Bayesian Adaptive Designs for Clinical Trials

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Phase 2

Why do we do clinical trials on new products?

A. To learn if the product is safe and effective

B. To ensure we deliver good medicine to patients

C. To see if the results are unusual assuming the product is ineffective and unsafe

D. To learn the probability the new drug is safe & effective

Bayesian vs. Frequentist

- P-value = Pr(Data or more extreme data | Ho is true)
- Posterior = Pr(Hypothesis | Data)
  - Insensitive to study design
  - Fit one model, calculate any posterior

Three people get a positive pregnancy test

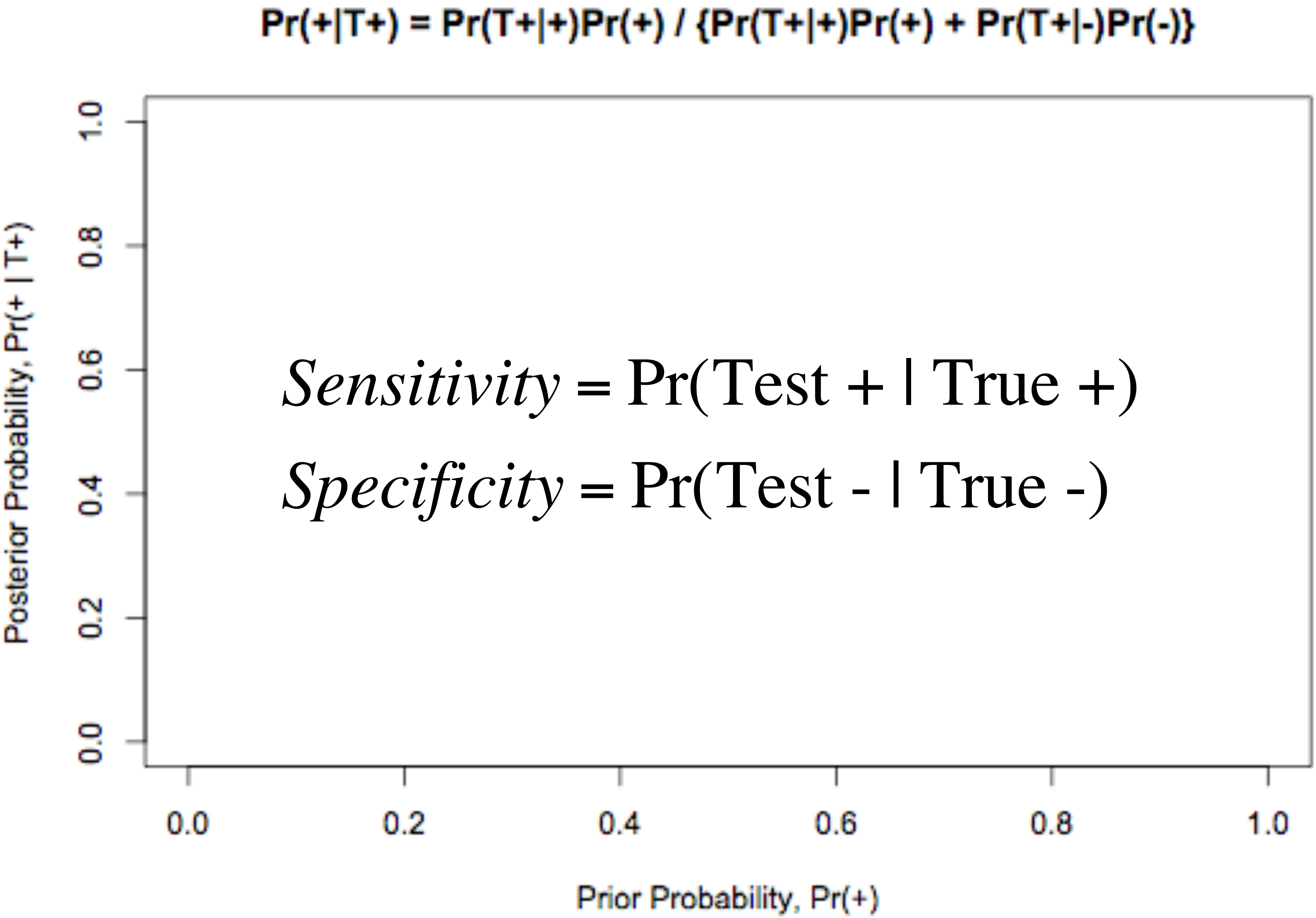
- My sister with 4 kids who I know wants more
- You or your wife/gf. Using oral contraception
- Me

- What is the probability each person is pregnant?

Three people get a positive pregnancy test

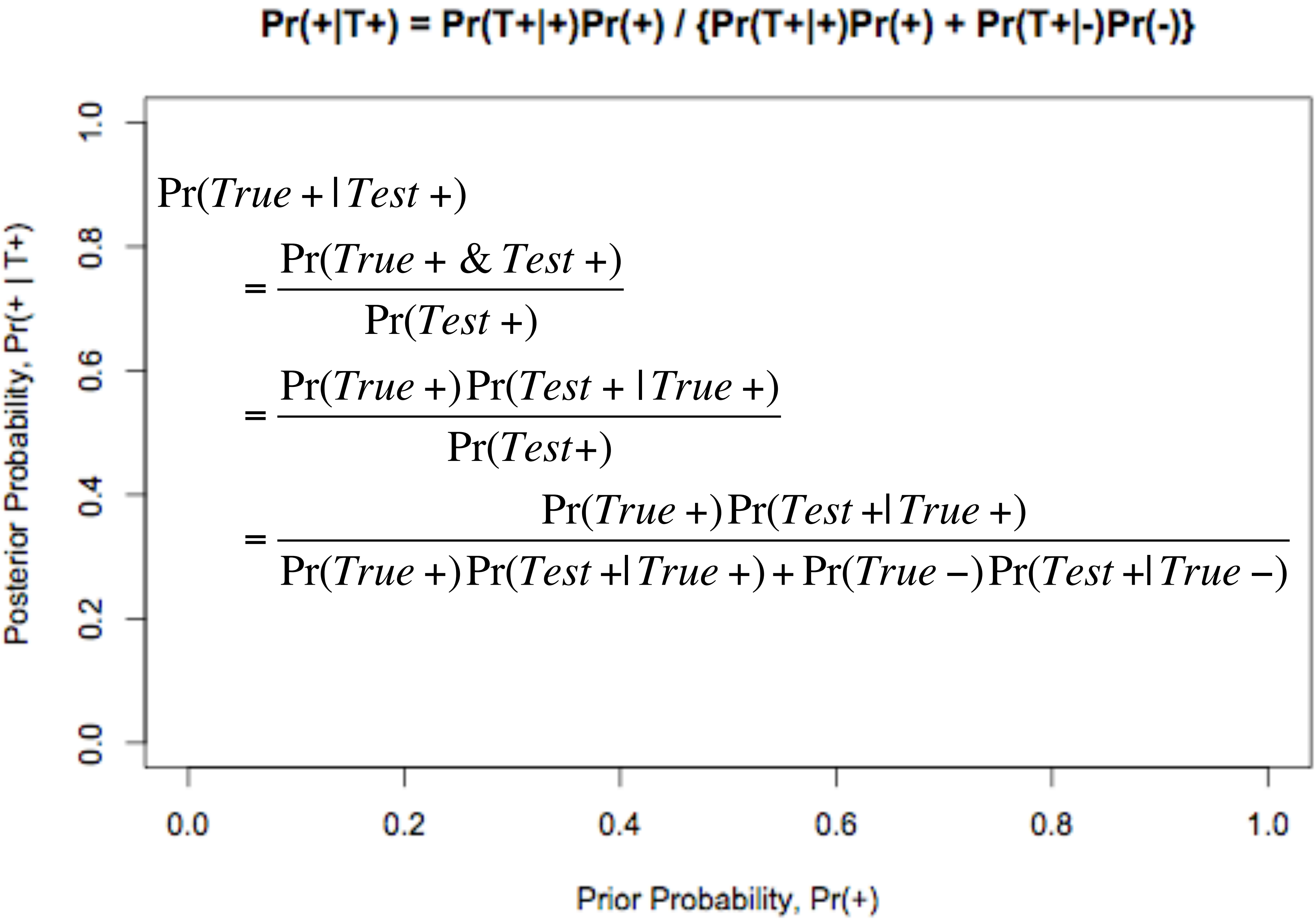
- My sister with 4 kids who I know wants more
- You or your wife/gf. Using oral contraception
- Me
  - Sensitivity 100%, Specificity 95%

- What is the probability each person is pregnant?



$$\textit{Sensitivity} = \mathrm{Pr}(\mathrm{Test}\ + \mid \mathrm{True}\ +)$$

$$\textit{Specificity} = \mathrm{Pr}(\mathrm{Test}\ - \mid \mathrm{True}\ -)$$



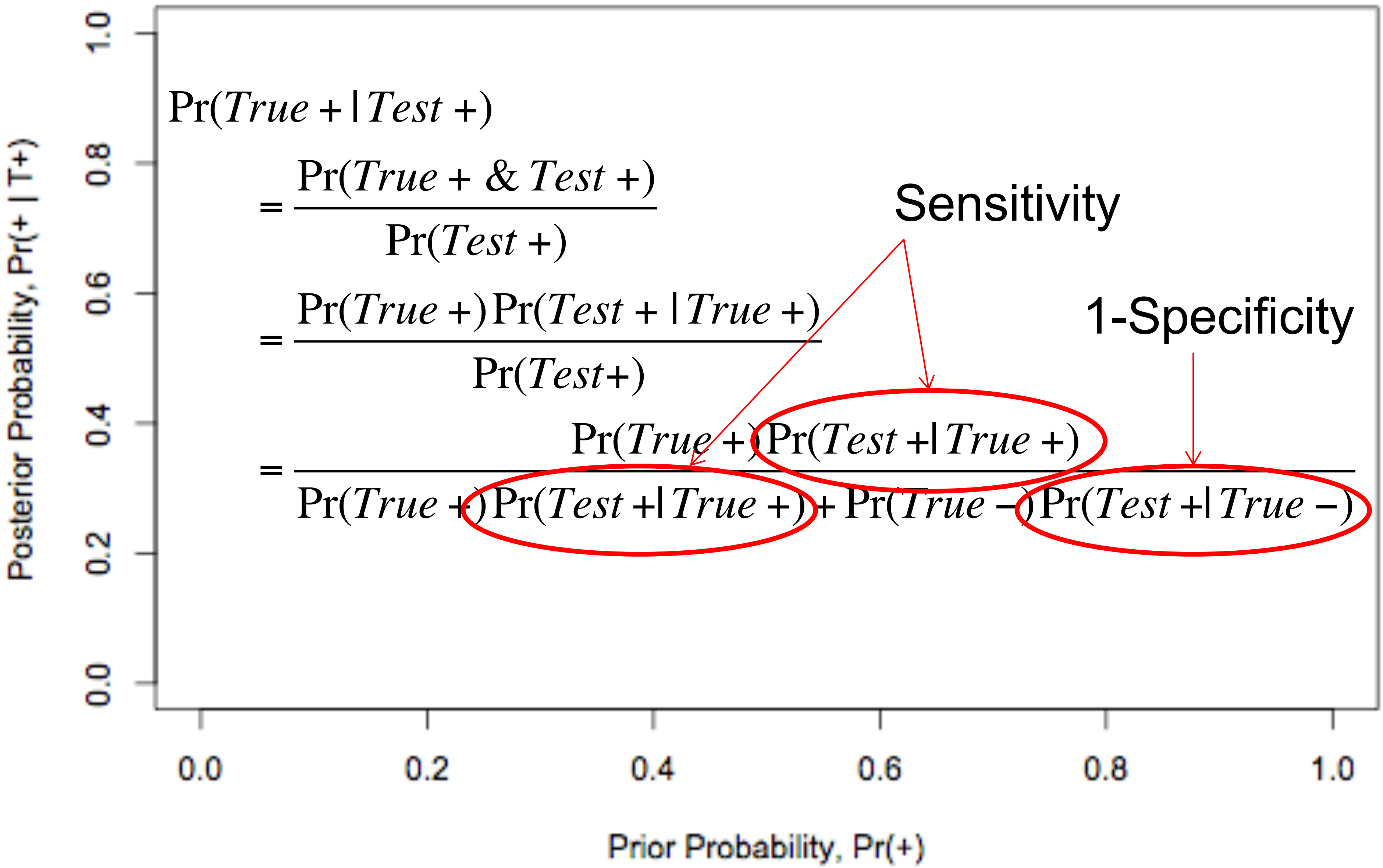
$$\Pr(True+ \mid Test+)$$

$$= \frac{\Pr(True+ \,\&\, Test+)}{\Pr(Test+)}$$

$$= \frac{\Pr(True+)\Pr(Test+ \mid True+)}{\Pr(Test+)}$$

$$= \frac{\Pr(True+)\Pr(Test+ \mid True+)}{\Pr(True+)\Pr(Test+ \mid True+) + \Pr(True-)\Pr(Test+ \mid True-)}$$

Pr(+|T+) = Pr(T+|+)Pr(+) / {Pr(T+|+)Pr(+) + Pr(T+|-)Pr(-)}

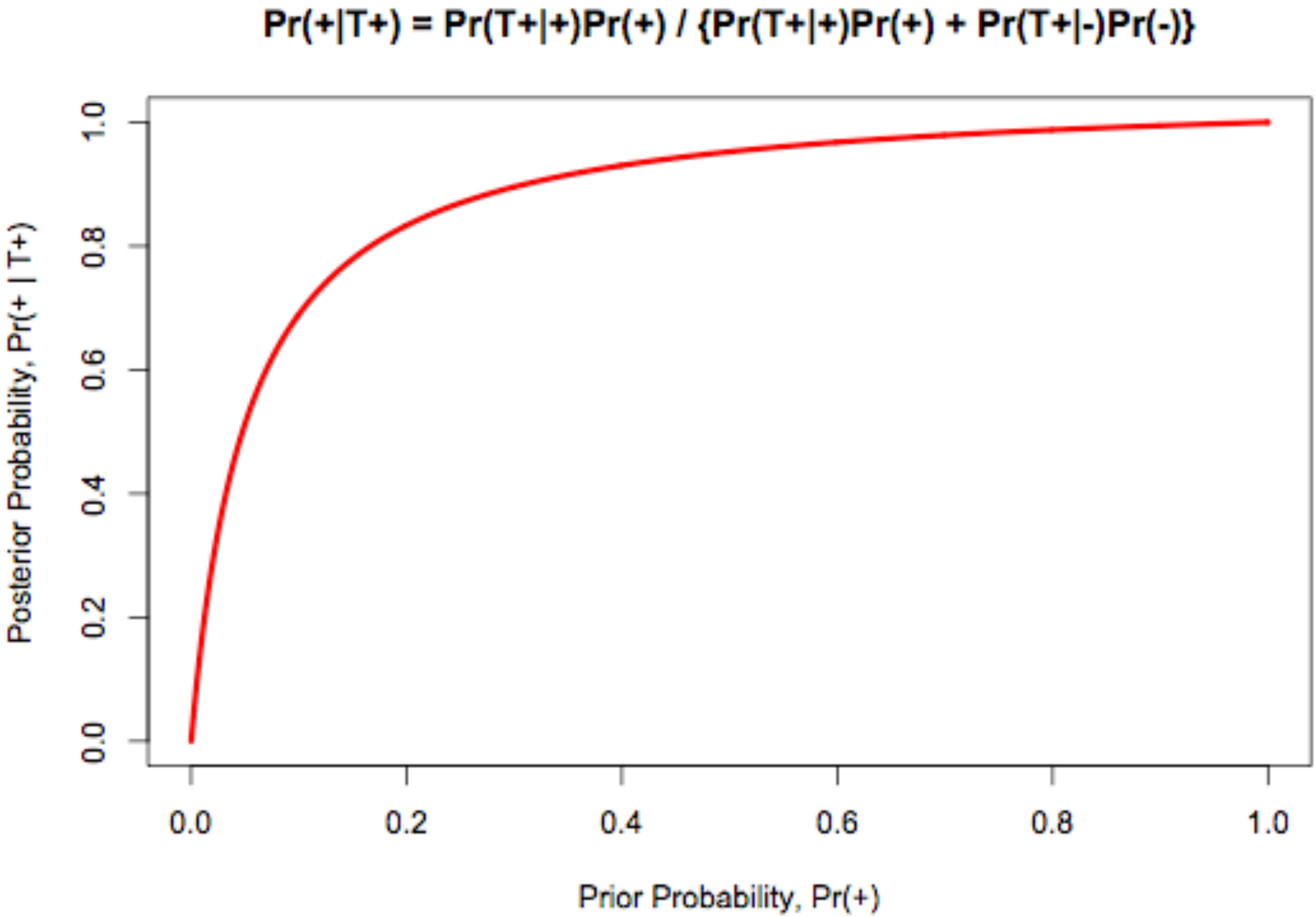


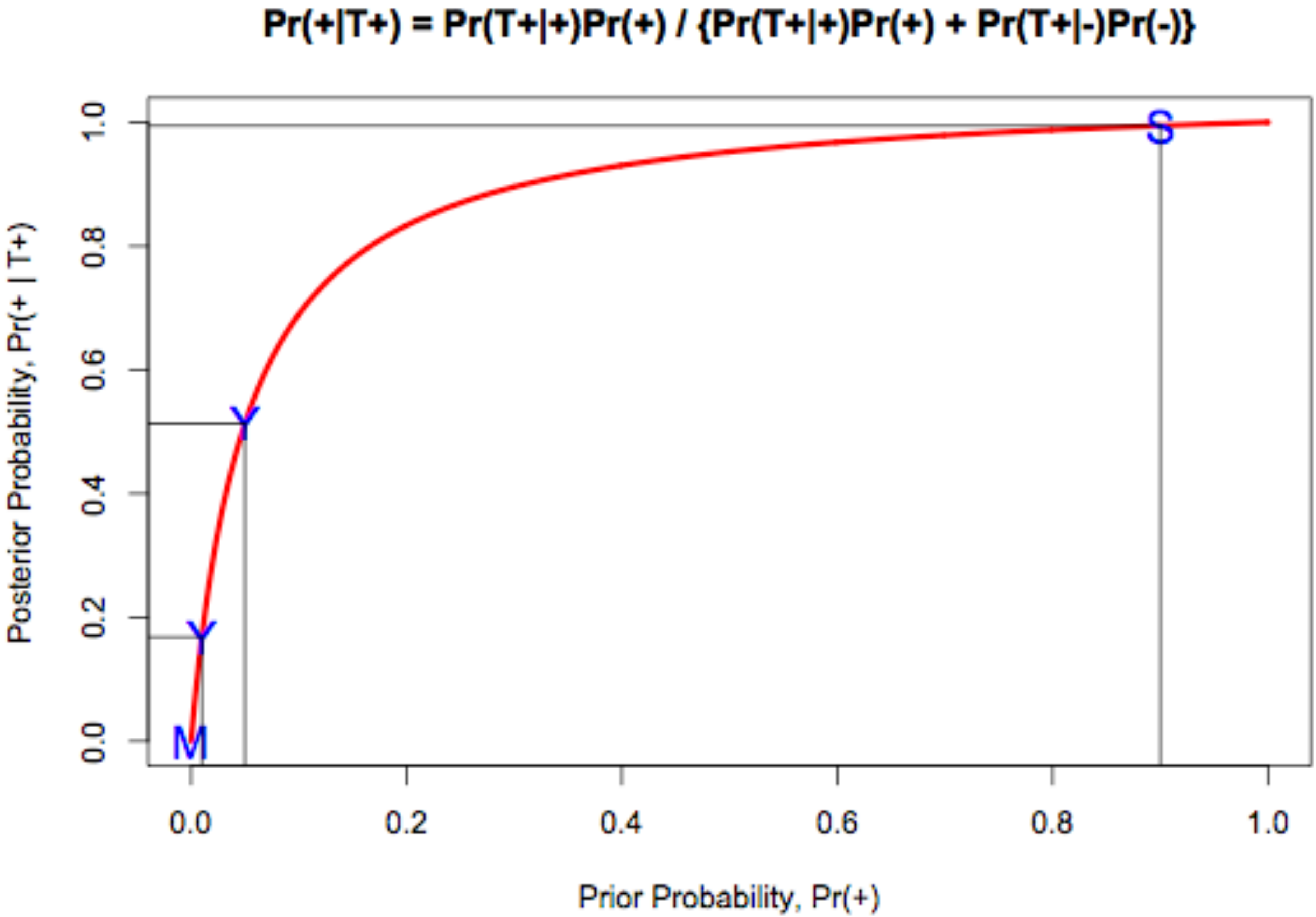
$$\Pr(True+ \mid Test+)$$

$$= \frac{\Pr(True+ \;\&\; Test+)}{\Pr(Test+)}$$

$$= \frac{\Pr(True+)\Pr(Test+ \mid True+)}{\Pr(Test+)}$$

$$= \frac{\Pr(True+)\Pr(Test+ \mid True+)}{\Pr(True+)\Pr(Test+ \mid True+) + \Pr(True-)\Pr(Test+ \mid True-)}$$


Pr(+|T+) = Pr(T+|+)Pr(+) / {Pr(T+|+)Pr(+) + Pr(T+|-)Pr(-)}
Posterior Probability, Pr(+ | T+)
0.0
0.2
0.4
0.6
0.8
1.0
Prior Probability, Pr(+)


Pr(+|T+) = Pr(T+|+)Pr(+) / {Pr(T+|+)Pr(+) + Pr(T+|-)Pr(-)}
Posterior Probability, Pr(+ | T+)
0.0
0.2
0.4
0.6
0.8
1.0
S
Y
Y
M
Prior Probability, Pr(+)

You read two abstracts

- A study for an experimental HIV vaccine shows that vaccinated subjects exposed to HIV were less likely to contract the disease vs. unvaccinated subjects (p=0.01)

- A study for a new experimental measles vaccine shows that vaccinated subjects exposed to measles were less likely to contract the disease vs. unvaccinated subjects (p=0.01)

- Do you believe one vaccine is more likely to work than the other?

Phase 2 Dose Finding Trials

Phase 2 Trials

- Early phase results
  - Animal studies showed promise for disease
  - Phase 1 showed non-toxic in healthy humans
- Questions for Phase 2
  - Does the treatment work in humans
  - Which dose is best
  - Which dose(s) to take to Phase 3
  - Is an dose with promising efficacy also safe
  - What is likelihood of Phase 3 success

Adaptive Randomization Strategies

- Bandits
- Play the Winner
- Randomized Play the Winner
- Randomize ~ Pr(Best Treatment)
- Randomize ~ *f*(Pr(Best Treatment))
- Randomize ~ Dose that gives the most information
- One of these with constraints

Adaptation

- Multiple trial characteristics may be changed during the course of the trial based on accumulating data
- Must pre-prescribe changes
  - Available Doses
  - Randomization proportions
  - Time of interim analyses
  - Maximum sample size
  - Dose dropping rules
  - Allow doses to re-enter?

