

## Ovarian Cancer

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SIOG 2012



## Clinical Trials

- Median age at diagnosis 64 years
- There have been no prospective randomized trials of older women in any gynecologic cancer
- Need to extrapolate from trials in which older patients make up small percentage of patients
  - Usually shows feasibility
- Few small (<50 pts) phase II in older patients



## Treatment Outline

- Primary surgical debulking
  - Optimal (no residual; <1 cm) vs. suboptimal
- Chemotherapy
  - IV
  - IP only for optimal patients



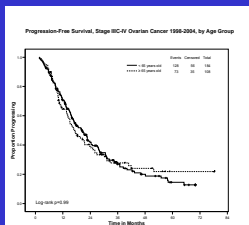
## Advanced Ovarian Cancer over 65 Years

- Older women have poorer survival
  - Possible causes:
    - Delay in diagnosis
    - Poor surgery
    - Undertreatment: more often chemotherapy delay; less chemotherapy
    - Biology
- Platinum based therapy effective

Wright, J., et al. Br J Cancer, 2008  
 Hershman D, et al. Gynecol Oncol, 2004



## MSKCC: Advanced Ovarian Cancer by Age (Retrospective)



- No difference:
  - PFS
  - OS
  - Chemotherapy regimens
  - Chemotherapy dose administered
  - Chemotherapy toxicity

Eisenhauer EL, et al. Gynecol Oncol, 2007



## Primary Therapy: 2012

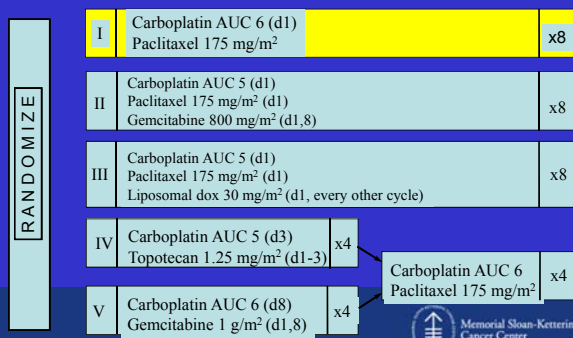


### Ovarian Cancer Landmarks in Therapy

1. Young, et al, showed combinations superior to single agent, 1978
2. Cisplatin effective in refractory disease
3. Carboplatin equivalent to cisplatin with less toxicity (Calvert formula)
4. Paclitaxel effective in platinum refractory patients
5. GOG 111: paclitaxel-cisplatin superior to cyclophosphamide-cisplatin
6. GOG 158: Paclitaxel-Carboplatin superior to paclitaxel-cisplatin; second look surgery not beneficial
7. GOG 182: 3 drugs vs. paclitaxel/carboplatin



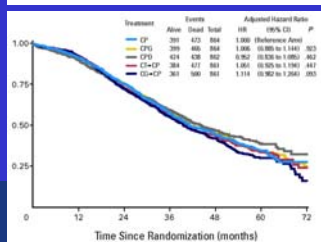
### GOG182: Ovarian Cancer (Stage III-IV)



Bookman, M. A. et al. J Clin Oncol; 27:1419-1425 2009



Treatment Regimen	CP (n = 864)	CPG (n = 864)	CPD (n = 862)	CT→CP (n = 861)	CG→CP (n = 861)
<b>Patient Characteristics</b>					
Median age (yr)	57.7	59.1	59.5	58.5	59.3
FIGO Stage 3 (%)	83.8	86.7	86.2	86.4	83.7
FIGO 4 (%)	16.2	13.3	13.8	13.7	16.3



#### Conclusions:

- Median Age = 59
- No survival improvement with a third agent.
- Carboplatin + Paclitaxel (CP) remains standard first-line treatment.



Bookman, M. A. et al. J Clin Oncol; 27:1419-1425 2009

### GOG 172: Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer

- Intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel improves survival in patients with optimally debulked stage III ovarian cancer:
  - Progression-free survival 18.3 vs. 23.8 months
  - Overall survival 49.7 vs. 65.6 months
- QOL decreased in IP arm, but equivalent at 12 months
- Markedly increased treatment related toxicity; patient selection important
- Work intensive; need experience

Armstrong, et al, 2006



### Issues in Primary Therapy

- Primary surgery vs. neoadjuvant therapy
- Role of intraperitoneal therapy; are there alternatives?
  - New drugs
  - Drug scheduling
- Role of bevacizumab



### JGOG: Phase III IV paclitaxel and carboplatin vs. dose dense (TC-T-T)

- JGOG: 637 patients randomized, Stage III diagnosis
- TC vs TC-T-T (80 mg/m<sup>2</sup>) weekly
- Primary endpoint PFS
  - 0.8 power to detect 5 month difference

