Multiplicity and other issues related to biomarker-based oncology trials
ASA NJ Chapter

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Abstract

With highly active targeted therapies becoming more commonplace in recent years, strategies for development become increasingly important in terms of time-to-market, clinical trials size and the breadth of patient population that may benefit from a drug. We discuss strategies and corresponding statistical tools that have been applied. Early single-arm trials followed quickly by randomized trials is a bedrock approach for many indications, but not without pitfalls. The possibility of doing trials that are target-based rather than histology-based as well as other novel approaches are considered. Another challenge is developing one or more biomarkers at the same time that a drug is being developed.

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Overview

- Examples of completed and ongoing biomarker-based studies
  - Generally based on checkpoint inhibitor MK-3475/pembrolizumab/Keytruda
- Progression of studies for a cancer type
- Companion vs. complementary diagnostic device
- Multiplicity control with the graphical method and group sequential design

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PD-1: Programmed Cell Death Protein 1

- Source: Wikipedia
  - PD-1 is a protein and cell-surface receptor
  - Binds to 2 ligands: PD-L1 and PD-L2
  - "PD-1, functioning as an immune checkpoint, plays an important role in down regulating the immune system by preventing the activation of T-cells, which in turn reduces autoimmunity and promotes self-tolerance."
  - "A new class of drugs that block PD-1, the PD-1 inhibitors, activate the immune system to attack tumors..."
  - "Many tumor cells express PD-L1, an immunosuppressive PD-1 ligand; inhibition of the interaction between PD-1 and PD-L1 can enhance T-cell responses in vitro and mediate preclinical antitumor activity."
- Pembrolizumab and nivolumab are examples of antibodies that inhibit PD-1
- Each has been studied in patients with a diagnostic measuring PD-L1

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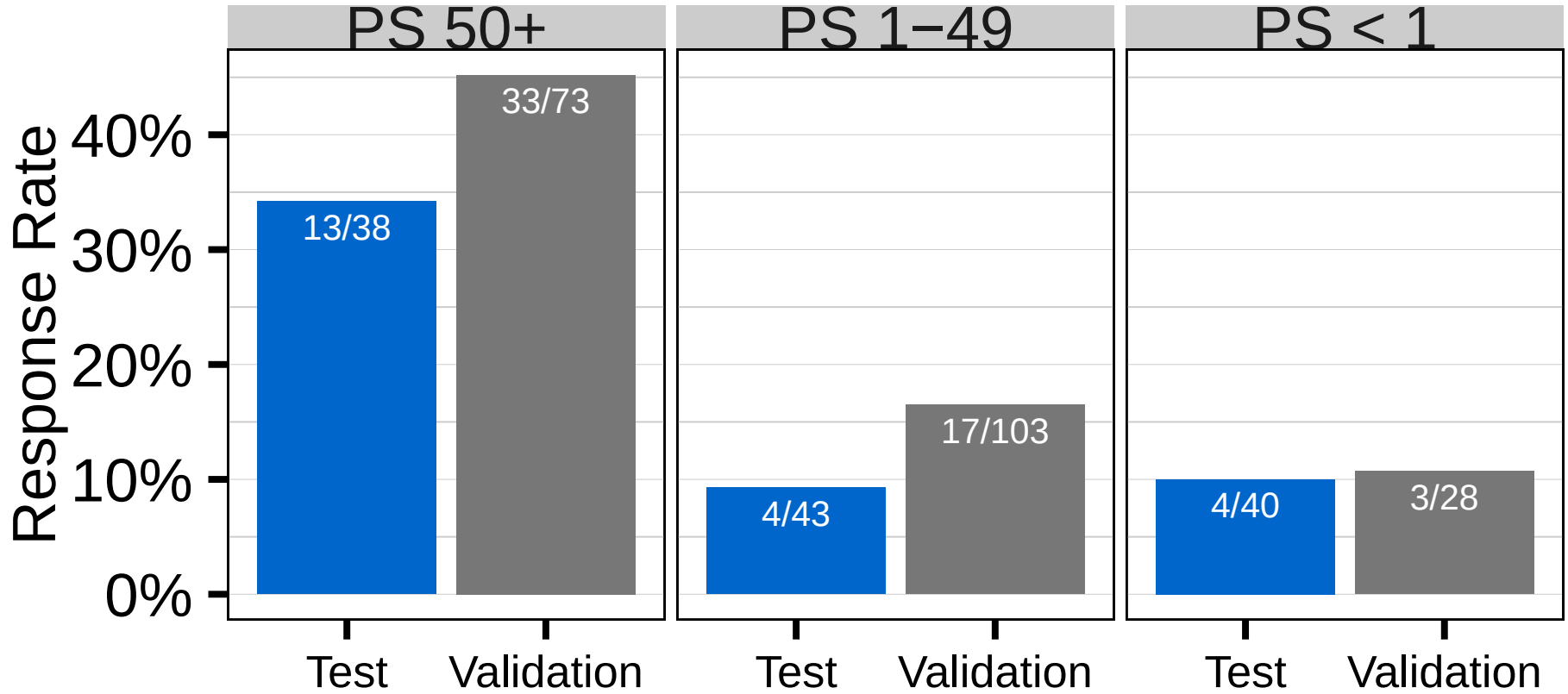
Keynote 001: Objective Response by Biomarker Level

Pembrolizumab for non-small-cell lung cancer; PS=proportion score
Early trial leading to randomized trial design



Garon et al. [2015]

