GPMA
MORSE – Health Technology Assessment Group

Crossover in Oncology Clinical Trials
Some case studies

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Disclaimer: Presentation is authors view only.

Of industry funded Oncology Phase III RCT how many are positive i.e. show a statistically significant benefit for the experimental therapy?

A. >75%

B. 50–75%

C. 25–50%

D. <25%

Of industry funded Oncology Phase III RCT how many are positive i.e. show a statistically significant benefit for the experimental therapy?

A. >75%

B. 50–75%

C. 25–50%

D. <25%

Answer: 43.2% are positive

Gan HK, You B, Pond GR, Chen EX. Assumptions of expected benefits in randomized phase III trials evaluating systemic treatments for cancer. J Natl Cancer Inst. 2012;104(8):590–598

Of industry funded Oncology Phase III RCT how many show a detriment for the experimental therapy?

A. >45%

B. 30–45%

C. 15–30%

D. <15%

Of industry funded Oncology Phase III RCT how many show a detriment for the experimental therapy?

A. >45%

B. 30–45%

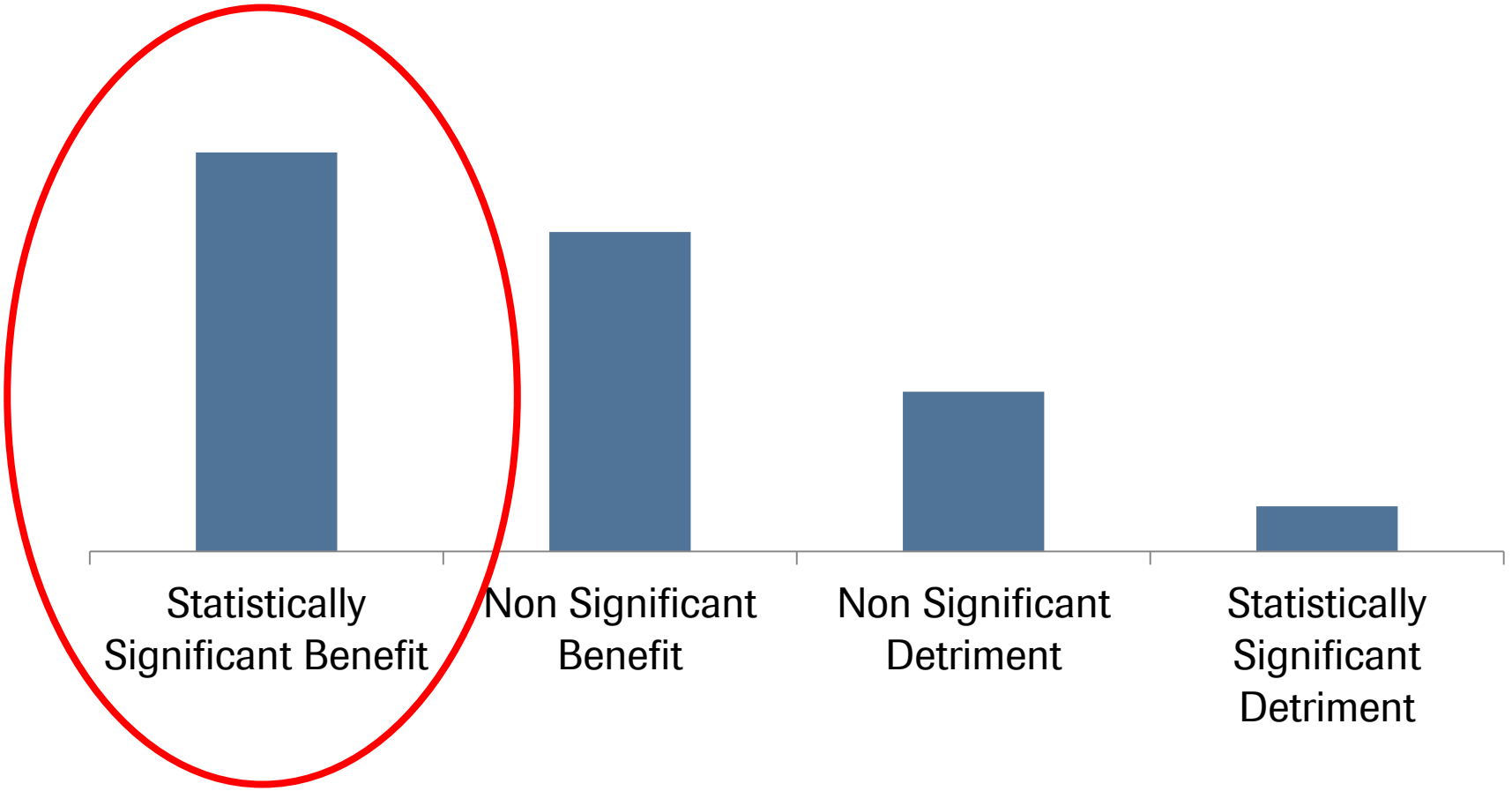
C. 15–30%

D. <15%

Answer: 22.2% show a detriment

Gan HK, You B, Pond GR, Chen EX. Assumptions of expected benefits in randomized phase III trials evaluating systemic treatments for cancer. J Natl Cancer Inst. 2012;104(8):590–598

Summary: Case Study RCT are from a subset of RCT with Statistically Significant Primary Endpoint

