Defining clinical and statistical improvement in consolidation or maintenance single-arm trials in Oncology

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What is consolidation /maintenance therapy?

- Patients are in Complete Response and the goal is to extend Progression Free Survival

- “Maintenance therapy” : using the same treatment continued until progression,

- “Consolidation therapy” using the same or a different treatment continued for a fixed period of time and then discontinued.

Background
Why is consolidation therapy useful?

- Treatment options are moving beyond classic cytotoxic chemotherapy to
  - novel hormones,
  - immune interventions, and
  - biologic agents.

- Offer the possibility of a non-toxic maintenance or consolidation therapy after they have achieved their 1st or 2nd remission.
- Toxicity should not outweigh benefit

Consolidation treatment in ovarian cancer

- 2nd remission population (as opposed to 1st) better suited to evaluate consolidation strategies
  - subjects = events
  - PFS is short (10 -12 months)
- Standard of care is observation (nothing else available)
- Fast accruing studies / Screen agents faster

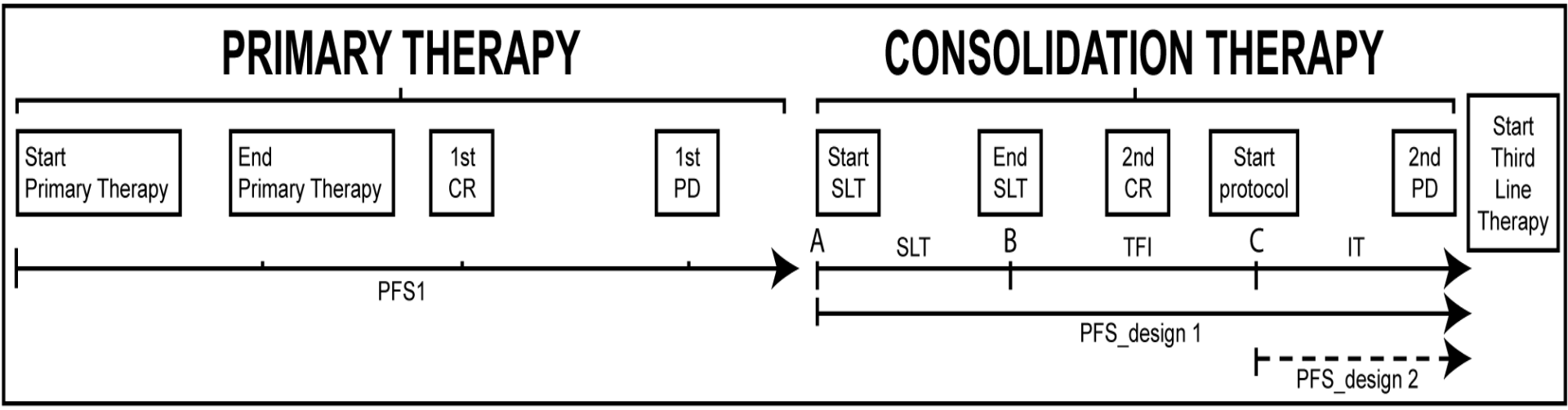
Purpose:
Extend PFS in Consolidation Single-arm Phase II Trials

- Endpoints (Response Rate is not appropriate)
- Meaningful improvement in PFS:
  - Historical data (single arm)
  - Patient population (in CR/PR or SD)
  - Statistical power

Questions

1. Where should we start time 0 for Progression-Free-Survival ?

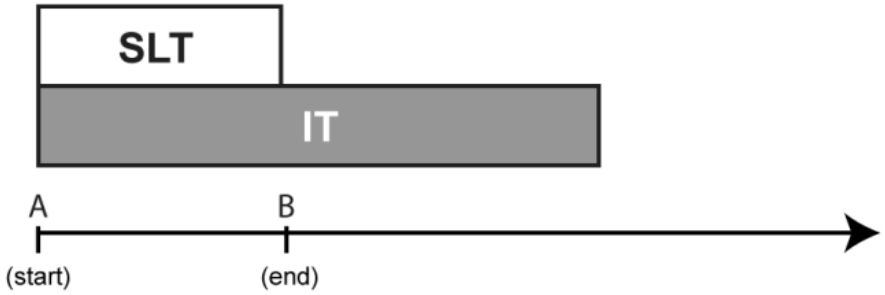
2. What represents a meaningful efficacy result from single-arm, non- comparative Phase II trials before committing to move on to a large Phase III trial?



