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# A PHASE III CLINICAL TRIAL OF BEVACIZUMAB WITH IV VERSUS IP CHEMOTHERAPY IN OVARIAN, FALLOPIAN TUBE AND PRIMARY PERITONEAL CARCINOMA NCI-SUPPLIED AGENT(S): BEVACIZUMAB (NSC #704865, IND #7921**)** **NCT01167712** a GOG/NRG Trial (GOG 252)

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# Verbal Disclosure

- This clinical trial was supported by Genentech for bevacizumab and drug distribution
- Dr. Walker has not personally received funding for this trial
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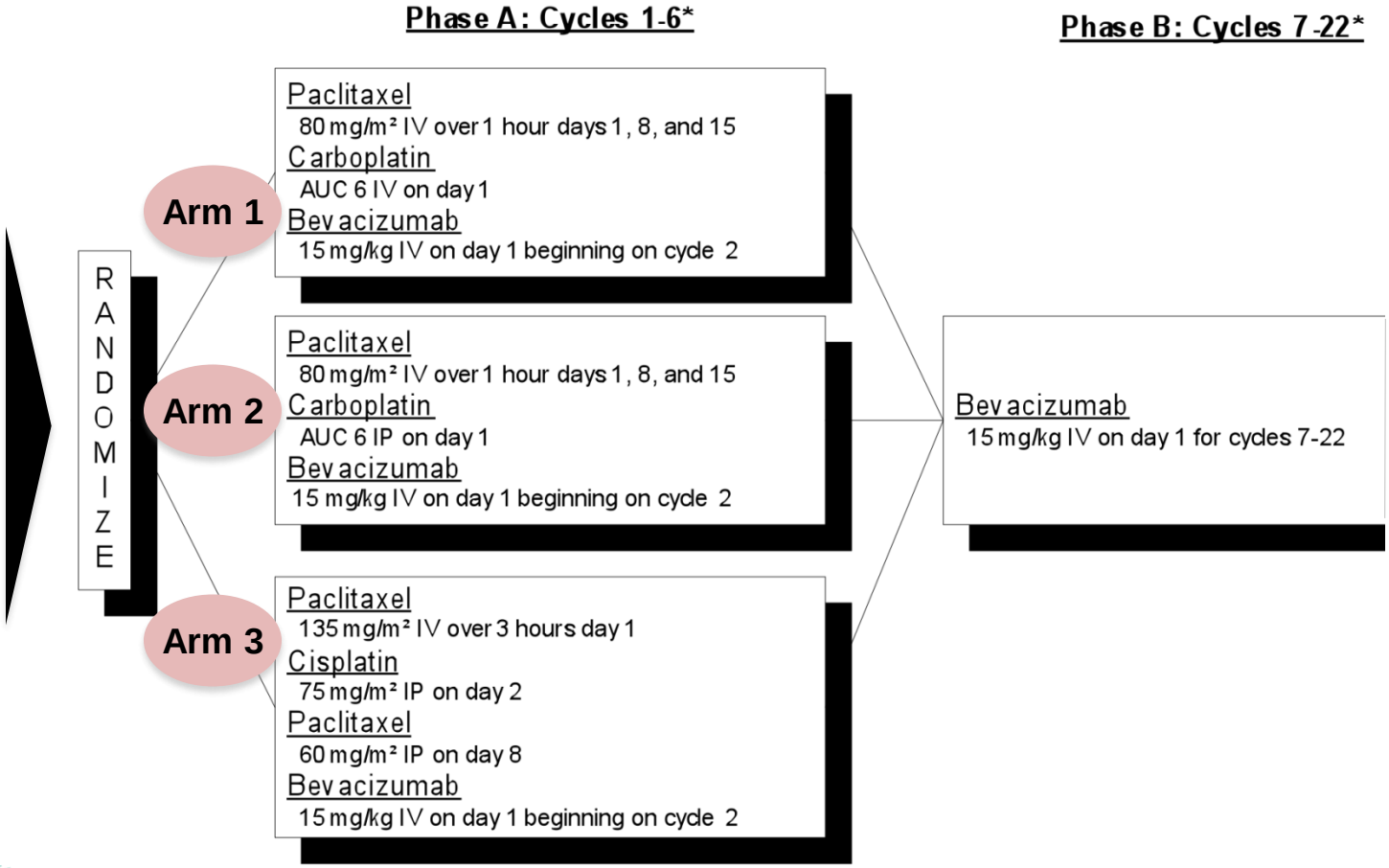
# GOG 252: IP chemo and dose dense Paclitaxel showed improved OS, both have toxicities; which is best?