Example In Uterine Cancer

- Phase 2 dose finding trial
- 3-armed RCT
  - Control chemotherapy
  - Control + experimental treatment q2w
  - Control + experimental treatment q1w
- Goals
  - Treat patients effectively & ethically
  - Learn about experimental treatment
  - Explore adaptive designs
    - This company's first attempt at an adaptive design

Trial Setup

- Primary Outcome
  - Progression Free Survival (PFS)
  - λ_c = Rate of PFS in Control population
  - λ_2 = Rate of PFS in Control + q2w population
  - λ_1 = Rate of PFS in Control + q1w population
- Expectation
  - Control mean PFS = 303 days, median = 210
  - Accrual
    - 1 patient every 3 days for first 45 pts (135 days)
    - 1 patient every 2 days thereafter
- Need to beat control by 10% to be marketable

Factors to Consider

- Statistical Model
  - Parametric dose-response curve, non-parametric, independent arms
  - Historical vs. vague priors
- How many doses
- Maximum sample size
- Timing of first interim analysis
- Timing of subsequent interim analyses
  - Time based or patient based
- Randomization scheme
- Rules to drop doses
- Rules to allow doses to re-enter
- Rules to stop for futility
- Rules to stop for success
- How long to track patients after last patient enrolled

Statistical Model

- Assume time-to-progression exponential
- Priors on rates:

  $\lambda_{c,} \lambda_{2,} \lambda_1 \sim \Gamma(1, 303 \text{ days})$
- Posteriors

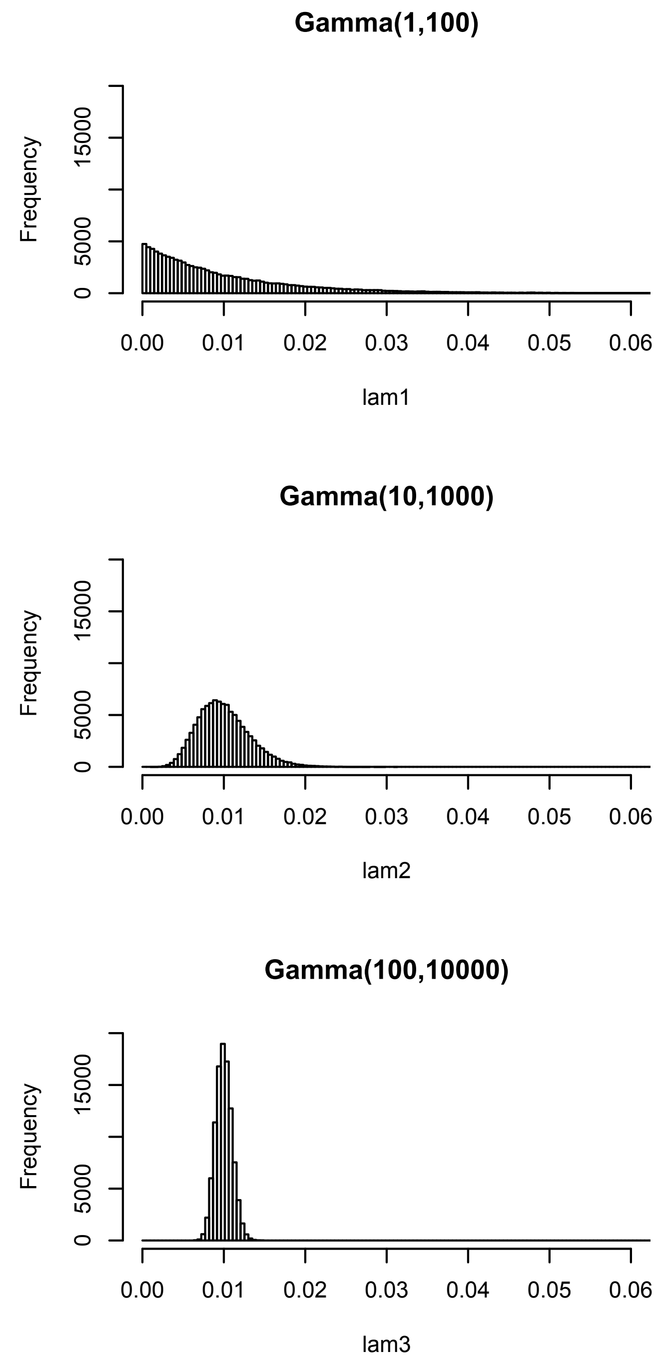
  $\lambda_d | \text{Data} \sim \Gamma(1+ \#\ \text{Progressors}, 303+\text{Exposure Time})$
- Also calculate probability each dose is best
  - "best" = has lowest PFS rate
  - $p_c = \Pr(\lambda_c < \lambda_2 \ \& \ \lambda_c < \lambda_1)$
  - $p_2 = \Pr(\lambda_2 < \lambda_c \ \& \ \lambda_2 < \lambda_1)$
  - $p_1 = \Pr(\lambda_1 < \lambda_c \ \& \ \lambda_1 < \lambda_2)$

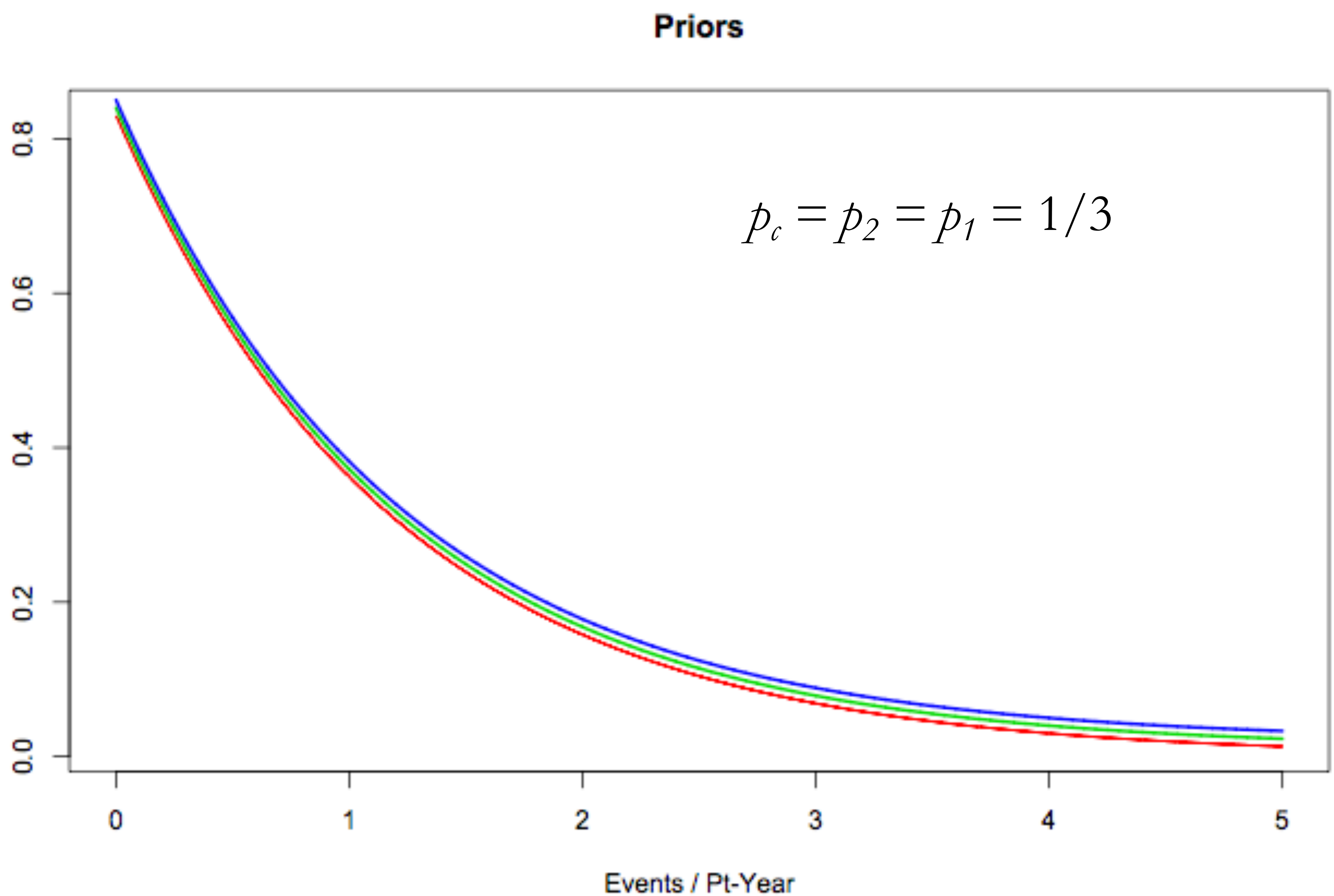
Example

```
> lam1 <- rgamma(100000,   1,   100)
> lam2 <- rgamma(100000,  10,  1000)
> lam3 <- rgamma(100000, 100, 10000)
> par(mfrow=c(3,1))

> mean(lam1 < lam2 & lam1 < lam3)
[1] 0.5738
> mean(lam2 < lam1 & lam2 < lam3)
[1] 0.24854
> mean(lam3 < lam1 & lam2 > lam3)
[1] 0.17766

>hist(lam1,breaks=seq(0,.12, length=250),
          xlim=c(0,.06), ylim=c(0,20000),
          main="Gamma(1,100)")
> hist(lam2,breaks=seq(0,.12, length=250),
          xlim=c(0,.06), ylim=c(0,20000),
          main="Gamma(10,1000)")
> hist(lam3,breaks=seq(0,.12, length=250),
          xlim=c(0,.06), ylim=c(0,20000),
          main="Gamma(100,10000)")
```




Priors
0.0
0.2
0.4
0.6
0.8
0
1
2
3
4
5
Events / Pt-Year
pc = p2 = p1 = 1/3

Statistical Summary

- Primary Outcome: Progression free survival
  - λ_t = PFS rate for Treatment *t*; *t* = A, B, C

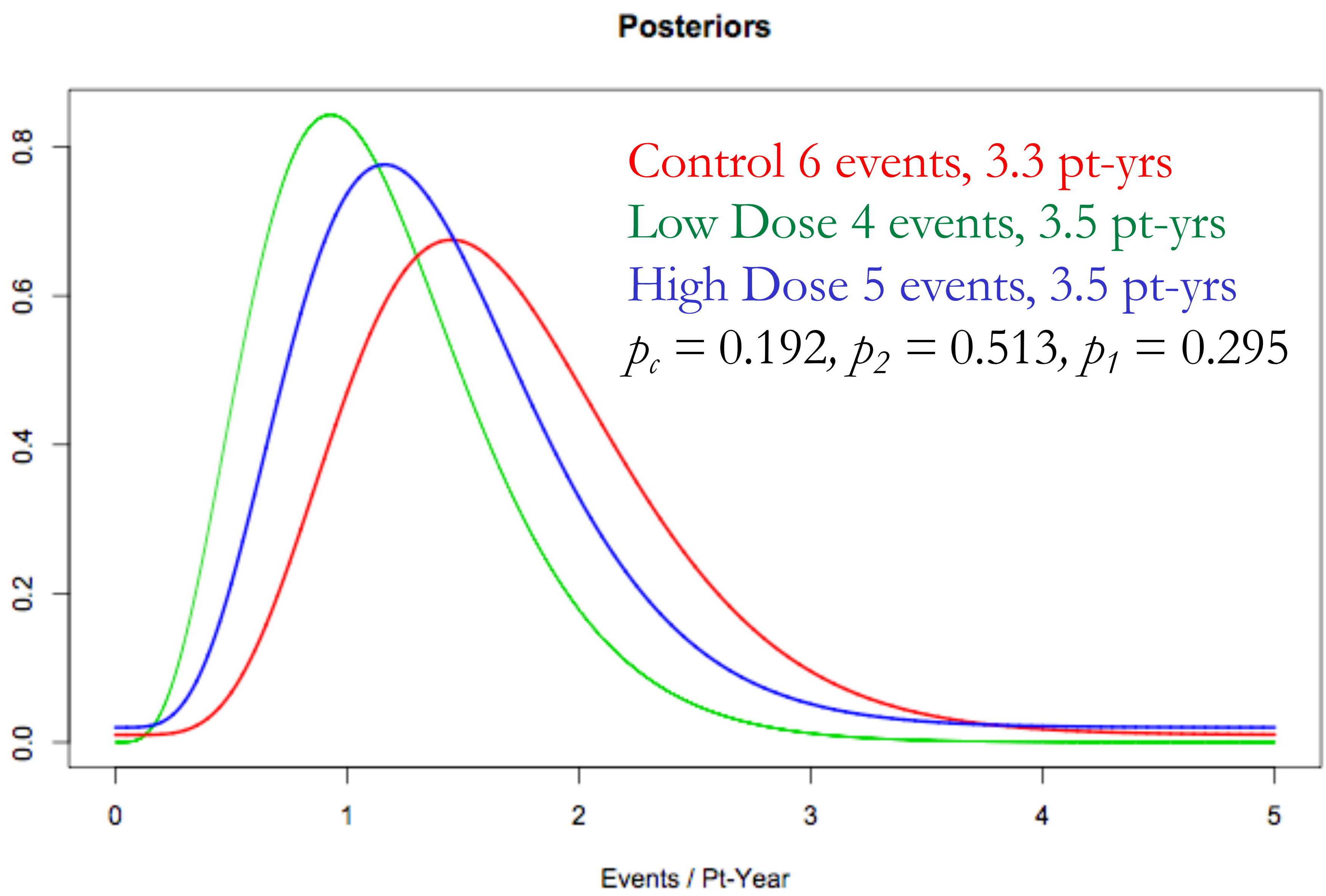
- Statistical Assumptions and Modeling
  - PFS distributed $y_{i,t} \sim \text{Exp}(\lambda_t)$; *t* = A, B, C
  - Priors: $\lambda_{A,} \lambda_{B,} \lambda_C \sim \Gamma(1, 303)$

    Equals 1 subject with mean 303 days

    median = 210 days

    Median = Mean × log(2) for gamma dist
  - Posteriors:

    $$\lambda_t \mid data \sim \Gamma(1 + \#\ \text{Events}_t, 303 + \text{Exposure}_t)$$


Posteriors
Control 6 events, 3.3 pt-yrs
Low Dose 4 events, 3.5 pt-yrs
High Dose 5 events, 3.5 pt-yrs
$p_c = 0.192, p_2 = 0.513, p_1 = 0.295$
0.0
0.2
0.4
0.6
0.8
0
1
2
3
4
5
Events / Pt-Year

Complication I'll ignore

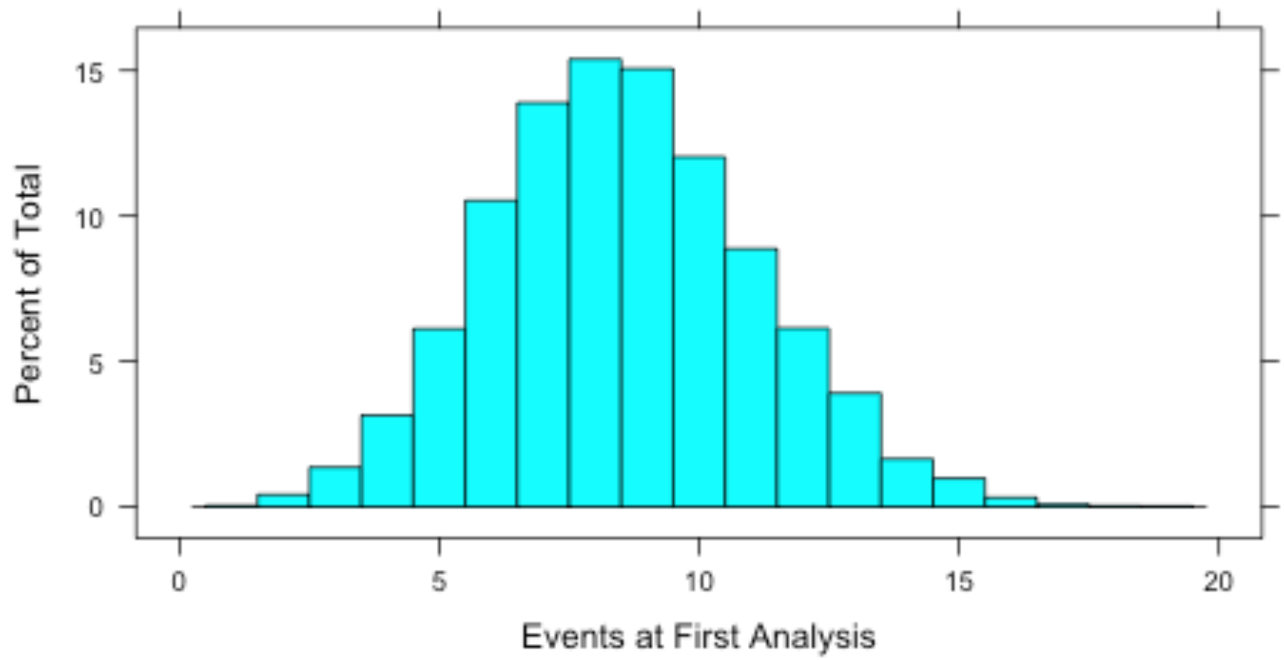
- In fact there were 2 types of patients
  platinum sensitive & platinum refractory
- Expect mean TTP shorter for refractory
    TTP in refractory = 2/7 that of sensitive
- Model event rates as $\gamma\lambda_d$ for refractory
    assume γ same across groups
- Prior on $\log(\gamma) \sim N(0,10^2)$
- Means we no longer have conjugate priors
    must use Metropolis-Hastings algorithm

Maximum Sample Size

- Oftentimes determined by company resources
- Considered 150 & 195

Timing of interim analyses

- Expected accrual rate = 3 days per patient
  - 45 patients take 135 days
  - With expected $\lambda_c = 1/303$
  - Expect 8.5 events by 135 days
  - Median 8, IQR 7-10



Randomization

- Randomize first 45 patients 15:15:15
- Start interim analysis after 45th patient enrolled
- Repeat interim analyses every 15 patients
  - Approximately every 1 month with expected accrual
  - This timing worked logistically
  - Allowed blocks of 15 to ensure patients on each dose
- Open question: How to randomize?

Randomization Options

- Let r_d = randomization probability to dose d
- Let p_d = probability arm d has lowest (best) progression rate
- Randomization weighting by C

$$r_d = \frac{p_d^C}{p_1^C + p_2^C + p_3^C + \ldots + p_D^C}$$

Randomization Options

$$r_d = \frac{p_d^C}{p_1^C + p_2^C + p_3^C + \ldots + p_D^C}$$

- $C = 0$, equal randomization ($r_d = 1/\text{Number of Groups}$)
- $C = 1$, proportional to probability best ($r_d = p_d$)
- $C \geq 1$
  - strongly favor 1 arm earlier in the trial, even when treatments are equal
  - more subjects likely assigned to the best treatment
  - C ➞ big means assign all to best treatment, play the leader
- $0 < C < 1$
  - weakly favor better
  - fewer subjects likely assigned to best treatment
  - more even distribution early in trials
  - randomization less affected by early events
- $C = n/N$, trial begins with c = 0 and ends with c = 1

Rules to Stop

- When to Stop for Success?
  - If $p_2 > 0.95$, stop for success
  - If $p_1 > 0.95$, stop for success
  - Take successful dose to Phase III

- What if experimental doses equally effective?

Rules to Stop

- When to Stop for Success?
  - If $p_2 > 0.95$, stop for success
  - If $p_1 > 0.95$, stop for success
  - Take successful dose to Phase III

- What if experimental doses equally effective?

- Instead use if $p_C < 0.10$, stop for success?

Rules to Stop

- When to Stop for Futility?
  - If $p_2 < 0.05$ drop q2w arm
  - If $p_1 < 0.05$ drop q1w arm
  - If both arms dropped, trial ends
  - Allow dropped arms to re-enter?

Rules to Stop

- When to Stop for Futility?
  - If $p_2 < 0.05$ drop q2w arm
  - If $p_1 < 0.05$ drop q1w arm
  - If $Pr(\lambda_c / \lambda_2 > 1.10 \mid \text{Data}) < 0.05$ drop q2w arm
  - If $Pr(\lambda_c / \lambda_1 > 1.10 \mid \text{Data}) < 0.05$ drop q1w arm
  - If both arms dropped, trial ends
  - Allow dropped arms to re-enter? Yes

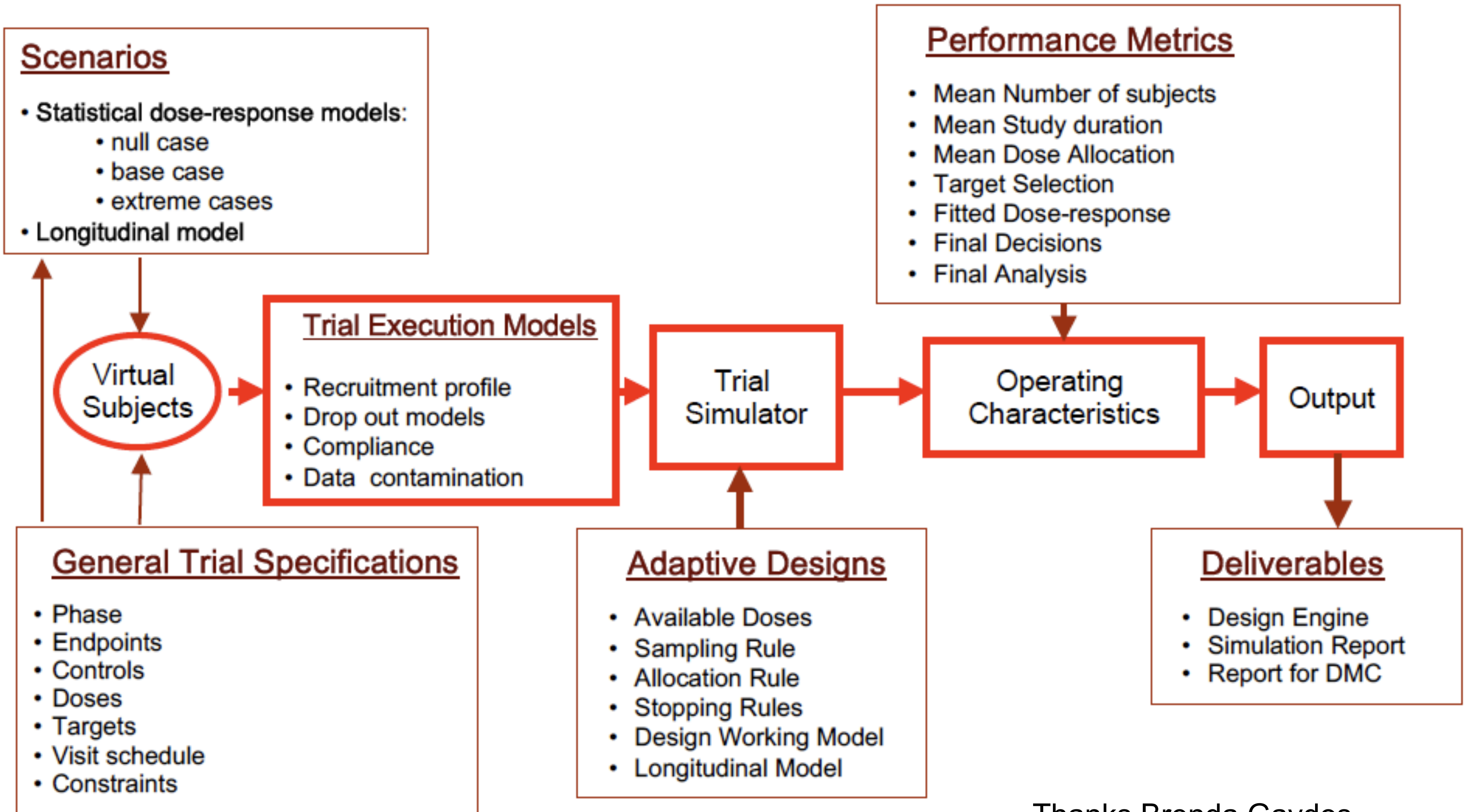
Post Accrual Tracking

- Choose to track patients for 1-year post accrual
- 70% chance last patient will have event

  $1 - e^{-365/303} = 0.70$

- Under assumed accrual rates & N=195, 83% of patients will have events if $\lambda = 1/303$.