Dizon DS, Hensley M, et al, JCO 2002

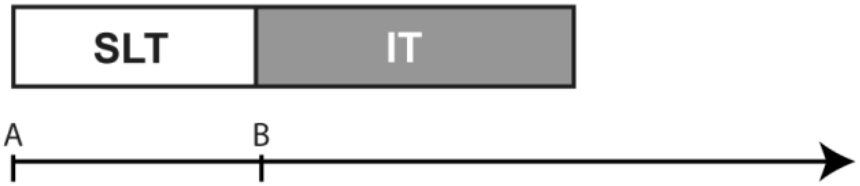
STRATEGY 1:

SLT and IT are given concurrently



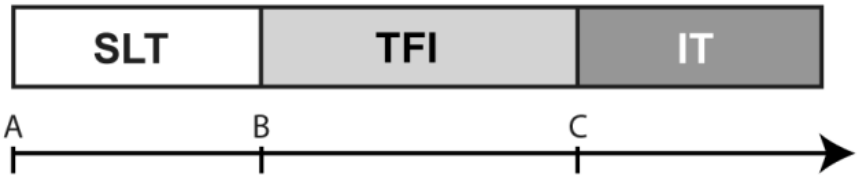
STRATEGY 2:

IT is given immediatly after the end of SLT



STRATEGY 3:

IT is given after a treatment free interval (TFI) has elapsed after the end of SLT



