First-line therapy in Ovarian Cancer
Surrogate endpoints for accelerated approval

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These preliminary results are part of work in progress.
Not to be used for publication or reference.

Six GOG Randomized Trials involving patients with recently diagnosed, optimally debulked, advanced epithelial ovarian cancer

Study Identifier	Control Regimen	Experimental Regimen	Target population	N of patients
GOG-25 (1977)	Mel 7 mg/m2 x 5 days q 28 days x 10/18 months	Mel 7 mg/m2 x 5 days q 28 days C.Parv 4 mg/m2 q 10/18 months	Opt Stage III	187
GOG-52 (1981)	Cisplatin 100 mg/m2 q 3 weeks x 6	Cisplatin 75 mg/m2 Tax 135 mg/m2 (24 hr) q 3weeks x 6	Opt stage III	349
GOG-104 (1988)	Ctx 600 mg/m2 IV Cisplatin 100 mg/m2 IV q 3 weeks x 6	Ctx 600 mg/m2 IV Cisplatin 100 mg/m2 IP q 3 weeks x 6	Opt Stage III	298*
GOG-114 (1992)	Tax 135 mg/m2 (24 hr) IV Cisplatin 75 mg/m2 IV q 3weeks x 6	Carbo AUC 9 IV 2 cycles + Tax 135 mg/m2 (24 hr) IV Cisplatin 100 mg/m2 IP q 3weeks x 6	Opt Stage III	462
GOG-158 (1995)	Tax 135 mg/m2 (24 hr) Cisplatin 75 mg/m2 q 3weeks x 6	Tax 135 mg/m2 (3 hr) Carbo AUC 7.5 mg/m2 q 3weeks x 6	Opt Stage III	792
GOG-172 (1998)	Tax 135 mg/m^2 (24 hr) IV Cisplatin 75 mg/m^2 IV q 3 weeks x 6	Tax 135 mg/m^2 (24 hr) IV Cisplatin 100 mg/m^2 IP Tax 60 mg/m^2 IP day 8 q 3weeks x 6	Opt stage III	415

* Includes patients enrolled through GOG institutions only.

Eight GOG Randomized Trials involving patients with recently diagnosed, suboptimally debulked advanced epithelial ovarian cancer

Study Identifier	Control Regimen	Experimental Regimen	Target population	N of patients
GOG-22* (1976)	Ctx 500 mg/m2 Dox 50 mg/m2 q 3 weeks x 18	Mel 7 mg/m2 +/- Hex 150 mg/m2 q 4 weeks x 18	Subopt stage III-IV	328
GOG-47 (1979)	Ctx 500 mg/m2 Dox 50 mg/m2 q 3 weeks x 8	Same regimen with cisplatin 50 mg/m2	Subopt stage III-IV	423
GOG-60 (1982)	Cisplatin 50 mg/m2 CTX 500 mg/m2 Dox 50 mg/m2 q 3 weeks x 8	Same regimen with BCG	Subopt Stage III-IV	411
GOG-97 (1986)	Cisplatin 50 mg/m2 Ctx 500 mg/m2 q 3 weeks x 8	Cisplatin 100 mg/m2 Ctx 1000 mg/m2 q 3 weeks x 4	Subopt stage III-IV	458
GOG-111 (1990)	Ctx 750 mg/m2 Cisplatin 75 mg/m2 q 3 weeks x 6	Tax 135 mg/m2 (24 hr) IV Cisplatin 75 mg/m2 q 3weeks x 6	Subopt stage III-IV	386
GOG-132a (1992)	Cisplatin 100 mg/m2 q 3 weeks x 6	Cisplatin75 mg/m2 Tax 135 mg/m2 (24 hr) q 3weeks x 6	Subopt stage III-IV	401
GOG-132b (1992)	Same as GOG-132a	Tax 200 mg/m2 (24 hr) q 3weeks x 6	Subopt stage III-IV	213
GOG-152 (1994)	Tax 135 mg/m2 (24 hr) Cisplatin 75 mg/m2 q 3weeks x 6	Same regimen with interval debulking after the 3rd cycle	Subopt stage III-IV	422
GOG-162 (1996)	Tax 135 mg/m2 (24 hr) IV Cisplatin 75 mg/m2 q 3weeks x 6	Tax 120 mg/m2 (96 hr) IV Cisplatin 75 mg/m2 q 3weeks x 6	Stage IV	280

* Combines melphalan +/- hexamethylmelamine into one treatment group.