Treatment	N	Median PFS	P value	HR	95% CI
TC	319	17.2 mos			
TC-T-T	312	28.0 mos	0.0015	0.71	0.581-0.88
		<b>3 year OS</b>			
TC	319	65.1%			
TC-T-T	312	72.1%	0.03	0.75	0.57-0.98

Katsumata et al. Lancet 374: 2009



### Primary Therapy Weekly Therapy

- Eligibility
  - Patients aged  $\geq 70$  years
  - Stage IC-IV ovarian cancer,
  - Performance status  $\leq 2$
- Treatment
  - Carboplatin (AUC 2) + paclitaxel (60 mg/m<sup>2</sup>) on days 1, 8, 15 every 4 weeks, up to six cycles
- Results
  - PFS 13.6 months
  - Acceptable toxicity

Pignata, et al 2008



### New Drug

- **IP Carboplatin**
- Should IP carboplatin be substituted for IP cisplatin due to issues of toxicity?



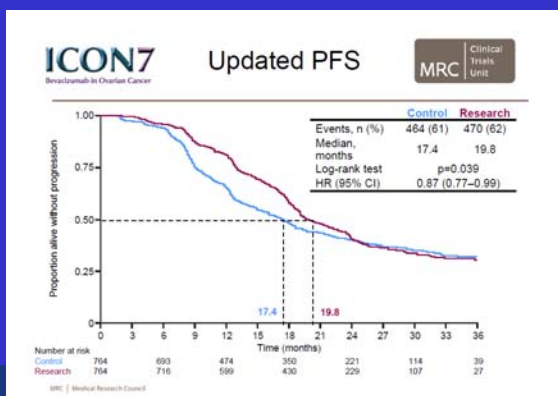
### New Drug: Bevacizumab (Avastin)

Not FDA approved for any gynecologic malignancy



### Bevacizumab: Randomized Trials

- Primary Therapy
  - paclitaxel/Carboplatin +/- bevacizumab
    - GOG 218
    - ICON 7



### Phase III GOG 218/ICON 7: Many Questions

- Will there be an overall survival benefit?
- Could it be given with same benefit later in disease course?
- How long should it be administered? Until PD? For life?
- What will the phenotype of relapsed disease look like? Is there rebound?
- What is the required dose? Is less equally effective?



### GOG 0252 (optimal)


**Stage II or III  
(≤1cm residual),  
Ovarian,  
primary  
peritoneal, or  
fallopian tube  
cancer**

R  
A  
N  
D  
O  
M  
I  
Z  
E

Paclitaxel 80 mg/m<sup>2</sup>/1h IV, Days 1, 8, 15, Cycles 1-6  
Carboplatin AUC 6 IV, Day 1, Cycles 1-6  
Bevacizumab 15 mg/kg IV, Cycles 2-22


Paclitaxel 80 mg/m<sup>2</sup>/1h IV, Days 1, 8, 15, Cycles 1-6  
Carboplatin AUC 6 IP, Day 1, Cycles 1-6  
Bevacizumab 15 mg/kg IV, Cycles 2-22

Paclitaxel 135 mg/m<sup>2</sup>/3h IV, Day 1, Cycles 1-6  
Cisplatin 75 mg/m<sup>2</sup> IP, Day 2, Cycles 1-6  
Paclitaxel 60 mg/m<sup>2</sup> IP, Day 8, Cycles 1-6  
Bevacizumab 15 mg/kg IV, Cycles 2-22



### Ovarian Cancer 2012

- Carboplatin and paclitaxel (or docetaxel) remain a standard of care (GOG 182)
- 3 randomized trials have shown a superiority for survival using IP therapy in optimal patients.
- IP regimen requires modification for toxicity.
- IV Bevacizumab prolongs PFS in first line therapy.
- JGOG suggests impact of paclitaxel schedule
  - Weekly therapy for older patients or limited to those who are vulnerable
- GOG 252 will answer some of these questions




### Considerations in Older Patients



### Role of Surgery

- Neoadjuvant chemotherapy vs. primary surgery
  - Can we identify the patient appropriate for neoadjuvant chemotherapy?
    - Over 80 years of age
    - Multiple comorbidities
    - Poor PS
    - Tumor bulk
    - Prospective study of geriatric assessment

Moore KN, et al. Gynecol Oncol, 2008  
McLean KA, et al. Gynecol Oncol, 2010



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### Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

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**Ovarian cancer in the elderly: Outcomes with neoadjuvant chemotherapy or primary cytoreduction<sup>12</sup>**

Kate A. McLean<sup>a</sup>, Chirag A. Shah, Sara A. Thompson, Heidi J. Gray, Ron E. Swensen, Barbara A. Goff

<sup>a</sup>Department of Obstetrics and Gynecology, University of Washington School of Medicine, Seattle, Washington, USA

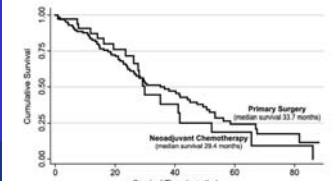



Fig. 1. Kaplan-Meier survival curves for neoadjuvant chemotherapy vs. primary surgery.