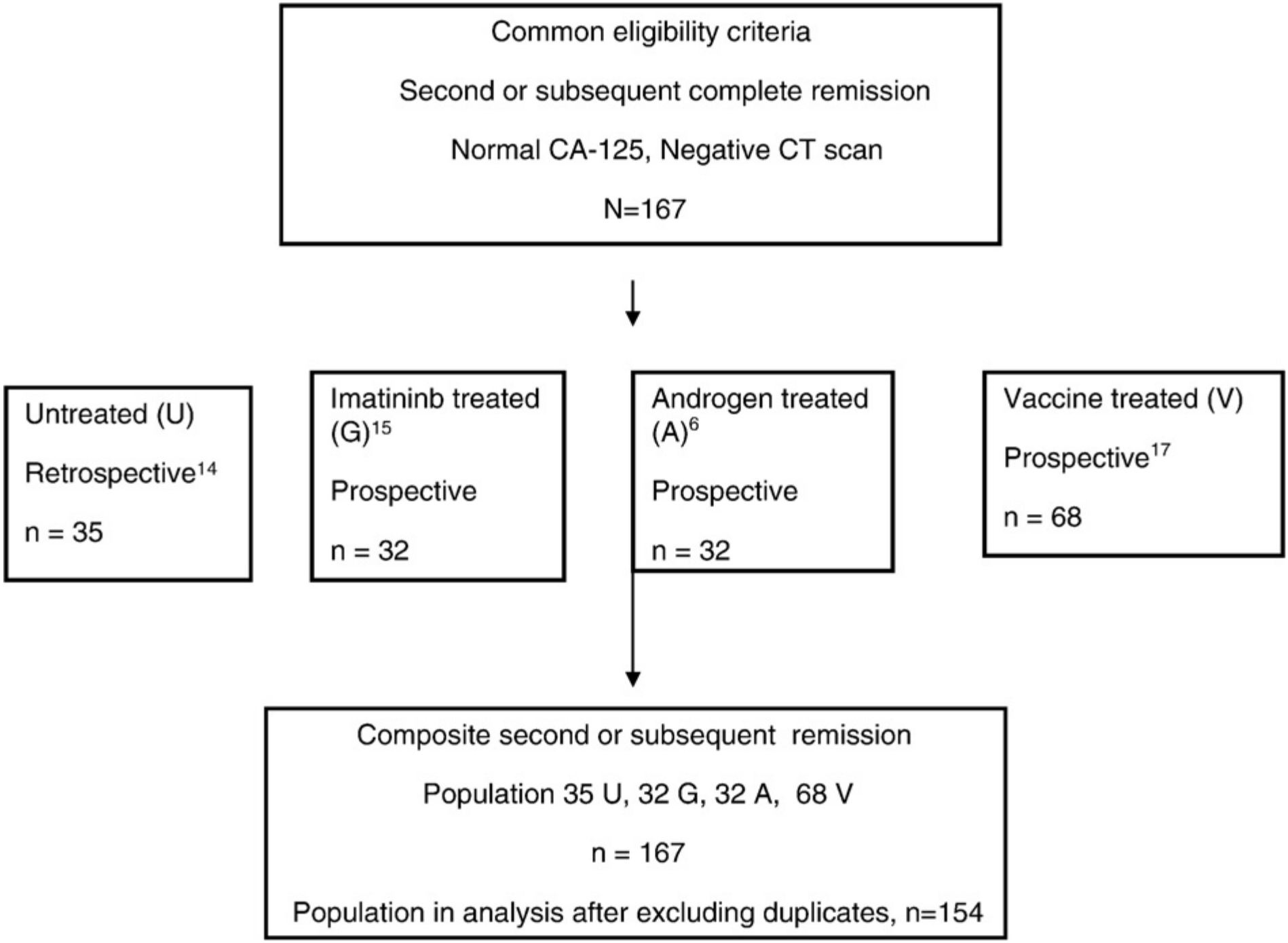
Lessons learned from MSKCC trials

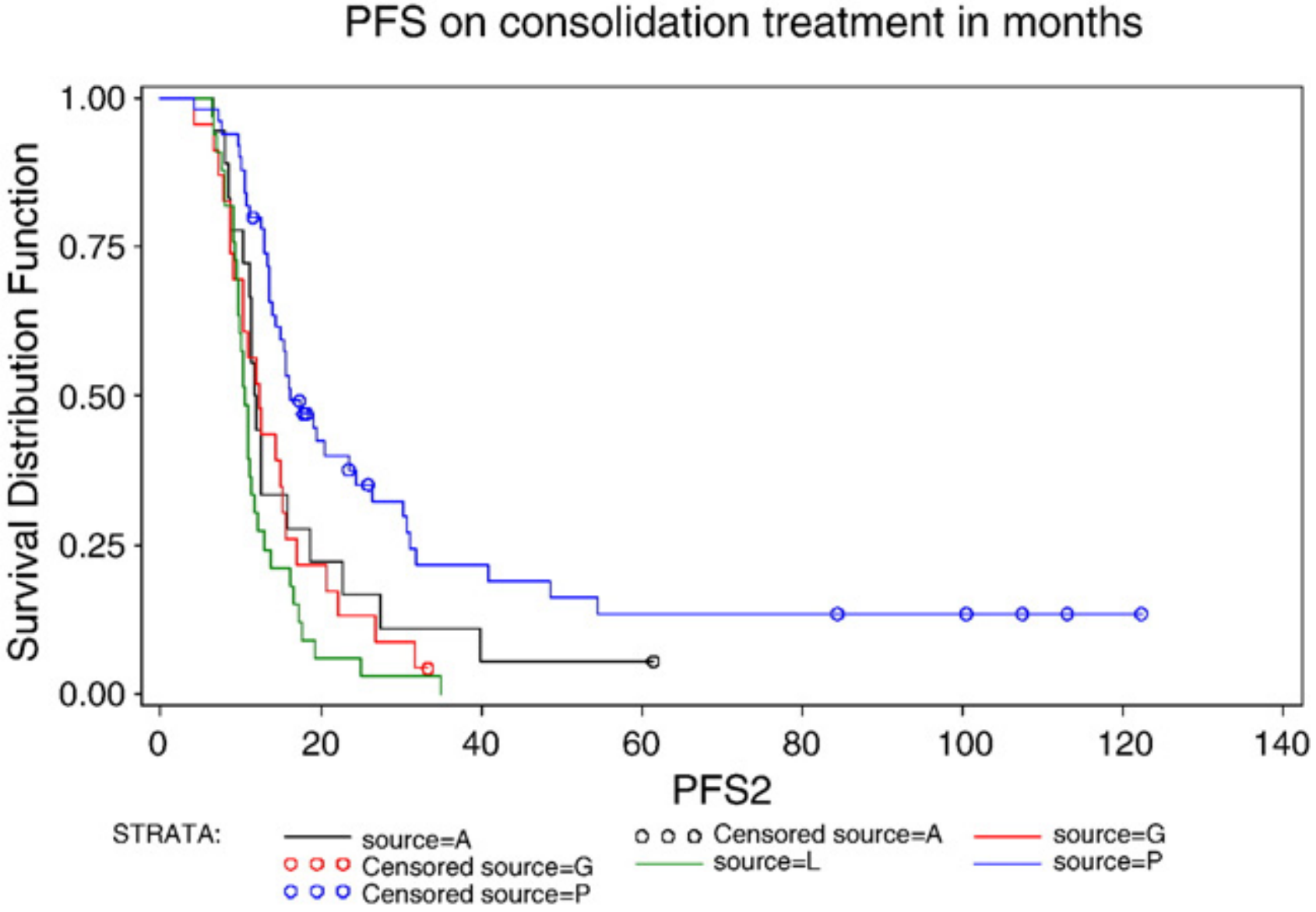
1) A phase II trial of goserelin (3.6 mg subcutaneously q 4 weeks) and bicalutamide (50 mg orally daily) enrolled 35 patients.
   - Median PFS was 11.8 mos (95% CI: 10.6 – 13.2 mos) [Levine D 2007]

