Testing Two Primary Endpoints for a Confirmatory Clinical Study

Ken-Ning Hsu (許根寧) Ph.D.
Senior Biostatistician, PAREXEL International
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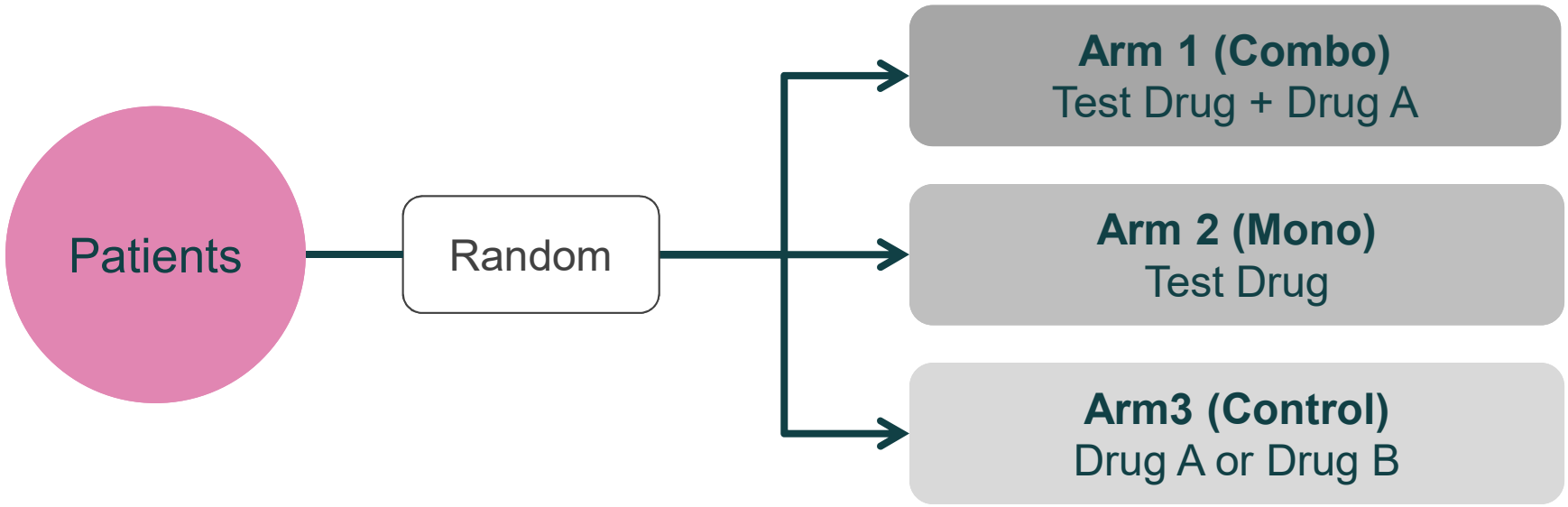
CLINICAL TRIAL – ONCOLOGY



Primary Endpoints

1. Objective Response Rate (ORR)
2. Overall Survival (OS)

Primary Objective At least one of Combo and Mono is effective.

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HISTORICAL CLINICAL RESULT

	Arm 1 (Combo) Test Drug + Drug A	Arm 2 (Mono) Test Drug	Arm3 (Control) Drug A or Drug B
Median OS	14 months	13 months	10 months
ORR	25%	15%	8%

