Clinical Trial Endpoints for Regulatory Approval

First-Line Therapy for Advanced Ovarian Cancer

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Options for Endpoints
First-Line Trials in Advanced OVCA

- Overall Survival: gold standard
- Disease Progression
  - Objective
  - CA125
  - Composite
- "Symptom-free" period or other QoL measure

Gynecologic Cancer Intergroup Consensus Statements

Two statements pertinent:

From Trial Methodology; Endpoints statement:

Advanced first-line – Both PFS and OS are important endpoints to understand the full impact of any new treatment. Thus either may be designated as the primary endpoint. Regardless of which is selected, the study should be powered so both PFS and OS can be appropriately evaluated.

From Standard Approaches: Post-progression therapy statement:

Although overall survival is an important endpoint, progression free survival may be the preferred primary endpoint for trials assessing the impact of 1st line therapy because of the confounding effect of the post-recurrence/progression therapy on overall survival. When progression free survival is the primary endpoint, measures should be taken to protect the validity of analysis of overall survival.

Focus for this Presentation: Progression Free Survival

- *Potential arguments in favour of PFS as endpoint for regulatory approval*:
  1. Its validity as a surrogate for overall survival
  2. The impact on survival of post-progression therapy
  3. Its value as an indicator of time without disease symptoms
- *Potential pitfalls in use of PFS*

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Progression Free Survival:
1. Surrogate for Overall Survival?

- Evidence:
  - Meta-analyses (Buyse)
  - Other trial results: hazard ratio relationships
  - Disease–related symptoms: inference

Relationship between PFS and OS: Recent front-line RCTs in OVCA

Trial (experimental vs standard)	**HR PFS**	**HR OS**

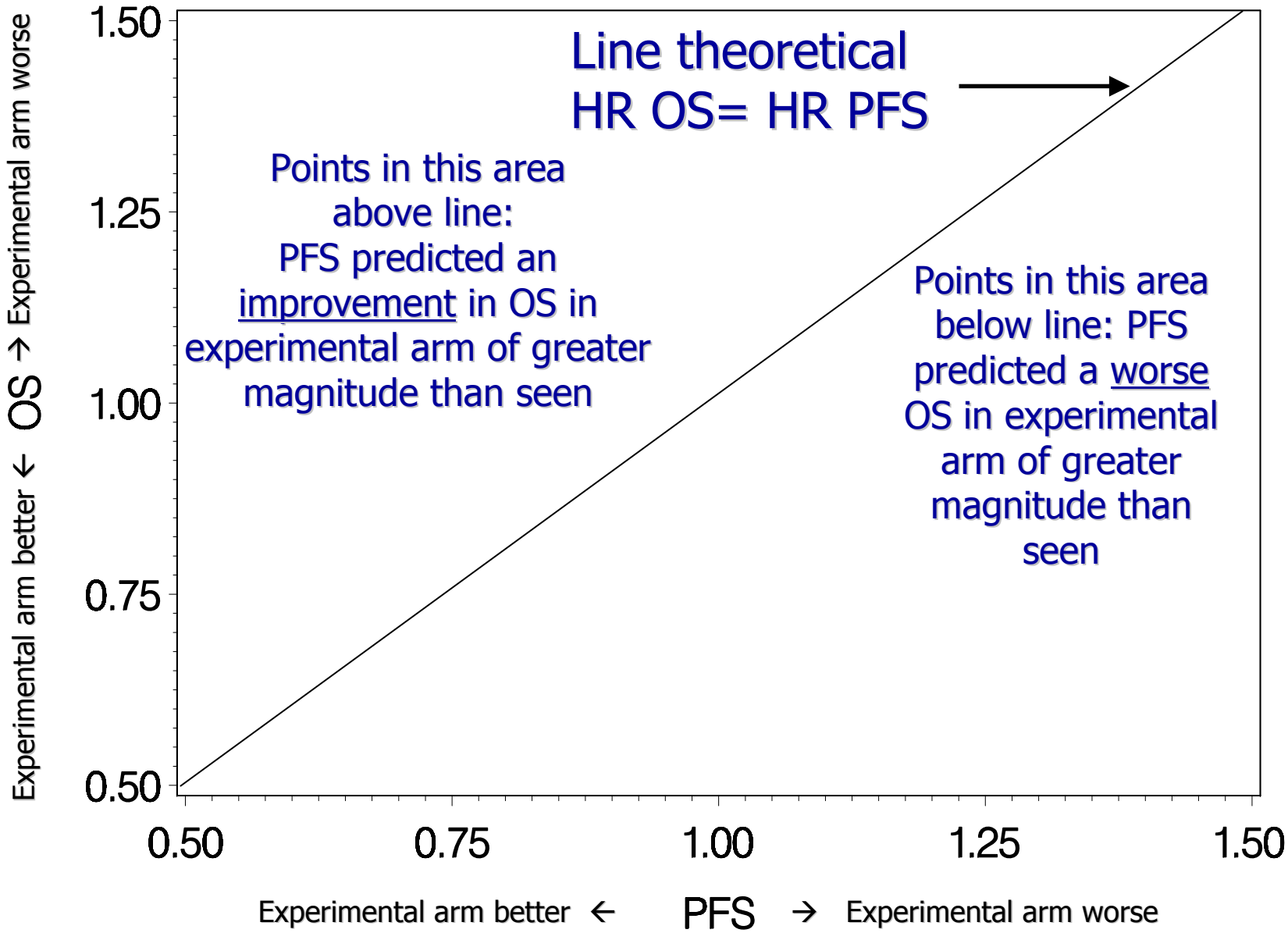
HR < 1: experimental arm “better”
HR > 1: standard arm “better”