2) A phase II trial of imatinib (Gleevec) given at 400mg daily orally enrolled 35 patients.
   - Median PFS was 12.1 mos (95% CI: 9.4 – 15.5 mos) [Juretzka M 2008].

3) an untreated population of 35 patients [Harrison ML 2007]
   Median PFS was 10.7 months (95% CI: 9.3–12.2 months).

4) A series of 6 phase I trials enrolling 68 patients evaluated monovalent or heptavalent conjugate antigen vaccine constructs mixed with an adjuvant. The duration of the second PFS for the composite vaccine population was
   - 16.1 months (95% CI: 13.6-24.2 mos) [Sabbatini P 2010]


Common eligibility criteria
Second or subsequent complete remission
Normal CA-125, Negative CT scan
N=167
Untreated (U)
Retrospective[14]
n = 35
Imatininb treated (G)[15]
Prospective
n = 32
Androgen treated (A)[6]
Prospective
n = 32
Vaccine treated (V)
Prospective[17]
n = 68
Composite second or subsequent remission
Population 35 U, 32 G, 32 A, 68 V
n = 167
Population in analysis after excluding duplicates, n=154

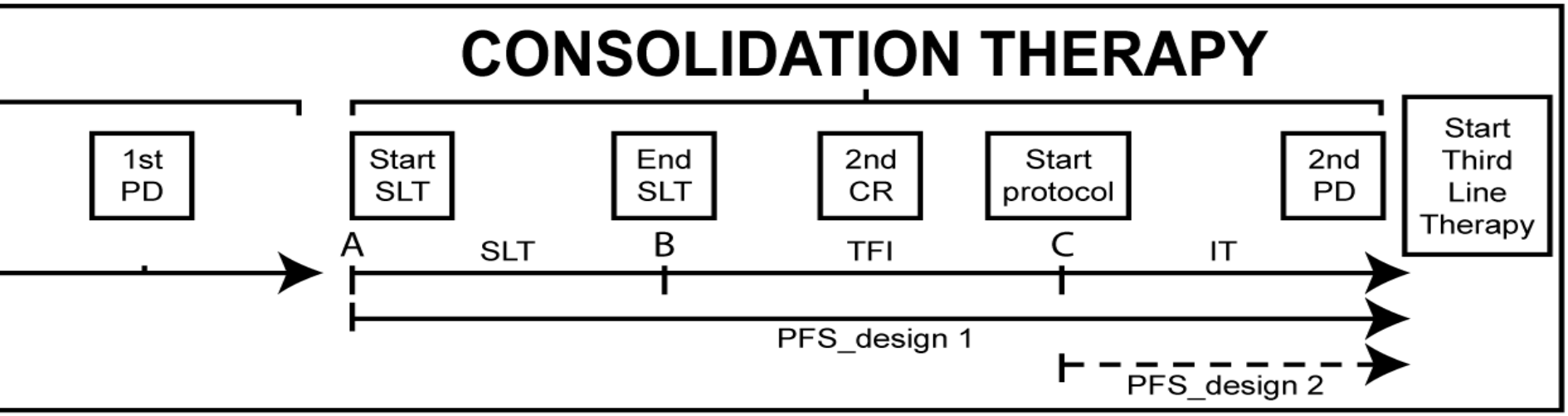

PFS on consolidation treatment in months
Survival Distribution Function
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
100
120
140
PFS2
STRATA:
source=A
Censored source=G
Censored source=P
Censored source=A
source=L
source=G
source=P