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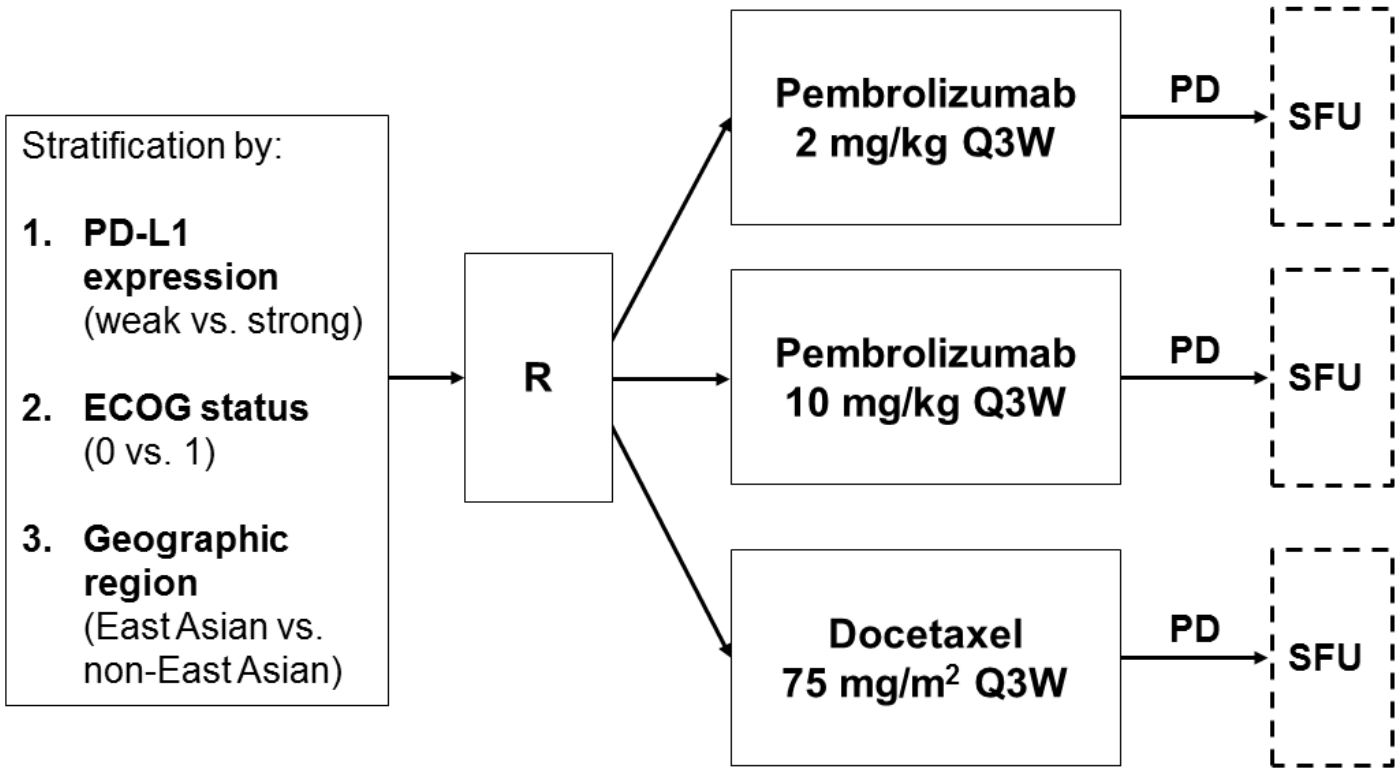
Keynote 010: Design (NSCLC, biomarker-based)

Previously Treated PD-L1 Positive Advanced Non-Small-Cell Lung Cancer

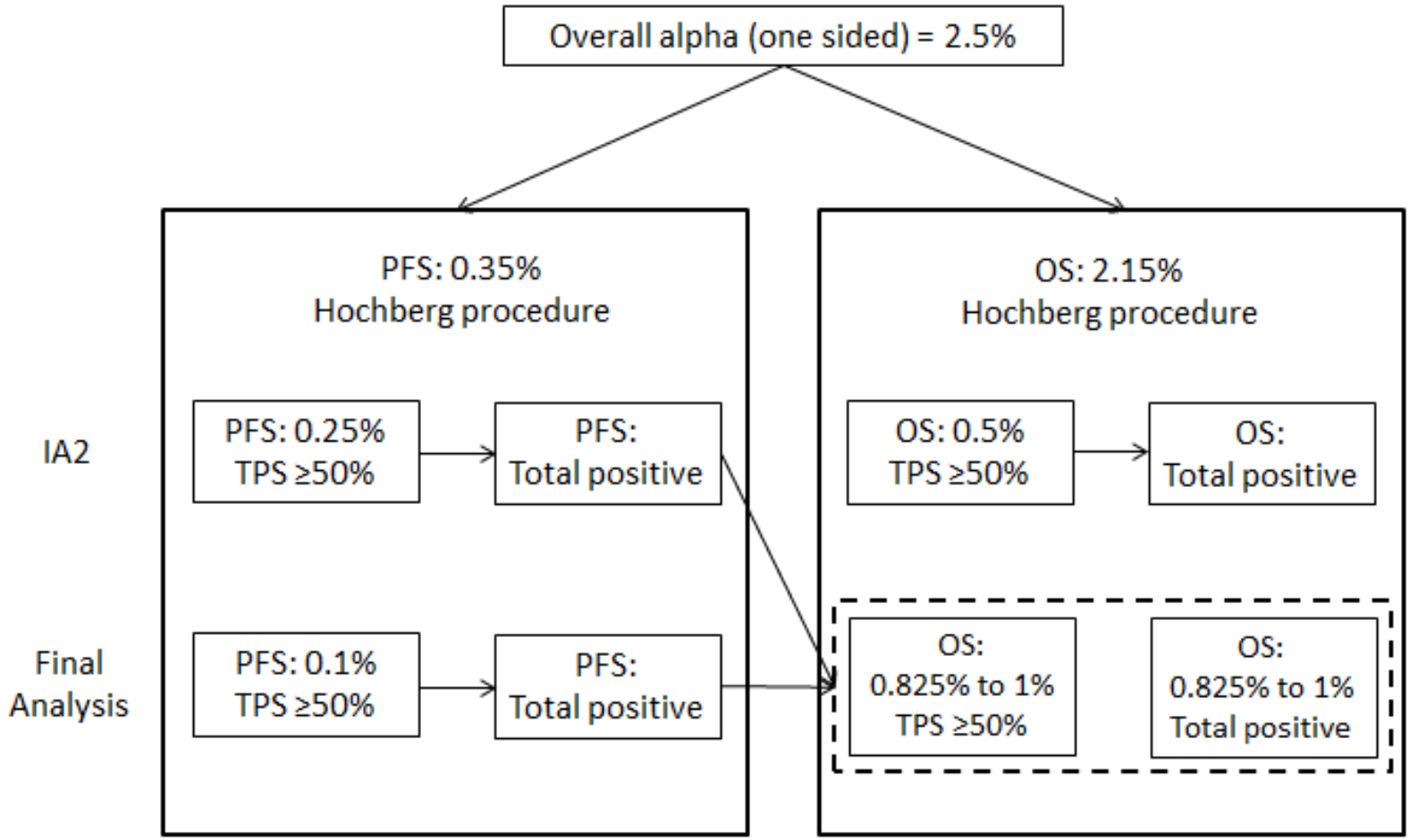


R = Randomization PD = Progressive Disease SFU = Survival Follow-up

Herbst et al. [2016]