| Key questions for GOG 252 | Indications and contemporary results | Implications for GOG 252 schema |
|---|---|---|
| Should we use dose dense Paclitaxel? | • JGOG 3016 showed improved OS, but not replicated in the US | **Arm 1:** Dose dense Paclitaxel |
| Should we use IP chemotherapy? | • GOG 172 showed survival advantage, but was toxic, with only 42% receiving 6 cycles; additional studies were done to address the toxicity:<br>-GOG9916/17 Substituted IP carbo for cisplatin<br>-GOG9921 Reduced IP cisplatin dose | **Arm 2:** IP Chemo substitute<br>**Arm 3:** IP chemo, reduced cisplatin dose |
| Should we use Bevacizumab? | • GOG 218 showed improved PFS with Bev, and feasibly safe with IP Chemo | **All:** Include Bevacizumab |

# GOG 252: Schema

## Eligibility

- Stage II-III Epithelial Carcinoma: Ovary, Fallopian Tube, Peritoneal
- Resected to optimal: less than or equal to 1 cm visible tumor by surgeon report
- Exploratory: suboptimal (7%) and Stage IV (5%)



# Differences in Dosing in GOG 252 Arm 3 IP Cisplatin compared to GOG 172

- Dose reduction cisplatin(100 down to 75 mg/$m^2$)
- Infusion time reduction 135 mg/$m^2$ paclitaxel(3 hr instead of 24h)
- All outpatient therapy
- Bevacizumab 15 mg/m2 for all arms on cycles 2-22
- Comparison arm dose dense paclitaxel with carbo IV AUC 6- GOG 262 (JGOG)
- Second experimental Arm IP carbo and dose dense paclitaxel

# GOG 252 accrual and demographics

- 1560 participants from July 2009-Nov 2011
- Median age - 58 years
- White 90%; Black 3%; Hispanic 3%
- Stage III- 84%
- Stage II- 10%
- Grade 3 Serous – 72%
- No visible residual disease per surgeon – 57%
- Exploratory aim:  suboptimal (7%) and Stage IV (5%)

# GOG 252 assigned treatment completion

| Arm | At least 6 cycles of Platinum | At least 6 cycles of taxane | # Bev Cycles |
|---|---|---|---|
| Arm 1: IV Carbo | 90% | 87% | 20 |
| Arm 2: IP Carb | 90% | 88% | 19 |
| Arm 3: IP Cisp | 84% | 87% | 17 |

Cross-over to the IV only therapy occurred in 16% randomized to IP carbo arm and 28% randomized to IP cis arm

Twice as many patients stopped protocol directed bevacizumab prior to completion of Cycle 6 on the arm 3 IP cisplatin (30% vs 15%)