Relationship between PFS and OS: Recent front-line RCTs in OVCA

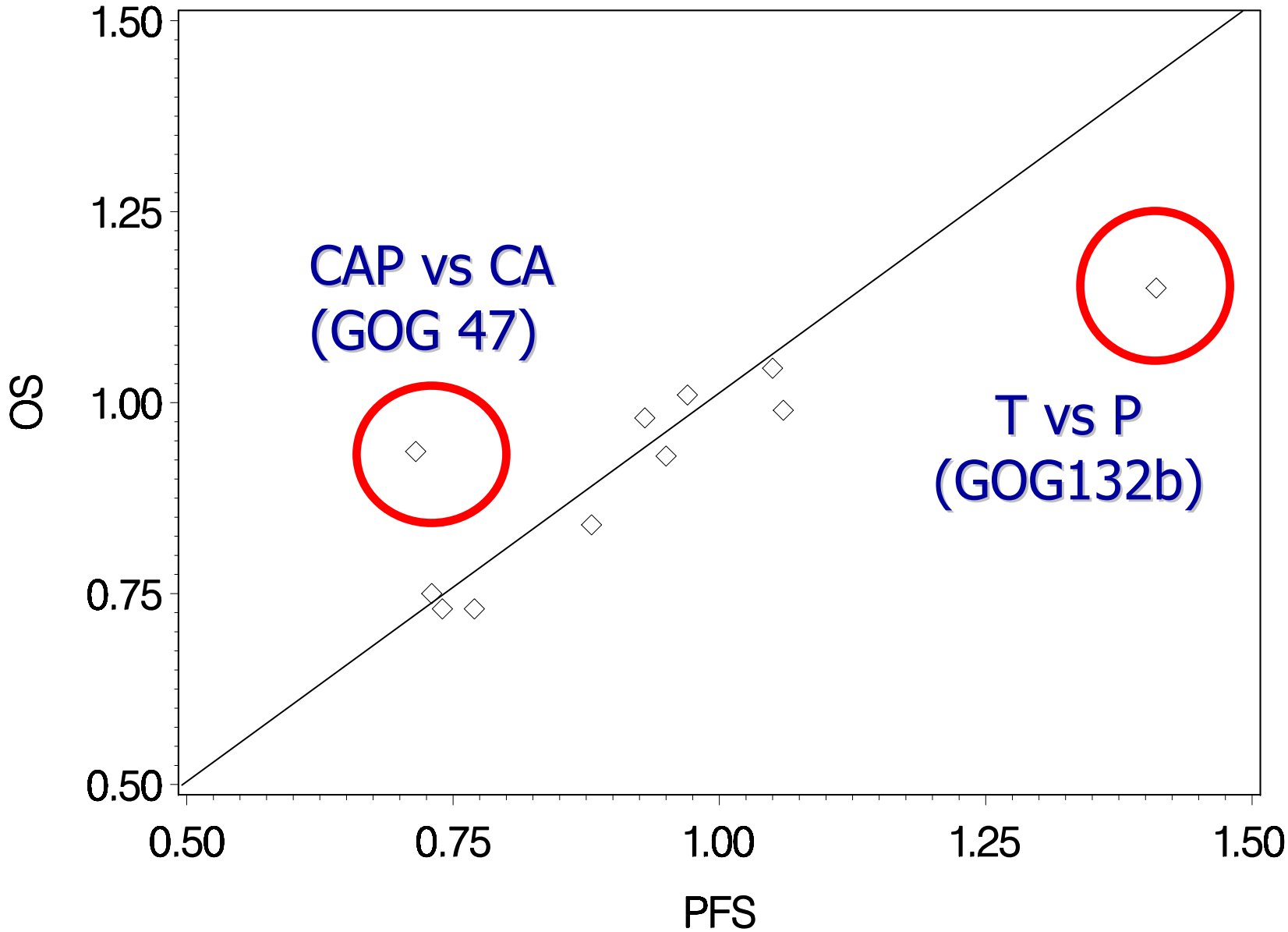
Trial (experimental vs standard)	**HR PFS**	**HR OS**
GOG 47 CAP vs CA	*0.715*	*0.936*
GOG 158: TC vs TP	0.88	0.84
GOG 132: TP vs P	1.06	0.99
GOG 132: T vs P	1.41	1.15
AGO: TEC vs TC	0.95	0.93
GOG 172: IP TP vs IV TP	0.77	0.73
AGO: TC vs TP	1.05	1.045
AGO: TC topo vs TC	0.97	1.01