Who/what do these analyses include?

Includes patients deemed eligible following GOG central pathology and surgical management review.

Excludes patients enrolled with recurrent disease even though they were eligible for some early trials

Includes patients regardless of compliance with their randomized study regimen.

Includes follow-up beyond the final study report.

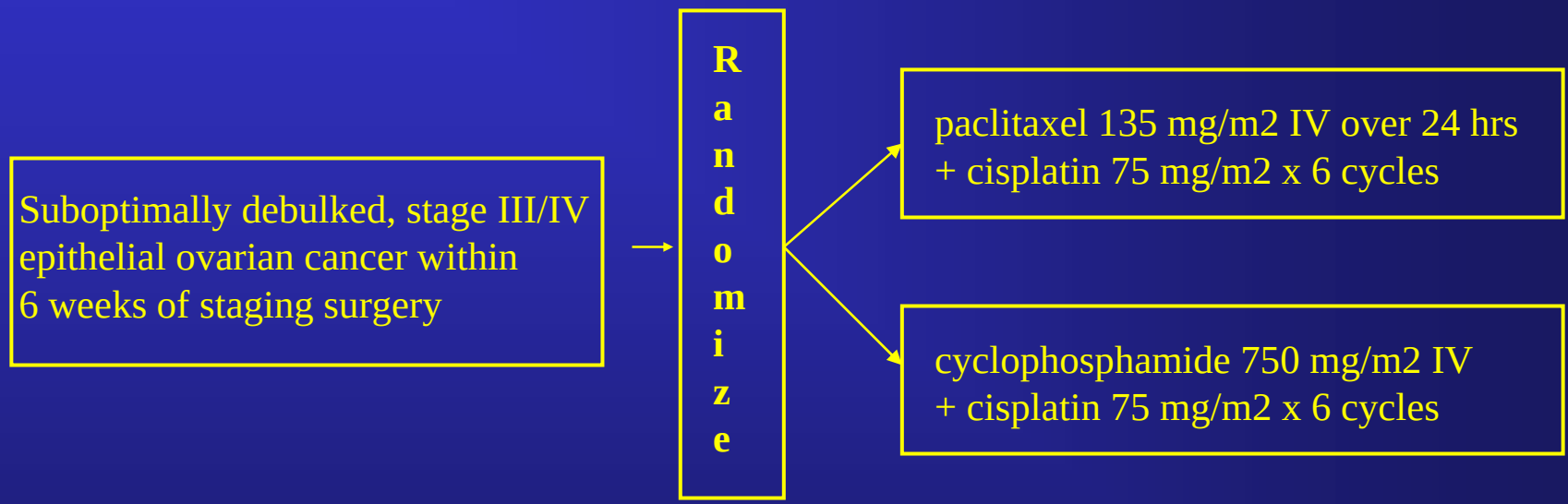
Summary of data available for these analyses