Keynote 010 Statistical Methods: Multiplicity

Type I error divided and reallocated between statistical tests



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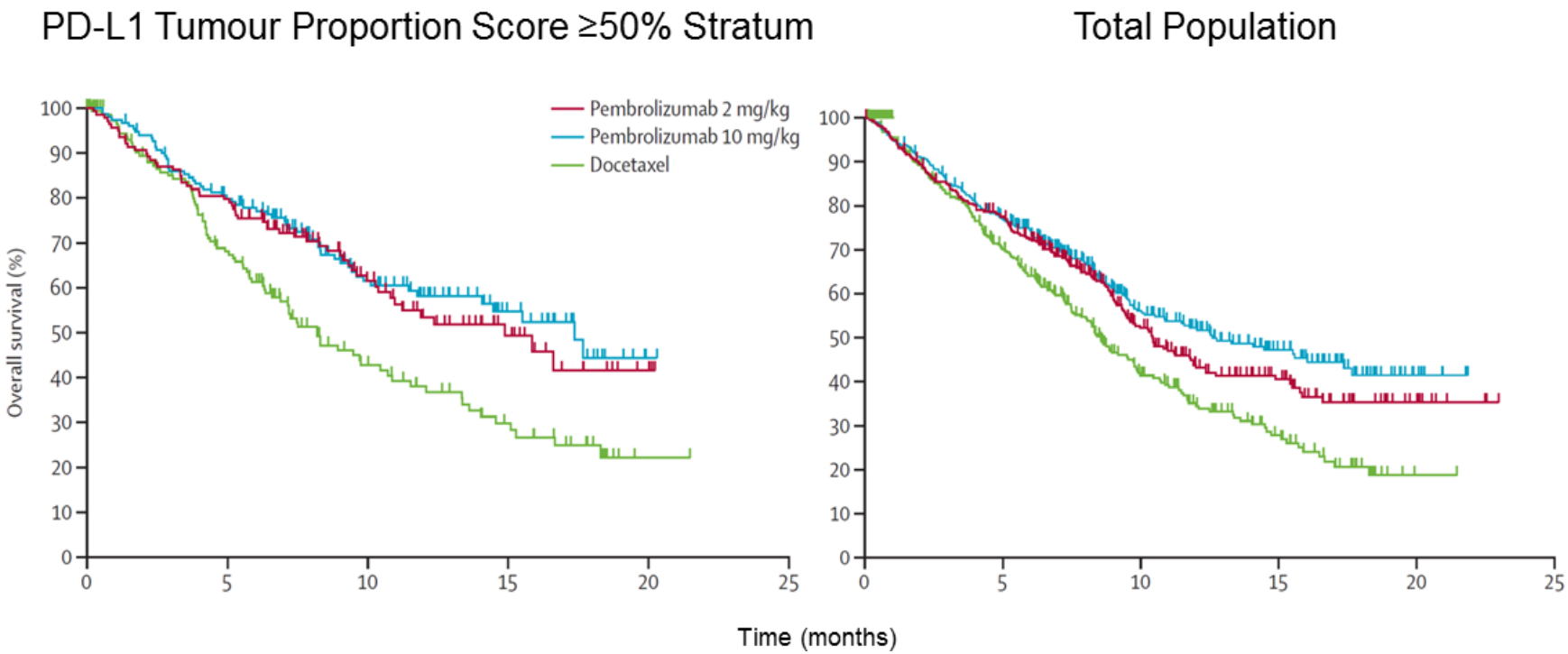
Herbst et al. [2016]

Keynote 010: Overall Survival (OS) by Biomarker at IA2



OS achieved statistical significance according to multiplicity plan in both treatment groups, total positive and TPS $\geq$ 50% populations
Herbst et al. [2016]; PFS=progression free survival

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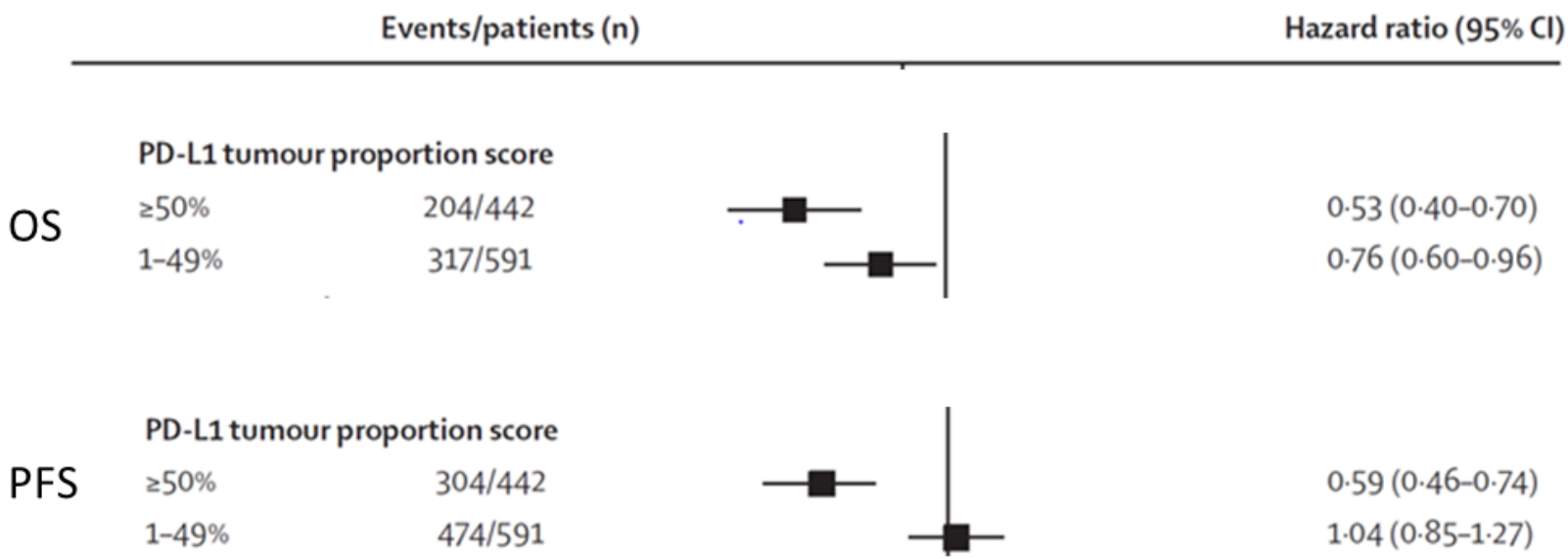
Keynote 010: OS and PFS Hazard Ratio by Biomarker