Maybe this is easier to "read" graphically!

Hazard ratio of PFS vs OS within trials



HR of PFS vs OS: Data from Table



Summary of Results Across Trials: PFS HR *vs* OS HR

- Hazard ratios of PFS and OS similar within trials suggesting strong relationship between behaviour of PFS and OS
- These data support the argument that: PFS is a surrogate for OS in 1st line OVCA
  - *Exception*: trial(s) where one arm does NOT contain platinum. In this case(s) salvage platinum therapy seems to overcome PFS disadvantage in the non-platinum arm to render survival similar.

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Progression Free Survival:
2. PFS useful since post-PD therapy obscures OS effect

- This argument is weakened by data just shown:
  - With the exception of administration of 2nd-line platinum (when it was not given 1st-line), other therapies do not seem to have obliterated the relationship between PFS and OS
  - Nonetheless, this is a theoretical possibility if:
    - New treatment in experimental arm is very active
    - Therapy after relapse is not balanced; a high proportion of standard arm patients get new therapy at relapse
  - Should not be issue if pattern of second-line care is similar between study arms

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Progression Free Survival:
3. PFS useful since it is a marker for time without disease symptoms

- In front-line OVCA, most patients respond to therapy
- At the end of treatment about 50-60% have either continuing NED or CR, and are thus clinically/radiologically disease free.
- Median time between end of therapy and progression is ~10-12 months

  (Calculated by subtracting median duration of therapy of 5-6 mo from median PFS of 16-18 mo)

Progression Free Survival:
3. PFS useful since it is a marker for time without disease symptoms (2)

- A long interval between the end of therapy and progression may be meaningful in its own right if, as is inferred, the majority of patients are without symptoms of disease for that period.
- Direct evidence to support this is not available:
  - data supporting this hypothesis may be found by mining disease symptom content of QoL information in many existing trials