# GOG 252 Toxicity

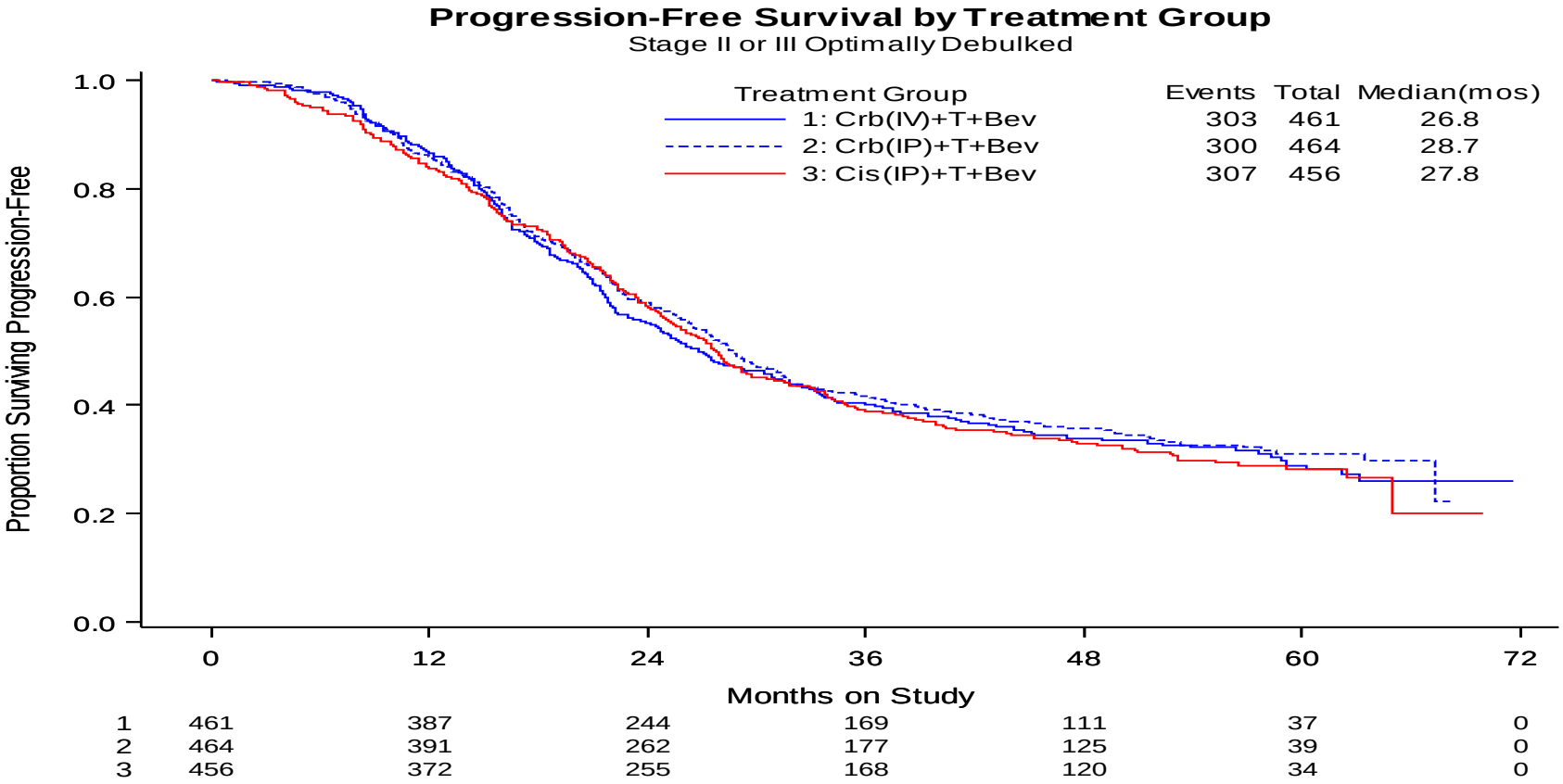
| Event | IV Carbo | | IP Carbo | | IP Cisp | |
|---|---|---|---|---|---|---|
| | G2 | ≥G3 | G2 | ≥G3 | G2 | ≥G3 |
| Feb/neut | | 2.5% | | 2.6% | | 3.3% |
| Neut | | 71% | | 68% | | 64% |
| Platelets | | 17.6% | | 15.1% | | 6.1% |
| HTN | | 11.9% | | 13.8% | | 20.5% |
| Thromb | | 6.3% | | 8.4% | | 9.0% |
| N/V | | 5.1% | | 4.7% | | 11.2% |
| Fistula | | 5.3% | | 3.7% | | 4.3% |
| Urine Prot | | 2.7% | | 3.1% | | 1.6% |
| Sens Neur | 24.1 | 5.7% | 22.6 | 4.5% | 21.3 | 5.5% |