Herbst et al. [2016]

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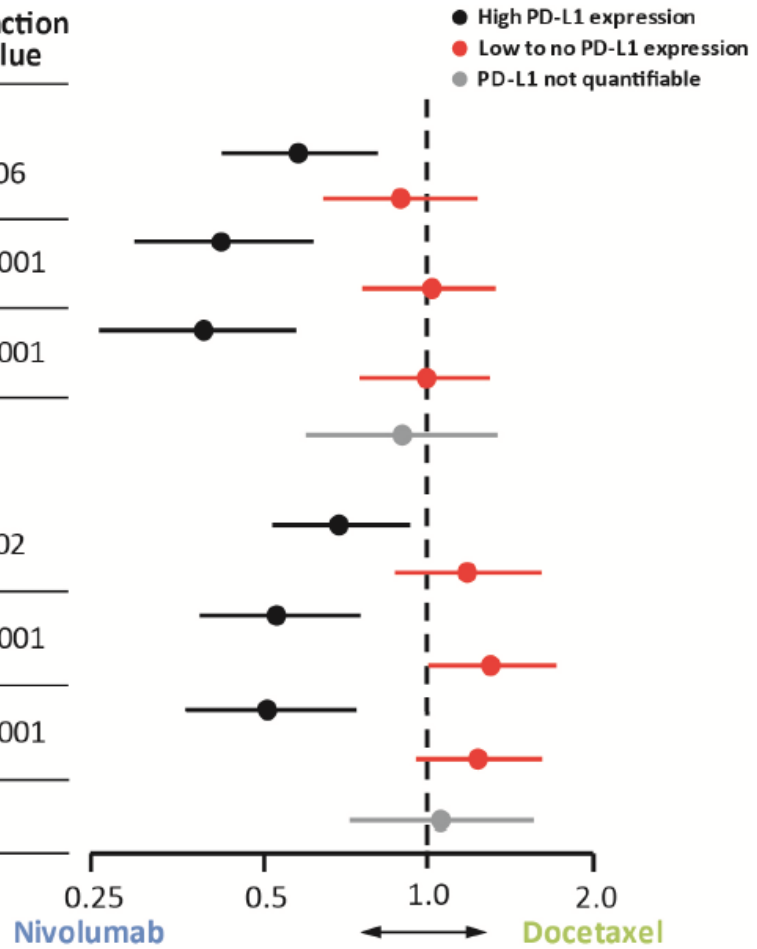
CheckMate 57 Efficacy by Biomarker Status (Exploratory)

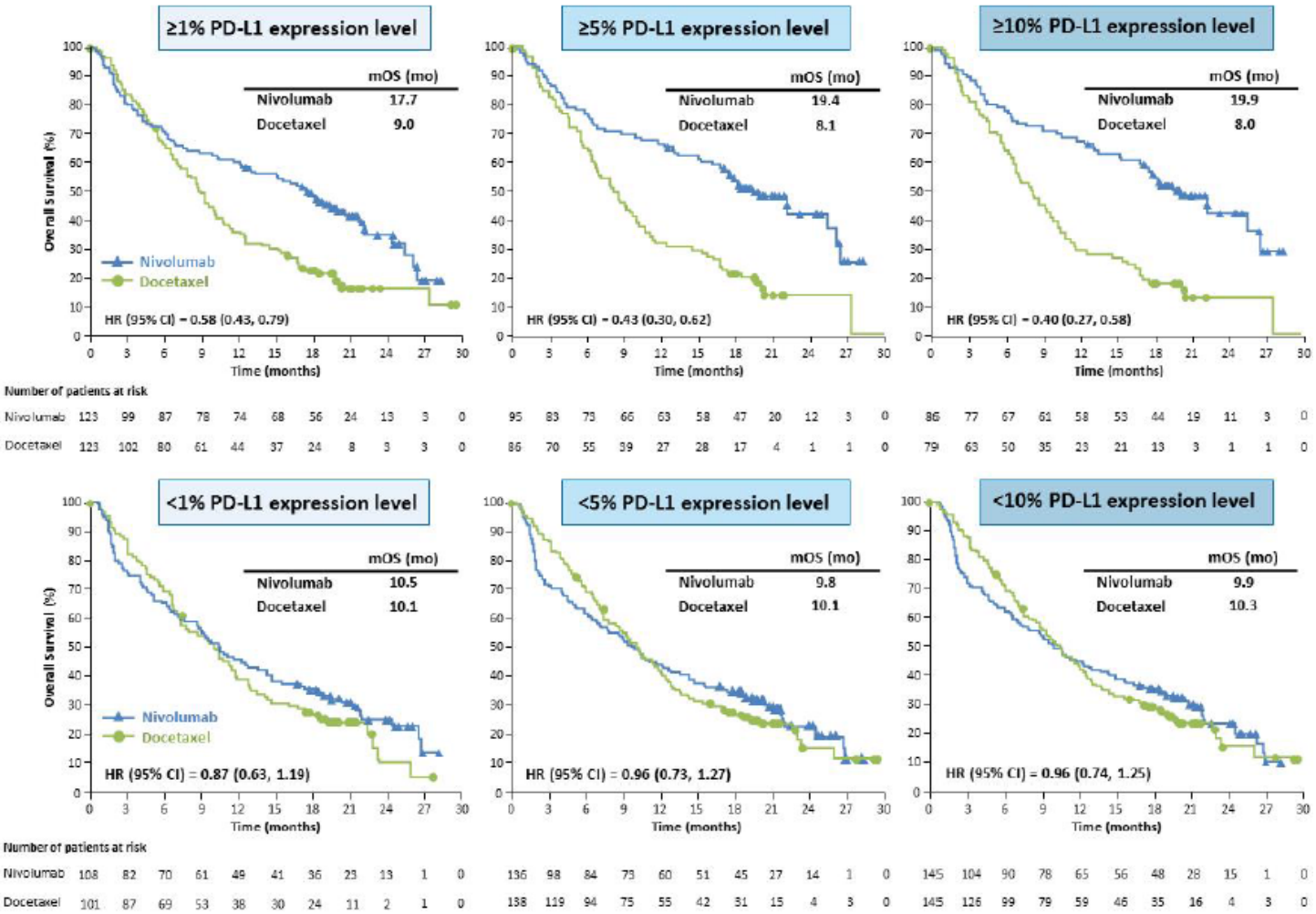
Primary evaluations and approval in broad population

