Dendreon Effect Size Estimates: Impact of Delayed Effect

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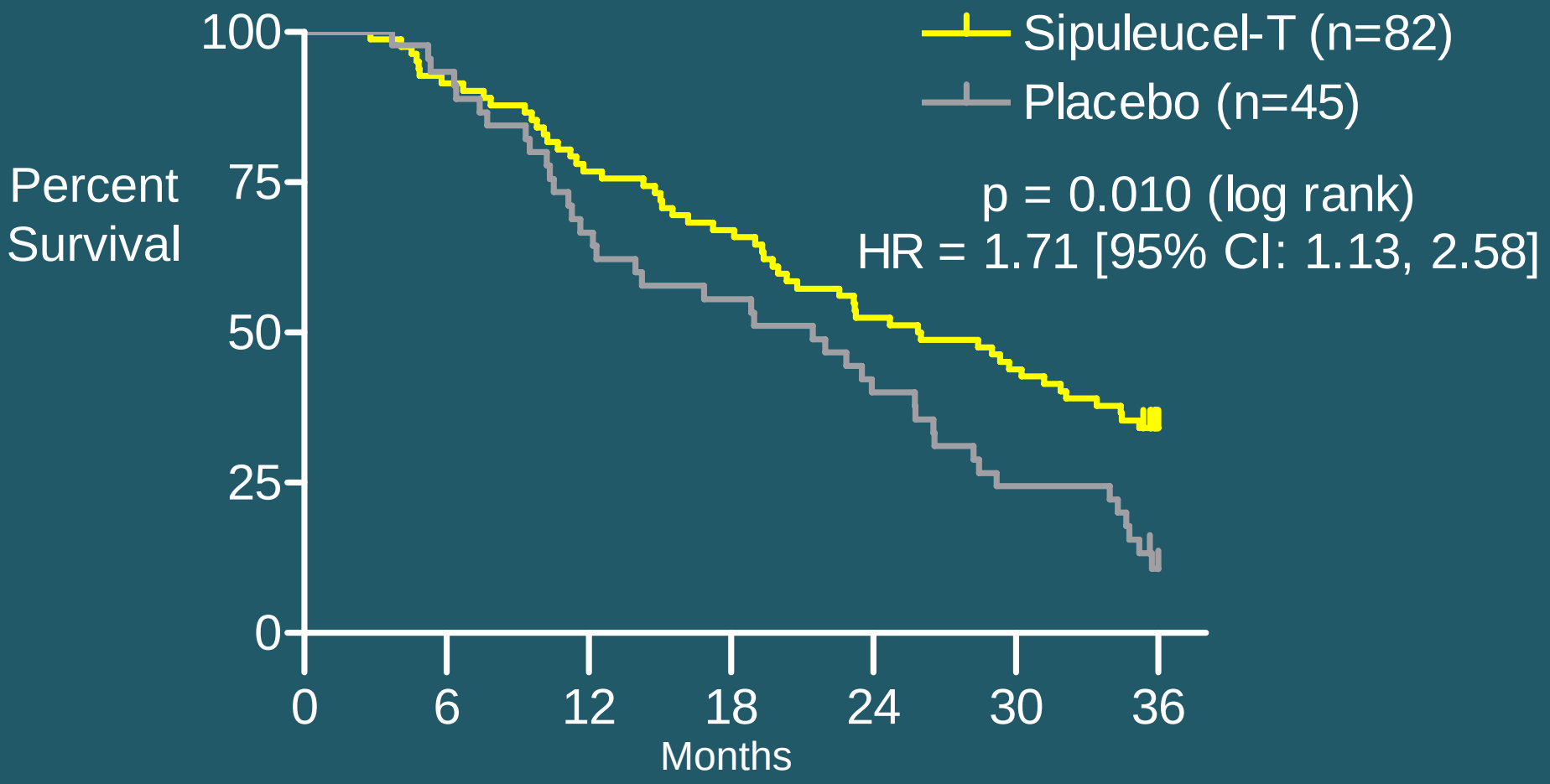
Presenter Disclosure Information

- Trial Architecture Consulting: Serve as consultant and receive consulting fees from numerous clients of Trial Architecture Consulting.
- Dendreon: Serve as consultant, receive consulting fees.
- This presentation is not sponsored by Dendreon.

Dendreon Survival

- Next slide shows 9901 survival outcome.
- P = 0.01 (two-sided).
- P value must be interpreted in the context of FDA standards, including:
  - "Two-trial rule",
  - Trial size,
  - Trial conduct,
  - …

Dendreon 9901 Survival (used with permission)