# Progression Free Survival Optimal Stage II-III (10% stage II)

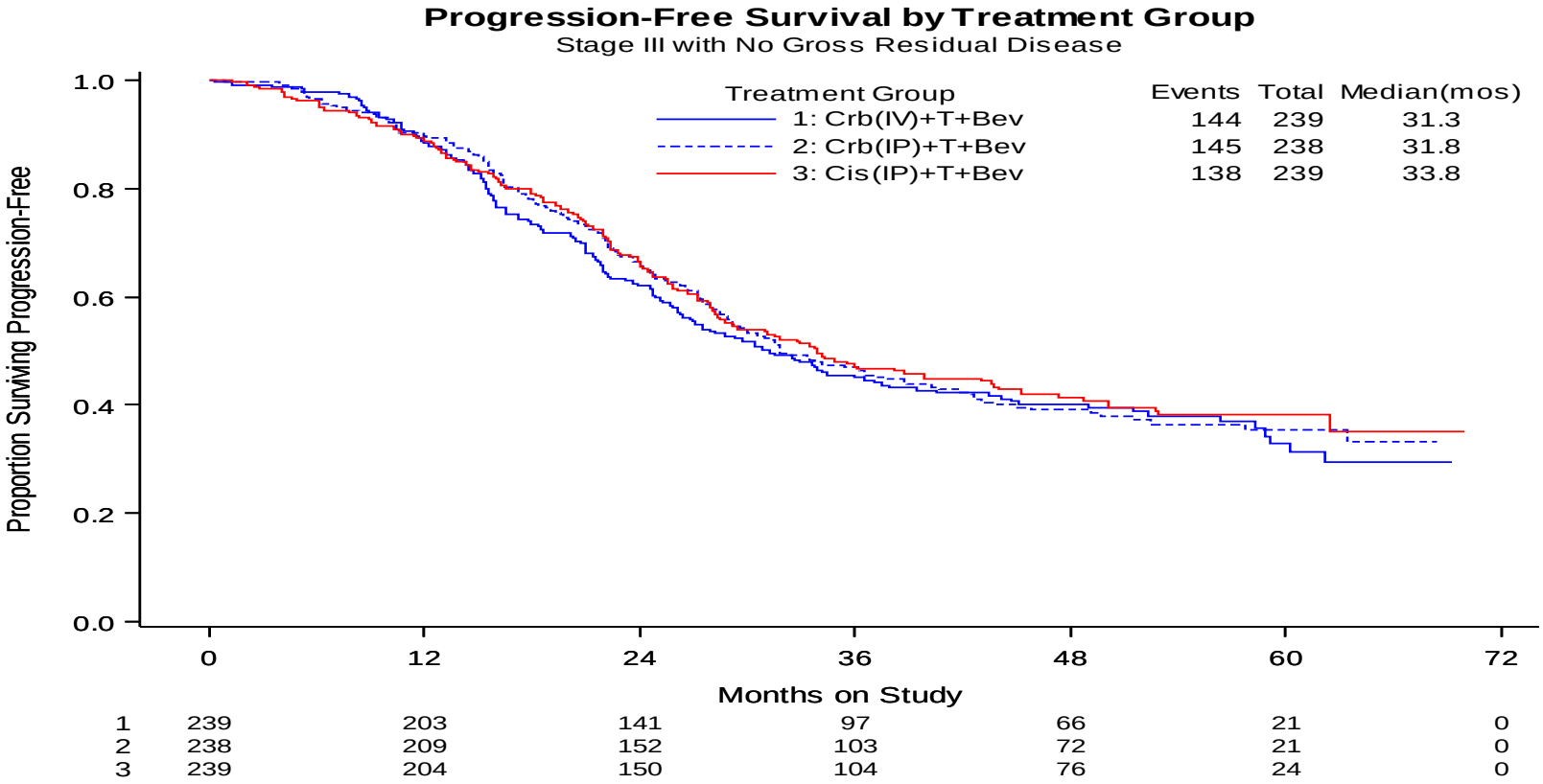
| Arm | N | Events | Median PFS | HR [95% CI] | Logrank | Logrank |
|---|---|---|---|---|---|---|
| IV Carbo | 461 | 303 | 26.8 months | Reference arm | P-value | Chi square |
| IP Carbo | 464 | 300 | 28.7 months | 0.947 [0.808-1.11] | 0.416 | 0.661 |
| IP Cisp | 456 | 307 | 27.8 months | 1.01 [0.858-1.18] | 0.727 | 0.122 |

- Estimated hazard ratios, and logrank tests are adjusted for stage of disease and size of residual disease micro vs < 1cm
- CT required every 6 months for surveillance (not required in GOG 114/172)

# Progression Free Survival Optimal Stage II-III



# Progression Free Survival Optimal Stage III NGR



# Across Study Comparisons for PFS

| Arm Study | PFS Median in mos No visible dx Stage 3 | PFS median mos 1 cm or less visible dx |
|---|---|---|
| GOG 114 & 172 IV cisplatin | 33.4 | |
| GOG 172 IV cisplatin | 43.2 | 18.3 |
| GOG 252 IV carbo | 31.3 | 26.8 (10% stage II) |
| GOG 114 & 172 IP cisplatin | 43.2 | |
| GOG 172 IP cisplatin | 60.4 | 23.8 |
| GOG 252 IP carboplatin | 31.8 | 28.7 (10% Stage II) |
| GOG 252 IP cisplatin | 33.8 | 27.8 (10% Stage II) |