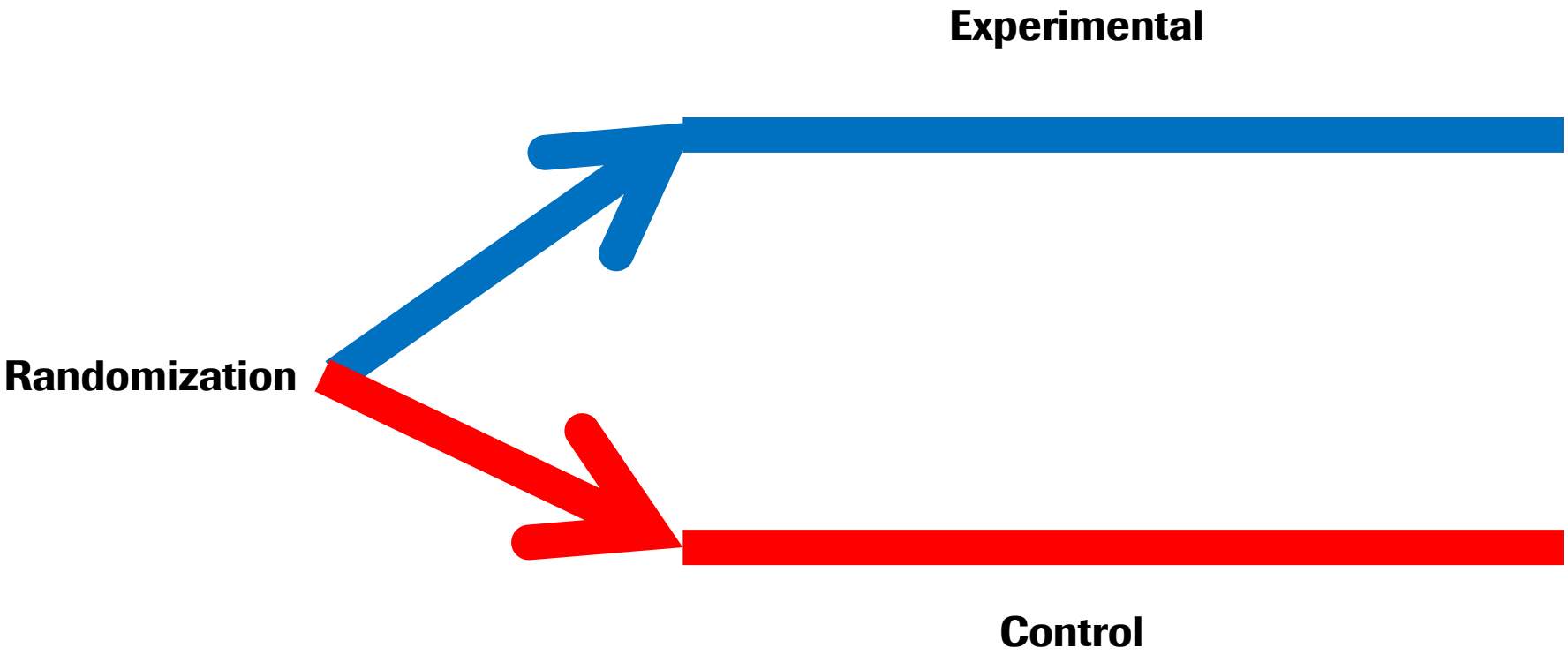


Gan HK, You B, Pond GR, Chen EX. Assumptions of expected benefits in randomized phase III trials evaluating systemic treatments for cancer. J Natl Cancer Inst. 2012;104(8):590–598