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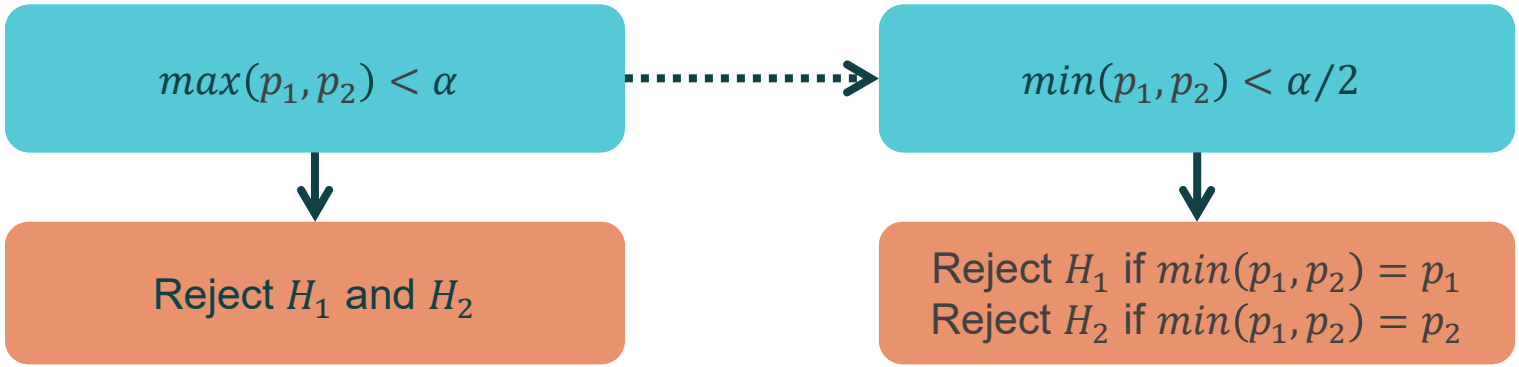
ONLY TESTING OS (1/2)

Strategy 1: Fixed-sequence Procedure

Strategy 2: Hochberg Test Procedure

Combo vs Control		Mono vs Control	
Null Hypothesis	P-value	Null Hypothesis	P-value
$H_1: \Lambda_{Combo}(t) = \Lambda_{Control}(t)$	p_1	$H_2: \Lambda_{Mono}(t) = \Lambda_{Control}(t)$	p_2



condition is met

condition is not met

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ONLY TESTING OS (2/2)

Table 1. Empirical Power for Strategy 1.

n	Scenario	Test Result	Power
259	1	$OS_{\text{Combo vs Control}}$	94.07%
	2	$OS_{\text{Combo vs Control}} \rightarrow OS_{\text{Mono vs Control}}$	86.15%
224	1	$OS_{\text{Combo vs Control}}$	90.09%
	2	$OS_{\text{Combo vs Control}} \rightarrow OS_{\text{Mono vs Control}}$	79.95%

Table 2. Empirical Power Strategy 2.

n	Scenario	Test Result	Power
259	1	$OS_{\text{Combo vs Control}}\ or\ OS_{\text{Mono vs Control}}$	96.09%
	2	$OS_{\text{Combo vs Control}}\ and\ OS_{\text{Mono vs Control}}$	86.12%
224	1	$OS_{\text{Combo vs Control}}\ or\ OS_{\text{Mono vs Control}}$	93.29%
	2	$OS_{\text{Combo vs Control}}\ and\ OS_{\text{Mono vs Control}}$	79.95%

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TESTING OS AND ORR (1/4)

	Null Hypothesis	
	Combo vs Control	**Mono vs Control**
OS	$H_1: \Lambda_{Combo}(t) = \Lambda_{Control}(t)$	$H_2: \Lambda_{Mono}(t) = \Lambda_{Control}(t)$
ORR	$H_3: \pi_{Combo} = \pi_{Control}$	$H_4: \pi_{Mono} = \pi_{Control}$

Strategy 3: Fixed-sequence Procedure (Combo then Mono)

$OS_{\text{Combo vs Control}}$ → $OS_{\text{Mono vs Control}}$ → $ORR_{\text{Combo vs Control}}$ → $ORR_{\text{Mono vs Control}}$

Strategy 4: Fixed-sequence Procedure (OS then ORR)

$OS_{\text{Combo vs Control}}$ → $ORR_{\text{Combo vs Control}}$ → $OS_{\text{Mono vs Control}}$ → $ORR_{\text{Mono vs Control}}$

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TESTING OS AND ORR (2/4)

Sample Size for Each Arm is 259 Subjects

Table 3. Empirical Power for Strategy 3.

Scenario	Test Result	Power
1	$OS_{\text{Combo vs Control}}$	94.35%
2	$OS_{\text{Combo vs Control}} \rightarrow OS_{\text{Mono vs Control}}$	86.21%
3	$OS_{\text{Combo vs Control}} \rightarrow OS_{\text{Mono vs Control}} \rightarrow ORR_{\text{Combo vs Control}}$	86.17%
4	$OS_{\text{Combo vs Control}} \rightarrow OS_{\text{Mono vs Control}} \rightarrow ORR_{\text{Combo vs Control}} \rightarrow ORR_{\text{Mono vs Control}}$	57.23%

Table 4. Empirical Power for Strategy 4.