PD-L1 expression level	Nivolumab n	Docetaxel n	Unstratified HR (95% CI)	Interaction *P*-value
OS				
≥1%	123	123	0.59 (0.43, 0.82)	0.06
<1%	108	101	0.90 (0.66, 1.24)	
≥5%	95	86	0.43 (0.30, 0.63)	<0.001
<5%	136	138	1.01 (0.77, 1.34)	
≥10%	86	79	0.40 (0.26, 0.59)	<0.001
<10%	145	145	1.00 (0.76, 1.31)	
Not quantifiable at baseline	61	66	0.91 (0.61, 1.35)	
PFS				
≥1%	123	123	0.70 (0.53, 0.94)	0.02
<1%	108	101	1.19 (0.88, 1.61)	
≥5%	95	86	0.54 (0.39, 0.76)	<0.001
<5%	136	138	1.31 (1.01, 1.71)	
≥10%	86	79	0.52 (0.37, 0.75)	<0.001
<10%	145	145	1.24 (0.96, 1.61)	
Not quantifiable at baseline	61	66	1.06 (0.73, 1.56)	



Borghaei et al. [2015], supplementary materials

CheckMate 57 OS by Biomarker Status (Exploratory)



Borghaei et al. [2015], supplementary materials

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PD-L1 Biomarker is Predictive

- Previously treated (non-squamous) NSCLC
- For high PD-L1 measures, PD-1 antibodies (nivolumab, pembrolizumab) are effective
- 'Exact' cutoffs for effectiveness unknown
- Companion diagnostic approach (pembrolizumab)
  - Trial and approval in targeted-population only
  - Possibility of patient benefit in broad population?
  - Likely higher probability of success from start

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  - Likely higher probability of success from start
- Complementary diagnostic approach (nivolumab)
  - No α-controlled subgroup testing
  - Approval in broad population
  - Diagnostic approved (first 'complementary' diagnostic)
  - Risk that overall population could have not demonstrated statistical significance

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Multiple histology, biomarker focused, single arm trials

- Key endpoints: response rate and duration of response
- Phase IB studies
  - Keynote 12: A Phase Ib Multi-Cohort Study of MK-3475 in Subjects With Advanced Solid Tumors
    - Cancer types: breast (triple negative), head and neck cancer, urothelial tract, gastric
  - Keynote 28: Phase IB Study of Pembrolizumab (MK-3475) in Subjects With Select Advanced Solid Tumors

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  - Keynote 28: Phase IB Study of Pembrolizumab (MK-3475) in Subjects With Select Advanced Solid Tumors
- Keynote 158: A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors
  - Cohorts A-J: 10 solid tumor types (overlap with Keynote 12, 28)
  - Cohort K: MSI-high (biomarker) selected population, any solid tumor type
  - N=1100

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Multiple histology, biomarker focused, single arm trials

- Key endpoints: response rate and duration of response

- Keynote 158: A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors
  - Cohorts A-J: 10 solid tumor types (overlap with Keynote 12, 28)
  - Cohort K: MSI-high (biomarker) selected population, any solid tumor type
  - N=1100

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Strong Type I error control for overall population and biomarker subgroups in randomized studies

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Hypotheses, analyses and test statistics

- $h > 1$ hypotheses
- $k > 1$ analyses
- $T_1 < T_2 \cdots < T_k$ calendar times of analyses
- For hypothesis $i = 1, \ldots, h$
  - May not test at all times for each hypothesis
  - $1 \leq k(i) \leq k$ analysis times $T_{i,1} < T_{i,2} \cdots < T_{i,k(i)}$
    - Some or all of $T_1 < T_2 \cdots < T_k$
  - $d_{i,1} < d_{i,2} \cdots < d_{i,k(i)}$ events for each analysis
  - $\mathcal{I}_{i,1} < \mathcal{I}_{i,2} \cdots < \mathcal{I}_{i,k(i)}$ statistical information for each analysis
    - For equal randomization with a time-to-event endpoint, this is approximated by $d_{i,j}/4$ [Schoenfeld, 1981]
  - $Z_{i,1}, Z_{i,2}, \ldots, Z_{i,k(i)}$ group sequential, normal test statistics with variance 1 to test hypothesis

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Example 1: Calendar-based

- $h = 2$ hypotheses (2 endpoints)
  - PFS: progression free survival; time until progression or death
  - OS: overall survival; time until death
- $k = 3$ analyses at given calendar times
  - PFS analyzed at $T_1 = 18$ and $T_2 = 24$ months
  - OS analyzed at $T_1 = 18$, $T_2 = 24$ and $T_3 = 36$ months
  - Number of events (d_{ij}) is random

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Example 2: Event-based

- $h = 2$, same hypotheses
  - PFS
  - OS
- $k = 3$ analyses at 3 times
  - PFS analyzed twice after $d_{1,1} < d_{1,2}$ endpoints
  - OS analyzed at same times plus final analysis with $d_{2,3}$ endpoints
  - Number of OS events at interims $(d_{2,1}, d_{2,2})$ are random
  - Analysis times $T_1,\ T_2,\ T_3$ are random

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Example 3: Add biomarker hypothesis