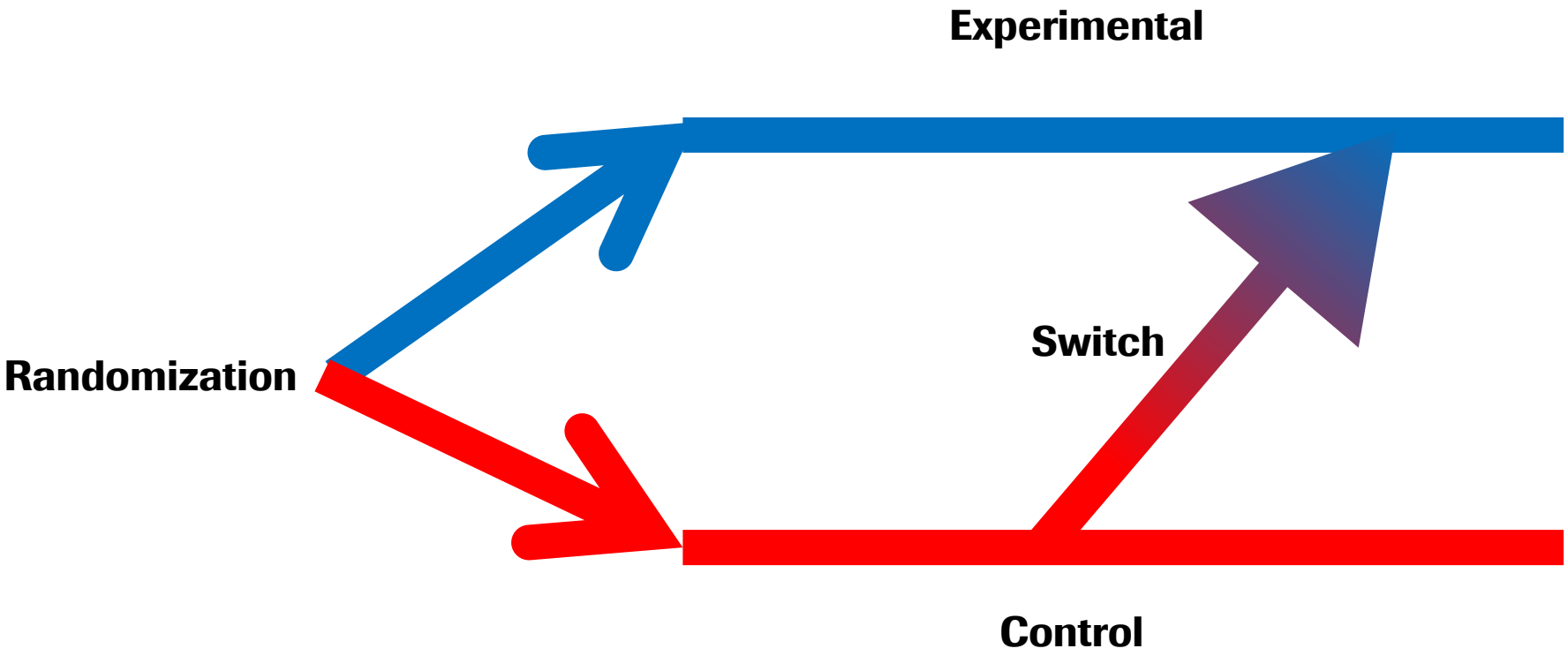
The case studies

- BRIM3
- BREAK-3
- CLEOPATRA
- TaNDEM
- TIVO-1

Trial with switch



Trial with switch



BRIM3

Population	**Patients with BRAF V600 positive advanced melanoma**			
Primary EP	PFS and OS (joint primary)			
Control	Dacarbazine (n=338)			
Experimental	Vemurafenib (n=337)			
Est. percent population eligible to switch	77% DSMB recommend switching be permitted based on compelling efficacy. No restriction on patients. (n=263)			
	% switch to		**Overall Survival**	
Analysis	**vem**	**any BRAFi**	**HR, 95% CI**	**Ctrl event n (%)**
Dec 2010	0		0.37 (0.26, 0.55)	75 (22%)
Mar 2011	15%	20%	0.47 (0.35, 0.62)	122 (36%)
Oct 2011	24%	30%	0.67 (0.54, 0.84)	175 (52%)
Feb 2012	25%	34%	0.76 (0.63, 0.93)	200 (59%)
Dec 2012	25%		0.79 (0.66, 0.96)	236 (69%)
Adjustment methods	Censoring at crossover (pre specified) for EMA and FDA. RPSFT performed for NICE, Historical control for IQWiG and NICE			

Chapman et al. Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation. N Engl J Med 2011;364:2507-16

McArther et al. Safety and efficacy of vemurafenib in BRAFV600E and BRAFV600K mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol 2014; 15: 323–32

BREAK3

Population	**Patients with BRAF V600 mutated metastatic melanoma**		
Primary EP	PFS		
Control	Dacarbazine (n=63)		
Experimental	Dabfrabenib (n=187)		
Est. percent population eligible to switch	100% Patients in the dacarbazine group were allowed to cross over to receive dabrafenib after progression was confirmed by independent review.		
Analysis	% switch	Overall Survival	
		HR, 95% CI	Ctrl event n (%)
Dec 2011	44%	0.61 (0.25, 1.48)	9 (14%)
Dec 2012	57%	0.76 (0.48, 1.21)	28 (44%)
Adjustment methods	RPSFT, IPE and 2 Stage AFT		

Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: A multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;**380**:358-365

Latimer NR, Abrams KR, Amonkar MM, Stapelkamp S, Swann S., Adjusting for the Confounding Effects of Treatment Switching—The BREAK-3 Trial: Dabrafenib Versus Dacarbazine;. The Oncologist;

TaNDEM

Population	**Postmenopausal women with HER2/hormone receptor–copositive metastatic breast cancer**
Primary EP	PFS
Control	anastrozole alone (n=103)
Experimental	trastuzumab plus anastrozole (n=104)
Est. percent population eligible to switch	100% At PD patients in the anastrozole alone arm could switch to a trastuzumab-containing regimen. (n=103)
Percent switch	70%
OS outcome	Median OS was 28.5 months in the trastuzumab plus anastrozole arm and 23.9 months in the anastrozole alone arm; this difference was not statistically significant (log-rank P = .325)
Adjustment methods	RPSFT performed for NICE submission

Kaufman et al. Trastuzumab Plus Anastrozole Versus Anastrozole Alone for the Treatment of Postmenopausal Women With Human Epidermal Growth Factor Receptor 2–Positive, Hormone Receptor–Positive Metastatic Breast Cancer: Results From the Randomized Phase III TAnDEM Study. J Clinical Oncology. 2009; 27(33):5529-5537

TIVO-1

Population	Patients with metastatic cc-RCC
Primary EP	PFS
Control	Sorafenib (n=257)
Experimental	Tivozanib (n=260)
Est. percent population eligible to switch	100% Patients randomly assigned to sorafenib who had RECIST-defined progressive disease (PD) per investigator assessment were given the option to cross over to receive tivozanib in a separate protocol.
Percent switch	60.7% (156/257)
OS outcome	Median OS was 28.8 months in the Tivozanib arm and 29.3 months in the Sorafanib arm; this difference was not statistically significant (log-rank P = .195) Hazard Ratio: 1.245; p=0.105
Adjustment methods	n/a

Motzer RJ, Nosov D, Eisen T et al. Tivozanib Versus Sorafenib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma: Results From a Phase III Trial. J Clin Oncol 31:3791-3799

CLEOPATRA

Population	**Women with HER2-positive metastatic breast cancer**		
Primary EP	PFS		
Control	Trastuzumab plus Docetaxel (n=406)		
Experimental	Pertuzumab plus Trastuzumab plus Docetaxel (n=402)		
Est. percent population eligible to switch	27% Patients still on placebo were offered crossover to pertuzumab after 2nd interim showed stat sig OS benefit at 2nd interim after 296 progression events (n=110)		
		Overall Survival	
Analysis	**% switch**	**HR, 95% CI**	**Ctrl event n (%)**
May 2011	0	0.64 (0.47, 0.88)* *Not statistically significant per interim stopping rules	96 (23%)
June 2012	0	0.66 (0.52, 0.84)	154 (38%)
Feb 2014	12%	0.68 (0.56, 0.84)	221 (54%)

Baselga et al. Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. N Engl J Med 2012; 366:109–119

Swain et al. Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer. N Engl J Med 2015;372:724–34

Trying to Group Case Studies: What design choices can be made?