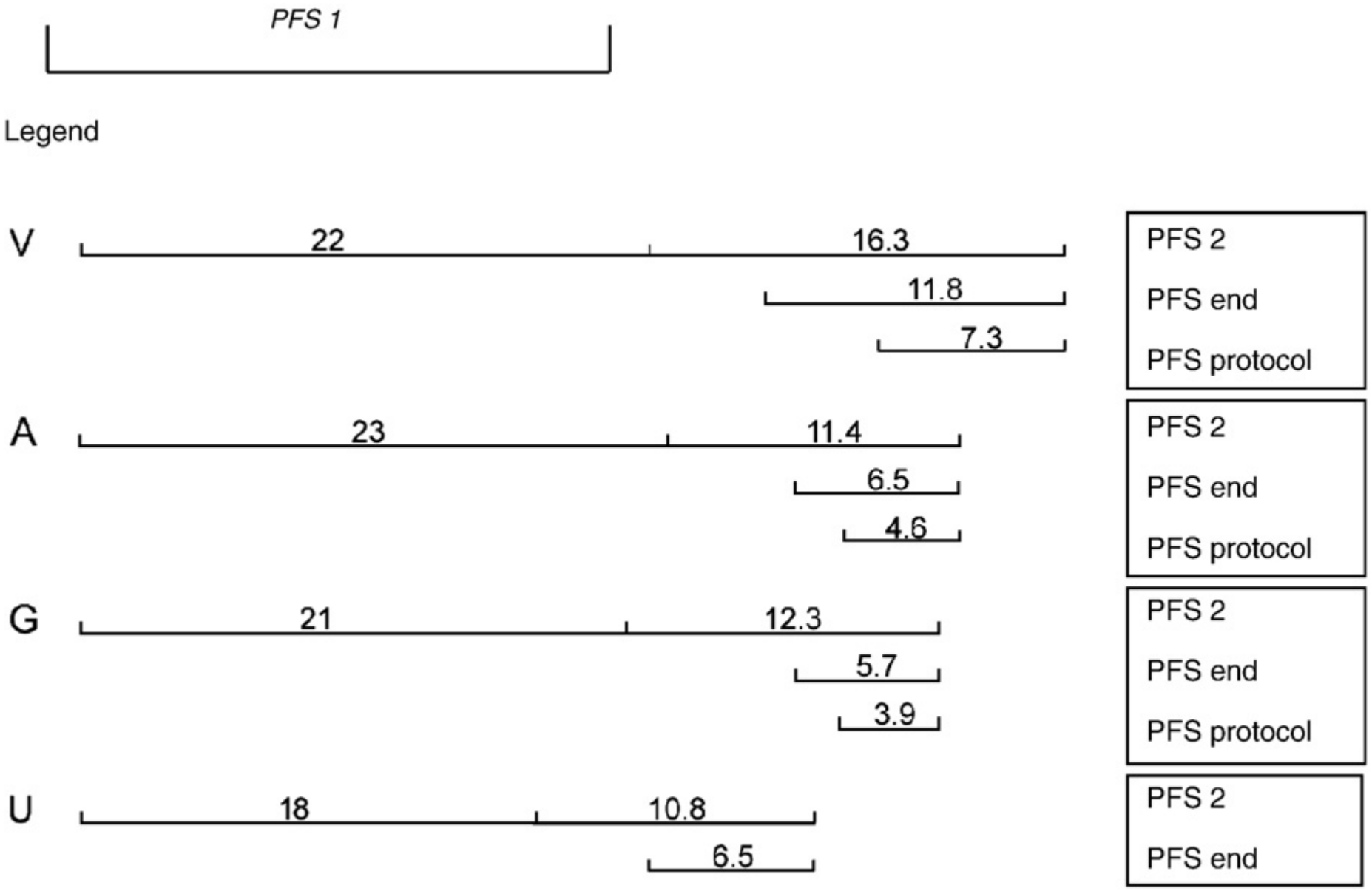
Lessons learned

- Standard definitions of PFS includes the duration of SLT:

  median SLT 4.5 mos (IQR 3.6 – 5.9; 13% had >8 months).