- $h = 4$ hypotheses (2 endpoints $\times$ 2 populations)
  - PFS
    - H_1: BM+ population (biomarker positive subgroup)
    - H_2: Overall population
  - OS
    - H_3: BM+ population
    - H_4: Overall population
- $k = 3$ analyses
  - PFS analyzed twice after $d_{1,1} < d_{1,2}$ endpoints
  - PFS endpoints for overall population $(d_{2,1}, d_{2,2})$ are random
  - OS analyzed at same times plus final analysis with $d_{3,3}$ endpoints
  - Number of OS events are random for BM+ at interims $(d_{3,1}, d_{3,2})$
  - Number of OS events are random for total population at all analyses $(d_{4,1}, d_{4,2}, d_{4,3})$
  - Analysis times T_1, T_2, T_3 are random

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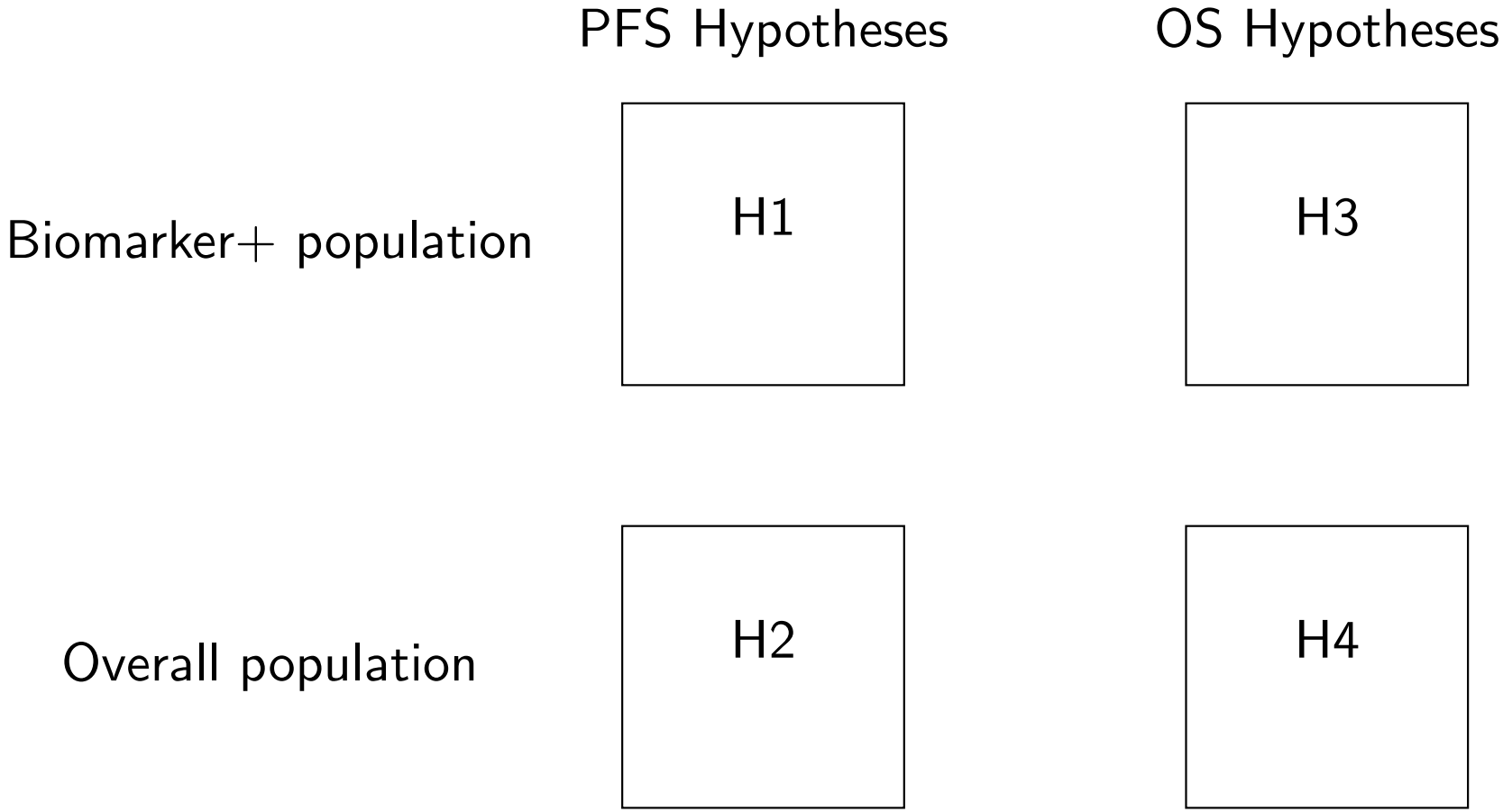
Example 3 graph



Methods summary

- Spending time concept importance when multiple hypotheses tested with varying rates of information accumulation
- Some key concepts for spending functions with group sequential combined with graphical multiplicity [Maurer and Bretz, 2013]
- Brief note on technical algorithm for testing

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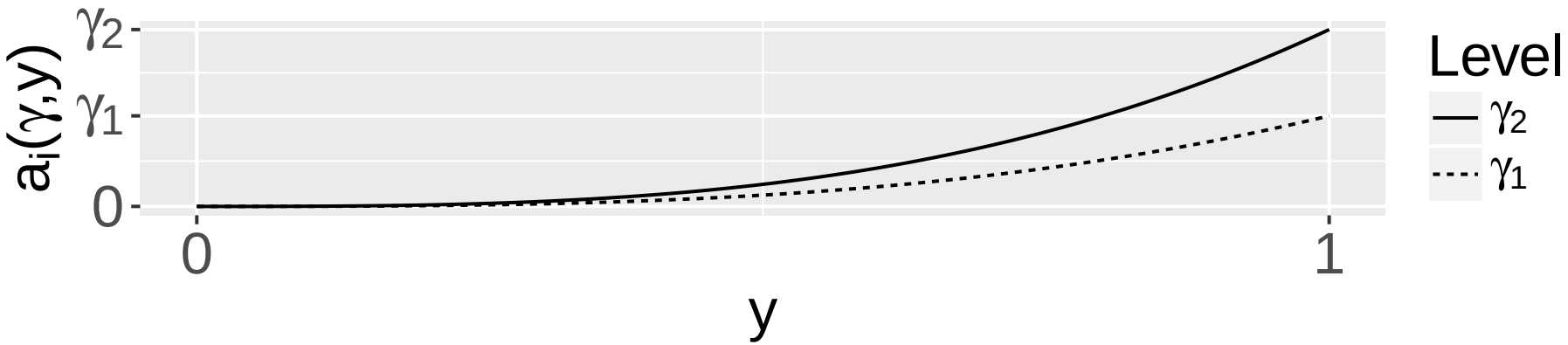
Spending functions