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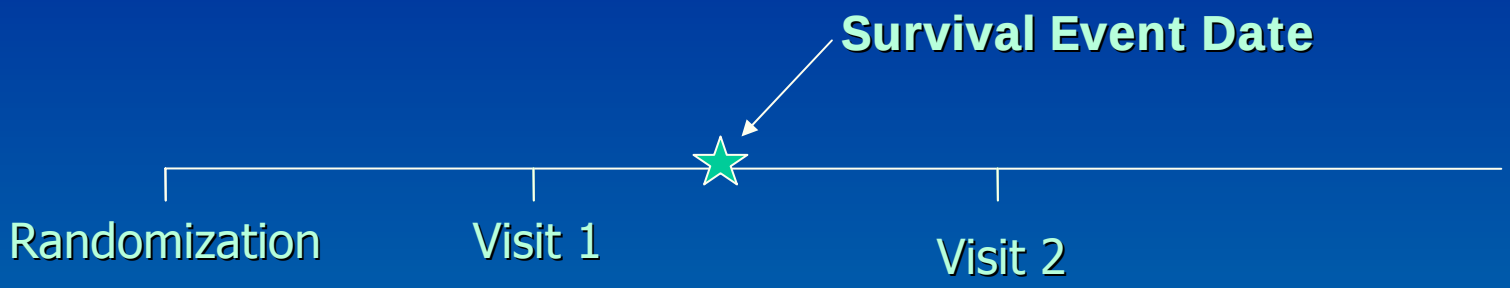
- ***Potential pitfalls in use of PFS***

Potential Pitfalls in Measuring PFS

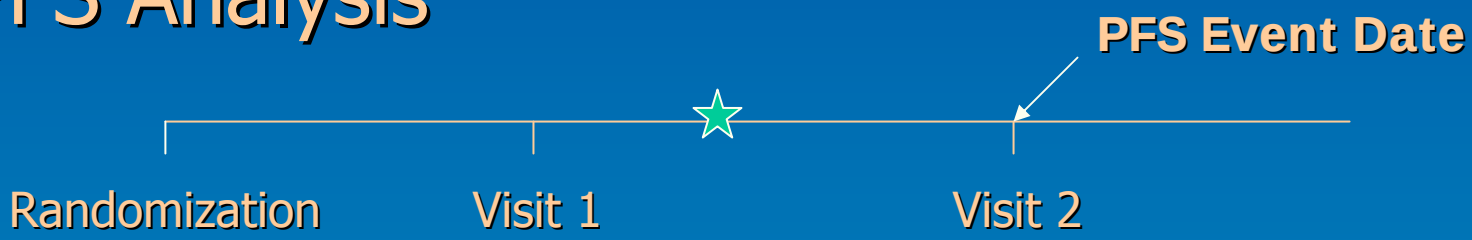
- Survival
  - only one date/one event possible
- Progression: Objective/CA125
  - *Sensitive to timing of investigation*
  - *Several Definitions*.
    - GCIG has adopted RECIST (objective) and own CA125 definitions (for front-line)