Simulation Plan



Thanks Brenda Gaydos

At each interim analysis

1. Calculate:

   Posteriors λ_t | *data*; $t \in$ A, B, C

   p_t = P(Treatment t is 'Best' treatment | *data*)

   e.g. $p_B = P(\lambda_B \leq \lambda_A \ \& \ \lambda_C \mid \text{data})$

   P(Treatment *t* is ≥10% better than A | *data*)

2. Check superiority and futility stopping/dropping rules
3. Randomize next 15 subjects with probability p_t
4. Repeat steps 1-4 up to 195 subjects

Simulation Output

```
 Doing Case =            9
Control           Mean TTP =  303.00
Control + q2w     Mean TTP =  606.00
Control + q1w     Mean TTP =  606.00


 Stop for Success   0.168
Stop for Futility   0.004
     Stop for Cap   0.828

        Name  Mean N    % N    SD N   Best    Win Beat P
Control        30.4850  0.214 10.8927  0.003  0.000  0.000
Control + q2w 55.8790  0.392 19.5526  0.492  0.059  0.682
Control + q1w 56.2410  0.394 19.0859  0.505  0.057  0.690

     Total N =    142.605      SD=  20.247
   Pr(Either Beats Placebo) =   0.853
```

Max N = 150

Doing Case = 1

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	303.00
Control + q1w	Mean TTP =	303.00

Stop for Success	0.049
Stop for Futility	0.073
Stop for Cap	0.878

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	47.6570	0.334	18.0027	0.342	0.000	0.000
Control + q2w	47.0040	0.330	19.2468	0.310	0.006	0.051
Control + q1w	47.9440	0.336	19.3273	0.348	0.008	0.052

Total N = 142.605 SD= 22.106

Pr(Either Beats Placebo) = 0.081

Doing Case = 9

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	606.00
Control + q1w	Mean TTP =	606.00

Stop for Success	0.168
Stop for Futility	0.004
Stop for Cap	0.828

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	**30.4850**	0.214	10.8927	0.003	0.000	0.000
Control + q2w	55.8790	0.392	19.5526	0.492	0.059	**0.682**
Control + q1w	56.2410	0.394	19.0859	0.505	0.057	**0.690**

Total N = 142.605 SD= 20.247

Pr(Either Beats Placebo) = **0.853**

Max N = 195

Doing Case = 1

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	303.00
Control + q1w	Mean TTP =	303.00

Stop for Success	0.070
Stop for Futility	0.103
Stop for Cap	0.827

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	60.3100	0.333	25.4370	0.331	0.000	0.000
Control + q2w	60.9040	0.336	28.1304	0.346	0.009	0.063
Control + q1w	59.9710	0.331	27.7830	0.323	0.006	0.061

Total N = 181.185 SD= 35.625

Pr(Either Beats Placebo) = 0.102

Doing Case = 9

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	606.00
Control + q1w	Mean TTP =	606.00

Stop for Success	0.208
Stop for Futility	0.002
Stop for Cap	0.790

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	**35.1840**	0.195	13.7992	0.001	0.000	0.000
Control + q2w	72.1780	0.400	27.5021	0.491	0.047	**0.757**
Control + q1w	72.9830	0.405	27.1835	0.508	0.053	**0.766**

Total N = 180.345 SD= 33.923

Pr(Either Beats Placebo) = **0.907**

Max N = 195, Firstlook=45

Doing Case = 1

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	303.00
Control + q1w	Mean TTP =	303.00

Stop for Success 0.070
Stop for Futility **0.103**
Stop for Cap 0.827

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	60.3100	0.333	25.4370	0.331	0.000	0.000
Control + q2w	60.9040	0.336	28.1304	0.346	0.009	0.063
Control + q1w	59.9710	0.331	27.7830	0.323	0.006	0.061

Total N = **181.185** SD= 35.625
Pr(Either Beats Placebo) = 0.102

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Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	606.00
Control + q1w	Mean TTP =	606.00

Stop for Success 0.208
Stop for Futility 0.002
Stop for Cap 0.790

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	35.1840	**0.195**	13.7992	0.001	0.000	0.000
Control + q2w	72.1780	**0.400**	27.5021	0.491	0.047	0.757
Control + q1w	72.9830	**0.405**	27.1835	0.508	0.053	0.766

Total N = **180.345** SD= 33.923
Pr(Either Beats Placebo) = **0.907**

Max N = 195, Firstlook=90

Doing Case = 1

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	303.00
Control + q1w	Mean TTP =	303.00

Stop for Success 0.057
Stop for Futility **0.089**
Stop for Cap 0.854

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	61.4750	0.332	19.4908	0.348	0.000	0.000
Control + q2w	62.2340	0.336	21.2199	0.322	0.005	0.042
Control + q1w	61.6460	0.333	21.2751	0.330	0.006	0.041

Total N = **185.355** SD= 27.081
Pr(Either Beats Placebo) = 0.071

Doing Case = 9

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	606.00
Control + q1w	Mean TTP =	606.00

Stop for Success 0.199
Stop for Futility 0.000
Stop for Cap 0.801

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	41.0450	**0.224**	9.0906	0.001	0.000	0.000
Control + q2w	70.8100	**0.387**	20.6464	0.499	0.044	0.806
Control + q1w	71.1900	**0.389**	20.7805	0.500	0.046	0.809

Total N = **183.045** SD= 28.766
Pr(Either Beats Placebo) = 0.931

Max N = 195, c = 1

Doing Case = 1

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	303.00
Control + q1w	Mean TTP =	303.00

Stop for Success	0.070
Stop for Futility	0.103
Stop for Cap	0.827

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	60.3100	0.333	25.4370	0.331	0.000	0.000
Control + q2w	60.9040	0.336	28.1304	0.346	0.009	0.063
Control + q1w	59.9710	0.331	27.7830	0.323	0.006	0.061

Total N = 181.185 SD= 35.625

Pr(Either Beats Placebo) = 0.102

Doing Case = 9

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	606.00
Control + q1w	Mean TTP =	606.00

Stop for Success	0.208
Stop for Futility	0.002
Stop for Cap	0.790

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	35.1840	0.195	13.7992	0.001	0.000	0.000
Control + q2w	72.1780	0.400	27.5021	0.491	0.047	0.757
Control + q1w	72.9830	0.405	27.1835	0.508	0.053	0.766

Total N = 180.345 SD= 33.923

Pr(Either Beats Placebo) = 0.907

Max N = 195, c = 0

Doing Case = 1

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	303.00
Control + q1w	Mean TTP =	303.00

Stop for Success	0.063
Stop for Futility	0.118
Stop for Cap	0.819

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	60.0350	0.333	12.3501	0.352	0.000	0.000
Control + q2w	60.0350	0.333	12.3501	0.331	0.009	0.044
Control + q1w	60.0350	0.333	12.3501	0.317	0.008	0.048

Total N = 180.105 SD= 37.050

Pr(Either Beats Placebo) = 0.083

Doing Case = 9

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	606.00
Control + q1w	Mean TTP =	606.00

Stop for Success	0.195
Stop for Futility	0.004
Stop for Cap	0.801

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	60.3950	0.333	11.0779	0.003	0.000	0.000
Control + q2w	60.3950	0.333	11.0779	0.488	0.046	0.828
Control + q1w	60.3950	0.333	11.0779	0.509	0.047	0.828

Total N = 181.185 SD= 33.234

Pr(Either Beats Placebo) = 0.931

Max N = 195, c = 1

Doing Case = 1

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	303.00
Control + q1w	Mean TTP =	303.00

Stop for Success	0.070
Stop for Futility	0.103
Stop for Cap	0.827

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	60.3100	0.333	25.4370	0.331	0.000	0.000
Control + q2w	60.9040	0.336	28.1304	0.346	0.009	0.063
Control + q1w	59.9710	0.331	27.7830	0.323	0.006	0.061

Total N = 181.185 SD= 35.625

Pr(Either Beats Placebo) = 0.102

Doing Case = 9

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	606.00
Control + q1w	Mean TTP =	606.00

Stop for Success	0.208
Stop for Futility	0.002
Stop for Cap	0.790

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Control	35.1840	0.195	13.7992	0.001	0.000	0.000
Control + q2w	72.1780	0.400	27.5021	0.491	0.047	0.757
Control + q1w	72.9830	0.405	27.1835	0.508	0.053	0.766

Total N = 180.345 SD= 33.923

Pr(Either Beats Placebo) = 0.907

Max N = 195, c = ∞

Doing Case = 1

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	303.00
Control + q1w	Mean TTP =	303.00

Stop for Success	0.047
Stop for Futility	0.092
Stop for Cap	0.861

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	60.4500	0.330	43.6835	0.347	0.000	0.000
Control + q2w	61.6800	0.336	45.8555	0.339	0.009	0.061
Control + q1w	61.2900	0.334	45.4790	0.314	0.002	0.057

Total N = 183.420 SD= 32.733

Pr(Either Beats Placebo) = 0.092

Doing Case = 9

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	606.00
Control + q1w	Mean TTP =	606.00

Stop for Success	0.201
Stop for Futility	0.003
Stop for Cap	0.796

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	24.1950	0.134	18.5007	0.004	0.000	0.000
Control + q2w	78.3450	0.435	51.8603	0.498	0.049	0.570
Control + q1w	77.7000	0.431	50.7603	0.498	0.043	0.561

Total N = 180.240 SD= 34.519

Pr(Either Beats Placebo) = 0.772

Max N = 195, c = ∞

Doing Case = 1

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	303.00
Control + q1w	Mean TTP =	303.00

Stop for Success	0.047
Stop for Futility	0.092
Stop for Cap	0.861

Name	Mean N	%N	SD N	Best	Win	Beat P
Control	60.4500	0.330	43.6835	0.347	0.000	0.000
Control + q2w	61.6800	0.336	45.8555	0.339	0.009	0.061
Control + q1w	61.2900	0.334	45.4790	0.314	0.002	0.057

Total N = 183.420 SD= 32.733

Pr(Either Beats Placebo) = 0.092

Doing Case = 9

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	606.00
Control + q1w	Mean TTP =	606.00

Stop for Success	0.201
Stop for Futility	0.003
Stop for Cap	0.796

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	24.1950	0.134	18.5007	0.004	0.000	0.000
Control + q2w	78.3450	0.435	51.8603	0.498	0.049	0.570
Control + q1w	77.7000	0.431	50.7603	0.498	0.043	0.561

Total N = 180.240 SD= 34.519

Pr(Either Beats Placebo) = 0.772

Max N = 195, c = ∞, every 1

Doing Case = 1

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	303.00
Control + q1w	Mean TTP =	303.00

Stop for Success	0.099
Stop for Futility	0.120
Stop for Cap	0.781

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	55.6170	0.319	40.6723	0.311	0.000	0.000
Control + q2w	61.1370	0.350	45.0447	0.352	0.006	0.047
Control + q1w	57.8350	0.331	44.5945	0.337	0.006	0.049

Total N = 174.589 SD= 44.094

Pr(Either Beats Placebo) = 0.081

Doing Case = 9

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	606.00
Control + q1w	Mean TTP =	606.00

Stop for Success	0.263
Stop for Futility	0.004
Stop for Cap	0.733

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	23.5280	0.136	17.2205	0.004	0.000	0.000
Control + q2w	75.4290	0.435	49.9018	0.514	0.043	0.582
Control + q1w	74.5200	0.430	50.4509	0.482	0.046	0.581

Total N = 173.477 SD= 42.012

Pr(Either Beats Placebo) = 0.770

Max N = 195, c = 1

Doing Case = 1

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	303.00
Control + q1w	Mean TTP =	303.00

Stop for Success	0.070
Stop for Futility	0.103
Stop for Cap	0.827

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	60.3100	0.333	25.4370	0.331	0.000	0.000
Control + q2w	60.9040	0.336	28.1304	0.346	0.009	0.063
Control + q1w	59.9710	0.331	27.7830	0.323	0.006	0.061

Total N = 181.185 SD= 35.625

Pr(Either Beats Placebo) = 0.102

Doing Case = 9

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	606.00
Control + q1w	Mean TTP =	606.00

Stop for Success	0.208
Stop for Futility	0.002
Stop for Cap	0.790

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	35.1840	0.195	13.7992	0.001	0.000	0.000
Control + q2w	72.1780	0.400	27.5021	0.491	0.047	0.757
Control + q1w	72.9830	0.405	27.1835	0.508	0.053	0.766

Total N = 180.345 SD= 33.923

Pr(Either Beats Placebo) = 0.907

Max N = 195, c = n/N

Doing Case = 1

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	303.00
Control + q1w	Mean TTP =	303.00

Stop for Success	0.070
Stop for Futility	0.106
Stop for Cap	0.824

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	61.3110	0.340	19.6030	0.335	0.000	0.000
Control + q2w	59.4440	0.330	22.8840	0.344	0.006	0.048
Control + q1w	59.6200	0.331	22.5230	0.321	0.007	0.049

Total N = 180.375 SD= 36.095

Pr(Either Beats Placebo) = 0.083

Doing Case = 9

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	606.00
Control + q1w	Mean TTP =	606.00

Stop for Success	0.212
Stop for Futility	0.001
Stop for Cap	0.787

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	40.8990	0.226	12.3915	0.000	0.000	0.000
Control + q2w	70.4020	0.389	21.1026	0.523	0.055	0.810
Control + q1w	69.4940	0.384	20.5548	0.477	0.063	0.804

Total N = 180.795 SD= 33.749

Pr(Either Beats Placebo) = 0.937

Max N = 195, c = 1

Doing Case = 1

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	303.00
Control + q1w	Mean TTP =	303.00

Stop for Success	0.070
Stop for Futility	0.103
Stop for Cap	0.827

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	60.3100	0.333	25.4370	0.331	0.000	0.000
Control + q2w	60.9040	0.336	28.1304	0.346	0.009	0.063
Control + q1w	59.9710	0.331	27.7830	0.323	0.006	0.061

Total N = 181.185 SD= 35.625

Pr(Either Beats Placebo) = 0.102

Doing Case = 9

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	606.00
Control + q1w	Mean TTP =	606.00

Stop for Success	0.208
Stop for Futility	0.002
Stop for Cap	0.790

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	35.1840	0.195	13.7992	0.001	0.000	0.000
Control + q2w	72.1780	0.400	27.5021	0.491	0.047	0.757
Control + q1w	72.9830	0.405	27.1835	0.508	0.053	0.766

Total N = 180.345 SD= 33.923

Pr(Either Beats Placebo) = 0.907

Max N = 195, c = n/N

Doing Case = 1

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	303.00
Control + q1w	Mean TTP =	303.00

Stop for Success	0.070
Stop for Futility	0.106
Stop for Cap	0.824

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	61.3110	0.340	19.6030	0.335	0.000	0.000
Control + q2w	59.4440	0.330	22.8840	0.344	0.006	0.048
Control + q1w	59.6200	0.331	22.5230	0.321	0.007	0.049

Total N = 180.375 SD= 36.095

Pr(Either Beats Placebo) = 0.083

Doing Case = 9

Control	Mean TTP =	303.00
Control + q2w	Mean TTP =	606.00
Control + q1w	Mean TTP =	606.00

Stop for Success	0.212
Stop for Futility	0.001
Stop for Cap	0.787

Fixed was 60

Name	Mean N	% N	SD N	Best	Win	Beat P
Control	40.8990	0.226	12.3915	0.000	0.000	0.000
Control + q2w	70.4020	0.389	21.1026	0.523	0.055	0.810
Control + q1w	69.4940	0.384	20.5548	0.477	0.063	0.804

Total N = 180.795 SD= 33.749

Pr(Either Beats Placebo) = 0.937

Design Parameters

- First look @ 45
- Interim analyses every 15 patients
- Maximum = 195 patients
- Success
  - If $P_2 > 0.95$, stop for success
  - If $P_1 > 0.95$, stop for success
  - Take successful dose to Phase III
- Futility
  - If $Pr(\lambda_c / \lambda_2 > 1.10 \mid \text{Data}) < 0.05$ drop q2w arm
  - If $Pr(\lambda_c / \lambda_1 > 1.10 \mid \text{Data}) < 0.05$ drop q1w arm
  - If both arms dropped, trial ends

Show Individual Trials

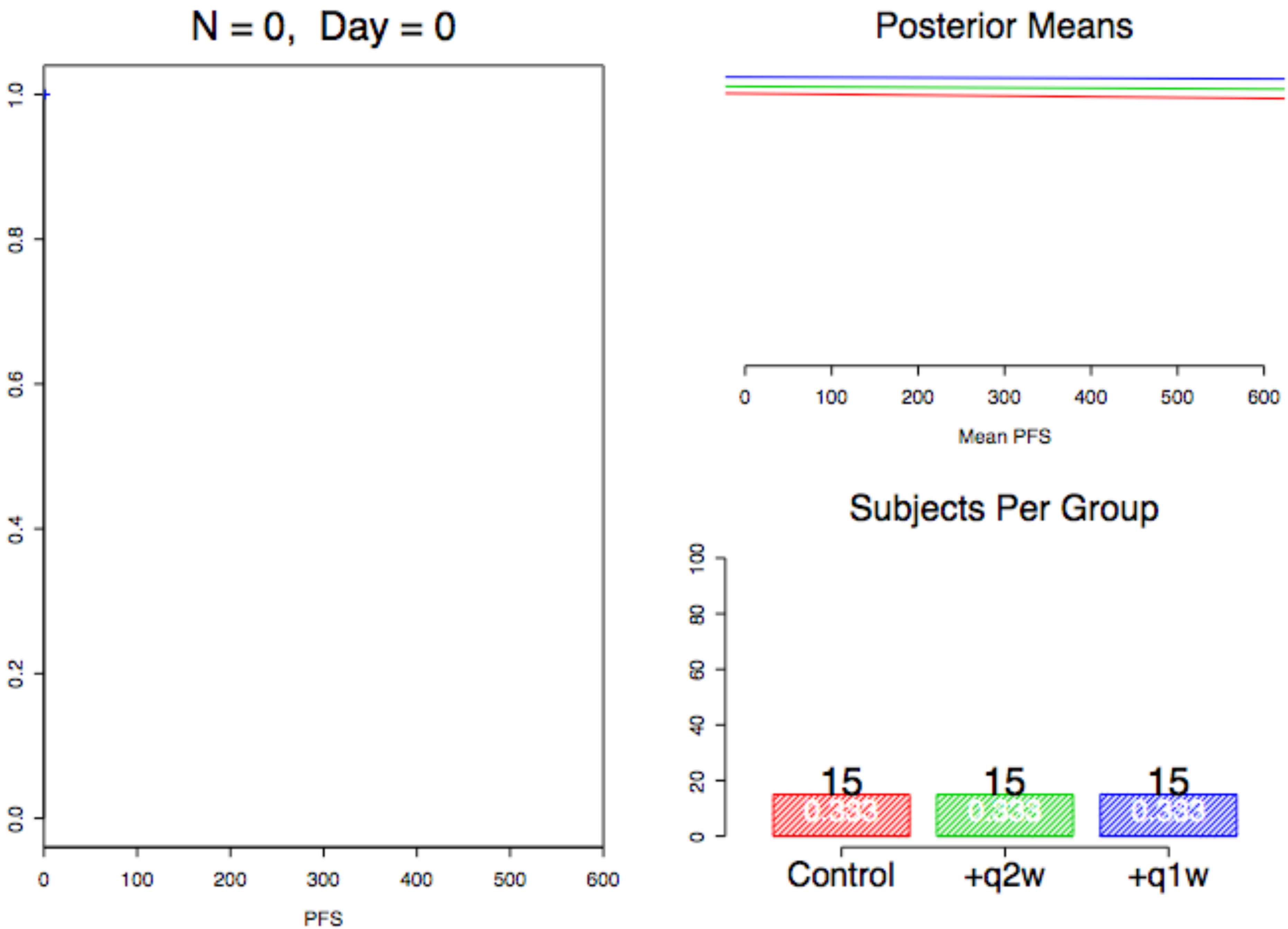
- Best way to illustrate the adaptive design is to show example trials to collaborators