- Slightly modified notation of Maurer and Bretz [2013]
- All hypotheses controlled at 1-sided level $0 < \alpha < 1$
- Spending function for hypothesis i
  - $a_i(\gamma, y)$
  - Non-decreasing for y on $[0, 1]$, γ on $[0, \alpha]$
  - $a_i(\gamma, 0) = 0$
  - $a_i(\gamma, y) = \gamma$ for $y = 1$



Spending times

For hypothesis $i = 1, \ldots, k$

- Test hypothesis at level γ_i
- $k(i) \leq k$ analysis times
- Spending times

$$0 = t_{i,0} < t_{i,1} \leq \cdots \leq t_{i,k(i)} = 1$$

- Type I error allocated to analysis $j = 1, \ldots, k(i)$

$$a(\gamma_i, t_{i,j}) - a(\gamma_i, t_{i,j-1})$$

- Bounds for Z-statistics then a standard group sequential calculation [Slud and Wei, 1982] based on statistical information (endpoint count; Tsiatis [1982])
- Any futility bound ignored in calculations per Liu and Anderson [2008]

Setting spending times

- $d_{i,\max}$: maximum planned endpoints for hypothesis i
- Information time [Lan and DeMets, 1983]:

$$t_{i,j} = \min(1, \mathcal{I}_{i,j}/\mathcal{I}_{i,\max} = d_{i,j}/d_{i,\max})$$

  - Under-running variation is to set $t_{i,k(i)} = 1$ if planned information level not reached for hypothesis i ($\mathcal{I}_{i,k(i)} < \mathcal{I}_{i,\max}$)
- Calendar time [Lan and DeMets, 1989]:

$$t_{i,j} = T_{i,j}/T_{i,k(i)}$$

- Alternate information time:
  - *e.g.*, set all OS hypotheses based on information time for biomarker positive subgroup OS hypothesis
  - Suggested in Proschan et al. [2006] (Section 5.1.1) based on the same logic as calendar time

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Key condition for spending time

- In words: Cannot choose spending time or information time for an analysis based on value of current or former test statistic for any hypothesis.
- Using notation: $t_{i,j}$ and $\mathcal{I}_{i,j}$ are conditionally independent of $Z_{i',j'} - E\{Z_{i',j'}\}$ for $T_{i',j'} \leq T_{i,j}$, $i' = 1, 2, \ldots, k$.

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Testing algorithm

For a given analysis

1. Test each null hypothesis i to be tested at or before this analysis
   a) Analysis index j, denote Type I error allocated to hypothesis γ_i
   b) Compute spending time $t_{i,j}$
   c) Compute boundaries $b_{i,j'}$, $j' = 1, \ldots, j$ based on
      - γ_i
      - $t_{i,j'}$, $j' = 1, \ldots, j$
      - $\mathcal{I}_{i,j'}$, $j' = 1, \ldots, j$
      - This is a standard group sequential design calculation
      - For $j' < j$, $b_{i,j'}$ will not change unless γ_i has changed due to reallocation
2. If $Z_{i,j'} > b_{i,j'}$ for any $j' = 1, \ldots, j$, reject null hypothesis i
3. If any hypothesis was rejected, reallocate γ_i per multiplicity graph [Bretz et al., 2009] and return to step 1

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Return to historical example; Type I error allocation

	PFS Hypotheses	OS Hypotheses
Biomarker+ population	H1 $\alpha_1 = 0.0025$	H3 $\alpha_2 = 0.01$
Overall population	H2 $\alpha_3 = 0.0025$	H4 $\alpha_4 = 0.01$