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1) **When** in study (will crossover start)

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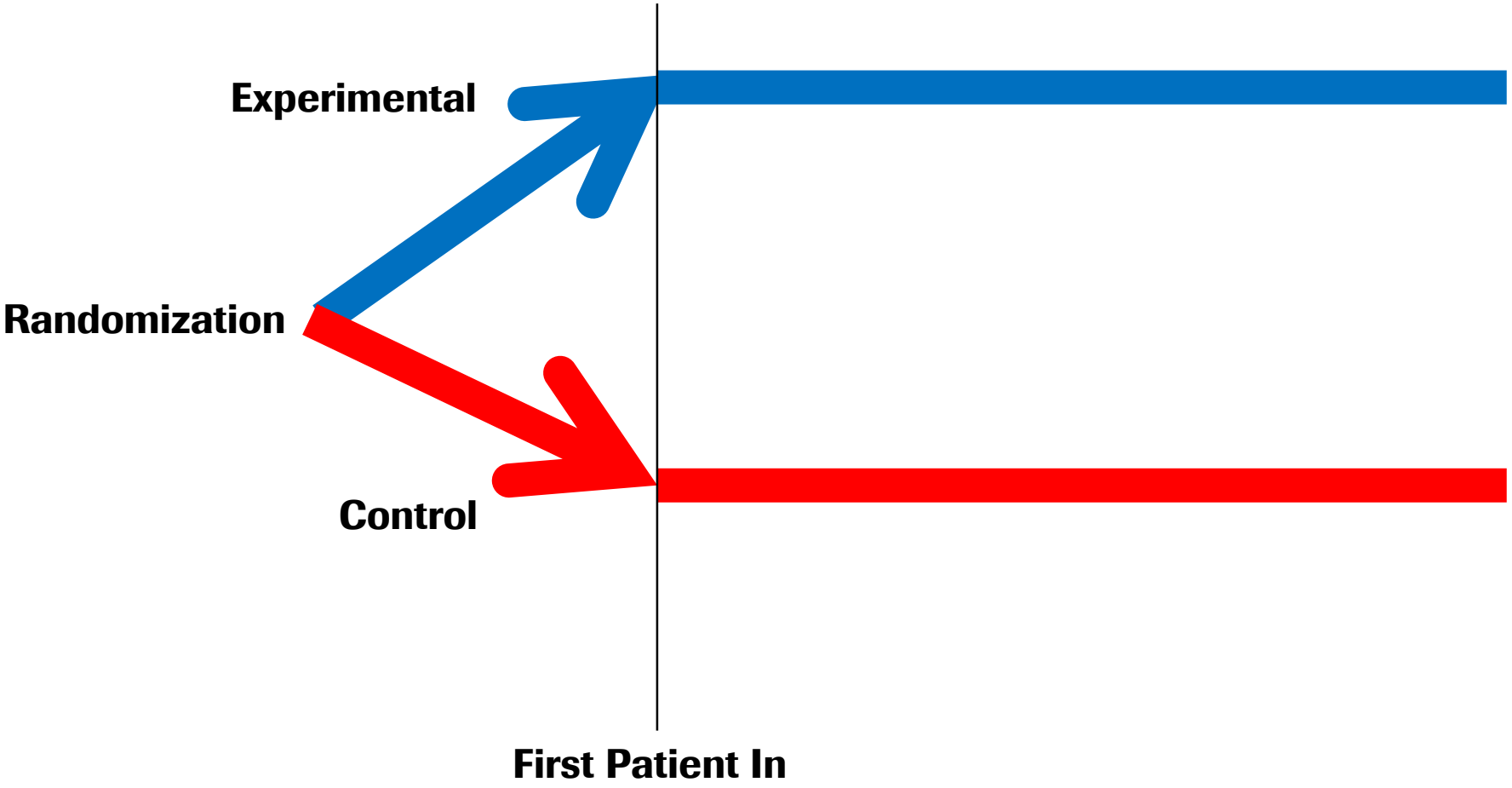
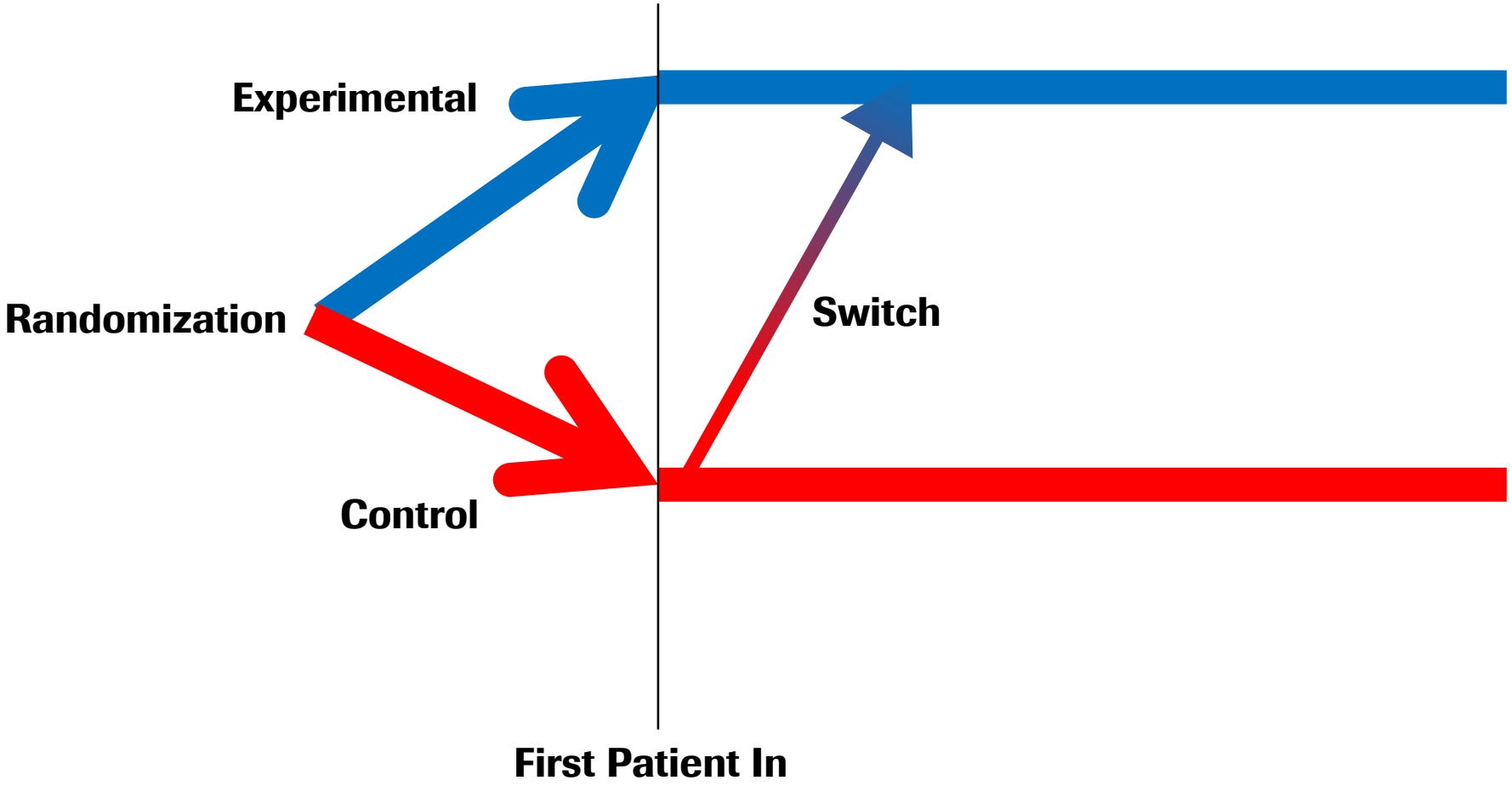
1) **When** in study (will crossover start)