5826 Patients involved in

14 Randomized clinical trials assessing

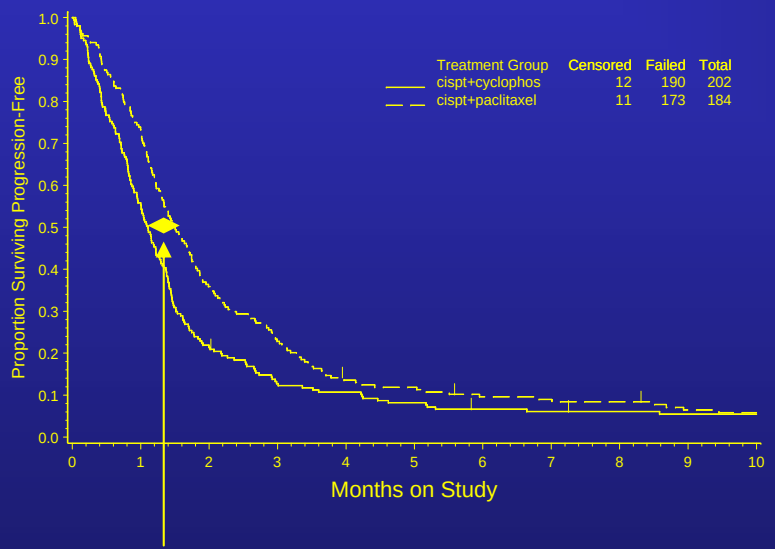
30 First-line treatment regimens

Schema for GOG Protocol 111



Progression-Free and overall survival by randomized treatment on GOG-111

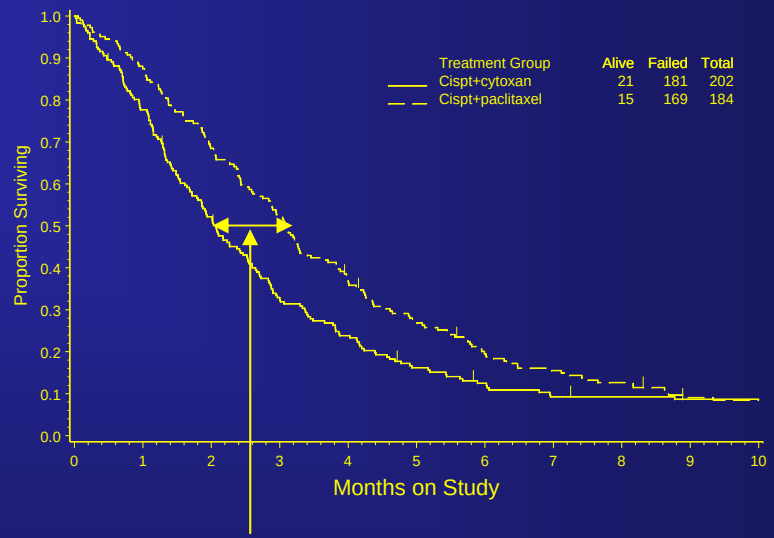
Progression-Free Survival



18.0 - 13.3 = 4.7 months

RH_{pfs} = 0.733

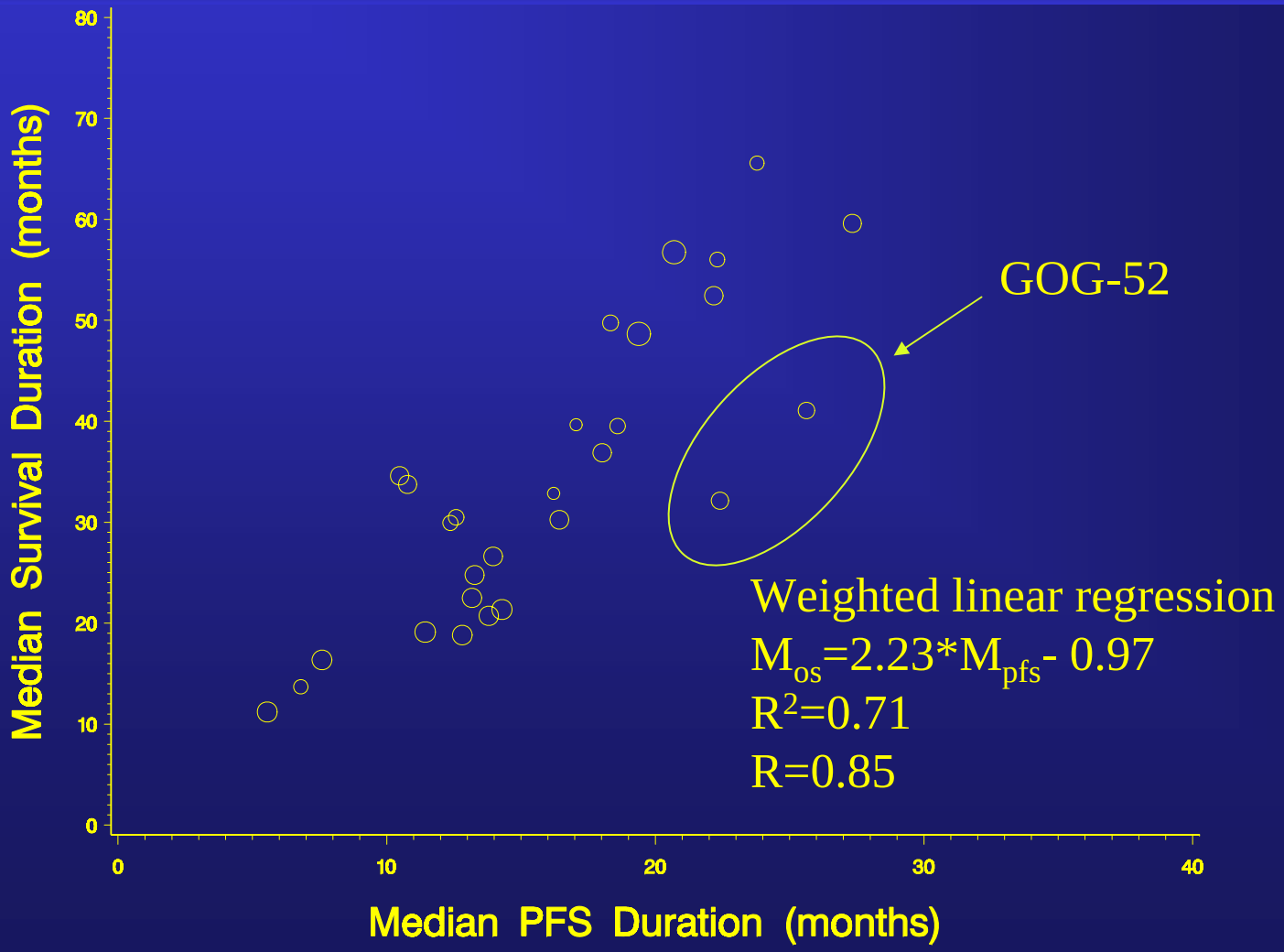
Overall Survival



36.9 - 24.8 = 12.1 months

$RH_{survival}$ = 0.745

Study arm-level of evidence: Median Progression-Free and overall survival