- Allocate most α to OS
- Equal split between populations

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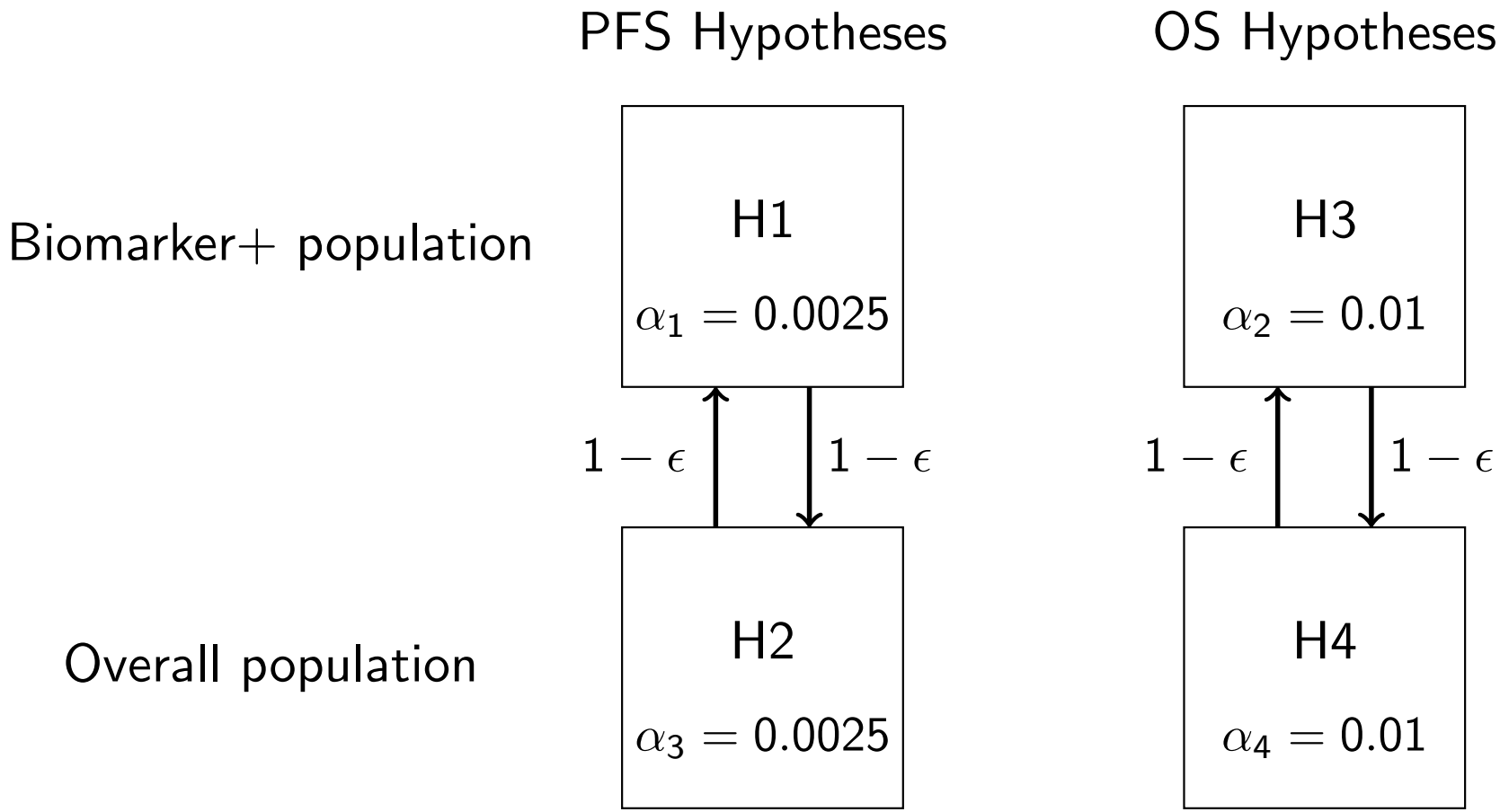
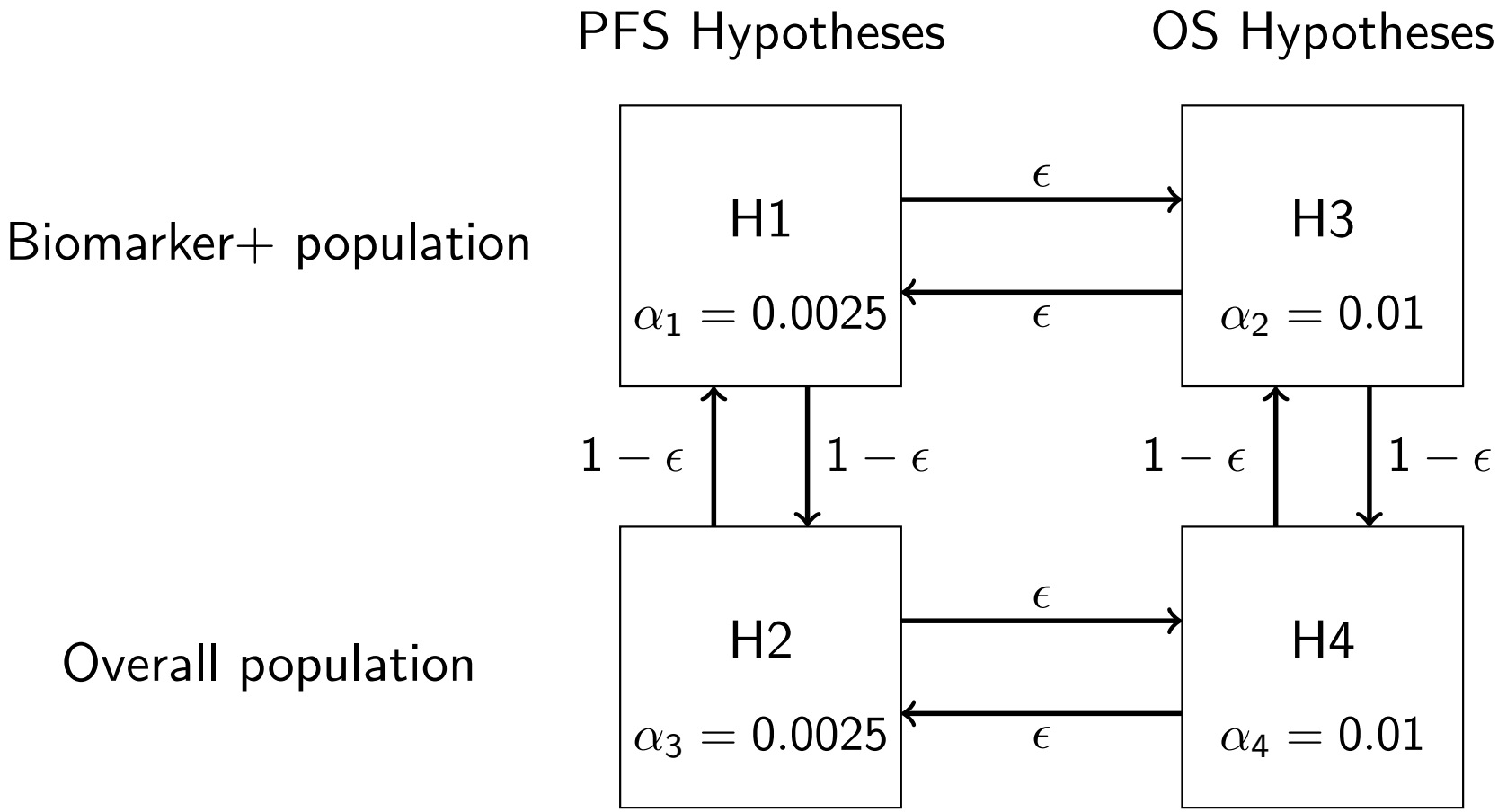
Main reallocation within endpoints



- Bonferonni-Holm between populations
- Motivated by PFS testing ending before OS testing

Final reallocation between endpoints



- Bonferonni-Holm between populations
- If both populations reject, reallocate to other endpoint [Bretz et al., 2009]

Summary and conclusions

- Biomarker-based development programs continue to be of interest
- Different approaches have been taken
- Personalized medicine results and multiple endpoints of interest can create a substantial multiplicity problem for oncology development
- Maurer and Bretz [2013] creates a framework for group sequential trials with multiple hypotheses
- Method extended here to apply to trials with time-to-event endpoints with varying rates of information (endpoint) accumulation

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