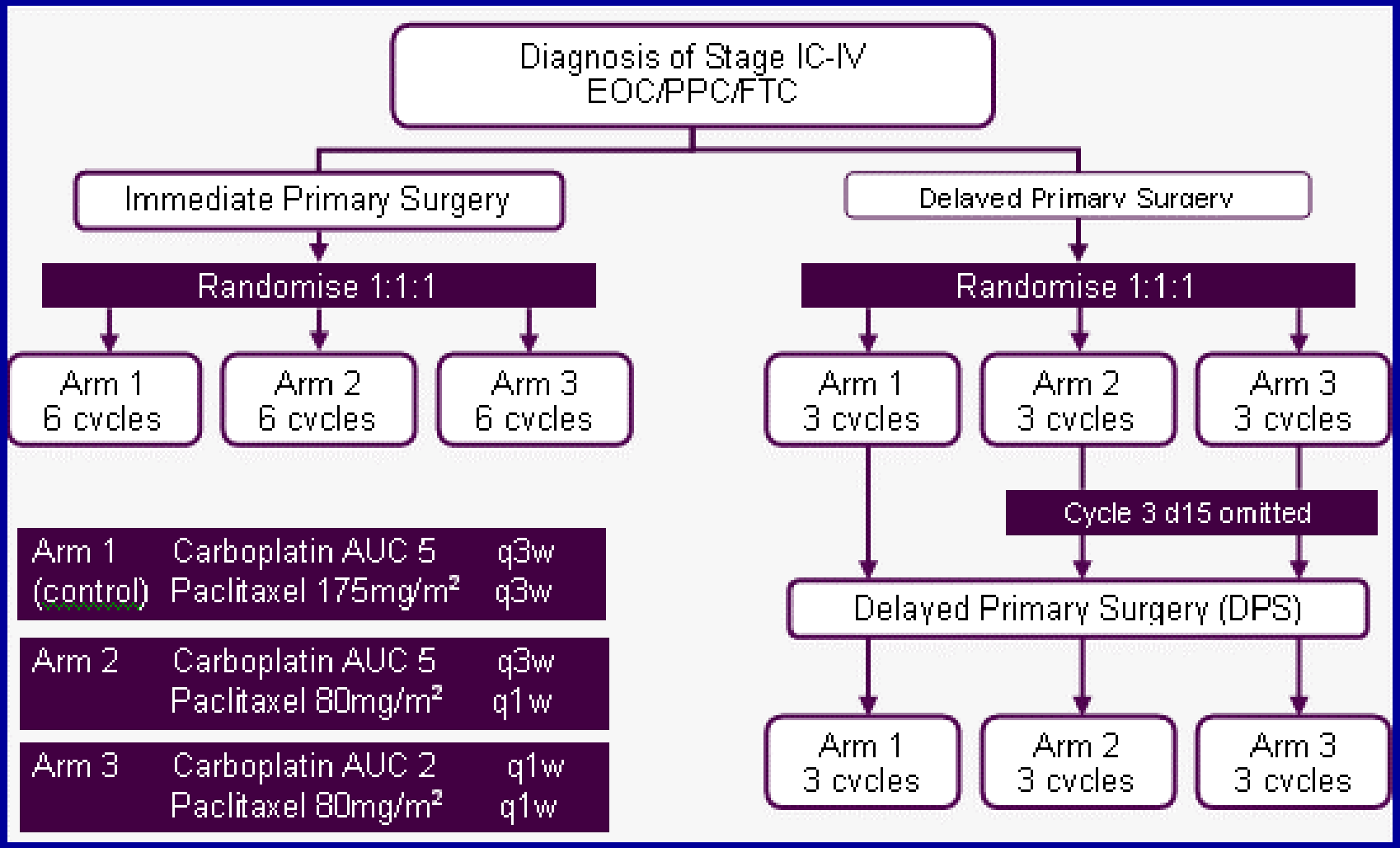
Dose-dense chemotherapy
Katsumata 2009

<u>Conventional</u>
3-weekly
- Carboplatin AUC6
- Paclitaxel 180mg/m2

<u>Dose-dense</u>
3-weekly
-Carboplatin AUC6
weekly
- Paclitaxel 80mg/m2



ICON 8


Diagnosis of Stage IC-IV
EOC/PPC/FTC
Immediate Primary Surgery
Delayed Primary Surgery
Randomise 1:1:1
Randomise 1:1:1
Arm 1
6 cycles
Arm 2
6 cycles
Arm 3
6 cycles
Arm 1
3 cycles
Arm 2
3 cycles
Arm 3
3 cycles
Cycle 3 d15 omitted
Arm 1 (control) Carboplatin AUC 5 q3w
Paclitaxel 175mg/m² q3w
Arm 2 Carboplatin AUC 5 q3w
Paclitaxel 80mg/m² q1w
Arm 3 Carboplatin AUC 2 q1w
Paclitaxel 80mg/m² q1w
Delayed Primary Surgery (DPS)
Arm 1
3 cycles
Arm 2
3 cycles
Arm 3
3 cycles