2) **Who** can crossover (which patients)

Trial with switch – choice – when in study?



Trial with switch – choice – when in study?



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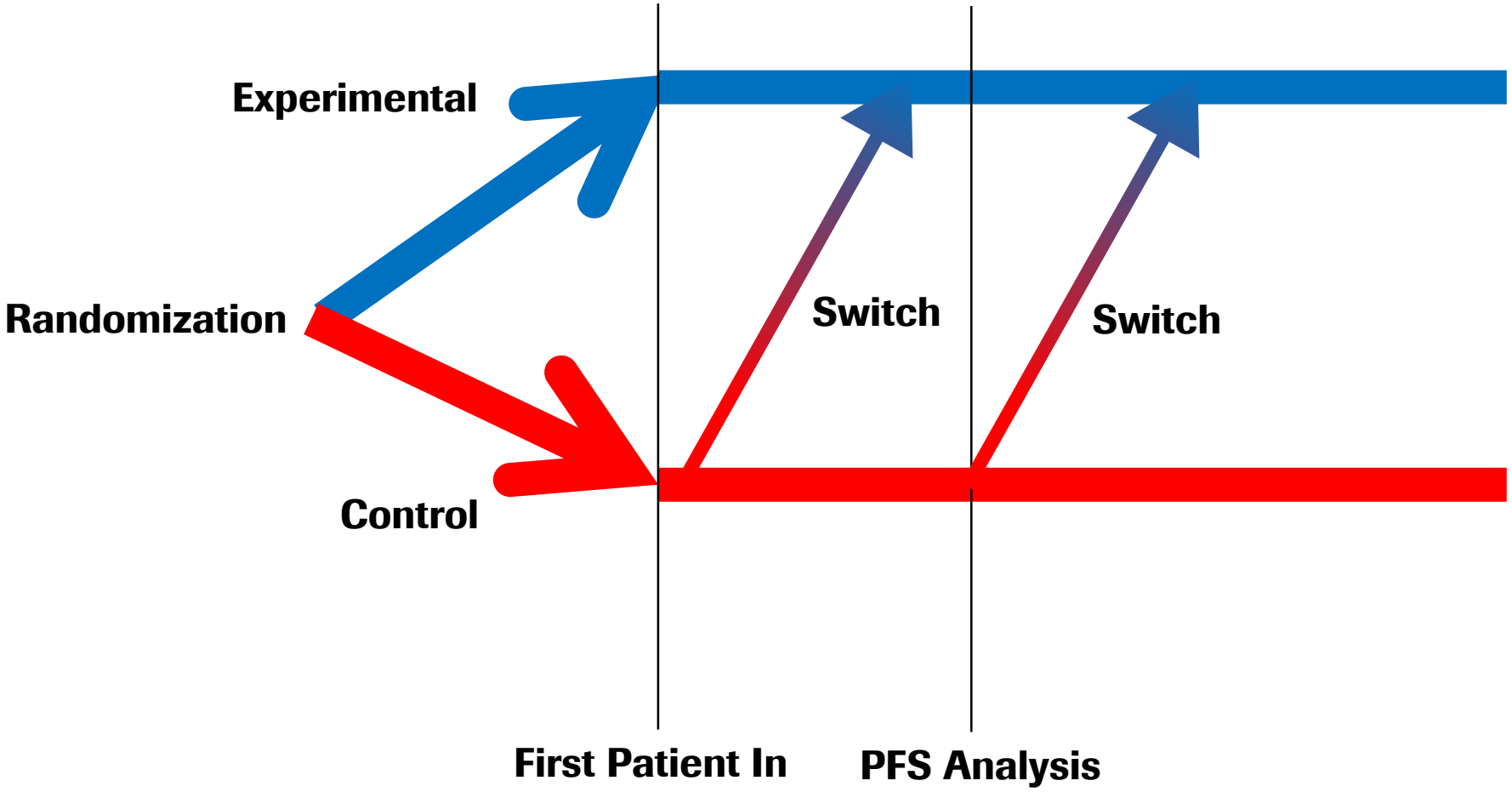
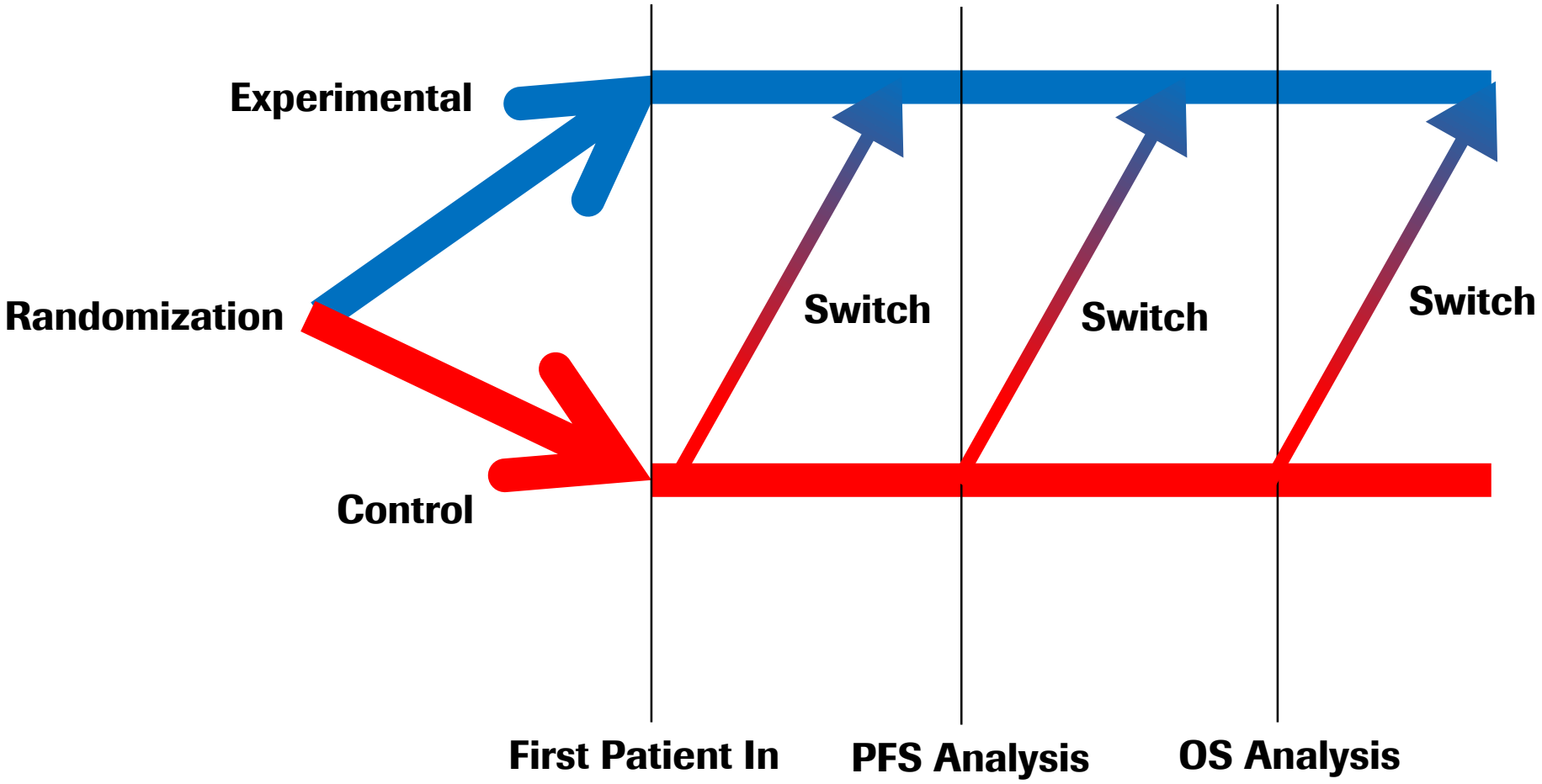
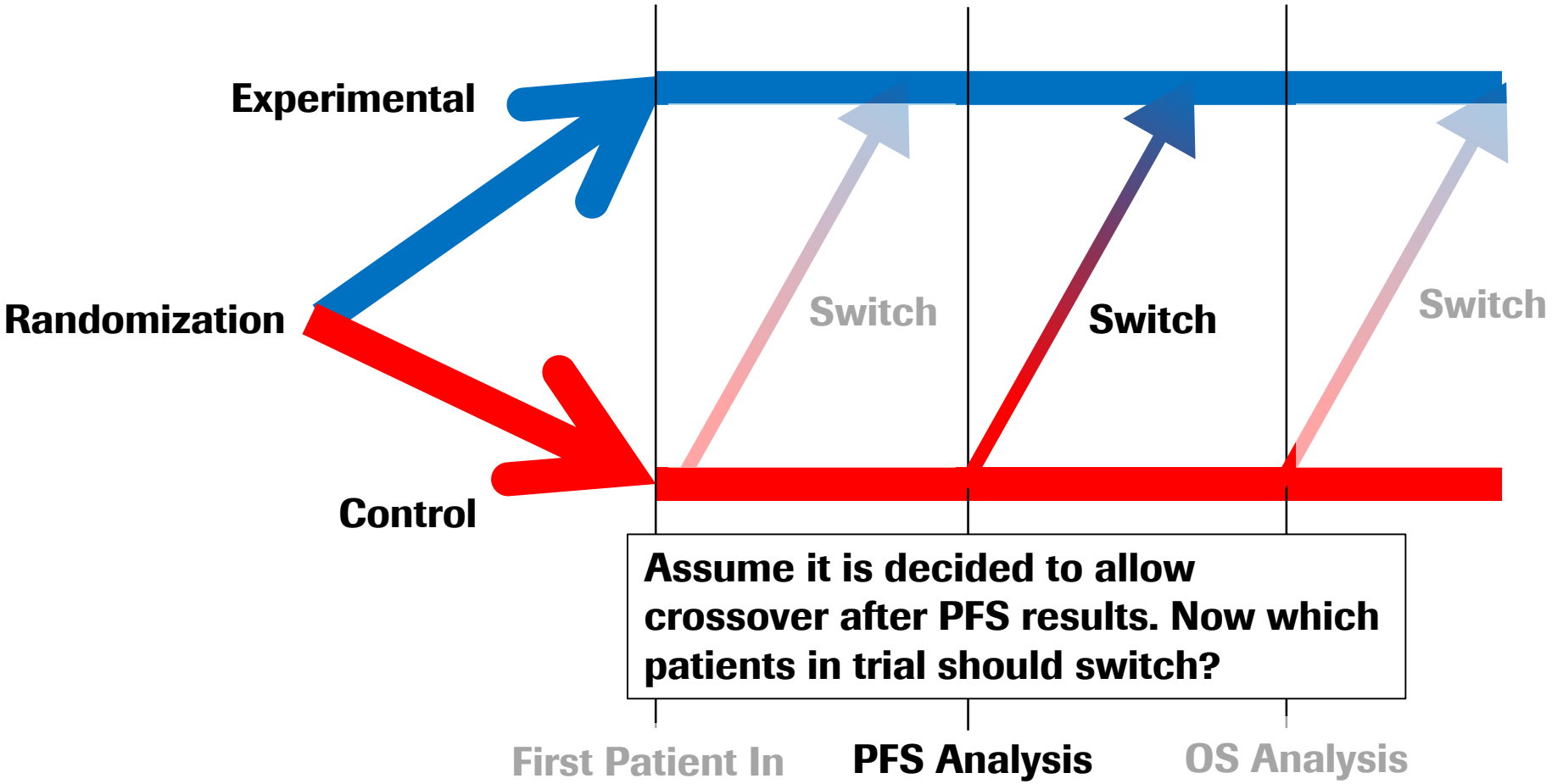