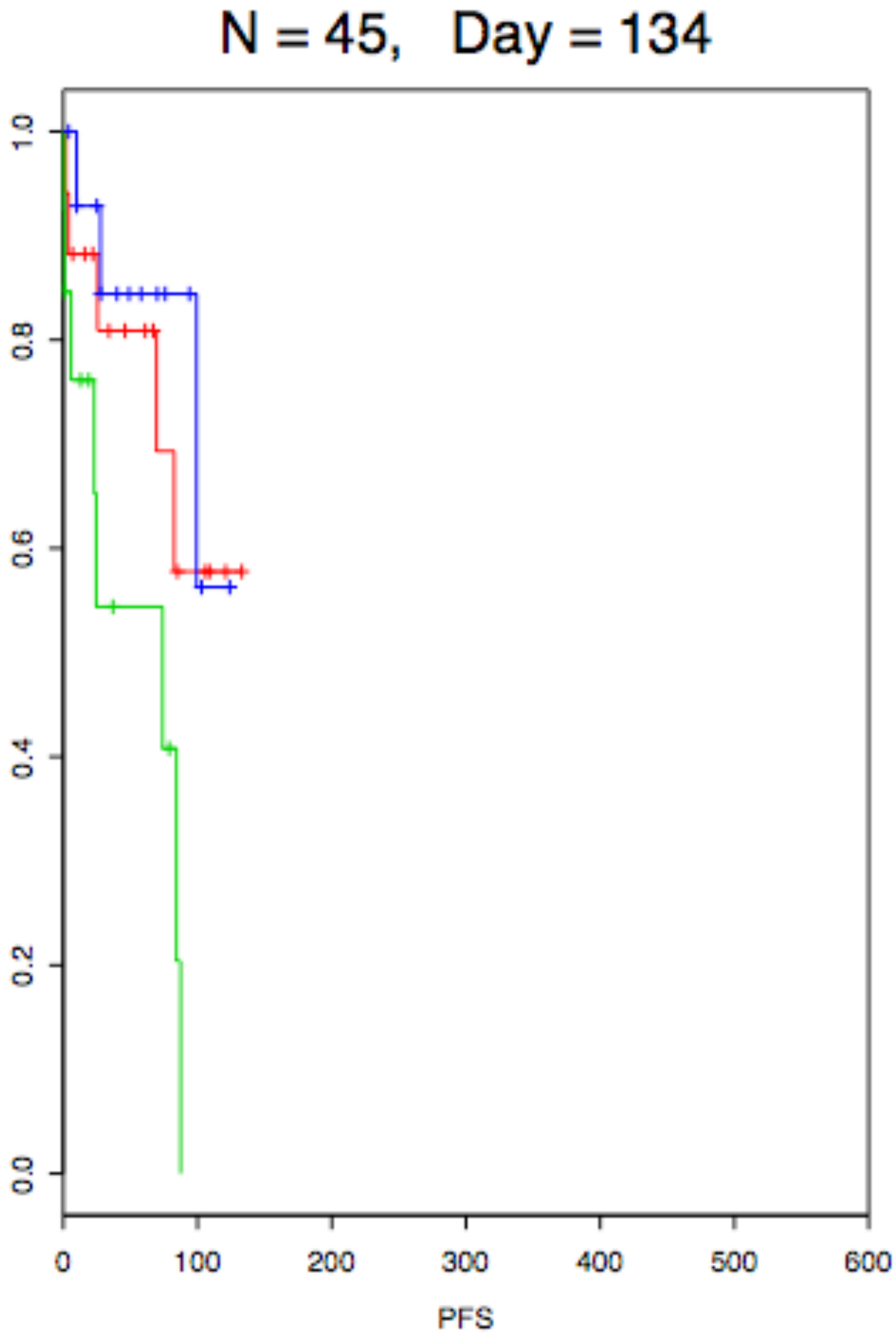
Show Individual Trials

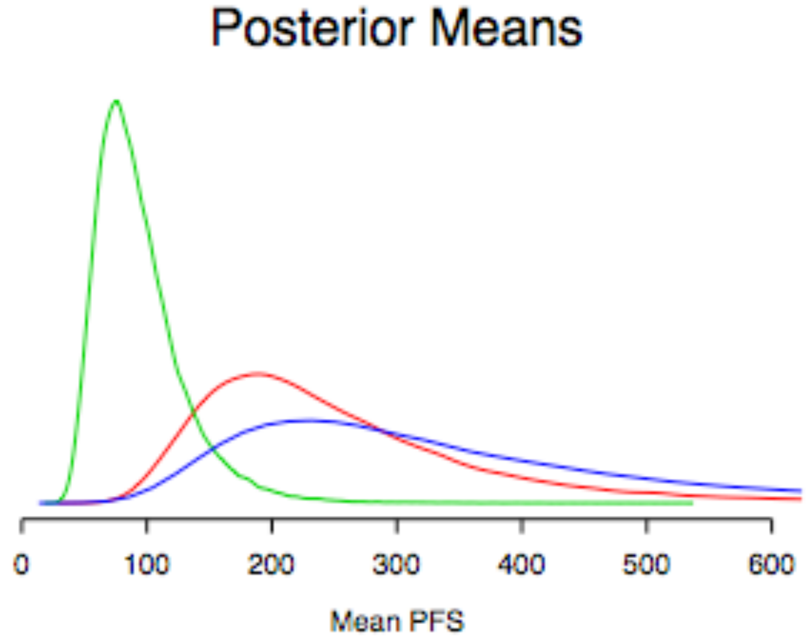
- Best way to illustrate the adaptive design is to show example trials to collaborators
- GREAT for debugging!

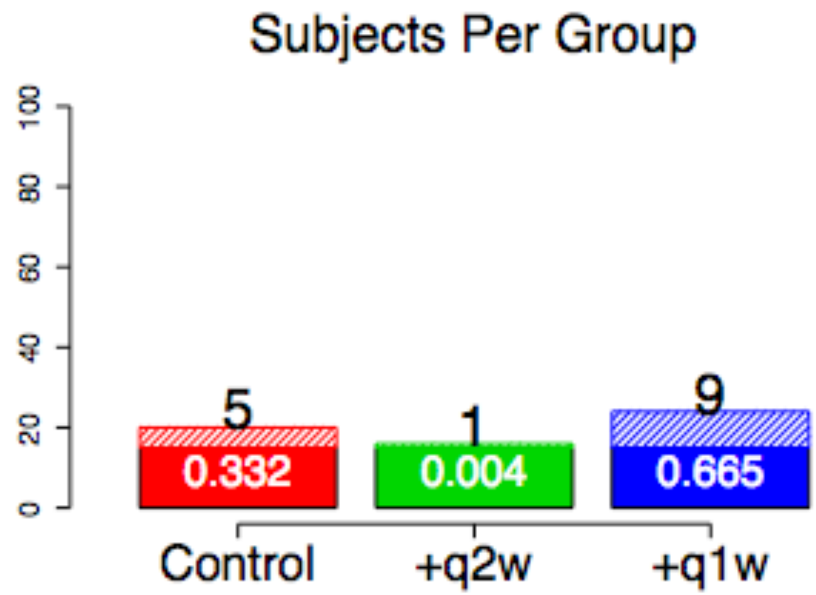
Simulation #1

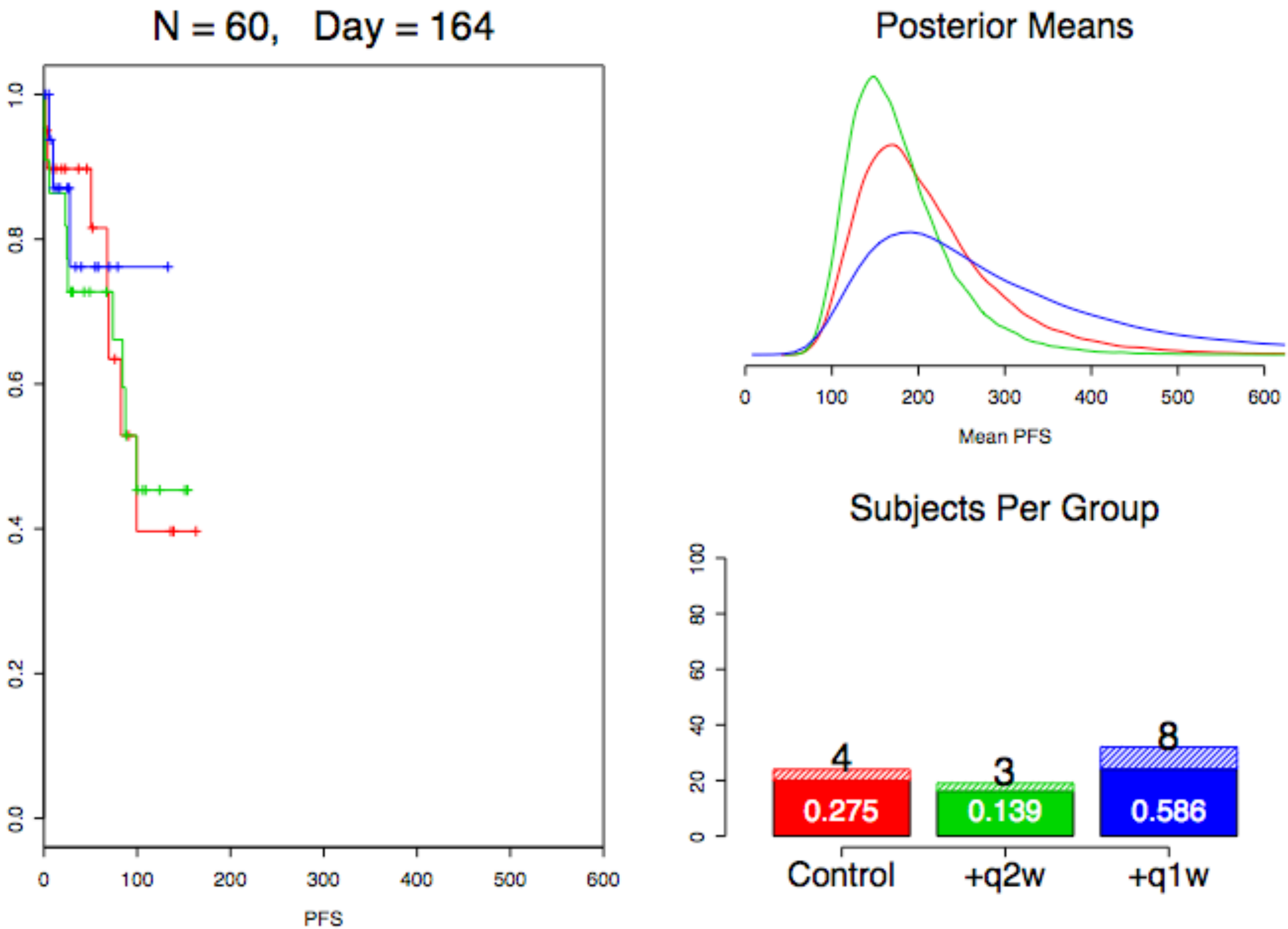
- Mean Progression Free Survival
  - Control = 303 days
  - Control + q2w = 303 days
  - Control + q1w = 303 days
- Accrual rate
  - 1 patient every 3 days for first 45 patients (~4mo)
  - 1 patient every 2 days thereafter
  - 435 days for 195 patients = 14.3 months
  - 1 year follow-up = 26.3 months


N = 0, Day = 0
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
PFS
Posterior Means
0
100
200
300
400
500
600
Mean PFS
Subjects Per Group
100
80
60
40
20
0
15
15
15
0.333
0.333
0.333
Control
+q2w
+q1w

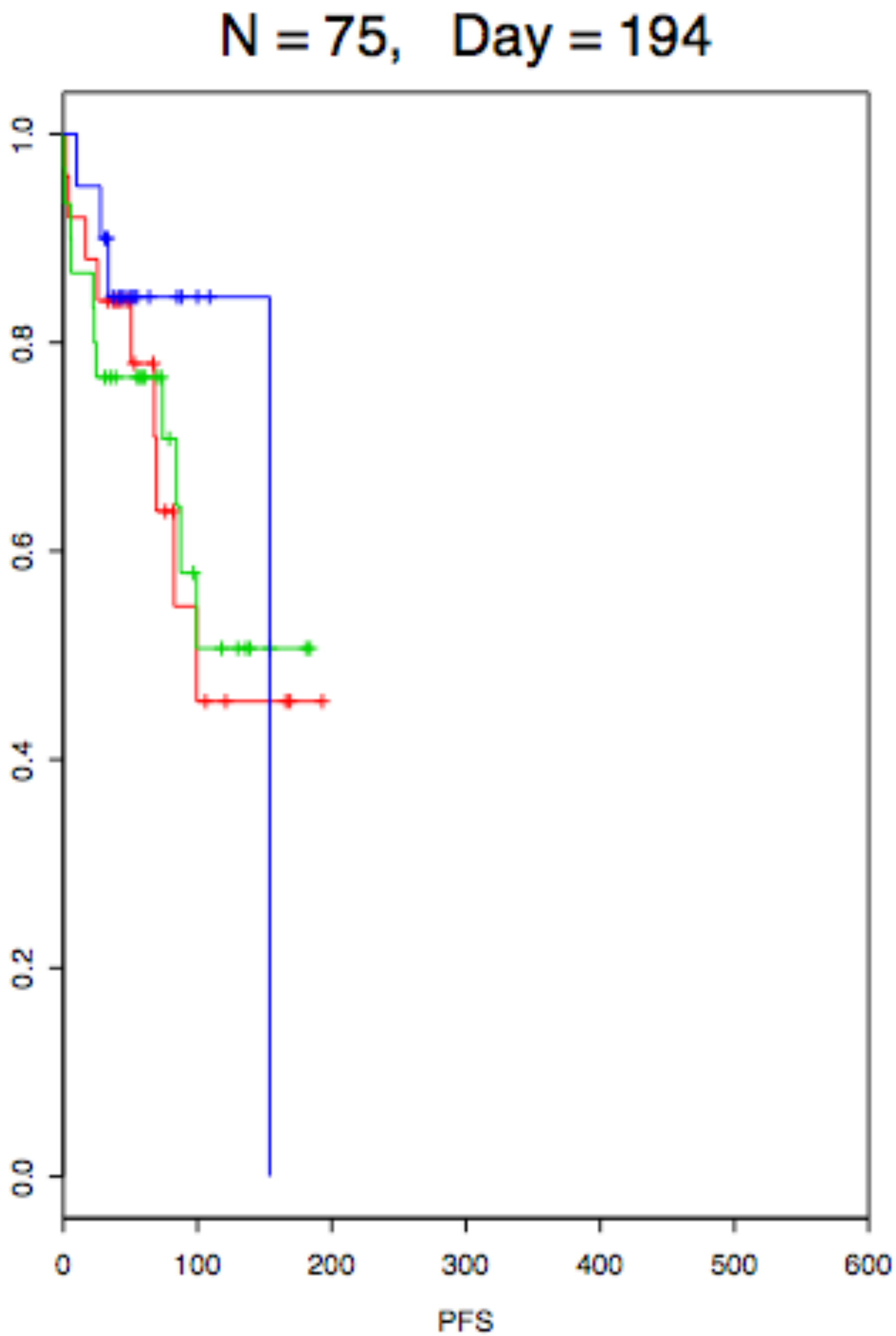

N = 45, Day = 134
PFS
0
100
200
300
400
500
600
0.0
0.2
0.4
0.6
0.8
1.0

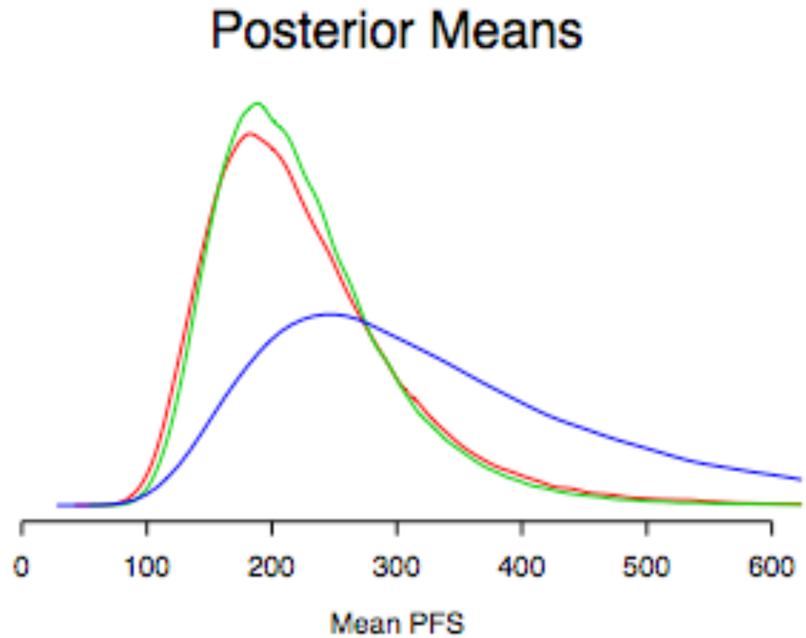

Posterior Means
Mean PFS
0
100
200
300
400
500
600

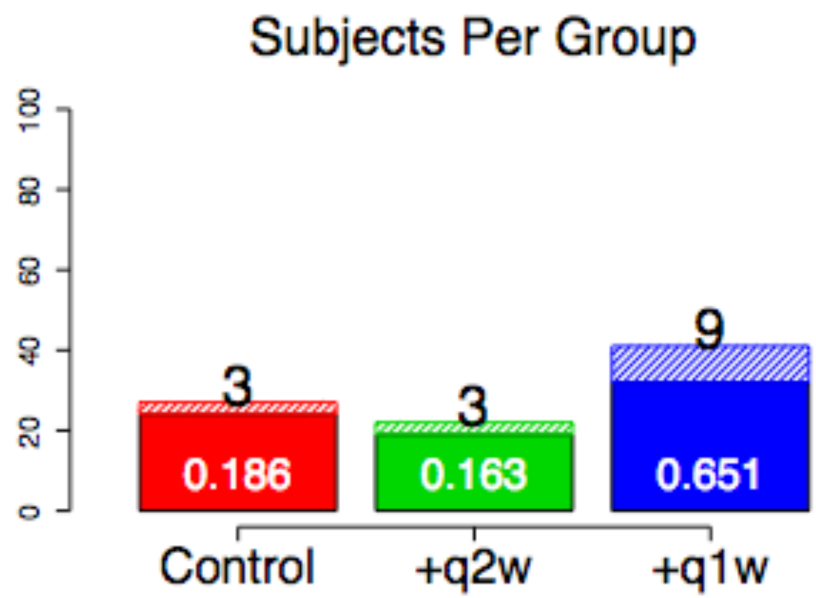

Subjects Per Group
0
20
40
60
80
100
5
0.332
1
0.004
9
0.665
Control
+q2w
+q1w

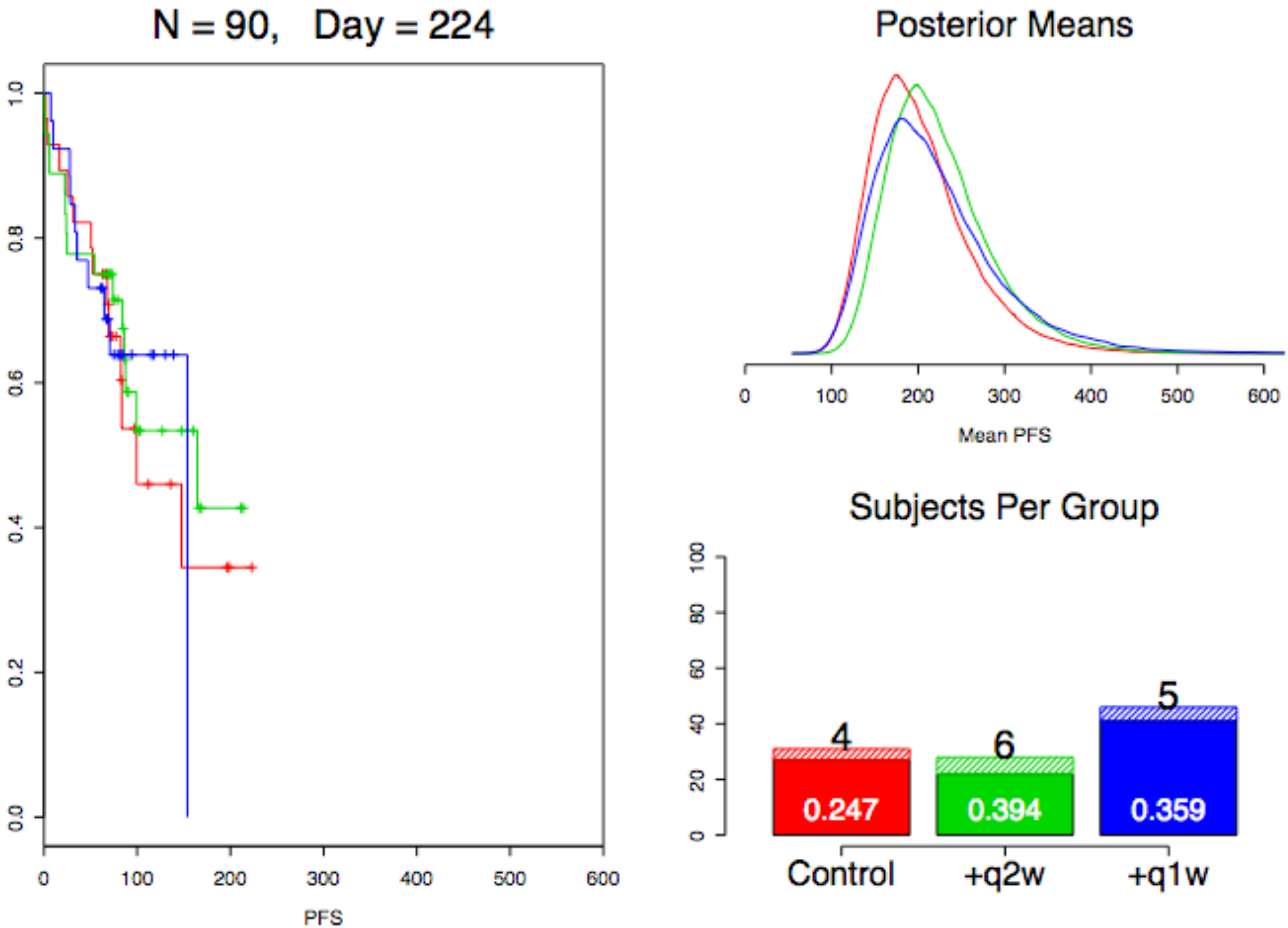


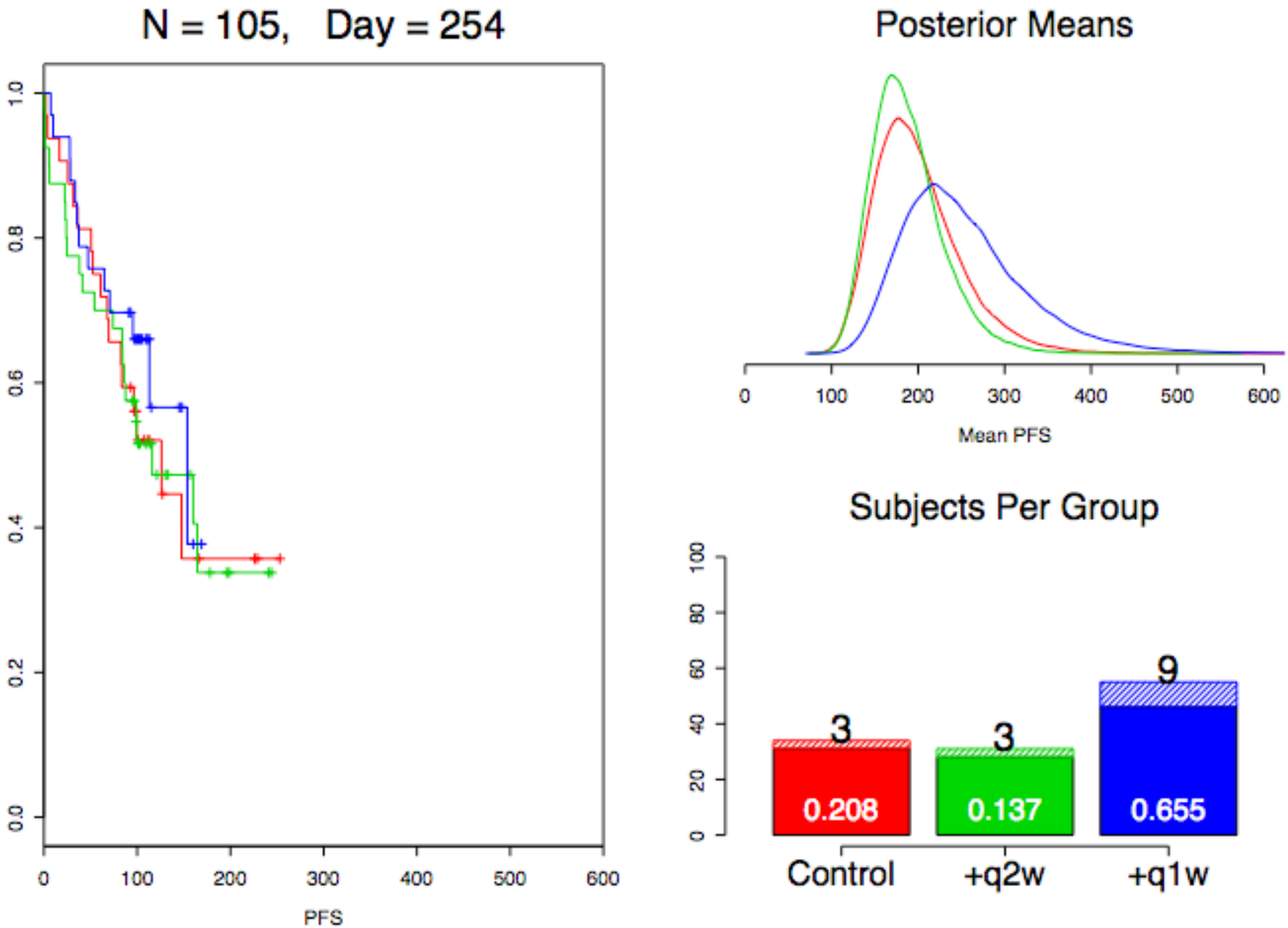
N = 60, Day = 164
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
PFS
Posterior Means
0
100
200
300
400
500
600
Mean PFS
Subjects Per Group
100
80
60
40
20
0
4
0.275
3
0.139
8
0.586
Control
+q2w
+q1w