Trial-level evidence:
Treatment hazard ratios for PFS and survival
Six trials in advanced, optimally debulked patients

	Treatment Hazard Ratios $\lambda_E(t)/\lambda_C(t)$	
Study identifier	**PFS**	**Survival**
GOG-25	0.821	0.835
GOG-52	0.796	0.835
GOG-104	0.828	0.788
GOG-114	0.829	0.854
GOG-158	0.896	0.931
GOG-172	0.812	0.746

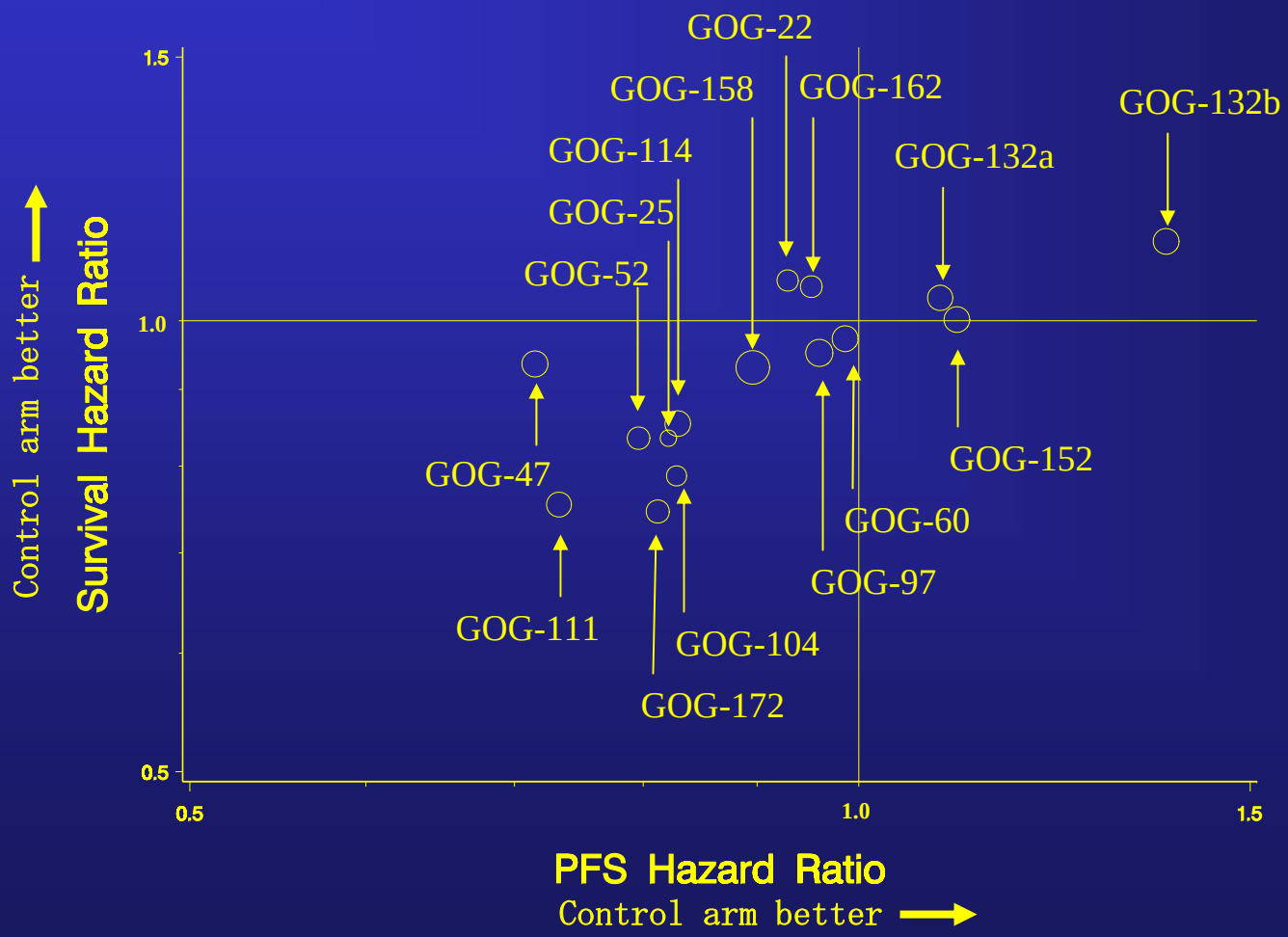
$\lambda_E(t)/\lambda_C(t)$ is the unadjusted ratio of the event rates for the experimental regimen to the control regimen.