### Chemotherapy



## Treatment Outcomes for Older Women with Advanced Ovarian Cancer: Phase III Clinical Trial (GOG182)


William Tew, Jim Java, Dennis Chi, Andrew Menzin, John Lovecchio, Michael Bookman, and Stuart Lichtman

Memorial Sloan-Kettering Cancer Ctr, NY, NY; Gynecologic Oncology Group, Buffalo, NY; Memorial Sloan-Kettering Cancer Ctr, NY, NY; North Shore Univ Hosp, Manhasset, NY; Arizona Cancer Center, Tucson, AZ; Memorial Sloan-Kettering Cancer Center, NY, NY

## GOG 182


- Patients ≥ 70yo = 620 (17%)
- Overall survival differences (older vs. younger):
  - 37.2 vs. 45 months (p<0.001)
  - PFS: PFS: 16 vs. 15 months; ?treatment at relapse
- Non-cancer death rate:
  - 13% vs. 7% (p<0.001)
- Relative risk of cancer-specific death:
  - RR = 1.14 (95% CI, 1.01-1.27, p =0.028)
- Survival differences observed in first 12-months




## GOG 182

- Women with ovarian cancer ≥ 70yo:
  - Poorer performance status
  - Less likely to complete 8 cycles of chemo
  - More toxicity (neuropathy, cytopenia)
    - Similar to paclitaxel in breast cancer\*
  - Similar optimal debulking rates, but longer post-operative recovery
  - Do we need elderly specific trials?

\*Lichtman, et al. Ann Oncol 2011

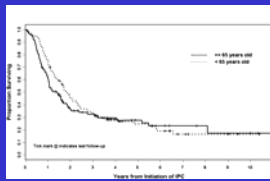


## Intraperitoneal Regimen: Should Older Patients Receive IP Therapy?



## IP Therapy by Age: MSKCC

### Survival




### Toxicity

Grade 3 or 4 toxicity <sup>a</sup>	Older (n=95)	Younger (n=99)	P value <sup>b</sup>
No	79 (83%)	78 (79%)	0.44
Yes	16 (17%)	21 (21%)	

<sup>a</sup> Five older and 1 younger patient did not get any IP chemotherapy due to cutaneous problems, and they were excluded from the analysis.  
<sup>b</sup> Based on  $\chi^2$  test, and available data.

Tew, et al, ASCO 2009; O’Cearbhaill, et al, JGO 2012



## Ovarian Cancer: Alternatives


- Frail
- Multiple comorbidities
- Poor performance status

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These represent different patient populations

- Weekly paclitaxel/carboplatin (not consecutive)
- Single agent, i.e. carboplatin or paclitaxel
- Liposomal doxorubicin/carboplatin (as per CALYPSO)

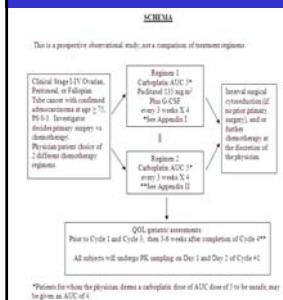
Pignata, et al. 2008



The next step...



## GOG 273: Ovarian Cancer in the Older Patients

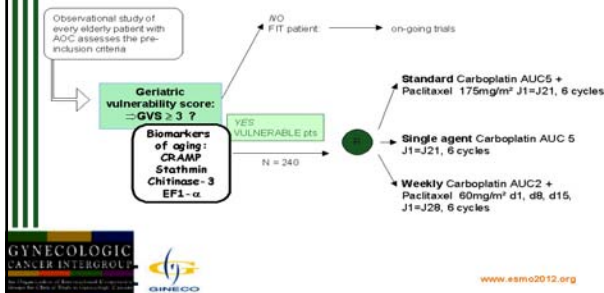


- Liberal eligibility criteria
- Patient and physician therapy choices-not randomized
- Prospective geriatric assessment
- Allows neoadjuvant

GOG Taskforce on Older Patients



## Towards a future challenge

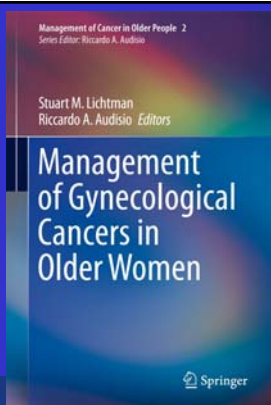


Provided by Claire Falandry, MD



## Conclusion

- Older patients with adequate performance status and functional status should receive current standard of care
- Encourage participation in clinical trials
- Off study
  - Consider intraperitoneal regimen
  - Standard IV paclitaxel/carboplatin
- Neoadjuvant chemotherapy may provide time to optimize patients for surgical resection



Thank you