Scenario	Test Result	Power
1	$OS_{\text{Combo vs Control}}$	94.35%
2	$OS_{\text{Combo vs Control}} \rightarrow ORR_{\text{Combo vs Control}}$	94.30%
3	$OS_{\text{Combo vs Control}} \rightarrow ORR_{\text{Combo vs Control}} \rightarrow OS_{\text{Mono vs Control}}$	86.17%
4	$OS_{\text{Combo vs Control}} \rightarrow ORR_{\text{Combo vs Control}} \rightarrow OS_{\text{Mono vs Control}} \rightarrow ORR_{\text{Mono vs Control}}$	57.23%

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TESTING OS AND ORR (3/4)

Strategy 5

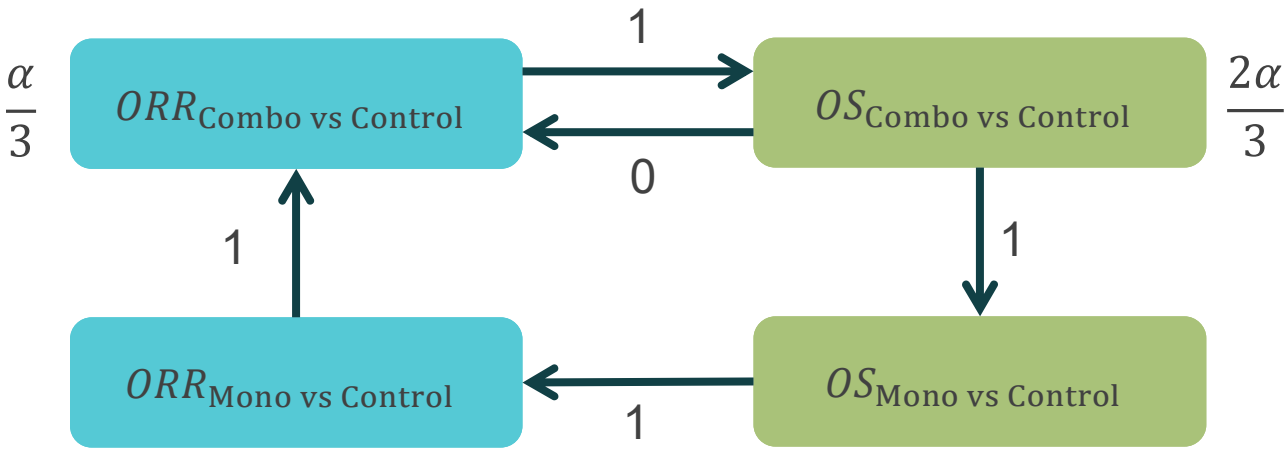

Table 5. Empirical power for Strategy 5.

Scenario	Test Result	Power
1	$ORR_{\text{Combo vs Control}}$	99.95%
2	$ORR_{\text{Combo vs Control}} \rightarrow OS_{\text{Combo vs Control}}$	95.77%
3	$ORR_{\text{Combo vs Control}} \rightarrow OS_{\text{Combo vs Control}} \rightarrow OS_{\text{Mono vs Control}}$	89.94%
4	$ORR_{\text{Combo vs Control}} \rightarrow OS_{\text{Combo vs Control}} \rightarrow OS_{\text{Mono vs Control}} \rightarrow ORR_{\text{Mono vs Control}}$	63.47%
5	$OS_{\text{Combo vs Control}}$	95.82%
6	$OS_{\text{Combo vs Control}} \rightarrow OS_{\text{Mono vs Control}}$	89.99%
7	$OS_{\text{Combo vs Control}} \rightarrow OS_{\text{Mono vs Control}} \rightarrow ORR_{\text{Mono vs Control}}$	64.07%
8	$OS_{\text{Combo vs Control}} \rightarrow OS_{\text{Mono vs Control}} \rightarrow ORR_{\text{Mono vs Control}} \rightarrow ORR_{\text{Combo vs Control}}$	63.47%