Trial with switch – choice – when in study?



Trial with switch – choice – who can crossover?



Trial with switch – choice – who can crossover?

At PFS analysis there will be 2 types of patients in the control arm

A

Those who have progressed (have experienced progression event).

B

Those who have not progressed (still on treatment).

Trial with switch – choice – who can crossover?

At PFS analysis there will be 2 types of patients in the control arm

A

Those who have progressed (have experienced progression event).

Option 1: Allow these patients to crossover

B

Those who have not progressed (still on treatment).

Trial with switch – choice – who can crossover?

At PFS analysis there will be 2 types of patients in the control arm

A

Those who have progressed (have experienced progression event).

Option 1: Allow these patients to crossover

B

Those who have not progressed (still on treatment).

Option 2: Allow these patients to crossover

Trial with switch – choice – who can crossover?

At PFS analysis there will be 2 types of patients in the control arm

A	B
Those who have progressed (have experienced progression event).	**Those who have not progressed (still on treatment).**

Option 1: Allow these patients to crossover

Option 2: Allow these patients to crossover

Option 3: Allow both types of patients to crossover meaning is investigator choice

Trying to group case studies: When is crossover allowed?

When in study?

Who can crossover?

	From Day 1	After analysis showed significant PFS benefit and OS trend	After analysis showed significant OS benefit	Never
All patients				
Restricted (Patients who progressed)	This split not applicable here			
Restricted (Patients still on treatment				

Trying to group case studies: When is crossover allowed?

When in study?

Who can crossover?

	From Day 1	After analysis showed significant PFS benefit and OS trend	After analysis showed significant OS benefit	Never
All patients	Not RCT?			Regulatory approval in at least one country will cause partial crossover
Restricted (Patients who progressed)	This split not applicable here			
Restricted (Patients still on treatment				

Trying to group case studies: When is crossover allowed?

When in study?

Who can crossover?

	From Day 1	After analysis showed significant PFS benefit and OS trend	After analysis showed significant OS benefit	Never
All patients	Not RCT?		BRIM3	Regulatory approval in at least one country will cause partial crossover
Restricted (Patients who progressed)	BREAK3 TaNDEM TIVO-1			
Restricted (Patients still on treatment			CLEOPATRA	

Primary Endpoint?

When in study?

Who can crossover?

	From Day 1	After analysis showed significant PFS benefit and OS trend	After analysis showed significant OS benefit	Never
All patients	Not RCT?		BRIM3 PFS & OS	Regulatory approval in at least one country will cause partial crossover
Restricted (Patients who progressed)	BREAK3 PFS TaNDEM PFS TIVO-1 PFS			
Restricted (Patients still on treatment			CLEOPATRA PFS	

How many patients could switch?

When in study?

Who can crossover?

	From Day 1	After analysis showed significant PFS benefit and OS trend	After analysis showed significant OS benefit	Never
All patients	Not RCT?		BRIM3 77%	Regulatory approval in at least one country will cause partial crossover
Restricted (Patients who progressed)	BREAK3 100% TaNDEM 100% TIVO-1 100%			
Restricted (Patients still on treatment			CLEOPATRA 27%	

How many patients did switch?

When in study?

Who can crossover?