# Discussion

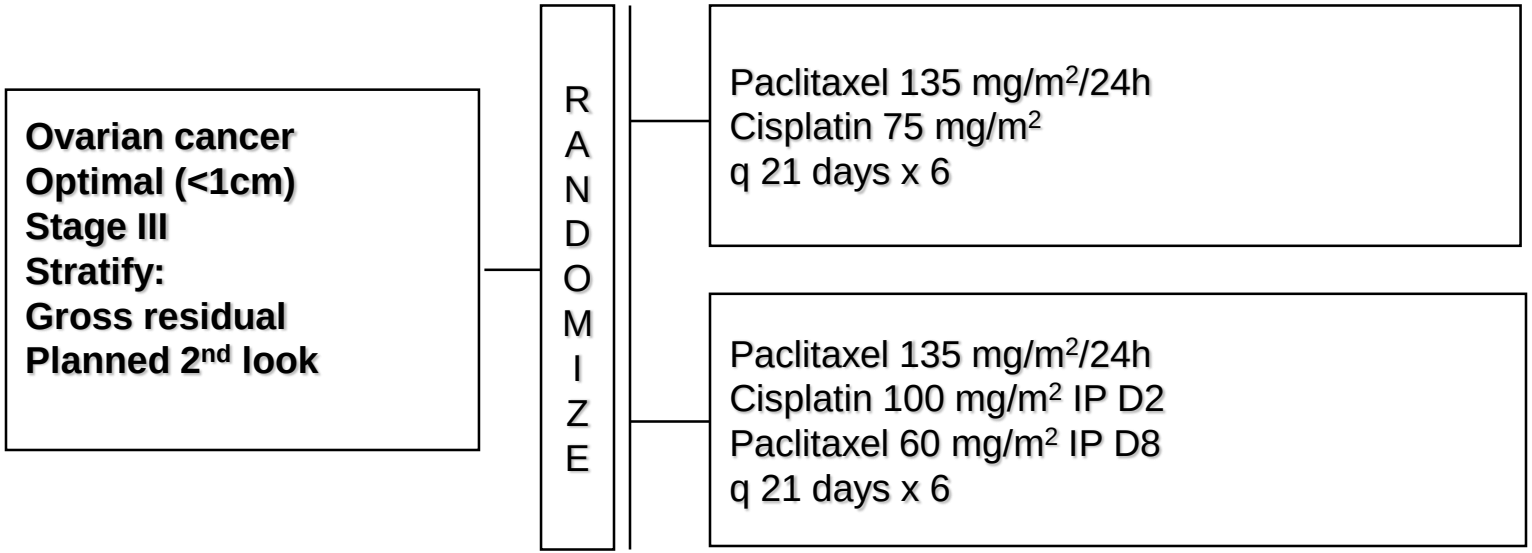
- Survival for optimal and no residual disease participants will not be available for a few years.
- Dose reductions of paclitaxel and cisplatin as well as cross- over may have compromised efficacy.
- Dose dense paclitaxel may have improved efficacy to allow us to abandon IP chemo-  must we wait- combine both?
- Bevacizumab interactions could have clouded analysis

# Conclusions

- All arms have excessive toxicity
- Neurotoxicity is similarly high in all arms
- Reserve changes in treatment recommendations until survival data available for no residual disease high grade serous Stage III participants.
- IP Cisplatin increases bevacizumab associated HTN