Sample Size for Each Arm is 286 Subjects

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TESTING OS AND ORR (4/4)

Strategy 6

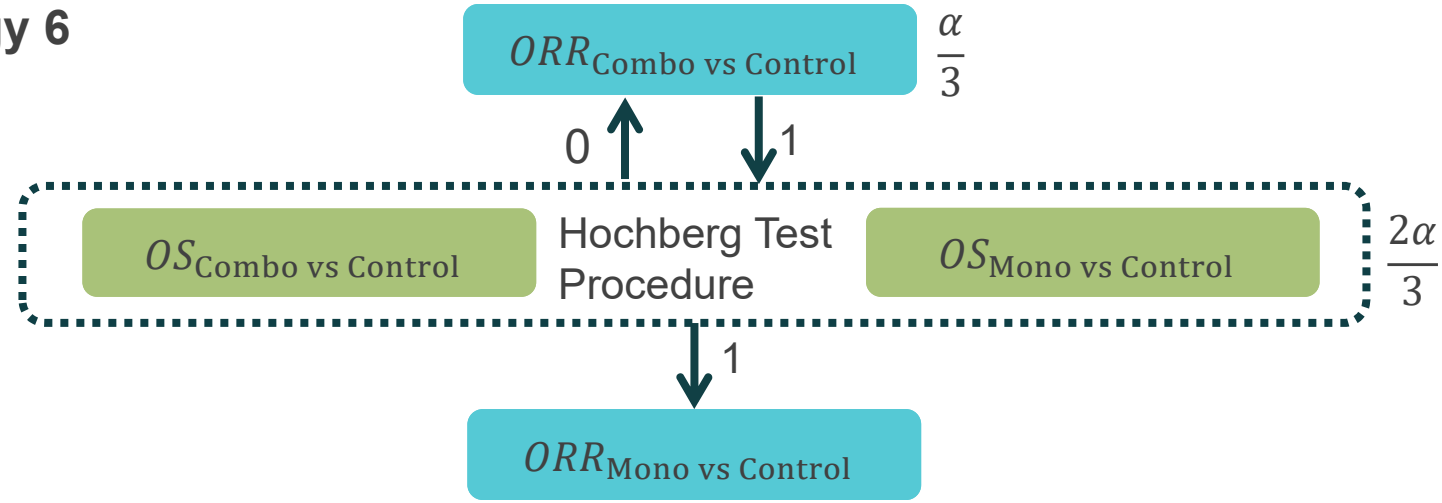

Table 6. Empirical power for Strategy 6.

Scenario	Test Result	Power
1	$ORR_{\text{Combo vs Control}}$	99.95%
2	$ORR_{\text{Combo vs Control}} \rightarrow (OS_{\text{Combo vs Control}}\ or\ OS_{\text{Mono vs Control}})$	97.19%
3	$ORR_{\text{Combo vs Control}} \rightarrow (OS_{\text{Combo vs Control}}\ or\ OS_{\text{Mono vs Control}}) \rightarrow ORR_{\text{Mono vs Control}}$	68.74%
4	$ORR_{\text{Combo vs Control}} \rightarrow (OS_{\text{Combo vs Control}}\ and\ OS_{\text{Mono vs Control}})$	89.94%
5	$ORR_{\text{Combo vs Control}} \rightarrow (OS_{\text{Combo vs Control}}\ and\ OS_{\text{Mono vs Control}}) \rightarrow ORR_{\text{Mono vs Control}}$	63.47%
6	$(OS_{\text{Combo vs Control}}\ or\ OS_{\text{Mono vs Control}})$	97.24%
7	$(OS_{\text{Combo vs Control}}\ or\ OS_{\text{Mono vs Control}}) \rightarrow ORR_{\text{Mono vs Control}}$	68.74%
8	$(OS_{\text{Combo vs Control}}\ and\ OS_{\text{Mono vs Control}})$	89.99%
9	$(OS_{\text{Combo vs Control}}\ and\ OS_{\text{Mono vs Control}}) \rightarrow ORR_{\text{Mono vs Control}}$	63.47%

Sample Size for Each Arm is 286 Subjects

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