Determining Event Dates

Survival Analysis



PFS Analysis

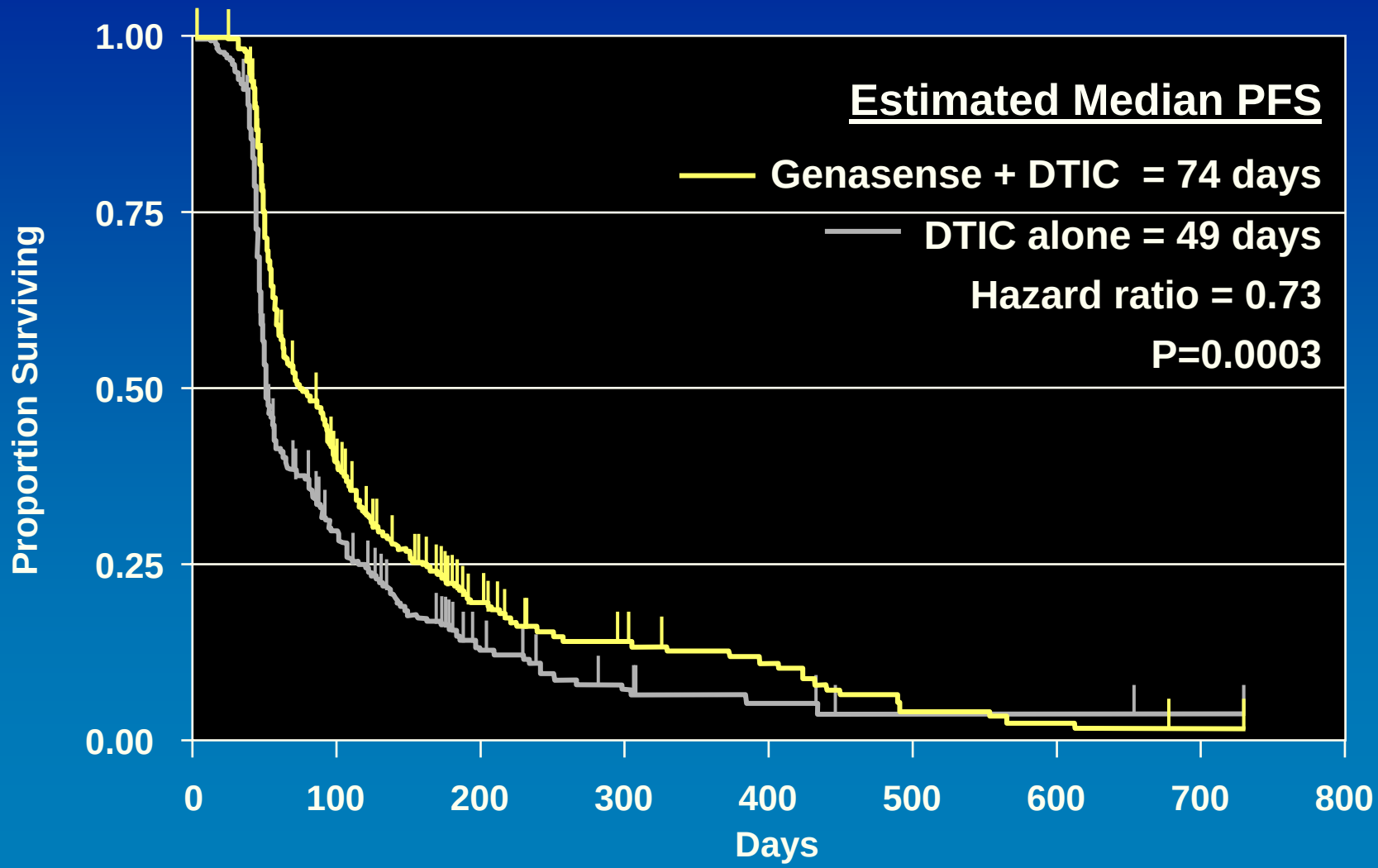


= Date of Death or actual tumor progression