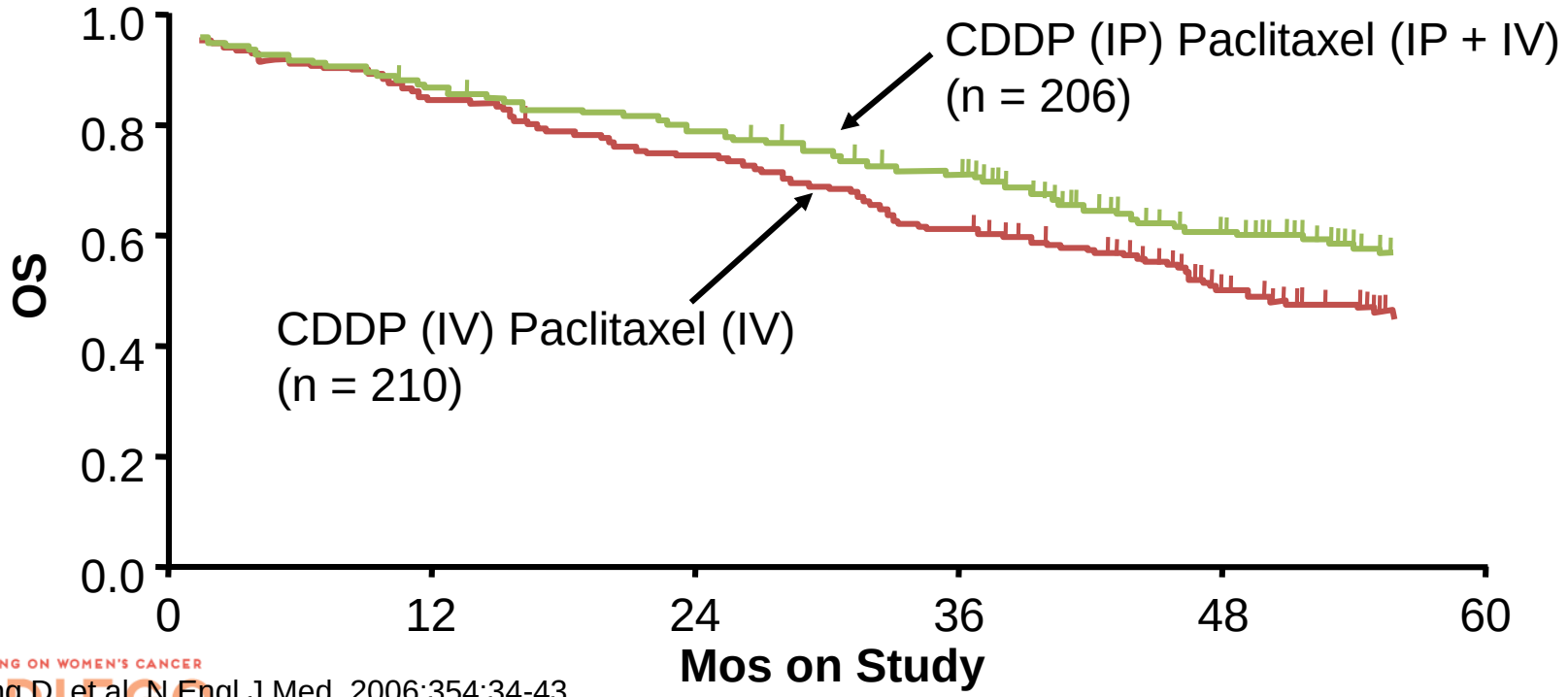
# APPENDIX

# GOG 172 Schema



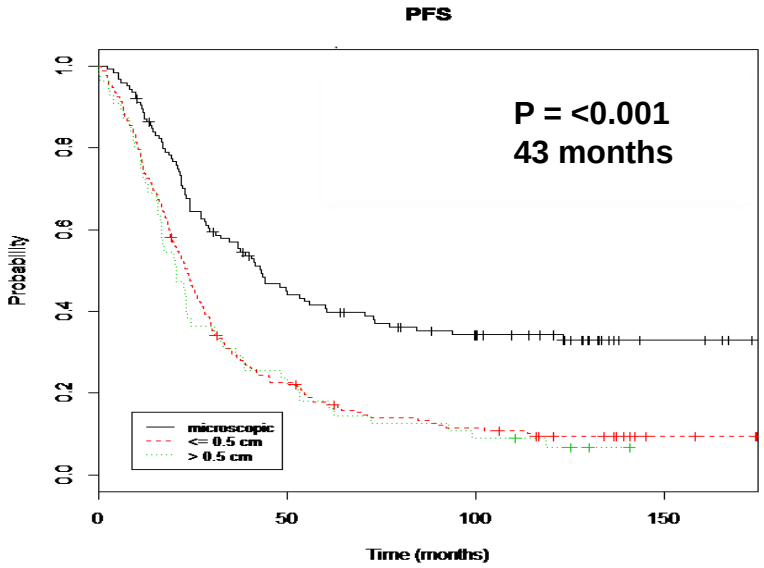

Armstrong et.al. N Engl J Med 2006;354:34-43

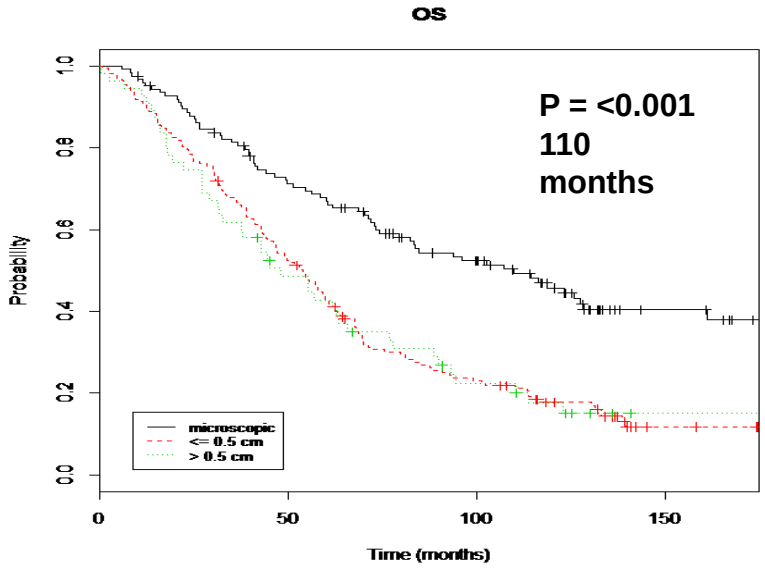
# GOG 172: Ovarian (Optimal III)




Armstrong D, et al. N Engl J Med. 2006;354:34-43.