Trial-level evidence: Treatment hazard ratios for PFS and survival from eight trials in advanced subopt debulked patients

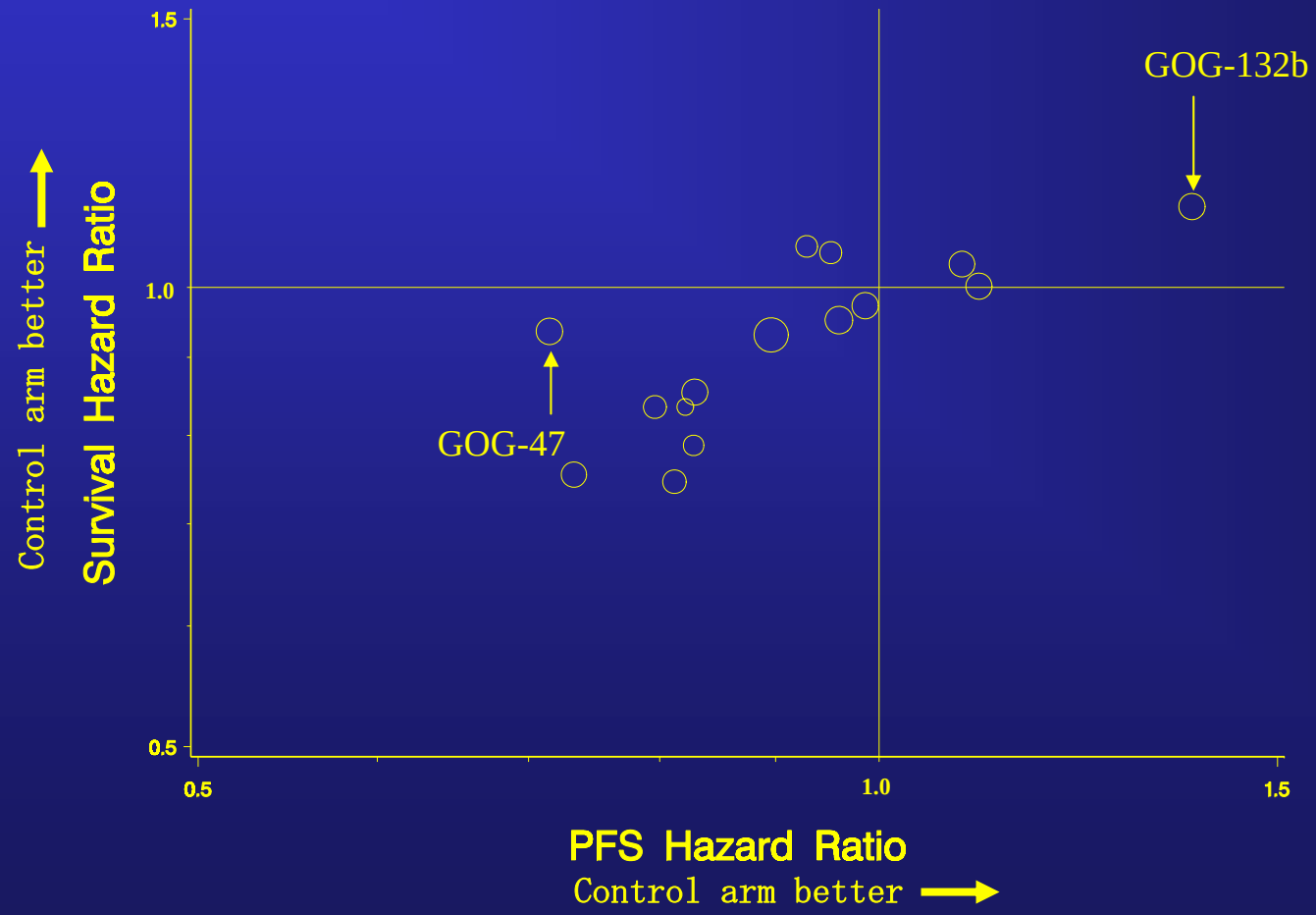
	Treatment Hazard Ratios $\lambda_E(t)/\lambda_C(t)$	
Study identifier	**PFS**	**Survival**
GOG-22*	0.952	1.054
GOG-47	0.715	0.936
GOG-60	0.986	0.973
GOG-97	0.960	0.952
GOG-111	0.733	0.754
GOG-132a	1.09	1.04
GOG-132b	1.39	1.17
GOG-152	1.11	1.00
GOG-162	0.939	1.06