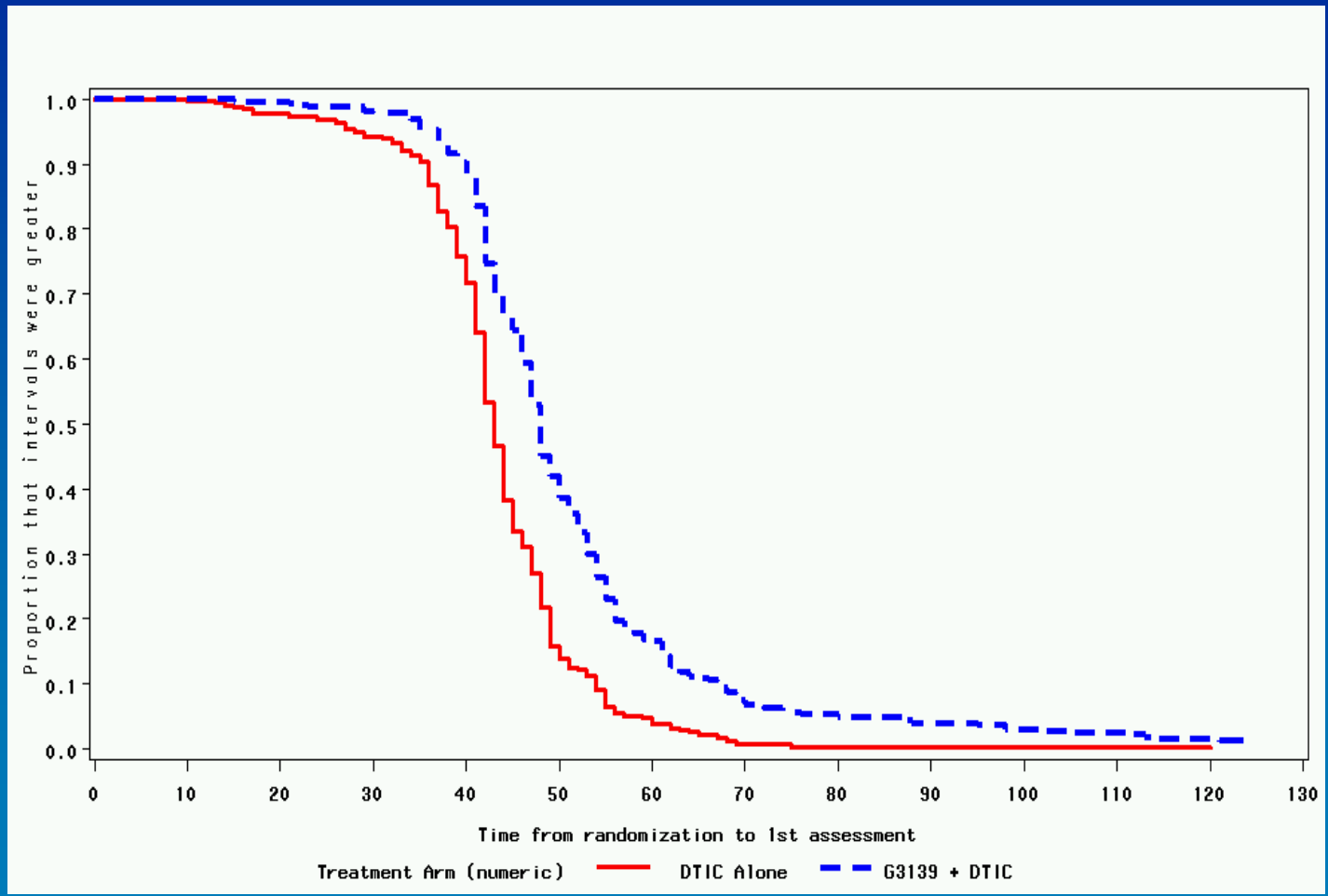
Measuring PFS

- Imbalance in assessment times can lead to apparent difference in PFS!
- Example:
  - Genasense trial in melanoma

