Maintenance Therapy in Ovarian Cancer

PFS and OS as Endpoints of Therapeutic Clinical Trials

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Potential impact of maintenance therapy in ovarian cancer

- **Early-stage disease**
  - 20-25% of all patients diagnosed with FIGO stage I and II
  - Essentially all patients will be in a clinical CR after surgery and chemotherapy
  - 25% of these patients will relapse
- **Advanced-stage disease**
  - 75-80% of patients diagnosed with FIGO stage III and IV disease
  - 75% of patients will achieve a clinical CR after cytoreductive surgery and carboplatin/paclitaxel therapy
  - Approximately 75% of patients in a CR will relapse
- **Overall**
  - 60-65% of all patients with ovarian cancer could potentially benefit from an effective maintenance therapy

Maintenance vs. Consolidation

- Arbitrary definitions
  - Consolidation
    - Relatively short therapy, such as high-dose chemotherapy with a transplant or intraperitoneal ^{32}P or whole abdominal radiation
  - Maintenance
    - Extended therapy for 6 or more months (with an arbitrary number of treatments) or continuous treatment until disease progression

Maintenance and Consolidation approaches in patients who respond to initial therapy

- **Maintenance**
  - Chemotherapy (IV or PO)
  - Biological agents
- **Consolidation**
  - Intraperitoneal ^{32}P or radioimmunoconjugates
  - Whole abdominal radiation
  - High-dose chemotherapy with transplant
  - Intraperitoneal chemotherapy

Randomized controlled trials of consolidation therapy in ovarian cancer

High-dose Chemotherapy	Randomization	N	Results
with PBSC (Cure et al., ASCO Abstract 22:450, 2004)	High-dose chemo vs. conventional maintenance	110 (III-IV)	94 pts. relapsed PFS = 12.2 mo. vs. 17.5 mo. (p=.22) OS = 56.6 mo. vs. 49.7 mo. (p = .43)
Intraperitoneal ^{32}P (Varia et al., JCO 21: 2149, 2003)	Patients with negative second-look laparotomy 15 m Ci IP ^{32}P vs. observation	202 (III)	131 pts. relapsed RR recurrence=0.9 [0.68-1.19] 5 yrs. survival 42% vs. 36% p = .27 RR death = 0.85 [0.62-1.16]
Intraperitoneal Yttrium-90 HMFG (Verheisen R et al., JCO 24: 571, 2006)	Patients with negative second-look laparotomy: 25 mg ^{90}Y-mu HMFG1 + standard therapy vs. standard therapy	447 (Ic-IV)	202 pts. relapsed & 131 pts. died (3.5 year f/u) RR recurrence = 0.90 p = .48 RR death = 1.16 p = .40

Intraperitoneal cisplatin as consolidation therapy

Randomization	N	Median F/U 8 yrs
pCR responses	153	52% progressed
at second-look		49% died
laparotomy		PFS RR=0.89
4 cycles IP cisplatin		(0.59-1.33)
(90 mg/m^2 q 3 wks)		OS RR = 0.82
vs. observation		(0.52-1.29)

Piccart MJ et al. Int J Gynecol Cancer 2003, 13 (suppl 2), 196-203

WAR Consolidation vs. Maintenance Chemotherapy

Whole Abdominal Radiotherapy

4 cycles CA followed by second-look laparotomy

172 pts. (III)

In pCR group: 64/98 recurred

WAR PFS significantly better (P = 0.034)

Recurrence rate =

50% for WAR

71% for chemo

74% for control

p = 0.027

OS = p = 0.084

In pPR group = no Δ PFS

pCR: WAR vs. chemo* vs. observation

pPR: WAR vs. chemo*

*Chemo = 6 cycles

CA or epirubicin

Sorbe B, Int J Gynecol Cancer 2003, 13 (suppl 2), 192

Randomized trials of extended initial chemotherapy*

Study	Randomization	N	Results
Hakes[1]	5 vs. 10 cycles of PAC	78 (IIc-IV)	No sig Δ
Bertelsen[2]	6 vs. 12 cycles of PAC	202	No sig Δ in response or survival
Lambert[3]	5 vs. 8 cycles of either cisplatin or carboplatin		No sig Δ in PFS or OS

*Not designed as classic maintenance trials

[1] Hakes TB et al. Gynecol Oncol 1992, 45:284-289

[2] Bertelsen K et al. Gynecol Oncol 1993, 49:30-36

[3] Lambert HE et al. Ann Oncol 1997, 8:327-333

RCT of IV chemotherapy [topotecan or epirubicin] as maintenance in ovarian cancer