# Residual disease and Survival: GOG 172, 114

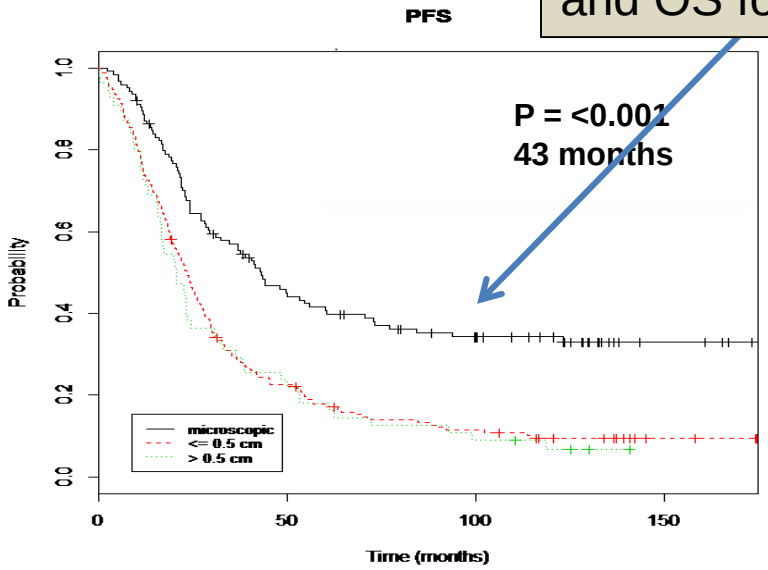


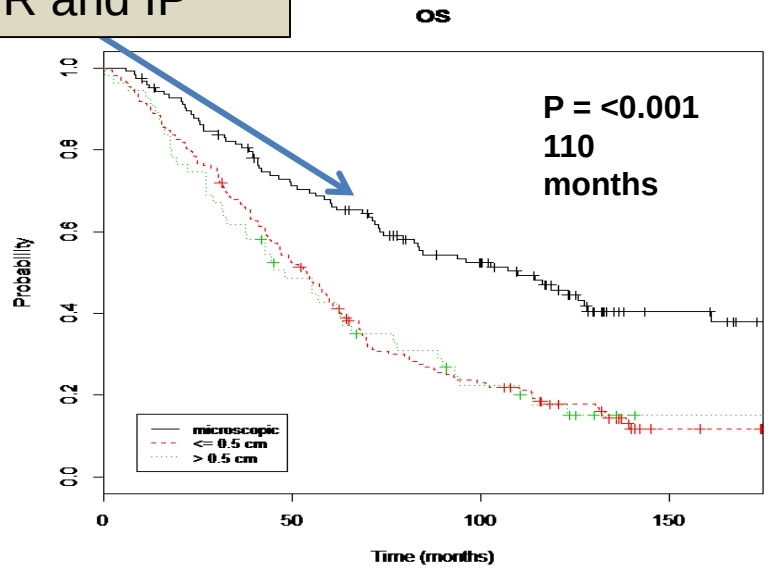




Landrum et al. Gyn Onc 2013

# RESIDUAL DISEASE AND SURVIVAL: GOG 172, 114

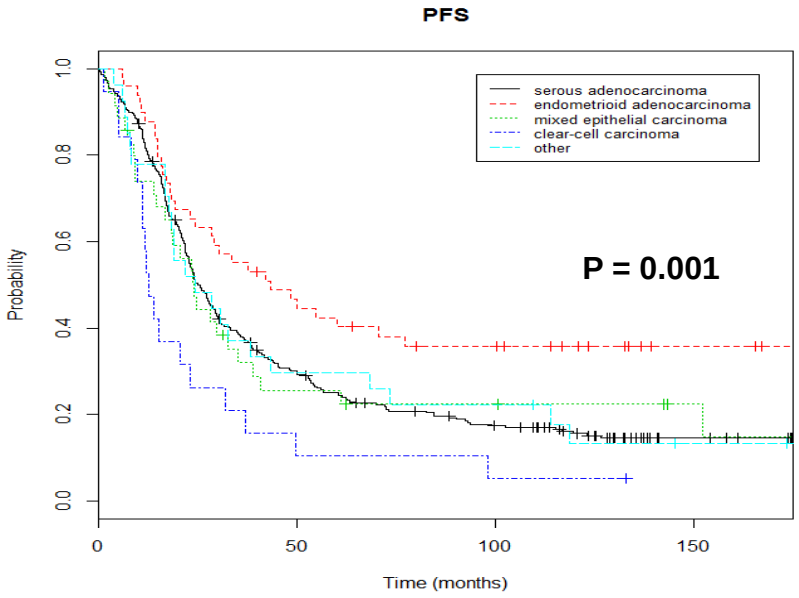
Significantly Longer PFS and OS for NGR and IP