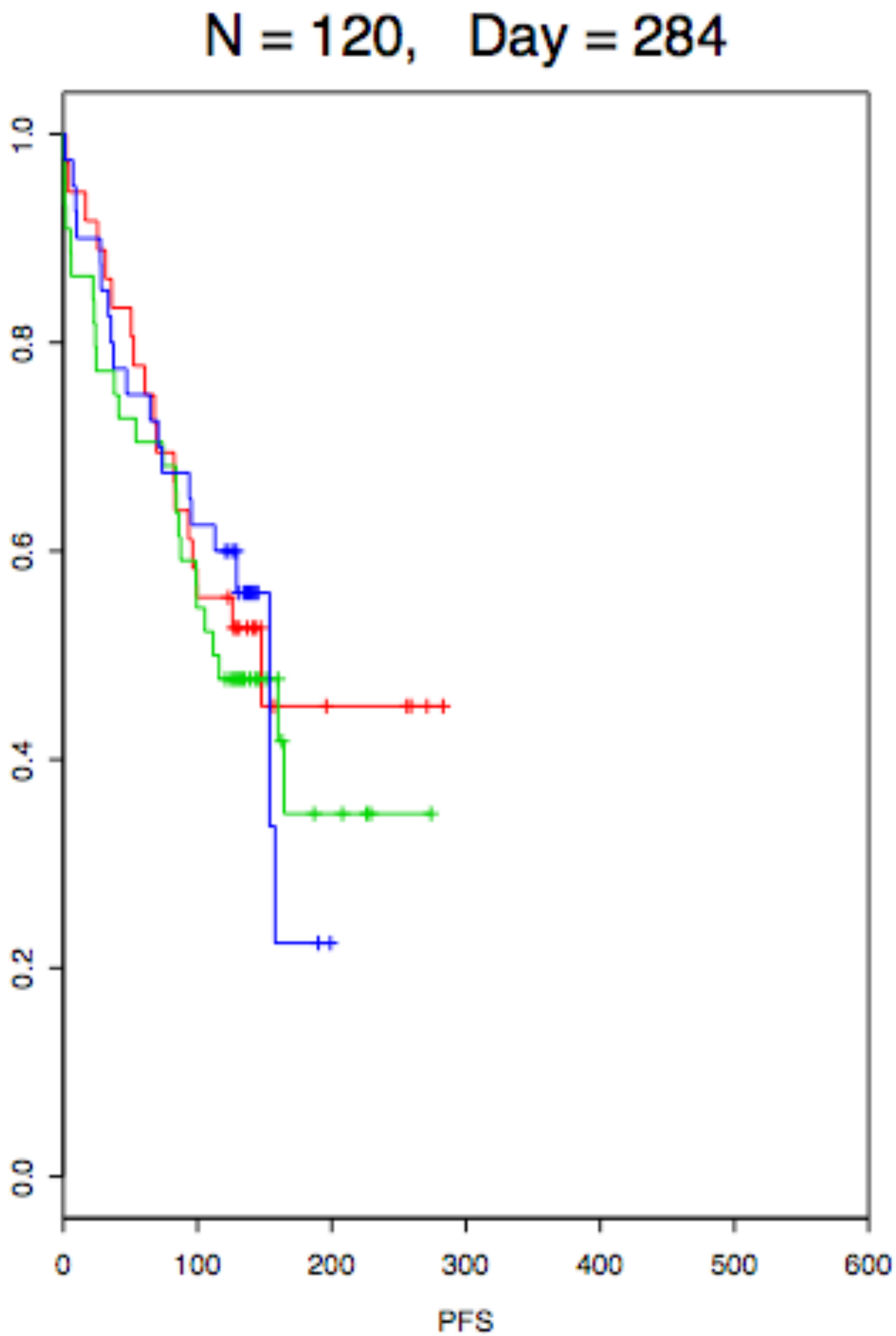

N = 75, Day = 194
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
PFS

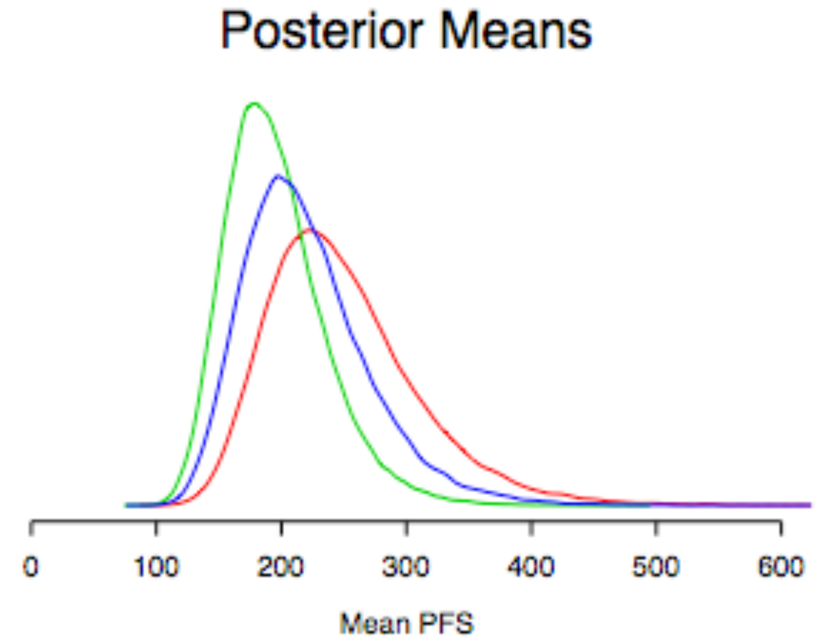

Posterior Means
0
100
200
300
400
500
600
Mean PFS

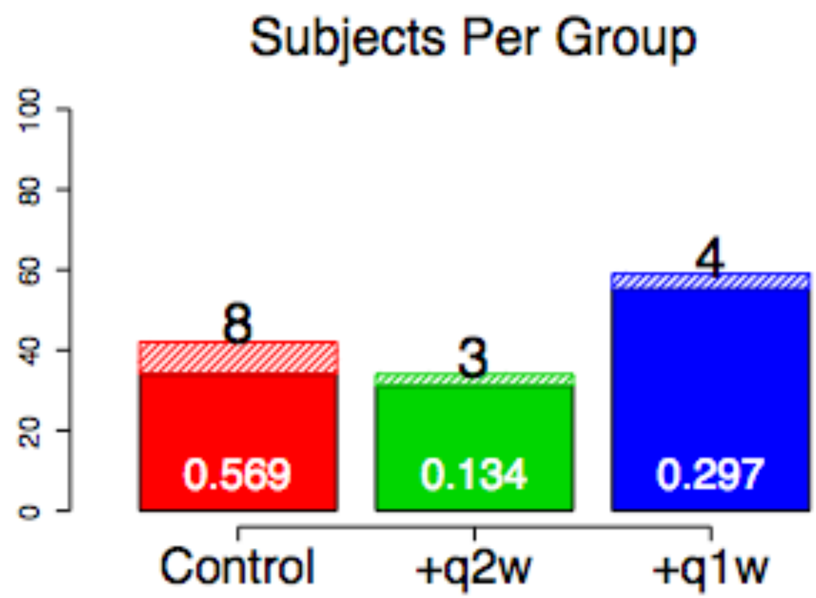

Subjects Per Group
100
80
60
40
20
0
3
0.186
3
0.163
9
0.651
Control
+q2w
+q1w

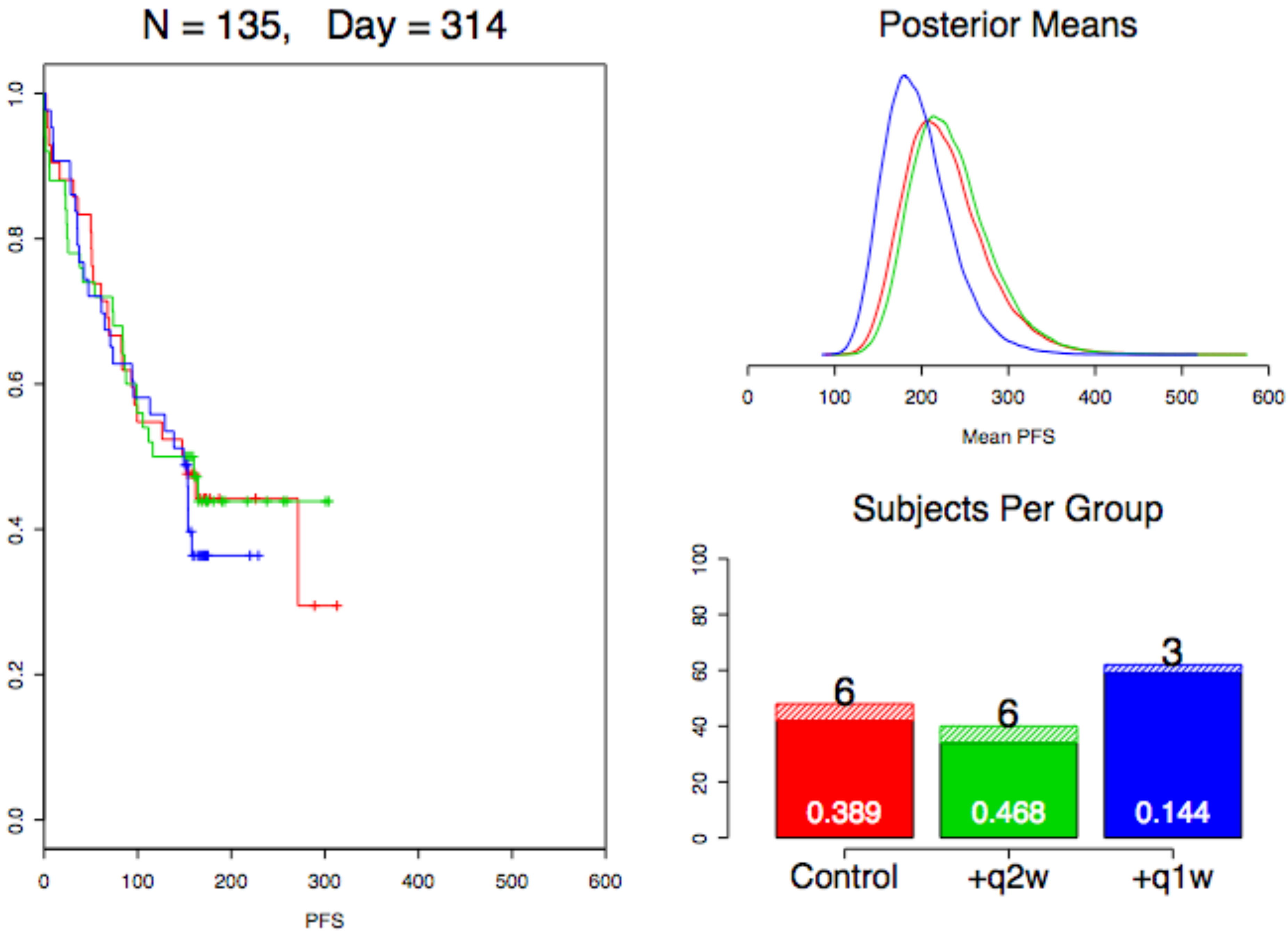

N = 90, Day = 224
PFS
Posterior Means
Mean PFS
Subjects Per Group
4
6
5
0.247
0.394
0.359
Control
+q2w
+q1w

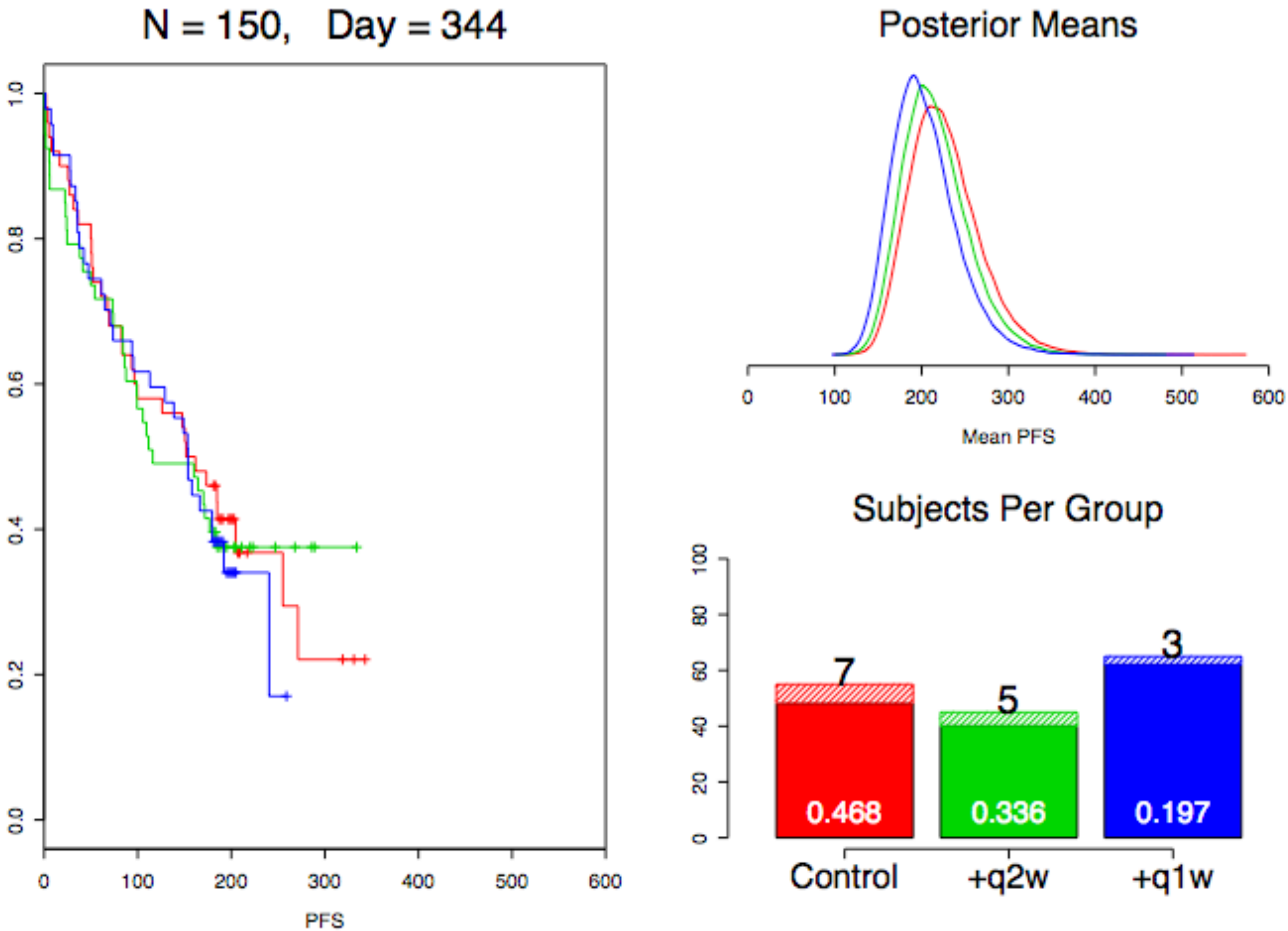

N = 105, Day = 254
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
PFS
Posterior Means
0
100
200
300
400
500
600
Mean PFS
Subjects Per Group
100
80
60
40
20
0
3
3
9
0.208
0.137
0.655
Control
+q2w
+q1w