	From Day 1	After analysis showed significant PFS benefit and OS trend	After analysis showed significant OS benefit	Never
All patients	Not RCT?		BRIM3 25%	Regulatory approval in at least one country will cause partial crossover
Restricted (Patients who progressed)	BREAK3 57% TaNDEM 70% TIVO-1 60.7%			
Restricted (Patients still on treatment			CLEOPATRA 12%	

How mature was last data cut without switch? (percent of control arm experiencing OS event)

When in study?

Who can crossover?

	From Day 1	After analysis showed significant PFS benefit and OS trend	After analysis showed significant OS benefit	Never
All patients	Not RCT?		BRIM3 22%	Regulatory approval in at least one country will cause partial crossover
Restricted (Patients who progressed)	BREAK3 0% TaNDEM 0% TIVO-1 0%			
Restricted (Patients still on treatment			CLEOPATRA 38%	

What do we want to learn from a clinical trial?

- Different bodies are asking different questions
- May lead to different requirements for data e.g. longer follow-up vs un-confounded analysis

Body	Research Question (simplified)
FDA, EMA	Benefit/Risk of an individual medicine
IQWiG	Additional benefit compared to standard of care
NICE	Additional benefit compared to standard of care extrapolated over patients life time

Did Trial Support FDA Approval?

When in study?

Who can crossover?

	From Day 1	After analysis showed significant PFS benefit and OS trend	After analysis showed significant OS benefit	Never
All patients	Not RCT?			Regulatory approval in at least one country will cause partial crossover
Restricted (Patients who progressed)	TIVO-1 NO BREAK3 YES			
Restricted (Patients still on treatment				

Did Trial Support FDA Approval?

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Was a benefit recognised by IQWiG?

When in study?

Who can crossover?

	From Day 1	After analysis showed significant PFS benefit and OS trend	After analysis showed significant OS benefit	Never
All patients	Not RCT?		BRIM3 YES	Regulatory approval in at least one country will cause partial crossover
Restricted (Patients who progressed)	BREAK3 NO			
Restricted (Patients still on treatment				

Was a benefit recognised by IQWiG?

IQWiG Institute for Quality and Efficiency in Health Care

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Press ▸ Press releases ▸ Dabrafenib in melanoma: added benefit not pro...

- Press releases
- Comments
- Press photos
- Contact

2014-01-02

Dabrafenib in melanoma: added benefit not proven

No differences could be shown for mortality, symptoms and quality of life / concerning side effects, data too uncertain

Dabrafenib (trade name: Tafinlar) has been approved in Germany since August 2013 for the treatment of advanced melanoma.In an early benefit assessment pursuant to the Act on the Reform of the Market for Medicinal Products (AMNOG), the German Institute for Quality and Efficiency in Health Care (IQWiG) examined whether this new drug offers an added benefit over the appropriate comparator therapy.

According to the findings, an added benefit of dabrafenib is not proven: Regarding mortality, symptoms, health-related quality of life and treatment discontinuation due to side effects, no advantage can be derived from the dossier. Concerning other side effects, the data were too uncertain to allow drawing any conclusions.

Who can crossover?

Were adjusted analysis accepted by NICE?

When in study?

Who can crossover?

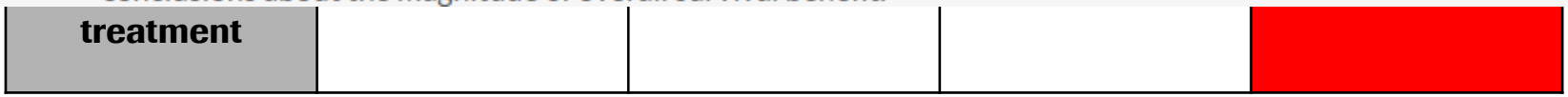
	From Day 1	After analysis showed significant PFS benefit and OS trend	After analysis showed significant OS benefit	Never
All patients	Not RCT?		BRIM3 YES	Regulatory approval in at least one country will cause partial crossover
Restricted (Patients who progressed)	BREAK3 YES			
Restricted (Patients still on treatment				

Were adjusted analysis accepted by NICE?

When in study?

Who can crossover?

4.4 The Committee examined the results of BREAK-3 presented by the company. It noted that dabrafenib reduces the risk of progression compared with dacarbazine, with a statistically significant difference of 4.2 months in median time to progression. The Committee was aware that for overall survival, the point estimate for the hazard ratio suggested that dabrafenib results in an overall survival benefit, but that the difference did not reach statistical significance. The Committee noted the high level of crossover (57%) in the trial and was aware that even after adjusting for crossover using the RPSFT method (see section 3.22) the company's estimate of overall survival gain did not reach statistical significance. The Committee was aware of the ERG's concerns about the appropriateness of the RPSFT method (see section 3.22); however, it did not think it was necessary to discuss the issue further because it considered vemurafenib to be the relevant comparator for this appraisal. The Committee noted that the relatively low numbers in the dacarbazine arm of the trial (3:1 randomisation) and the high rates of crossover made it very difficult to draw a firm conclusion about the precise effect on overall survival. The Committee concluded that compared with dacarbazine, dabrafenib significantly improved progression-free survival and probably improved overall survival, but it was unable to draw firm conclusions about the magnitude of overall survival benefit.



Suggested implications to consider when designing trials

- Not all Phase 3 RCT are positive
- Crossover can be considered a choice of when and who and should be specified in advance (for informed consent and to collect data for adjustment methods)
- There is a trade-off between the amount of patients eligible for crossover, the proportion of patients who do switch and the maturity of uncontaminated data
- PFS without an OS trend may not be enough for regulatory approval
- Even if crossover is delayed until significant OS benefit observed the information gained may not be mature enough for all decision makers e.g. NICE HTA requirement to extrapolate over life time
- HTA bodies show different willingness to except adjusted analysis

Doing now what patients need next