Progression-Free Survival

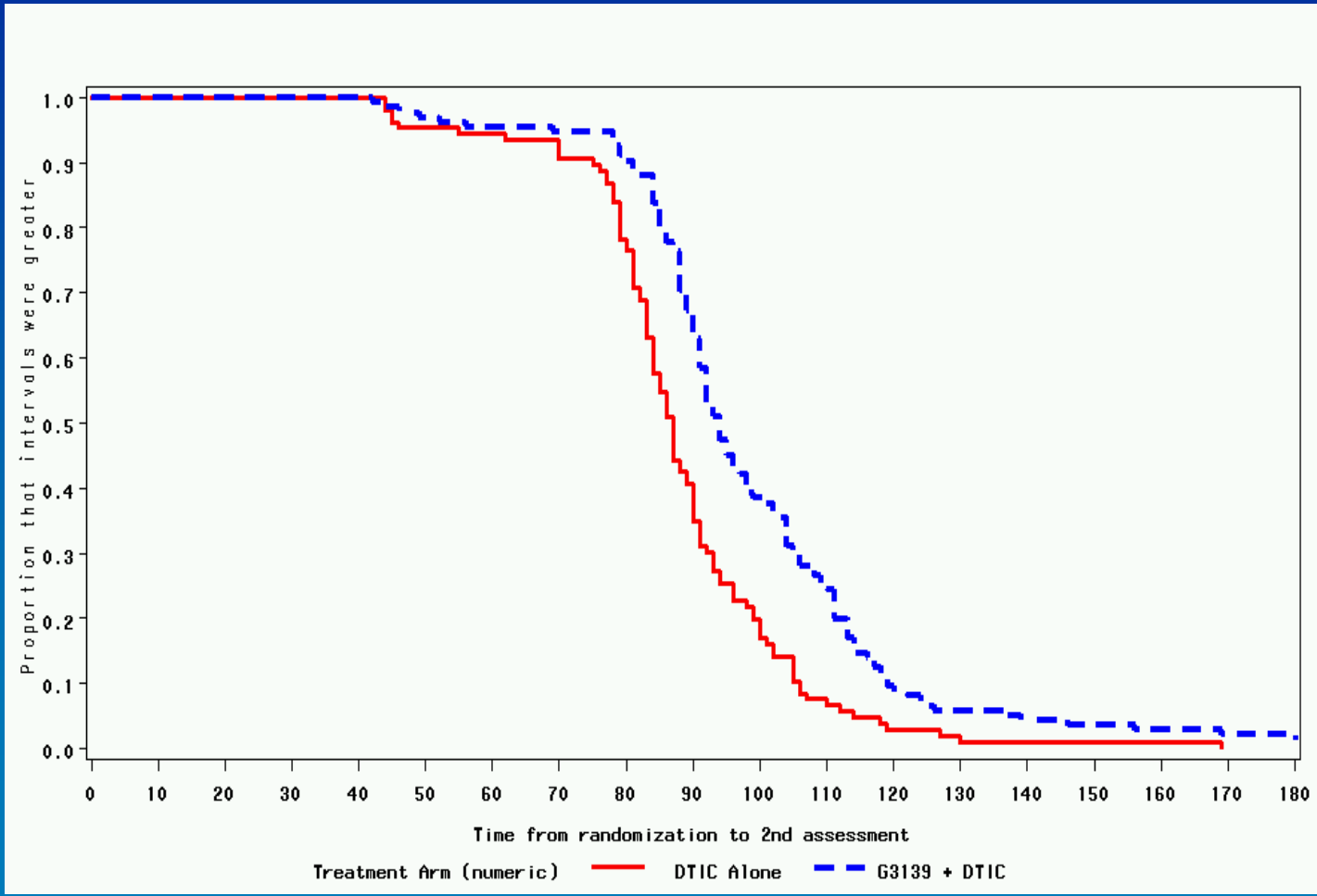


Time to 1st Assessment (Trial Data)



From presentation of FDA review of Genasense data. ODAC meeting May 2004

Time to 2nd Assessment (Trial Data)



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Pitfalls in Measuring PFS: Timing of Investigations

This issue is most problematic when small absolute improvement in PFS is being sought since then *the interval of improvement ≈ the interval of assessment*

Standard arm PFS (Months)	Experimental arm hypothesis (Months)	Absolute increase (Months)	%
3	4	1	33%
6	8	2	33%
9	12	3	33%
12	16	4	33%
18	24	6	33%

Not likely to be a relevant issue in *first-line* trials

Potential Pitfall: Definitions of Progression

- Objective (RECIST or WHO):
  - Basis of PD definition for historical data that supports PFS as surrogate for OS
  - Problem in measuring PD in patients who have non-measurable disease AND who do not have CR
- CA125:
  - More recently defined. Use is increasing in trials
- Many recent protocols assign PD date based on which of CA125 or objective PD occurs first.
- *What is impact of this on relationship of PFS to OS?*

Summary:
Endpoints for Regulatory Approval in First-line Advanced OVCA

- Overall survival is gold standard and trials should be powered to assess it.
- Nevertheless, Progression Free Survival is also appropriate endpoint for regulatory approval:
  - Good evidence it is surrogate for OS
  - Second-line therapy appears to have little impact but it could if highly active post-progression treatment is substantially imbalanced in randomized arms
  - PFS may also correlate with freedom from disease related symptoms (need data here)

Summary (2): Endpoints for Regulatory Approval in First-line Advanced OVCA

- Potential pitfalls of PFS:
  - Sensitive to timing of investigation
    - This is unlikely to be relevant in first-line trials but may be more so in second-line
  - PFS definitions shifting to incorporate CA125.
- **Questions to be addressed:**
  - Does PFS correlate with freedom from symptoms?
  - Does use of CA125 to define PD change the relationship of PFS to OS?