  median Trt Free Interval 2.5mos (range: 0.3 – 45)


CONSOLIDATION THERAPY
1st PD
Start SLT
End SLT
2nd CR
Start protocol
2nd PD
Start Third Line Therapy
A
SLT
B
TFI
C
IT
PFS_design 1
PFS_design 2


PFS 1
Legend
V
22
16.3
11.8
7.3
PFS 2
PFS end
PFS protocol
A
23
11.4
6.5
4.6
PFS 2
PFS end
PFS protocol
G
21
12.3
5.7
3.9
PFS 2
PFS end
PFS protocol
U
18
10.8
6.5
PFS 2
PFS end

Multivariate analysis
[Sabbatini et al 2010, Gyn Oncology]

Table 2
Multivariate analysis (patients in second complete remission with non-missing values).

Covariate	HR (95% CI)	*p*-value	Reference group
Duration of PFS 1			
PFS 1 (<12 months)	3.5 (1.6–7.8)	0.0024	PFS 1 (>18 months)
PFS 1 (12–18 months)	1.7 (1.03–2.9)		PFS 1 (>18 months)
Source population			
Imatinib (G)	1.6 (0.9–3)	0.0027	Vaccine (V)
Androgen (A)	1.6 (0.9–2.9)		Vaccine (V)
Untreated (U)	3.0 (1.7–5.5)		Vaccine (V)
Low stage	0.5 (0.2–1.03)	0.0595	High stage
Optimal debulking	0.6 (0.3–0.99)	0.0473	Suboptimal
Serous histology	1.2 (0.3–4.4)	0.0954	Other histology
Endometrioid histology	0.6 (0.16–2.6)		
Grade 3	1.6 (0.96–2.5)	0.0726	Grade 1–2

Objective

- We wanted to design a Ph III comparative study to show that vaccines are efficacious

- Goal is to derive meaningful historical estimates from single-arm trials to use in the design of Ph III study.

Efficacy estimates depend on:

- Patient Cohort (eligibility criteria):
  - CR/PR or CR only
  - Some trials enroll patients at the time of recurrence, while others only enroll patients who have achieved CR after the completion of second-line therapy.

  - 2^{nd} or greater CR
    - 3 pts were excluded b/c 1^{st} CR (total sample =32)
    - 23 pts in 2^{nd} CR
    - 9 pts in 3^{rd} CR
    - 1 pt in 7^{th} CR

Illustrate how the sample size is affected by the starting point of IT

We varied the starting point of IT after the start of SLT.

Starting time point of IT	
0 months	starting IT concurrently with SLT (strategy 1)
4.5 mos (6 cycles)	implies starting IT immediately after the end of SLT assuming SLT is given for 6 cycles every 3 weeks (strategy 2)
6 Mos (6 cycles + 6 wks) 7.5 (6 cycles + 12 wks)	starting point allows for a TFI interval of 6 and 12 weeks respectively after the end of SLT (strategy 3)

Design 1	Design 2
Endpoint PFS starting at the start of SLT.	Endpoint PFS starting at the start of IT; includes time on protocol/investigational therapy (IT) only.
Null Hypothesis: PFS follows exponential distribution with median of 9 months	
Alternative Hypothesis: with added treatment at point B (consolidation therapy), there is a new exponential distribution with a larger mean after point B (ie lower but constant hazard).	Alternative Hypothesis: An increase in median PFS from 9 to 13.5 mos is equivalent to 33% hazard reduction.
Power calculations are based on intent to treat analysis since PFS starts at point A; include all eligible patients at the start of SLT.	However, the eligibility criteria at the start of IT for Design 2 include patients who are in CR/PR/SD (ie exclude pts who had early PD). Power calculations are based on conditional analysis at point B or C.