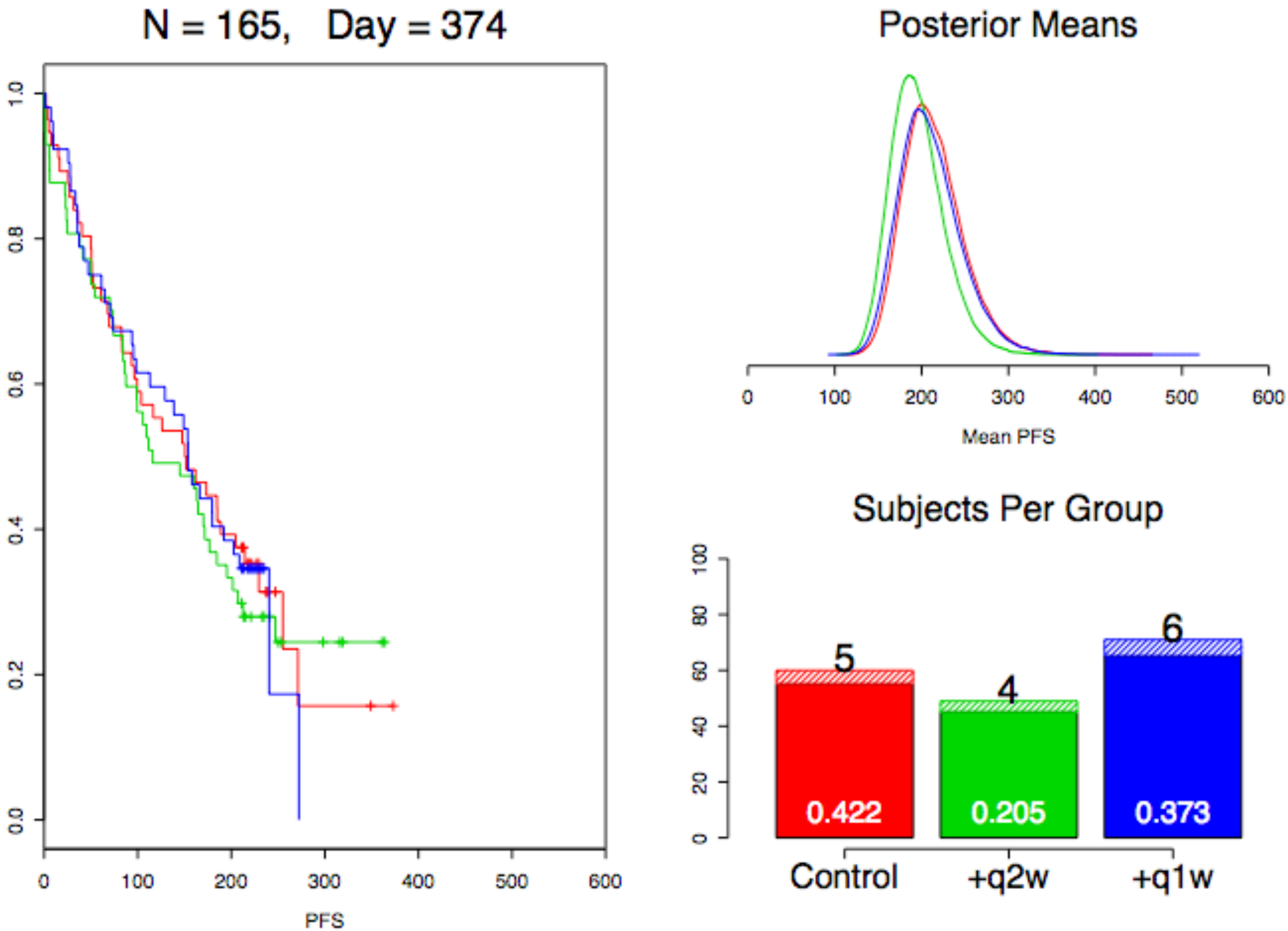

N = 120, Day = 284
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
PFS

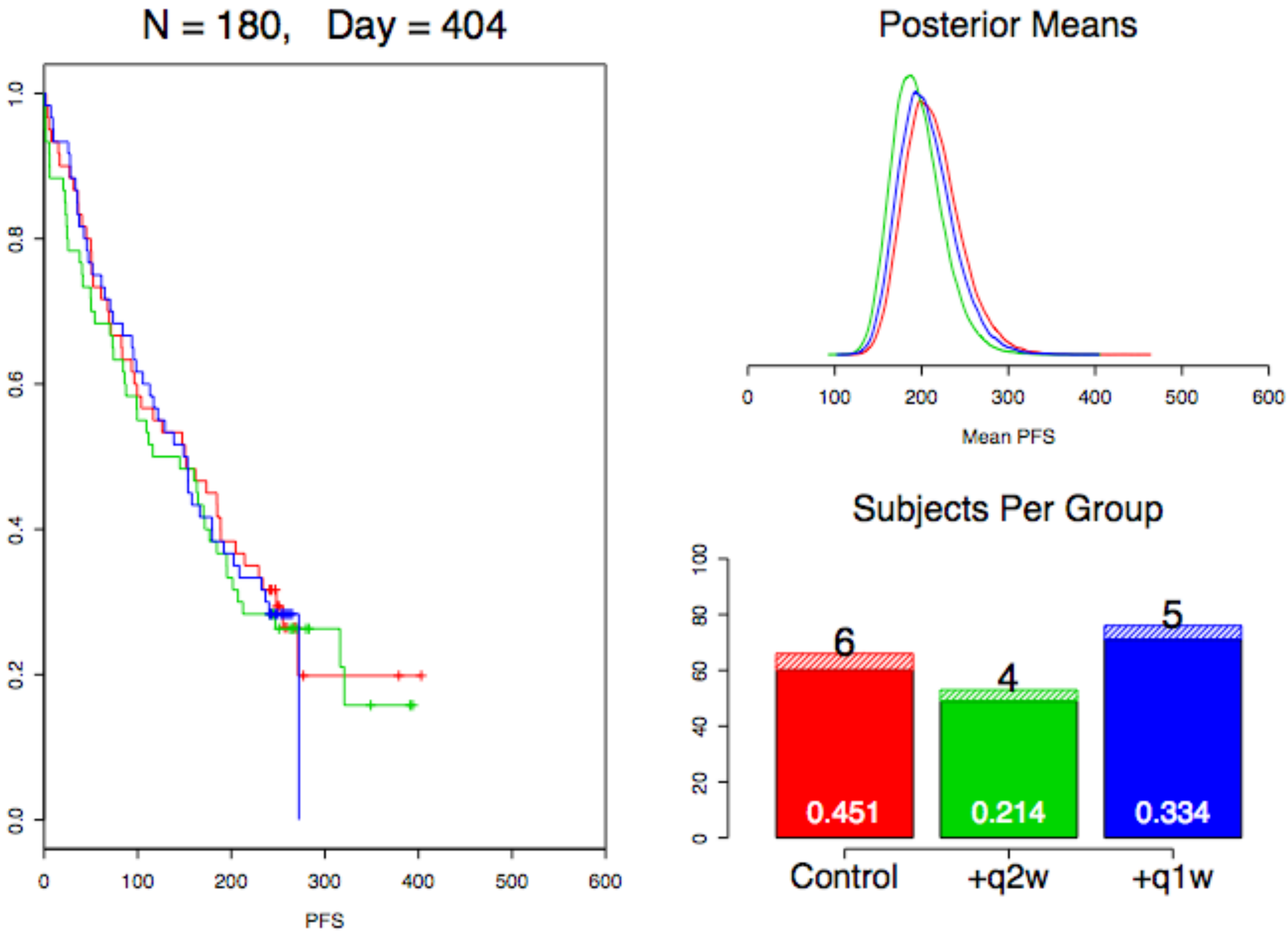

Posterior Means
0
100
200
300
400
500
600
Mean PFS

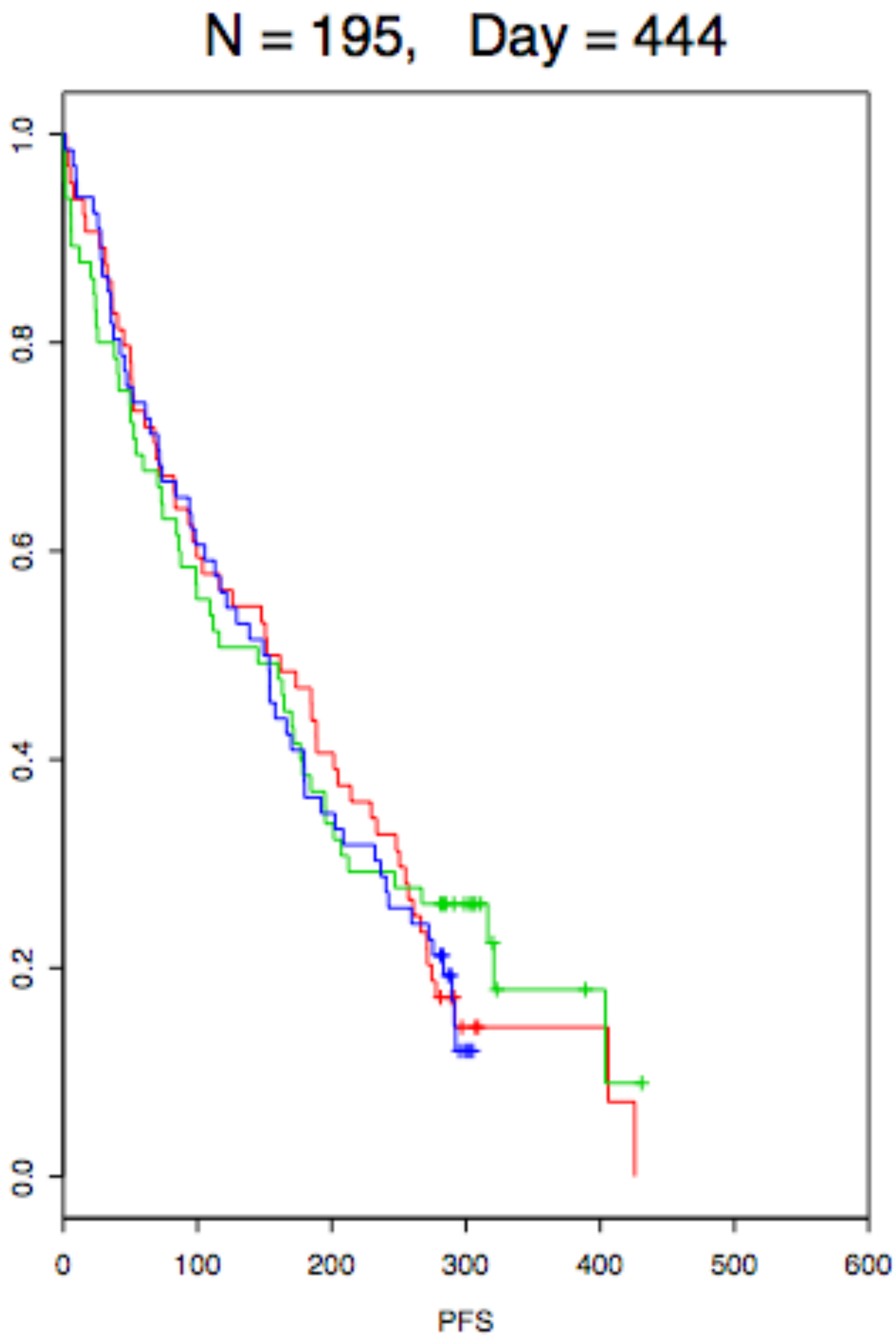

Subjects Per Group
100
80
60
40
20
0
8
3
4
0.569
0.134
0.297
Control
+q2w
+q1w

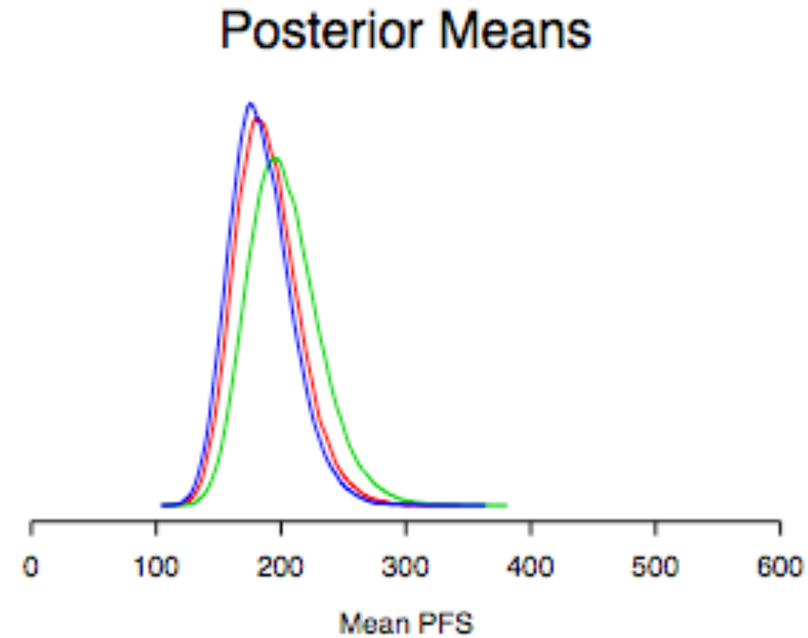

N = 135, Day = 314
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
PFS
Posterior Means
0
100
200
300
400
500
600
Mean PFS
Subjects Per Group
100
80
60
40
20
0
6
6
3
0.389
0.468
0.144
Control
+q2w
+q1w

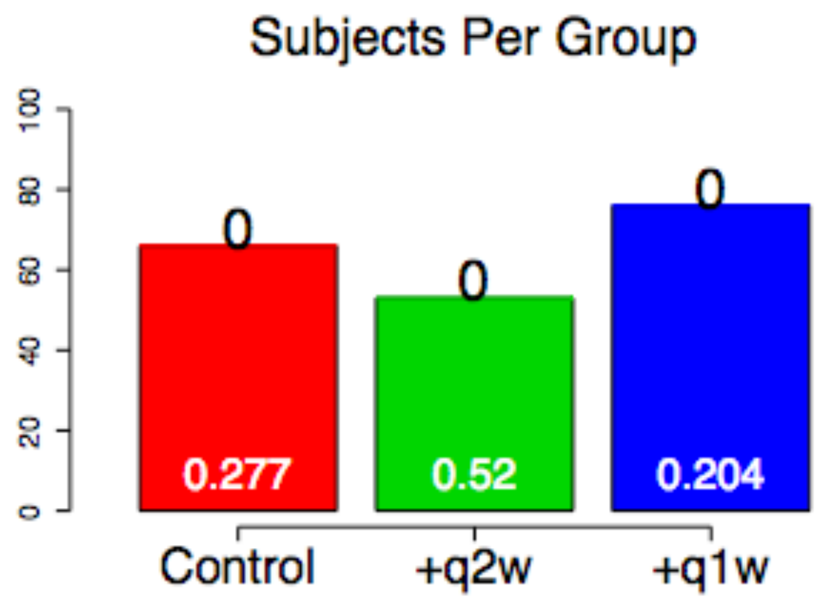

N = 150, Day = 344
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
PFS
Posterior Means
0
100
200
300
400
500
600
Mean PFS
Subjects Per Group
100
80
60
40
20
0
7
5
3
0.468
0.336
0.197
Control
+q2w
+q1w

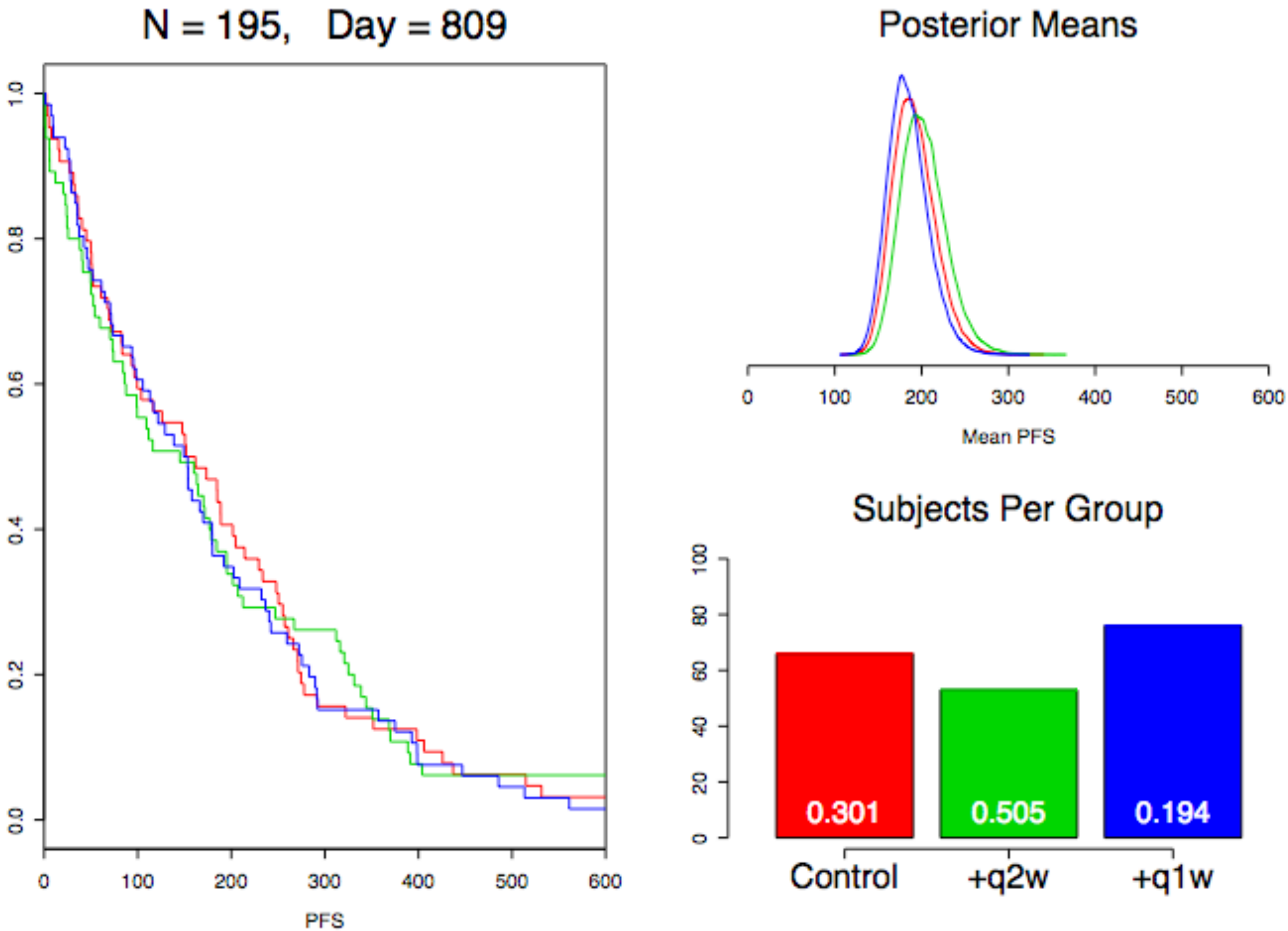

N = 165, Day = 374
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
PFS
Posterior Means
0
100
200
300
400
500
600
Mean PFS
Subjects Per Group
100
80
60
40
20
0
5
4
6
0.422
0.205
0.373
Control
+q2w
+q1w


N = 180, Day = 404
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
PFS
Posterior Means
Mean PFS
Subjects Per Group
6
4
5
0.451
0.214
0.334
Control
+q2w
+q1w


N = 195, Day = 444
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
PFS

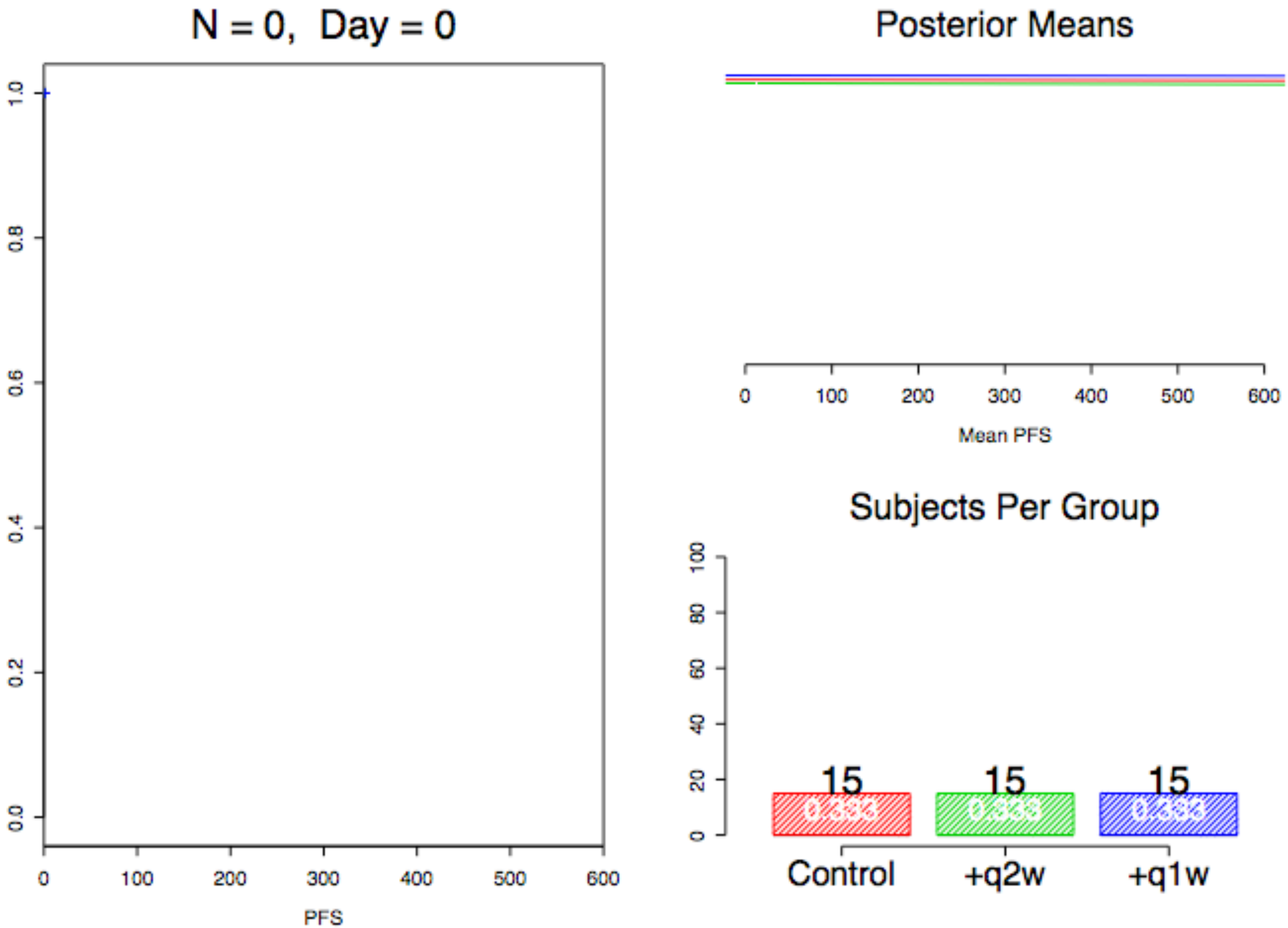

Posterior Means
0
100
200
300
400
500
600
Mean PFS


Subjects Per Group
100
80
60
40
20
0
0
0
0
0.277
0.52
0.204
Control
+q2w
+q1w

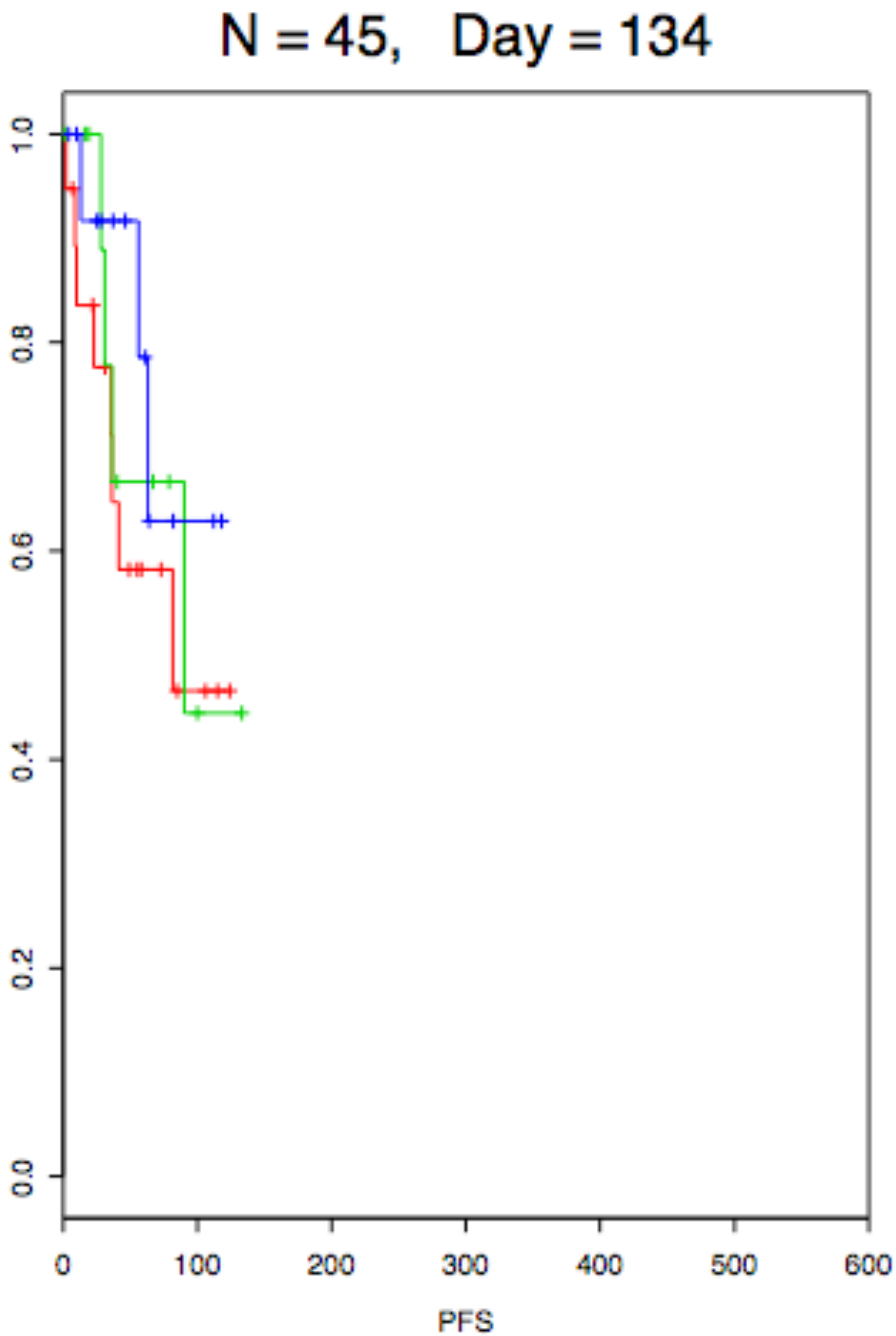

N = 195, Day = 809
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
PFS
Posterior Means
0
100
200
300
400
500
600
Mean PFS
Subjects Per Group
100
80
60
40
20
0
0.301
0.505
0.194
Control
+q2w
+q1w