* Two melphalan regimens combined

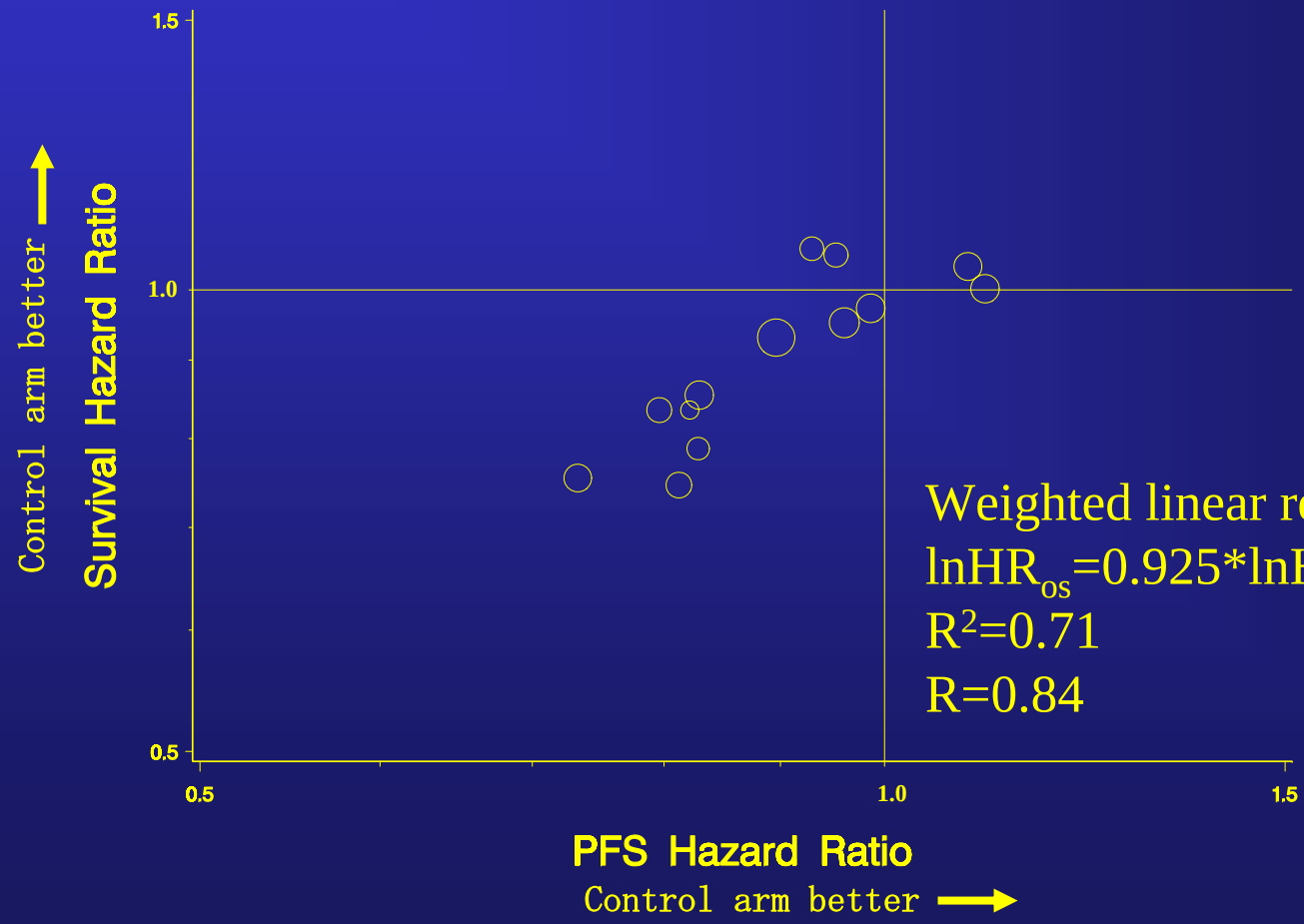
Trial-level evidence:
Treatment hazard ratios for PFS vs Survival