Sample size required under Design 1 (regardless of treatment strategy)

Time of initiating investigational therapy (IT)	33% Hazard Reduction Sample Size (Number of patients entered at the start of SLT, ie point A)	Average number of patients treated at the end of SLT (at point B)
0 mos (at start SLT)	34	34
4.5 mos	67	58
6 mos	84	69
7.5 mos	104	81

Sample size required under Design 2 (regardless of treatment strategy)

Time of initiating investigational therapy (IT)	33% Hazard Reduction Sample Size (Number of patients entered at the start of IT which can be point A, B, C)	Average number of patients ineligible at the start of IT (number of patients to be screened prior to initiation of IT)
0 mos (at start SLT)	34	0 (34)
4.5 mos	34	6 (40)
6 mos	34	8 (42)
7.5 mos	34	10 (44)

Pros /Cons for Design 1

- The results are generalizable to the patient population observed right after first PD
- Historical estimates of PFS are available

- However, all patients must be followed-up from point A, even if a reduced number of patients receive the IT at point B.
    - longer follow-up, larger SS and more resources.

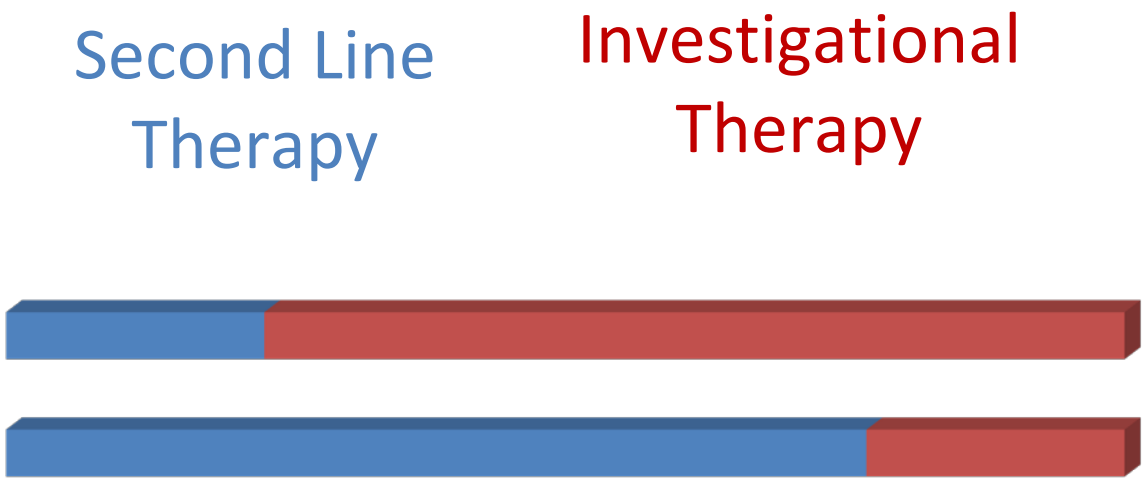
Pros / Cons for Design 2

1. A smaller sample size is needed since the power of the study is not affected by the interval on SLT
2. The time on SLT would affect the number of patients ineligible at initiation of IT (some patients PD), but the increase in SS is minimal.
3. PFS endpoint focuses on the time period during which the hazard is reduced by the IT

Limitations

- lack of historical estimates (ovarian ca)
- Eligibility criteria at the start of SLT allow all comers on study (Design 1), whereas for Design 2 we require patients in CR
- Whether these patients are healthier or patients who robustly responded to SLT cannot adequately be addressed by the design.

Current challenges



- If both strategies have a PFS of 13 months but which strategy warrants a phase III trial?

Conclusions

- The longer the time on SLT, the larger the sample size or the greater the magnitude must be to show an improvement.

- For sample size calculations, a varying SLT and IT start time would compromise statistical power and comparability with historical data from other single-arm Phase II studies.

- As a result, consolidation trials might be underpowered for the primary endpoint.

We recommend that designs of consolidation trials take into account the duration of SLT

- excluding SLT duration from the definition of PFS
- restricting SLT duration per protocol
  - patients achieve CR at variable time points (restrict SLT to 5-6 cycles).
  - the logistics of multicenter trial enrollment
  - allow for a TFI that can range between 2-8 weeks for administrative reasons

THANK YOU

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Joint work with:

- Sabbatini Paul, MD
- Spriggs David, MD
- Thaler Howard, PhD

Iasonos A, Sabbatini P. et al,

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