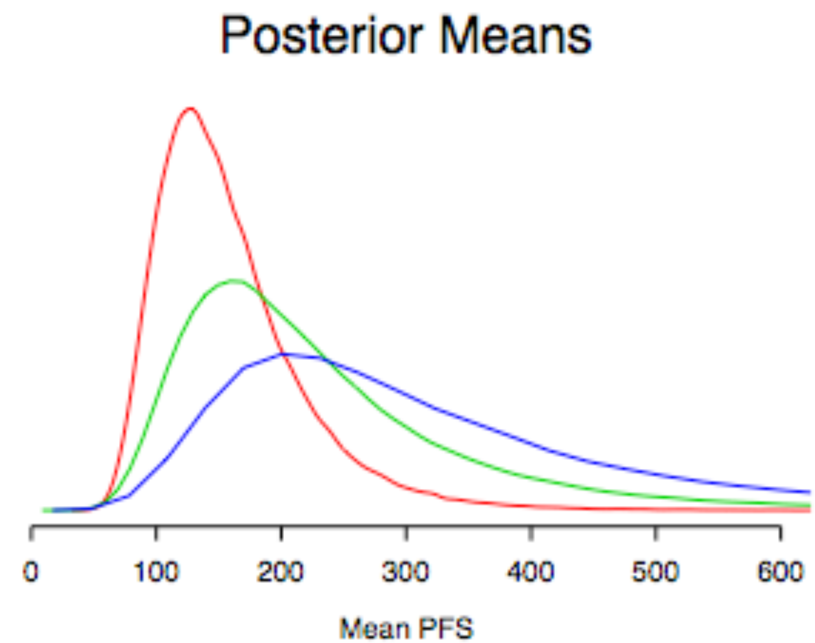
Simulation #2

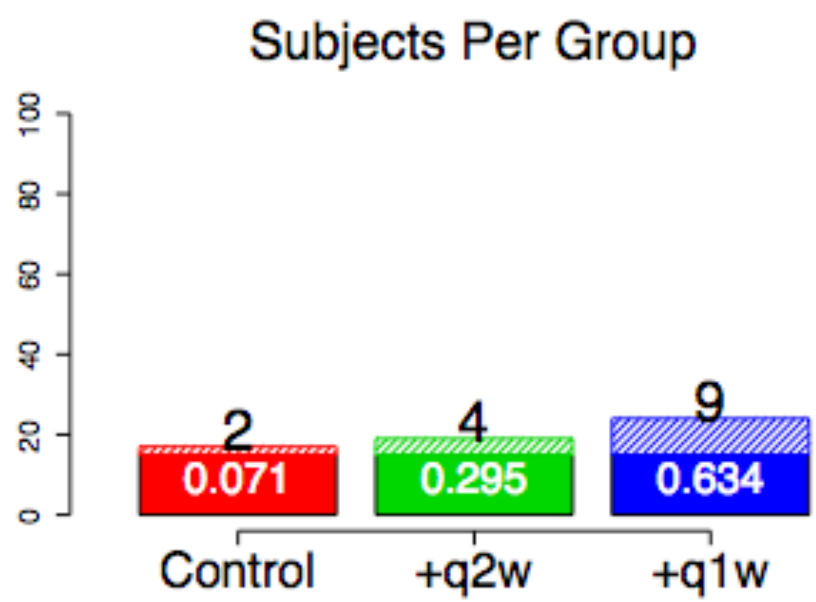
- Mean Progression Free Survival
  - Control = 303 days
  - Control + q2w = 303 days
  - Control + q1w = 606 days
- Accrual rate
  - 1 patient every 3 days for first 45 patients (~4mo)
  - 1 patient every 2 days thereafter
  - 435 days for 195 patients = 14.3 months
  - 1 year follow-up = 26.3 months

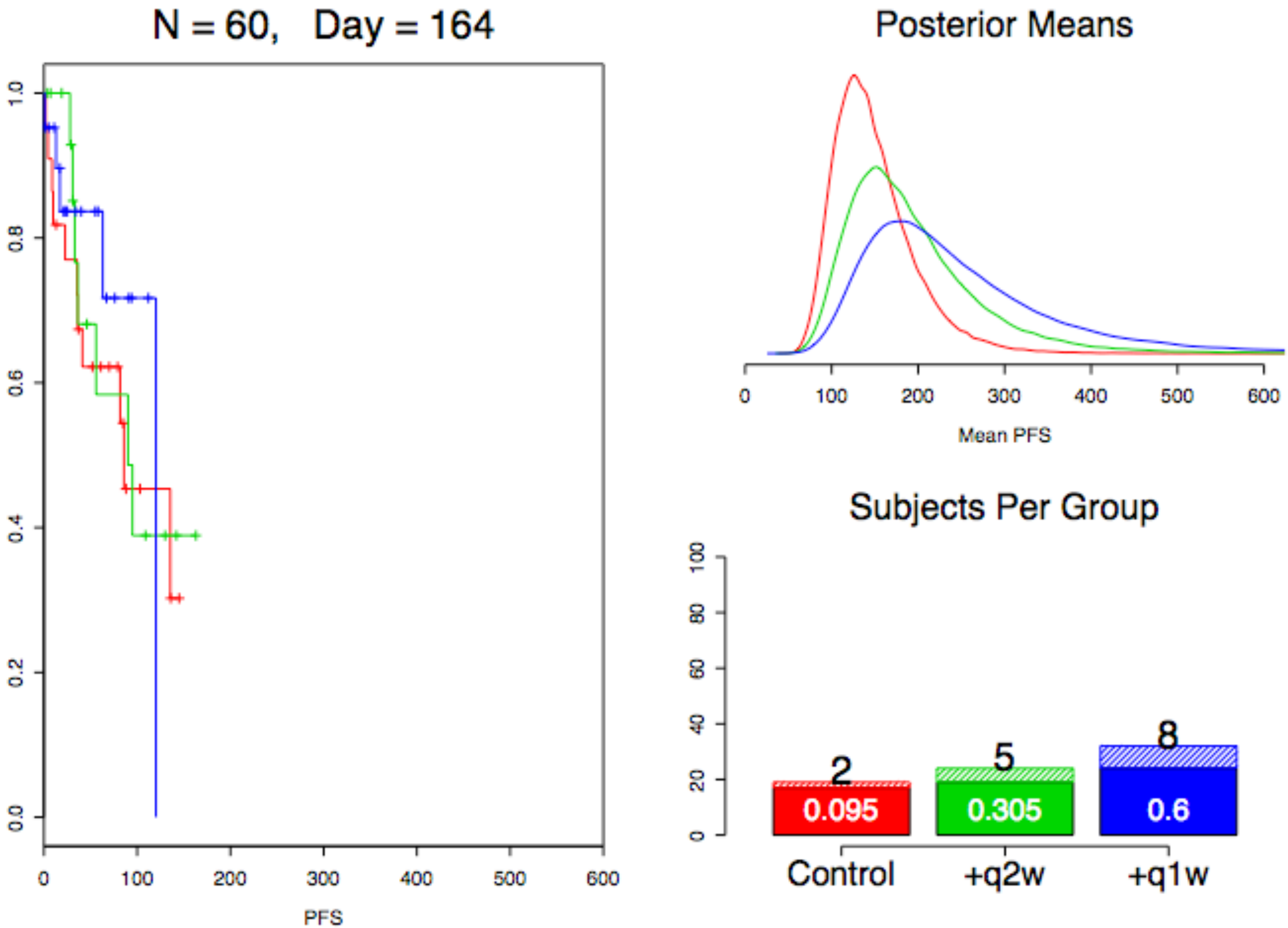


N = 0, Day = 0
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
PFS
Posterior Means
0
100
200
300
400
500
600
Mean PFS
Subjects Per Group
100
80
60
40
20
0
15
15
15
0.333
0.333
0.333
Control
+q2w
+q1w

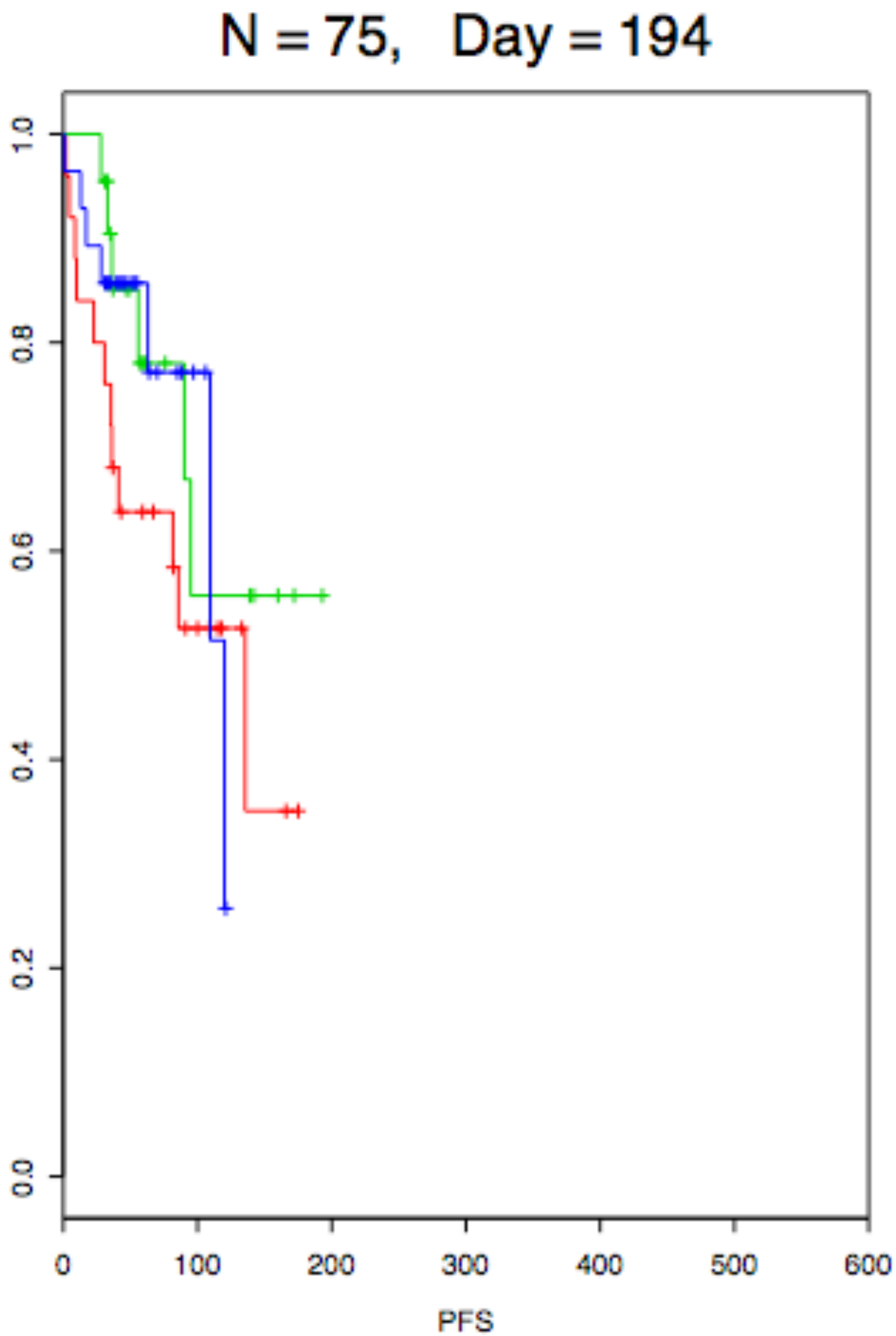

N = 45, Day = 134
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
PFS

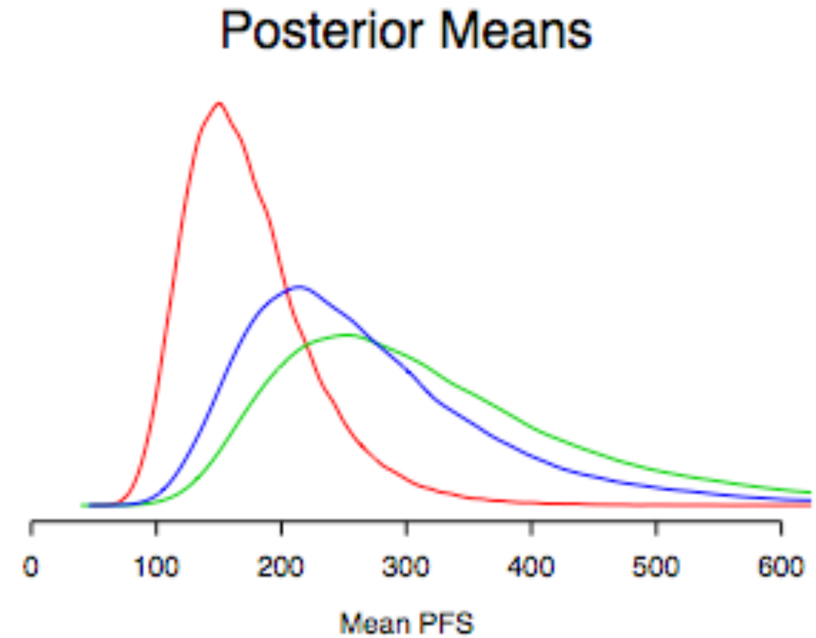

Posterior Means
0
100
200
300
400
500
600
Mean PFS

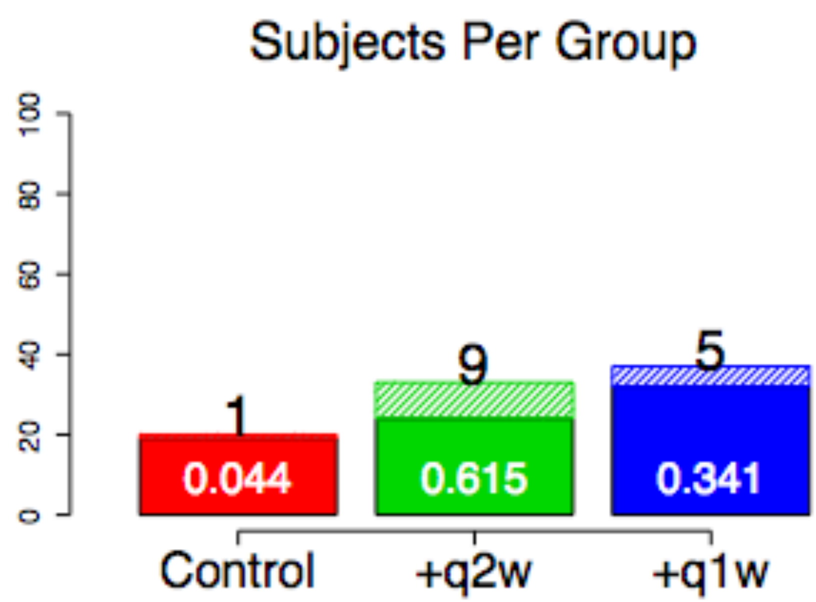

Subjects Per Group
100
80
60
40
20
0
2
0.071
4
0.295
9
0.634
Control
+q2w
+q1w

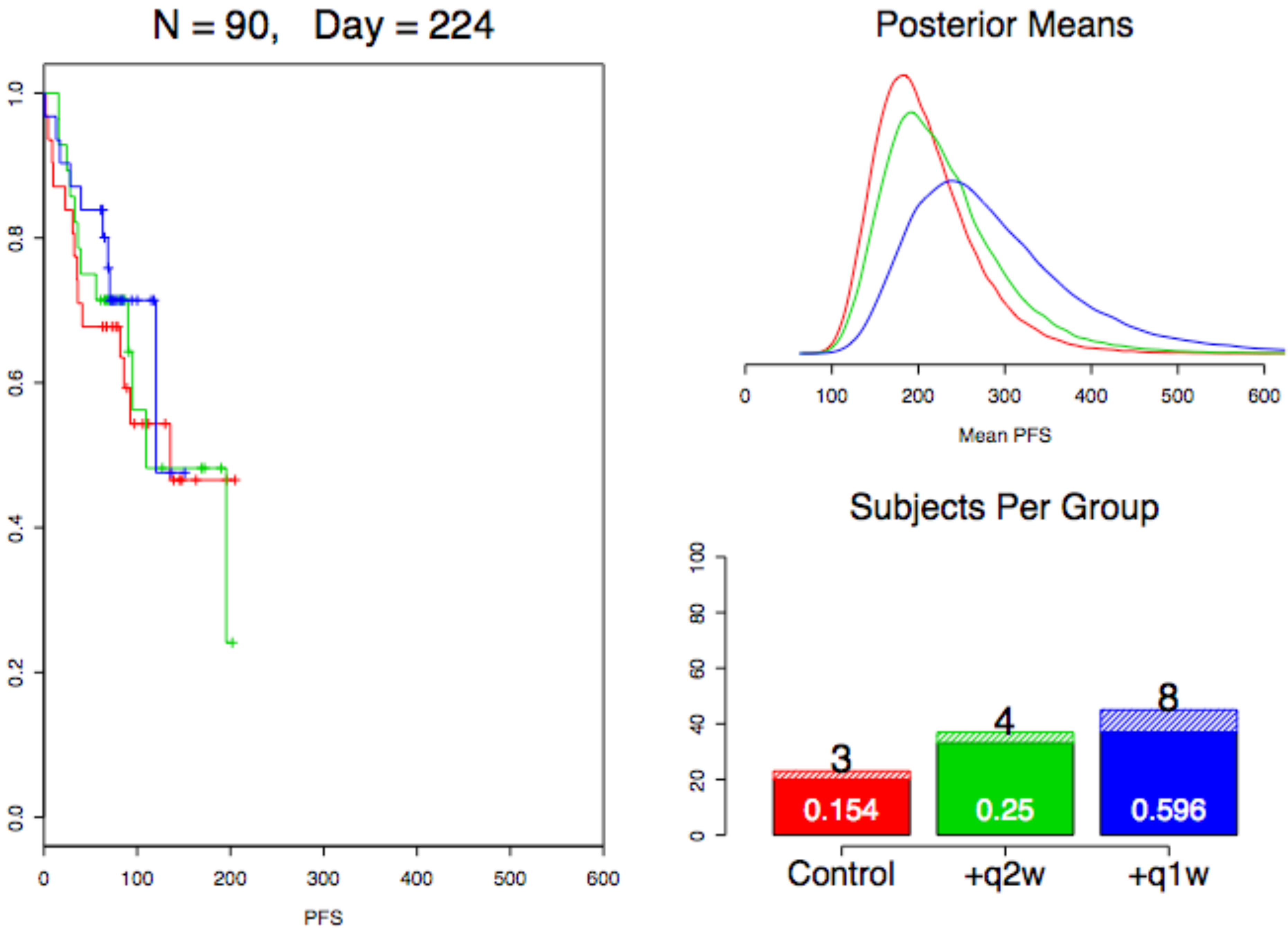


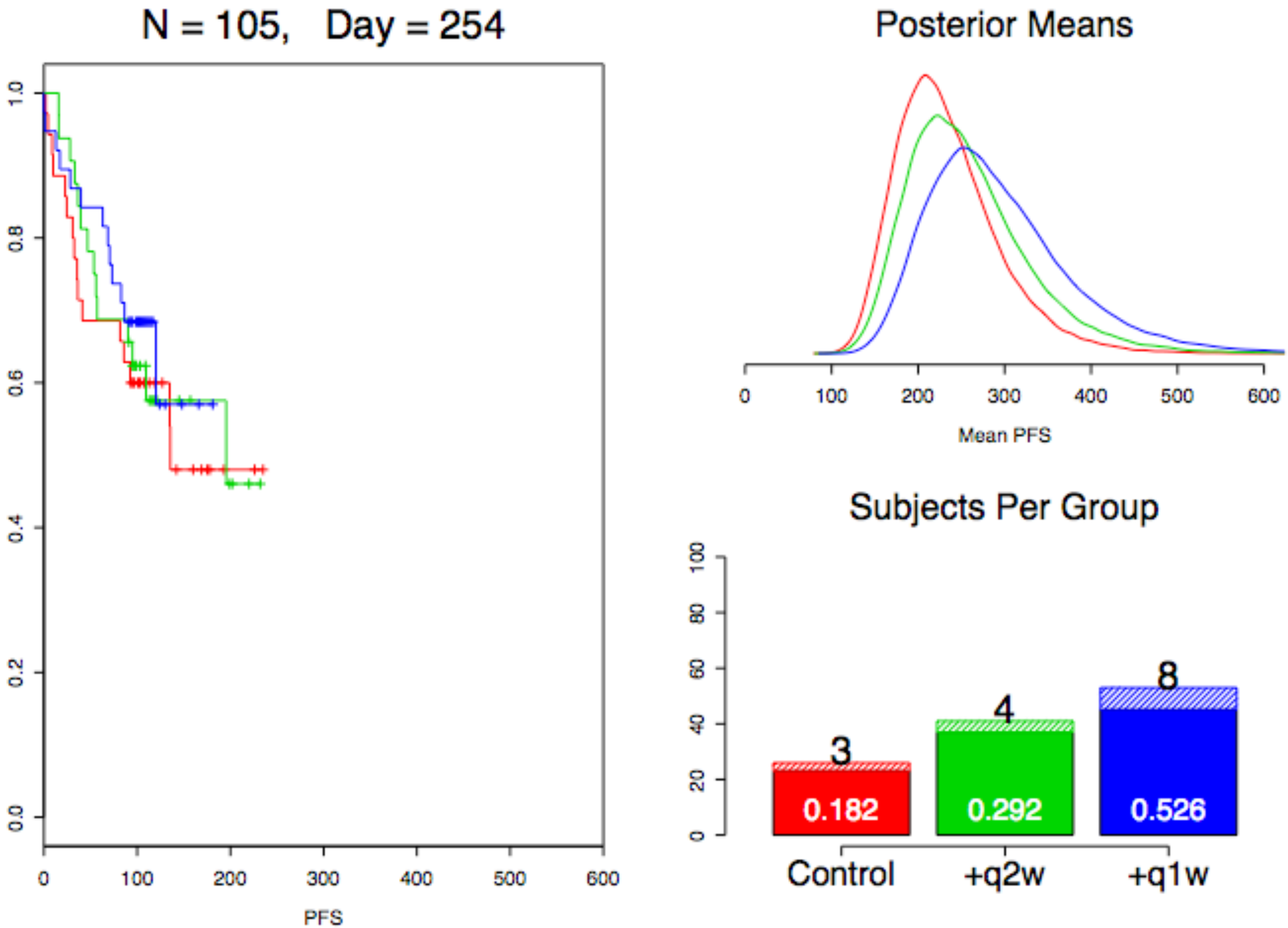
N = 60, Day = 164
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
PFS
Posterior Means
0
100
200
300
400
500
600
Mean PFS
Subjects Per Group
100
80
60
40
20
0
2
5
8
0.095
0.305
0.6
Control
+q2w
+q1w