Trial-level evidence:
Treatment hazard ratios for PFS vs Survival



Trial-level evidence: Treatment hazard ratios for PFS vs Survival



Weighted linear regression

$lnHR_{os}=0.925*lnHR_{pfs}- 0.0006$

$R^2=0.71$

$R=0.84$

Patient-level measures of concordance
Optimally debulked, advanced ovarian cancer trials

Study identifier	Kendall's Tau[1]	Median Concordance
GOG-25	0.66	0.82
GOG-52	0.67	0.80
GOG-104	0.70	0.85
GOG-114	0.70	0.83
GOG-158	0.64	0.77
GOG-172	0.66	0.84*

* 12% of patients not classifiable due to recently completed study

[1] Brown et al (1974) procedure for estimating Kendall's Tau for censored data.

Patient-level measures of concordance
Suboptimally debulked advanced ovarian cancer trials

Study identifier	Kendall's Tau[1]	Median Concordance
GOG-22	0.66	0.82
GOG-47	0.67	0.80
GOG-60	0.70	0.85
GOG-97	0.70	0.83
GOG-111	0.64	0.77
GOG-132a	0.66	0.84
GOG-152	0.55	0.77
GOG-162	0.61	0.79

[1] Brown et al (1974) procedure for estimating Kendall's Tau for censored data.

Justification for using PFS as a surrogate endpoint

- Increasing disease burden is in the etiologic pathway to death.
- Clinical symptoms sometime accompany progression.
- PFS duration is usually unperturbed by salvage therapies.
- PFS comparisons mature more quickly than survival.

Drawbacks for using PFS as a surrogate endpoint

- The onset of clinical progression depends on assessment timing.
- PFS is susceptible biases due to differential timing of assessments.
- PFS may not capture all of the direct effects of treatment.

The difference between a surrogate and a true endpoint is like the difference between a cheque and cash. You can often get the cheque earlier, but then, of course, it may bounce.

- Stephen Senn, 1997

When PFS and Survival do not agree

- PFS leads to false prediction of survival benefit
  Incomparable assessment times/procedures (Genesense)

- Survival leads to “false” prediction of survival benefit
  Treatment crossover (platinum vs no platinum trials)

Which endpoint?

Conclusion:

Good phase III trial designs in AOC implement procedures that protect the validity of ***both*** PFS and overall survival endpoints.

Protecting the validity of PFS and survival in phase III trials

If PFS is the primary endpoint:

Consider double-blind treatments.

Standardize the schedule and procedures for disease assessments.

Observing a small but statistically significant difference may not be enough. Consider:

- Direct clinical relevance of PFS effect size.
- Predicted benefit in the true clinical endpoint.

Interim analyses based on PFS should also consider the interpretability of 2ndary endpoints, (ie survival).

Protecting the validity of PFS and survival in phase III trials

If survival is the primary endpoint:

- Evaluate the potential for treatment crossover