Study	Randomization	N	Results
Scarfone[1]	pCR after SLL Epirubicin vs. observation	162 (III-IV)	OS: no sig Δ
Pfisterer[2]	6 cycles paclitaxel + carboplatin: randomized to no further Rx or 4 cycles topotecan (1.25 mg/m^2 IV d1-5)	1308 (IIb-IV)	PFS: No sig Δ OS: No sig Δ
De Placido[3]	6 cycles paclitaxel + carboplatin: pCR + CCR: randomized to no further Rx or 4 cycles topotecan	273 (III-IV)	PFS: No sig Δ 18.2 mo (topo) vs. 28.4 mo (control) RR = 1.18 [.86-1.63]

[1] Scarfone G et al. Proc Am Soc Clin Oncol 2002, 21:204 (abstr 812)

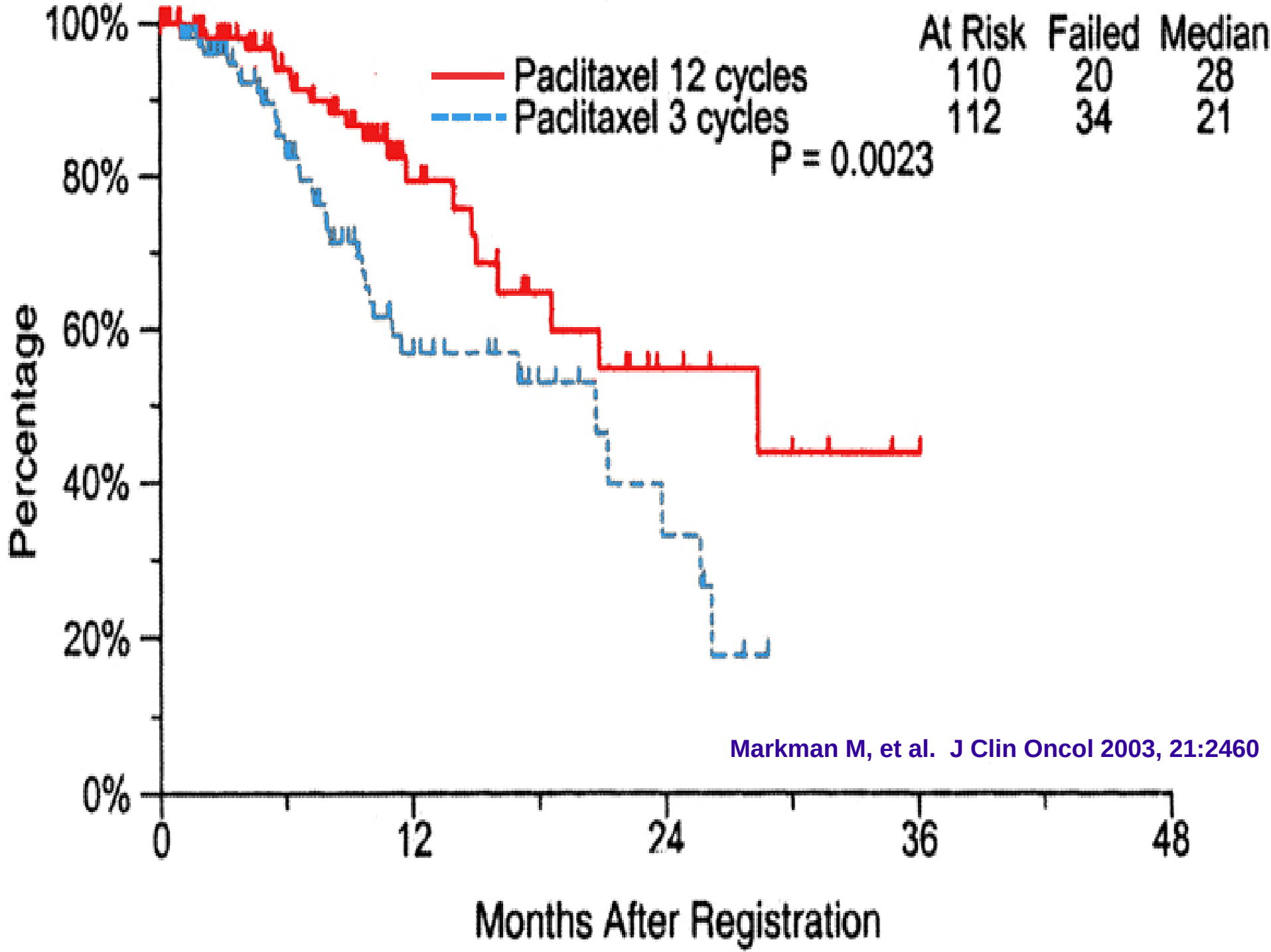
[2] Pfisterer J et al. Proc Am Soc Clin Oncol 2005, 23:456s (abstr LBA5007)