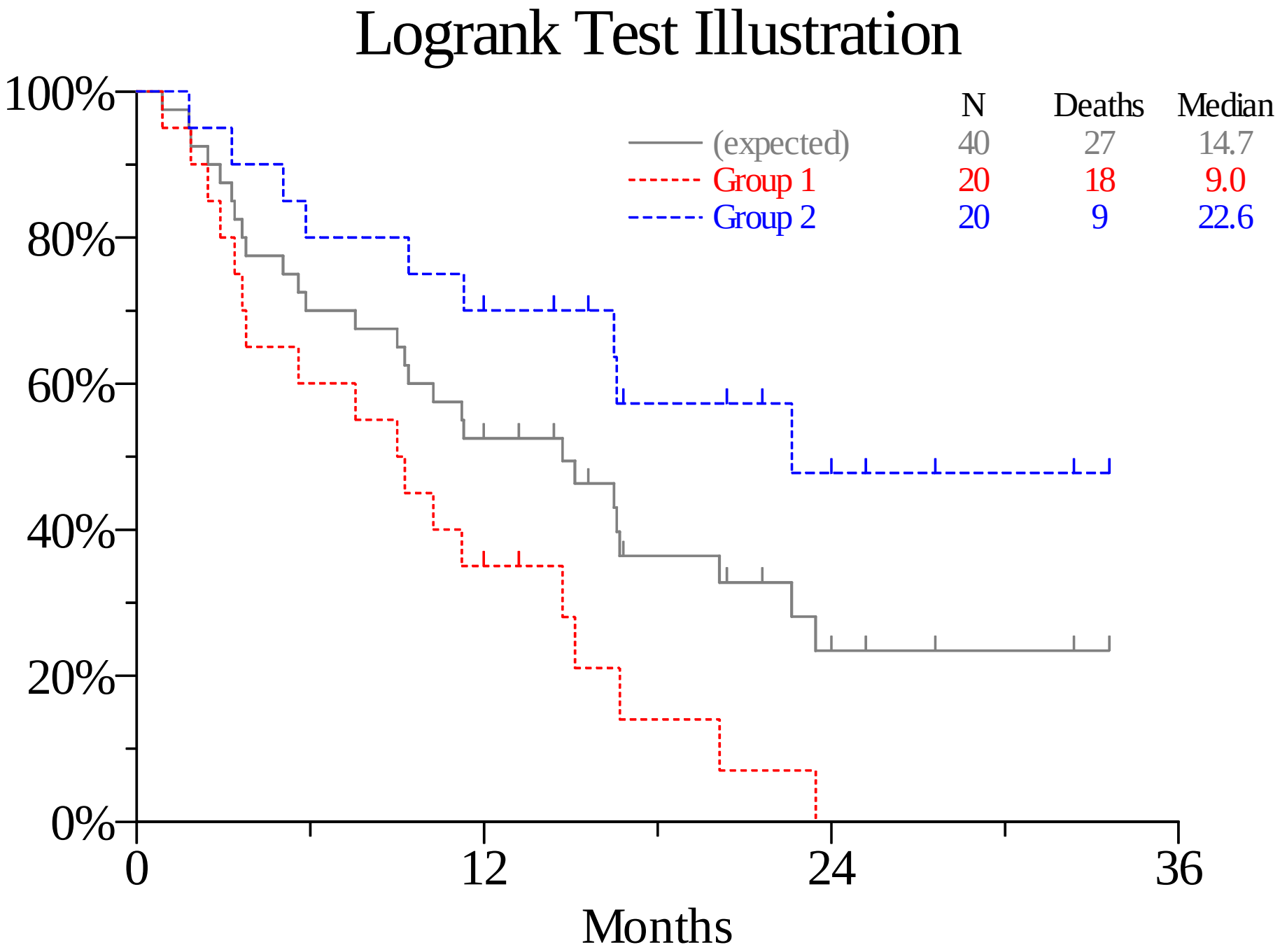


Dendreon Effect Size
(P = placebo, S = Sepuleucel)

Hazard ratio (P:S)	Estimated using proportional hazard regression, smoothes data wobble	1.71 (95% CI 1.13 to 2.58)
Median survival difference (S – P)	Susceptible to data wobble	4.5 months (= 25.9 - 21.4)
3-year survival (S vs P)	Susceptible to data wobble	34.1% vs 10.7%

Overview of Computation of 2-Group Logrank Test

- Compute Kaplan-Meier estimate for each group.
- Compute KM of pooled data (expected).
- Arbitrarily pick a group, say group 1.
- For each event time in group 1 compute sum of the differences in number of events between group 1 and the pooled data (exprected).
- Square the sum of the differences and divide by variance (very complicated).
- Refer result to chi-square distribution.


Logrank Test Illustration
100%
80%
60%
40%
20%
0%
0
12
24
36
Months
N
Deaths
Median
(expected)
40
27
14.7
Group 1
20
18
9.0
Group 2
20
9
22.6

Notes on Logrank Test

- Event times are used only to order the data (distance between event times is not used).
- Measures “distance” between Kaplan-Meier plots of one group to pooled data over the whole range of event times
- Optimal under proportional hazards.
- Widely used (not using logrank is weird).

Hazard Ratio

- Hazard rate ratio: P:S (definition used).
- Hazard rate: Instantaneous probability of event at time t given no event prior to time t.
- Hazard Ratio (HR) = 1 → equal rates.
- HR > 1 → higher rate in control arm.
- HR usually estimated using proportional hazard regression (Cox regression).
- Statistician like HR because all data used and there is smoothing.

Evidence of NonProportional Hazards (NPH) in Dendreon Survival Data

- Visual evidence of delayed effect, a form of NPH.
- Under exponential model:
  - HR is ratio of medians: S:P.
  - HR is ratio of the logs of T-year survivals: P:S.
- Under exponential, following should be equal:
  - Cox regression estimated HR = 1.71.
  - Median ratio: 25.9/21.4 = 1.21.
  - Ratio of logs of 3-year survivals = 2.08.
- Dendreon statisticians report evidence of NPH using more definitive methods.

Which Effect Size Estimate?

Type	Estimate	Susceptibility			
		Wobble	Deviation from Exponential	NPR / delayed effect	Underuse of early data
HR from PH regression	1.71	No	No	Yes	No
Median difference	4.5 months	Yes	No	No	Yes
HR estimated from medians	1.21	Yes	Yes	Yes	Yes
3-year survival difference	34.1% v 10.7 %	Yes, but minimal censoring	No	No	No
HR estimated from 3-year survival	2.08	Yes	Yes	Yes	No

Final Comment

- Ideally, HR estimated using parametric modeling because of greater data smoothing.
- Parametric modeling would use survival functions that closely fit the data and express biologic theory, such as Weibull with delayed effect.
- Parametric model could test for existence and magnitude of delayed effect.