Primary treatment

Advanced disease

Bevacizumab

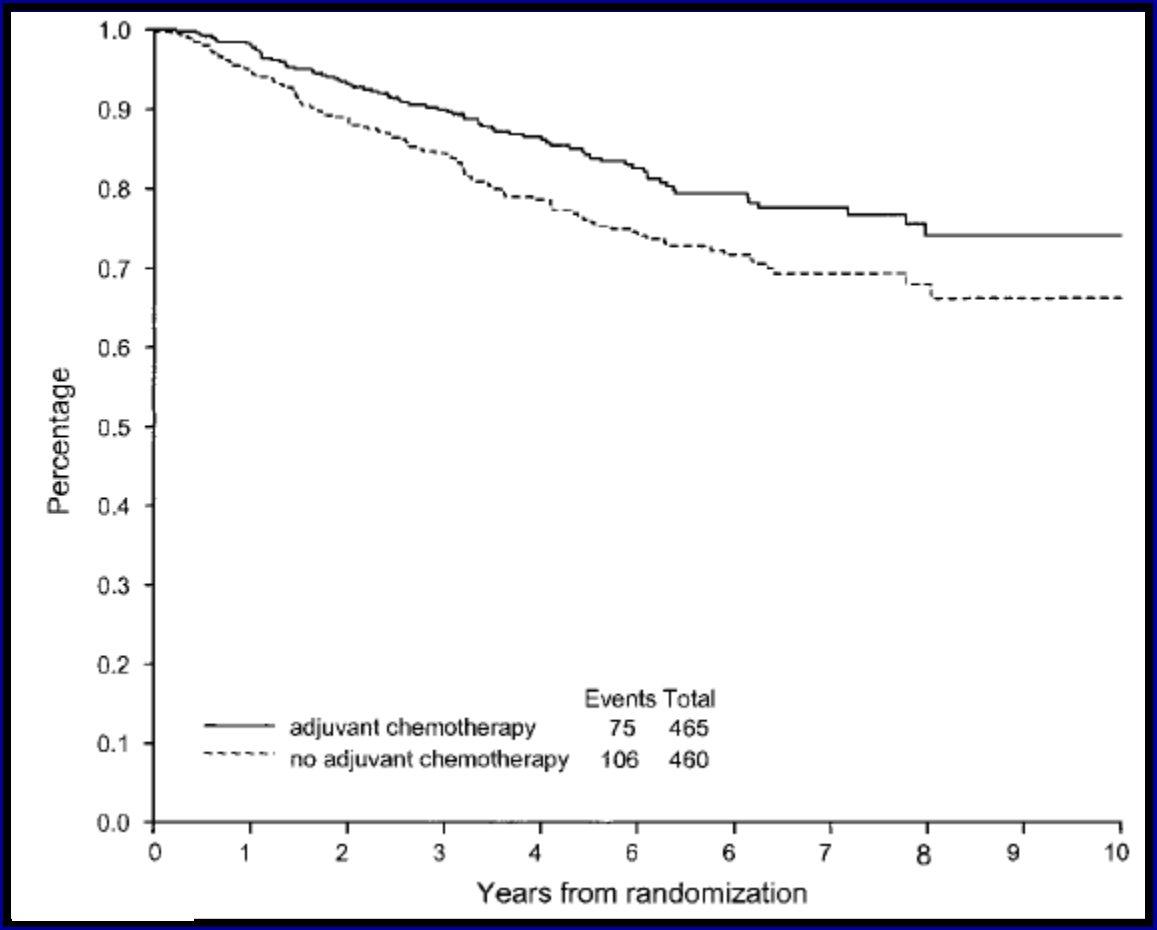
Primary treatment

Early stage disease

Adjuvant chemotherapy

Early stage disease

- Stage I & II
  - Adjuvant Chemotherapy - Increase chance of cure



5 yr OS
- 74 v 82%

ICON1/Action: JNCI 2003

Early stage disease

- Current practice
  - Likely benefit
    - Stage 1c or higher
    - Grade 3
    - Clear cell histology
  - Uncertainty
    - Peri-operative rupture (surgical 1c)
    - Inadequate staging
      - Chemotherapy vs repeat staging procedure

Relapsed disease

What is the aim of chemotherapy?