[3] De Placido S et al. J Clin Oncol 2004, 22:2635-2642

GOG 178:
Patients in clinical CR randomized to maintenance paclitaxel for 3 or 12 cycles

	Maintenance Paclitaxel	
	12 cycles	*3 cycles*
Patients	120	107
Recurrences	20	34
Progression-free Survival	28 mo	21 mo
Significance	p < 0.0028	

Markman M, et al. J Clin Oncol 2003, 21:2460


At Risk Failed Median
Paclitaxel 12 cycles 110 20 28
Paclitaxel 3 cycles 112 34 21
P = 0.0023
100%
80%
60%
40%
20%
0%
Percentage
0
12
24
36
48
Months After Registration
Markman M, et al. J Clin Oncol 2003, 21:2460

Biological maintenance therapy

Study	Randomization	N	Results
Hall[1]	INFα 2a vs. no Rx following chemotherapy	300	PFS: RR 0.96 (.75-1.22) OS: RR 1.06 (.82-1.38)
Alberts[2]	pCR at SLL: IP IFN α-26 vs. observation	70	PFS: No sig Δ OS: No sig Δ
Berek[3]	CCR: Oregovomab vs. placebo	145	PFS: 13.3 vs. 10.3 p = .71
Hirte[4]	6-9 cycles of paclitaxel + platinum: at least a PR with <2 cm disease: placebo vs. BAY12-9566 (MMPI)	243	No sig Δ PFS or OS

[1] Hall GD et al. Br J Cancer, 2004, 91:621-626

[2] Alberts DS et al. Gynecol Oncol 2006, 100:133-138

[3] Berek JS, et al. J Clin Oncol 2004, 22:3507-3516

[4] Hirte HW et al. Proc Am Soc Clin Oncol 2001, 20:211a (abstr 843)

Conclusions regarding Consolidation or Maintenance

- Neither maintenance nor consolidation has been shown to improve survival
- One trial of WAR and one trial of IV paclitaxel demonstrated improvement in PFS
- Toxicity of WAR and paclitaxel substantial

Consensus Statement of GCIG OCCC 2004

- What are the recommended primary endpoints for future phase II and randomized phase III clinical trials in ovarian cancer?
- The recommended primary endpoints for future clinical trials in ovarian cancer are:

  Maintenance following first-line: OS[1]

  10/13 vote

[1] Minority vote: In certain situations, PFS can also be considered a primary endpoint in maintenance trials following first-line therapy

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du Bois A et al. Ann Oncol 2005, 16 (suppl 8): viii7-viii12

“Certain situations?”

- Nontoxic therapy
- Biological therapy that will not affect subsequent chemotherapy
- Clinically significant improvement in PFS

Reasons for PFS as an endpoint in maintenance therapy

- Clinical benefit of PFS
  - Relapse linked with death
  - Delay further therapy
- Treatment effect not confounded by second- and third-line treatments
- Faster evaluation of new treatments

Reasons why PFS is not recommended endpoint in maintenance therapy

- Toxicity of maintenance therapy
  - Quality of life
- May make treatment at clinical progression more difficult
- Approximately 50% of patients have macroscopic/microscopic disease detectable only by SLL
  - Not “maintaining” a CR but treating residual disease

Current ongoing RCT of maintenance therapy

Agent Under Study	Trial	Endpoints
Oregovomab	Two placebo-controlled trials of 177 pts., each with 2:1 randomization	TTR = 1º obj QoL, immune response Safety - 2º obj Pts. will be followed for survival
Bevacizumab	GOG 3-arm trial: 2000 pts: 3 yr accrual - chemo (Carbo/Pac) + placebo maintenance vs. chemo + bevacizumab + placebo maintenance vs. chemo + bevacizumab maintenance	OS = 1º obj (increase median OS from 30-39 months – Death rate ↓ by 23%) PFS = 2º obj (accelerated approval will be sought on basis of 30% improvement in PFS [4 mo])
Paclitaxel-polyglutamate polymer	GOG 3-arm trial: paclitaxel vs. new agent vs. observation 1,550 eligible pts. with 3.1 years for accrual plus 2 years for survival	OS = primary endpoint (12 mo) PFS = secondary endpoint Safety and QoL endpoints