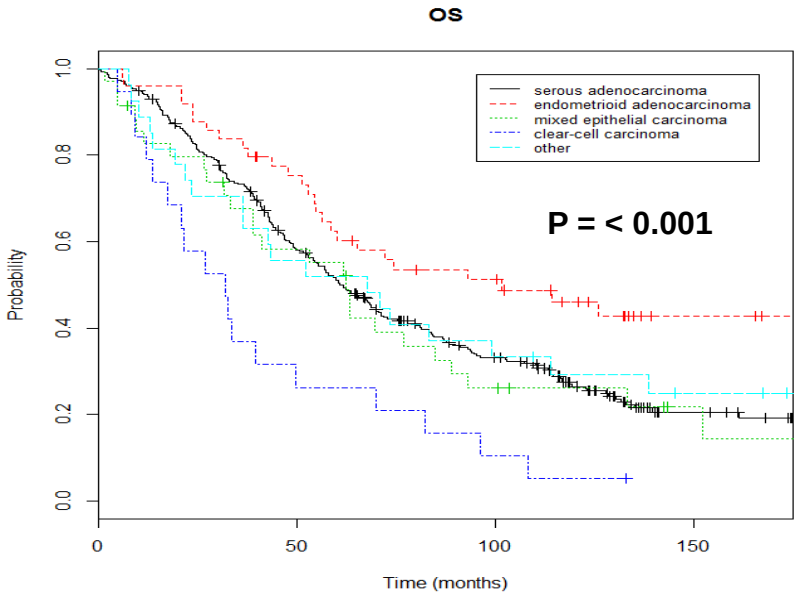



Landrum et al. Gyn Onc 2013

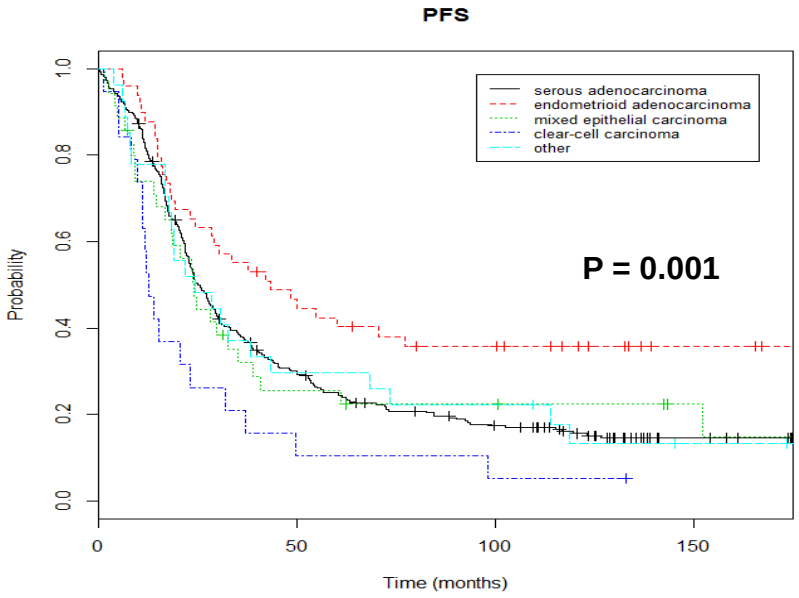
# Histology and Survival: GOG 172,114

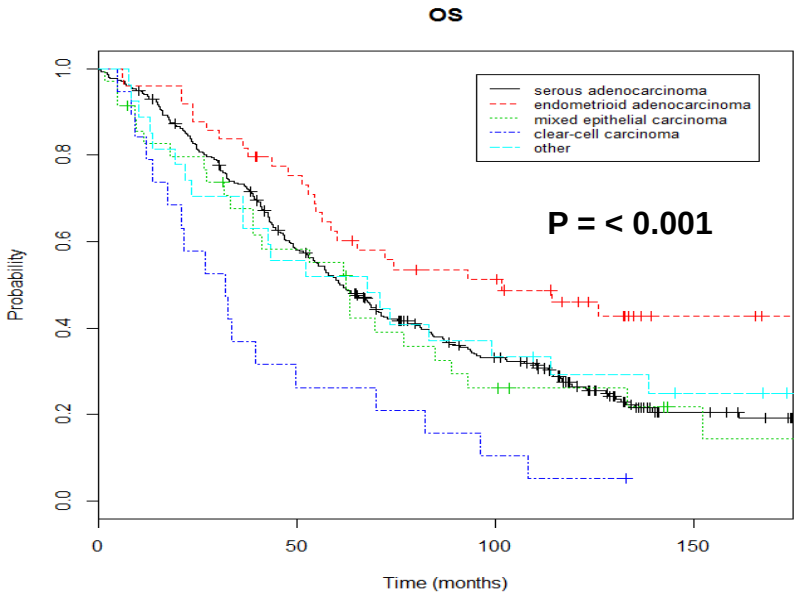



Landrum et al. Gyn Onc 2013

# Histology and Survival: GOG 172,114

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