- Relapsed disease
  - Control cancer
  - Prolong life
  - Improve symptoms
    - Ascites
    - Bowel dysfunction / obstruction

} Palliative

Relapsed disease

- Chemotherapy
  - Carboplatin
  - Paclitaxel (Taxol)
  - Liposomal doxorubicin (Caelyx)
  - Topotecan

  }
  - Single agent
  - Combination
  - 3-weekly
  - Weekly

  – Choice of drugs
    - Depending on
      – performance status; comorbidity
      – response to previous treatment; duration of response
      – time since previous exposure
      – allergy; previous toxicity - patient choice

Outcome of Recurrent Ovarian Cancer Patient by Treatment-Free Interval (TFI)

E. Pujade-Lauraine et al. Proc Am Soc Clin Oncol 2002

Relapsed disease

Platinum resistant

- Liposomal doxorubicin
- Topotecan

Table 4. Treatment Response for the Intent-to-Treat Population

	Pegylated Liposomal Doxorubicin (n = 239)		Topotecan (n = 235)	
	No.	%	No.	%
Intent-to-treat population				
Overall response (P = .390)				
Total	47	19.7	40	17.0
Complete	9	3.8	11	4.7
Partial	38	15.9	29	12.3
Stable disease	77	32.2	95	40.4
Median PFS, weeks (P = .095)	16.1		17.0	
Median survival, weeks (P = .341)	60		56.7	
Intent-to-treat population—platinum-sensitive tumors	109	45.6	111	47.2
Overall response (P = .964)				
Total	31	28.4	32	28.8
Complete	8	7.3	10	9.0
Partial	23	21.1	22	19.8
Stable disease	41	37.6	42	37.8
Median PFS, weeks (P = .037)	28.9		23.3	
Median survival, weeks (P = .008)	108.0		71.1	
Intent-to-treat population—platinum-resistant tumors	130	54.4	124	52.8
Overall response (P = 0.118)				
Total	16	12.3	8	6.5
Complete	1	0.8	1	0.8
Partial	15	11.5	7	5.6
Stable disease	36	27.7	53	42.7
Median PFS, weeks (P = .733)	9.1		13.6	
Median survival, weeks (P = .455)	35.6		41.3	

Gordon JCO 2001

Relapsed disease

- Dose-dense weekly chemotherapy
  - Platinum resistant disease

Table 4. Response, PFS, and overall survival of the patients treated with weekly paclitaxel/carboplatin according to platinum sensitivity

PFI after platinum therapy	*N*	Response RR/CR (%)	PFS	Overall survival
Platinum refractory, PFI <6 months	23	61/13	11 (1–15)	15 (1–40^{+})
Platinum intermediate sensitive, PFI 6–12 months	19	84/42	11 (3–17)	NR (3–35^{+})
Platinum sensitive, PFI >12 months	20	80/20	11 (2–39^{+})	NR (3–44^{+})

RR, response rate; CR, complete response; NR, not reached.

Van der Burg IJGC 2005

Relapsed disease

- Repeated courses of chemotherapy
  - Reducing response rate
  - Reducing duration of response
  - Chemotherapy resistance
    - Symptomatic care

Relapsed disease

Diagnosis:

1. Stage 3 ovarian carcinoma with peritoneal involvement, diagnosed 2003.

Treatment history:

1. Jun to Oct 03: Primary **Carboplatin** x 6 IDS (TAH, BSO) to no residual disease. Complete Ca125 and CT response

2. Jun 05: Relapsed disease - **Carboplatin** x 6. Complete radiological response

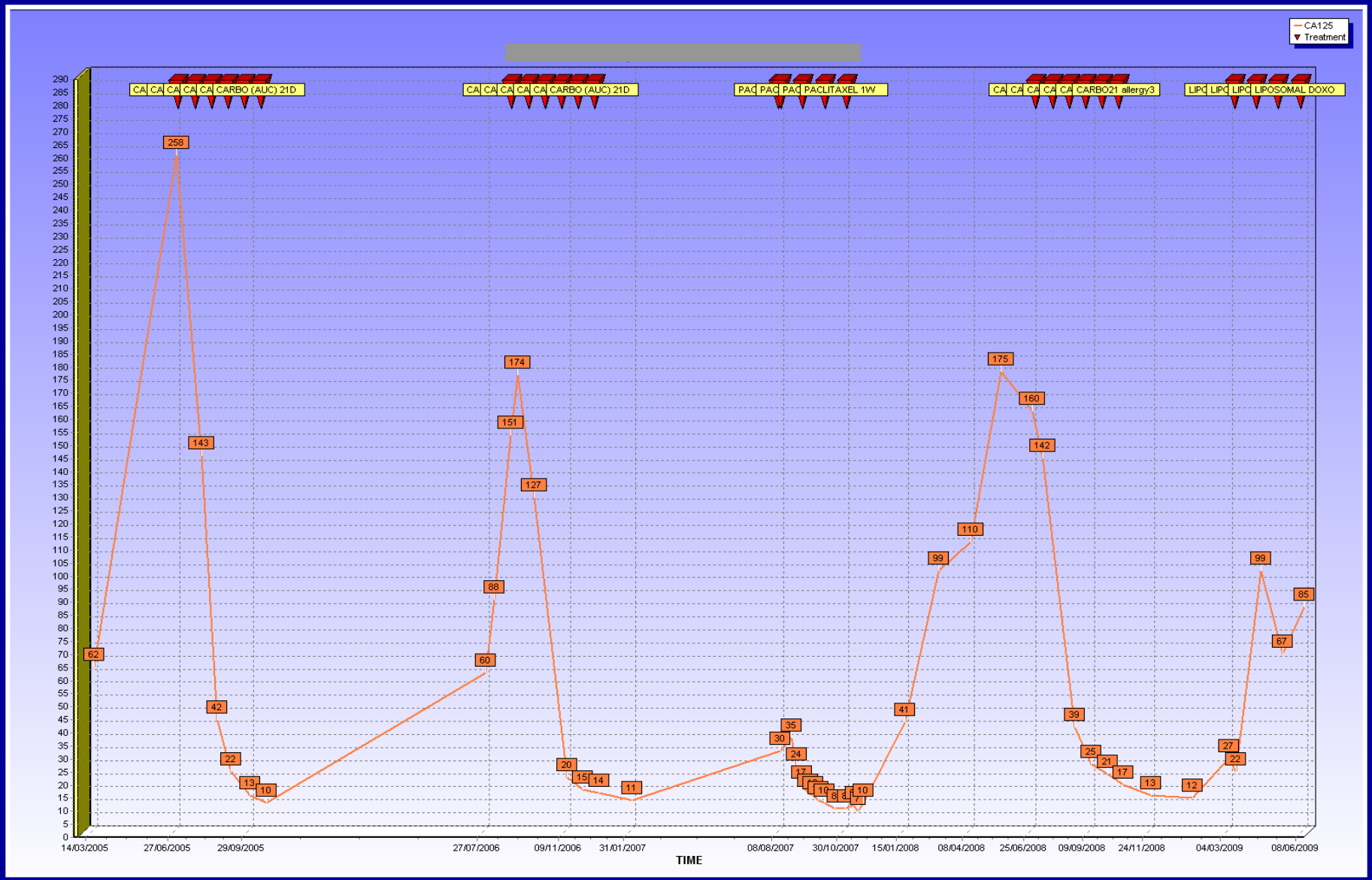
3. Aug 06: Recurrent disease - **Carboplatin** x 6. Complete radiological response

4. Aug 07: Recurrent disease (pleural effusion) - Weekly **paclitaxel** x 10 weeks. CT no measurable disease

5. Jun 08: Recurrent disease - **Carboplatin** x 6. Good CT response

6. Mar 09: Progressive disease, recurrent left pleural effusions. Commenced **Liposomal Doxorubicin** x 6

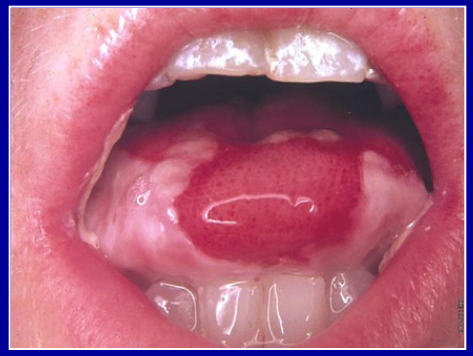
Relapsed disease



Side effects

Chemotherapy

- Side effects
  - Fatigue
  - Nausea & vomiting
  - Myelosupression
    - Anaemia, risk of infection
  - Hair loss
  - Neuropathy
  - Mucositis
  - Skin & nail changes
  - Allergic reactions



Side effects

- Neutropenia
  - Febrile neutropenia / neutropenic sepsis
    - Potentially life-threatening, within hours
      - Requires urgent treatment

    - Patient education
    - 24 hour telephone advice line
    - Urgent FBC
    - Urgent broad spectrum antibiotics

Side effects

- Intent of chemotherapy
  - Adjuvant
    - ↓ risk of recurrence / ↑ chance of cure
  - Palliative
    - Improve/maintain quality of life

Acceptability of toxicity

Benefit

Toxicity

Symptom Control

- Ascites
  - Chemotherapy
  - Repeated drainage
  - PleurX drain
- Bowel dysfunction/obstruction
  - Chemotherapy
  - Surgical defunctioning
  - Palliative care

Summary

- Systemic therapy for ovarian cancer
  - Early stage disease
    - Increase chance of cure
  - Advanced & Relapsed disease
    - Control disease, prolong life, improve symptoms
    - Effective over several years
  - Balance benefits vs side effects
    - Quality of Life

Good palliative & supportive care