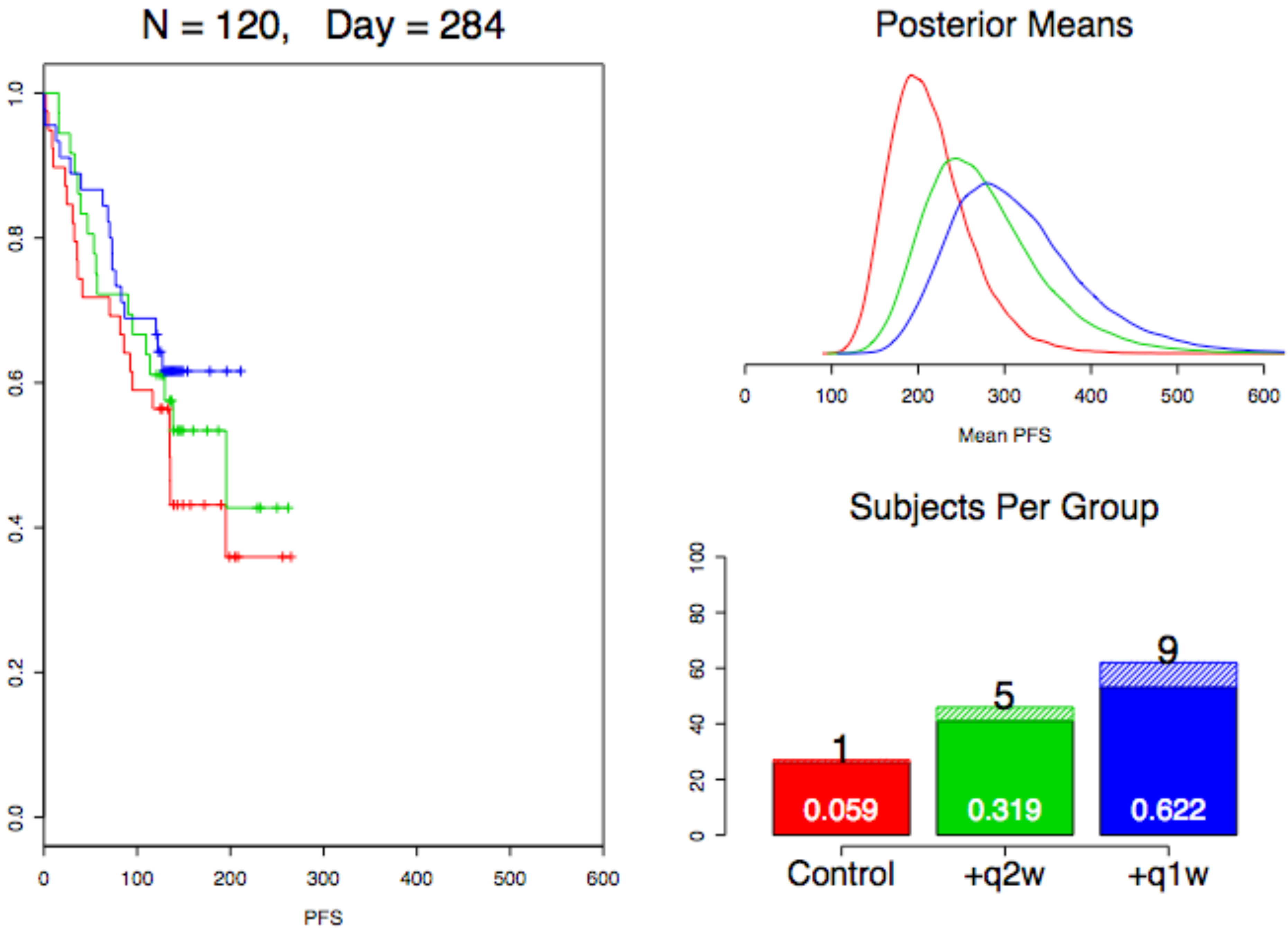

N = 75, Day = 194
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
PFS

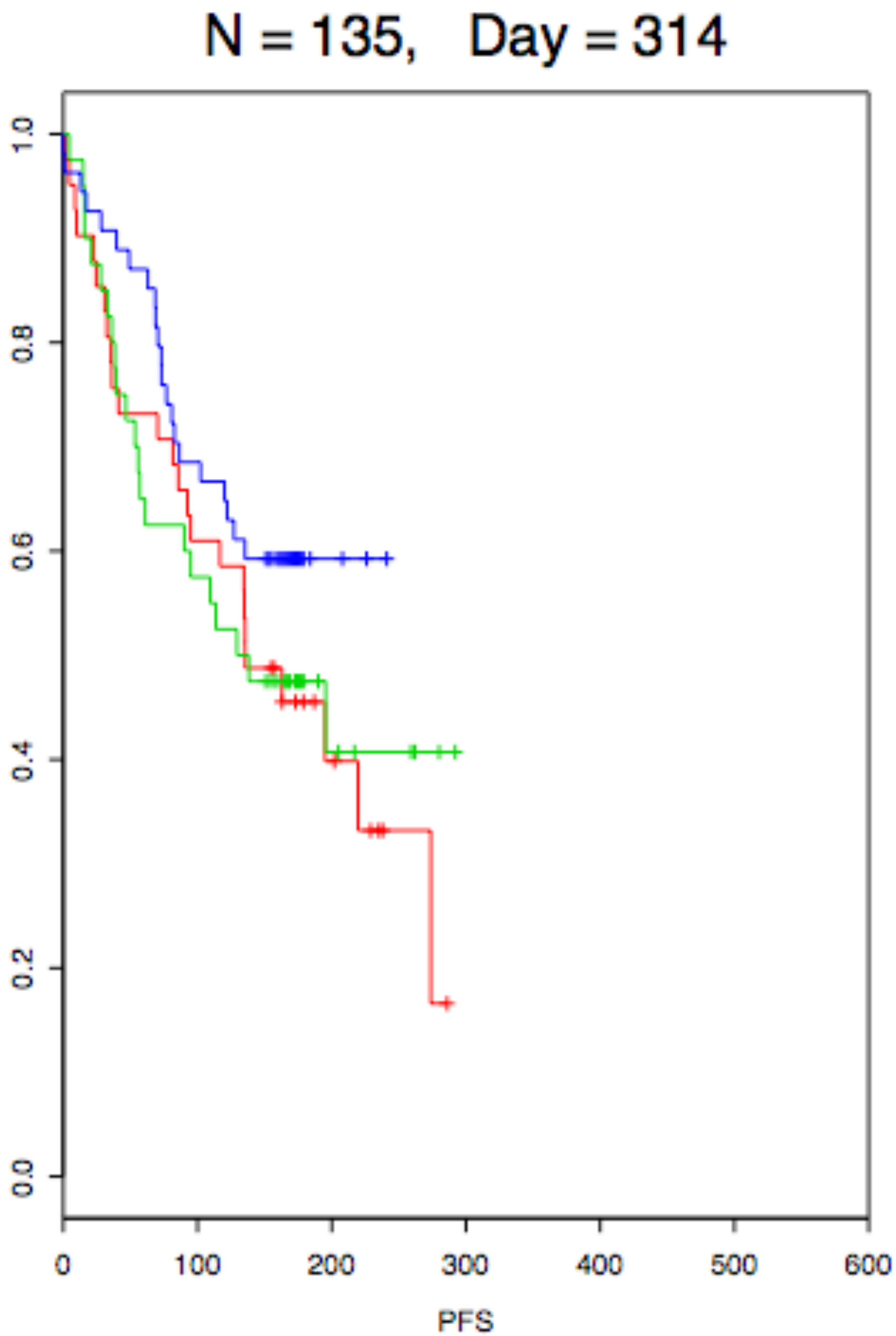

Posterior Means
0
100
200
300
400
500
600
Mean PFS

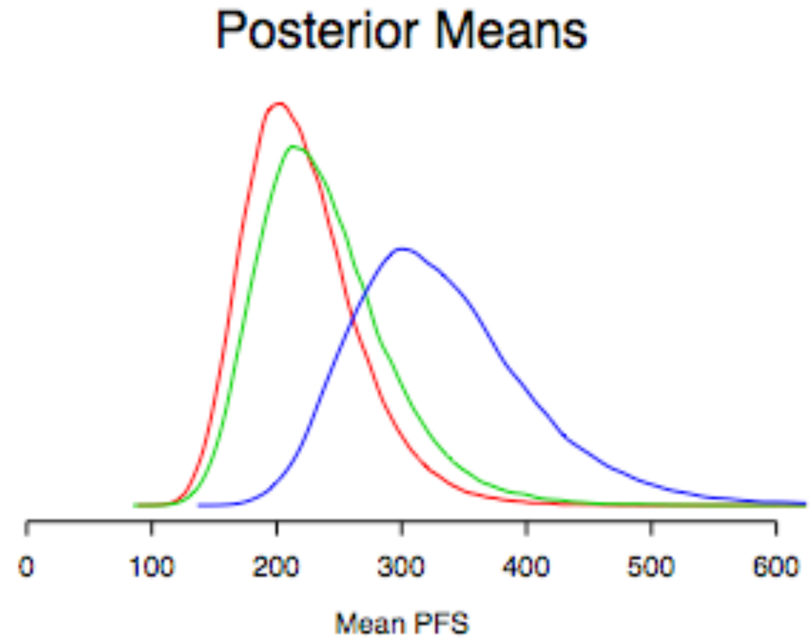

Subjects Per Group
100
80
60
40
20
0
1
9
5
0.044
0.615
0.341
Control
+q2w
+q1w

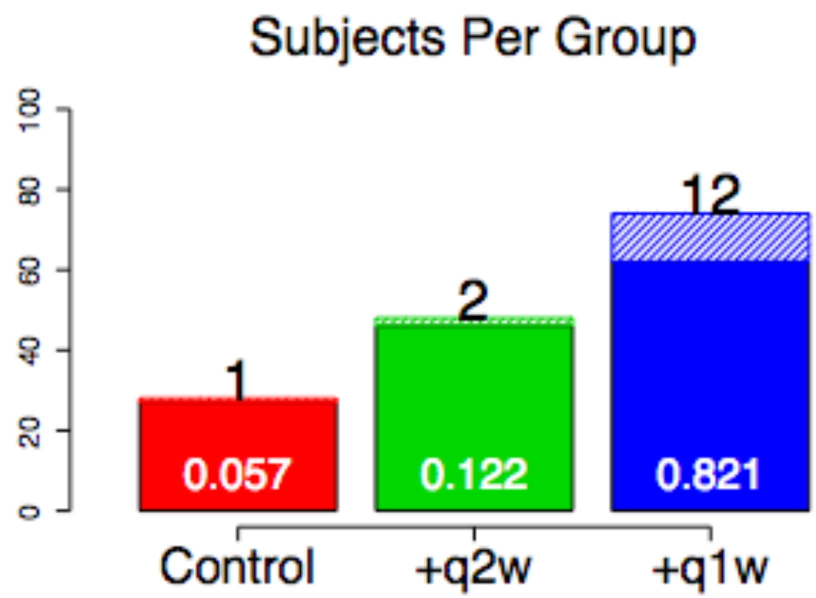

N = 90, Day = 224
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
PFS
Posterior Means
0
100
200
300
400
500
600
Mean PFS
Subjects Per Group
100
80
60
40
20
0
3
4
8
0.154
0.25
0.596
Control
+q2w
+q1w

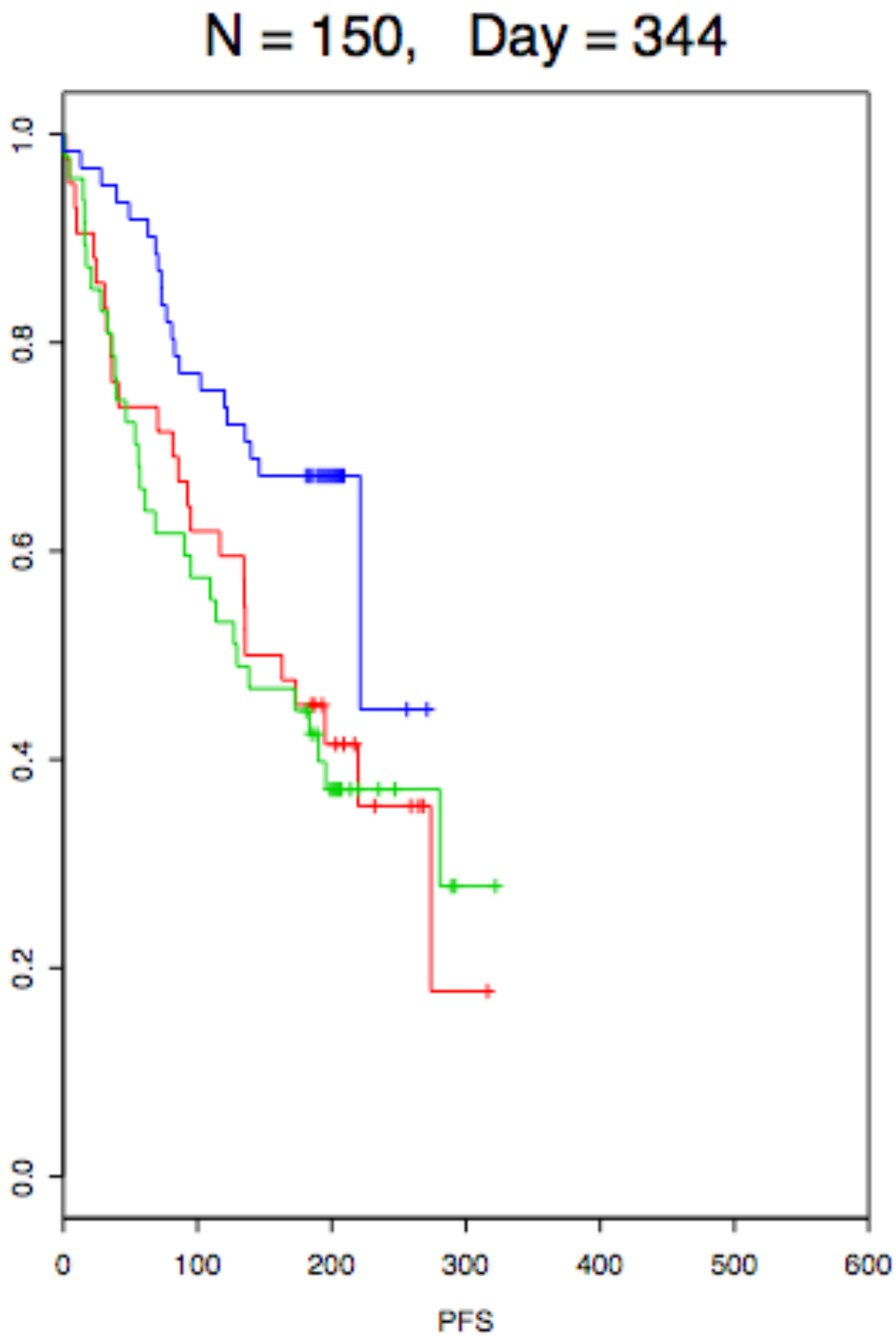

N = 105, Day = 254
PFS
Posterior Means
Mean PFS
Subjects Per Group
3
4
8
0.182
0.292
0.526
Control
+q2w
+q1w


N = 120, Day = 284
PFS
0
100
200
300
400
500
600
0.0
0.2
0.4
0.6
0.8
1.0
Posterior Means
Mean PFS
Subjects Per Group
1
5
9
0.059
0.319
0.622
Control
+q2w
+q1w
0
20
40
60
80
100

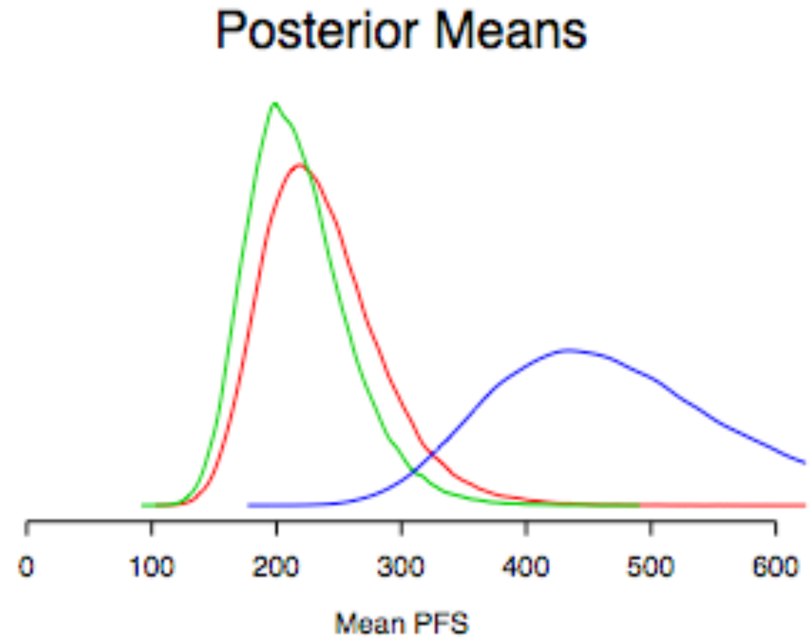

N = 135,   Day = 314
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
PFS


Posterior Means
0
100
200
300
400
500
600
Mean PFS

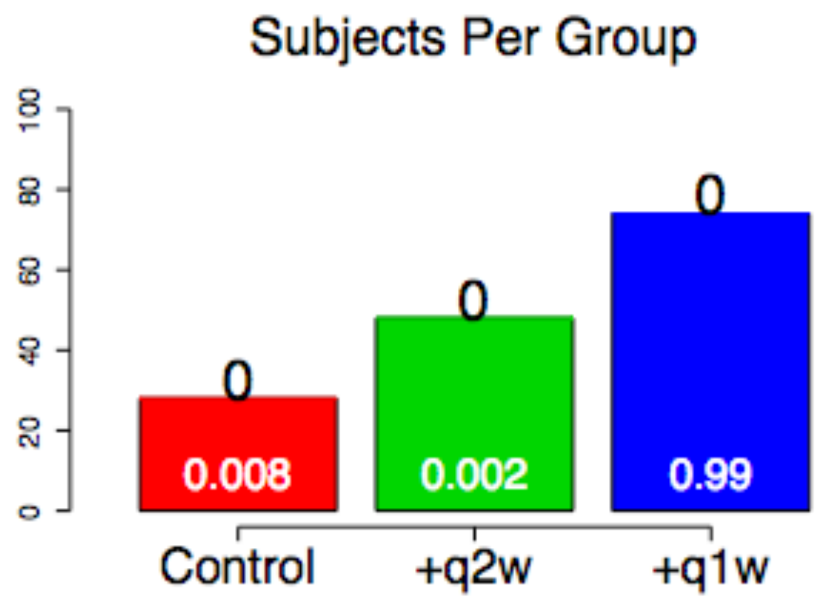

Subjects Per Group
100
80
60
40
20
0
1
2
12
0.057
0.122
0.821
Control
+q2w
+q1w



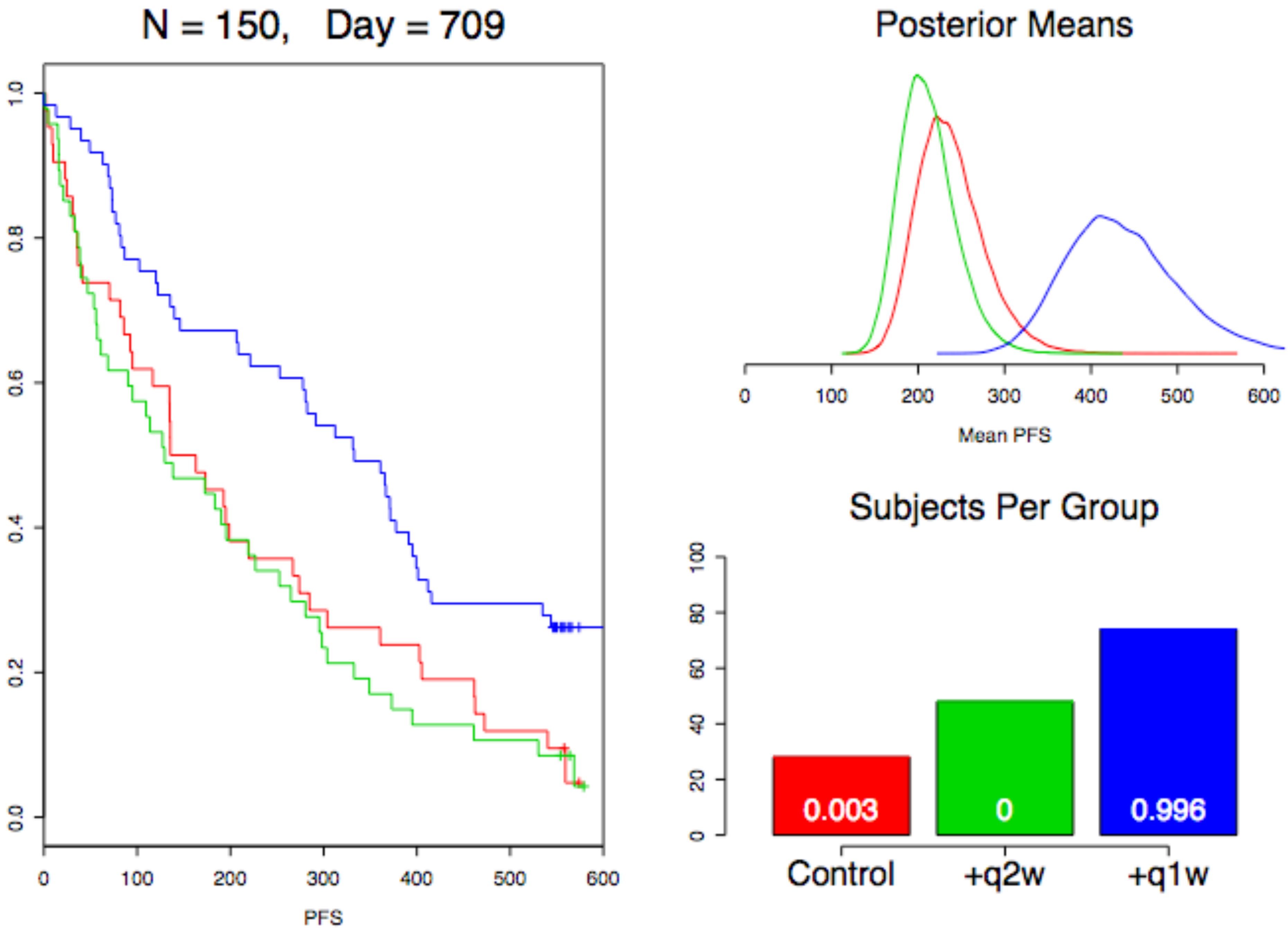
N = 150, Day = 344
0.0
0.2
0.4
0.6
0.8
1.0
0
100
200
300
400
500
600
PFS



Posterior Means
0
100
200
300
400
500
600
Mean PFS



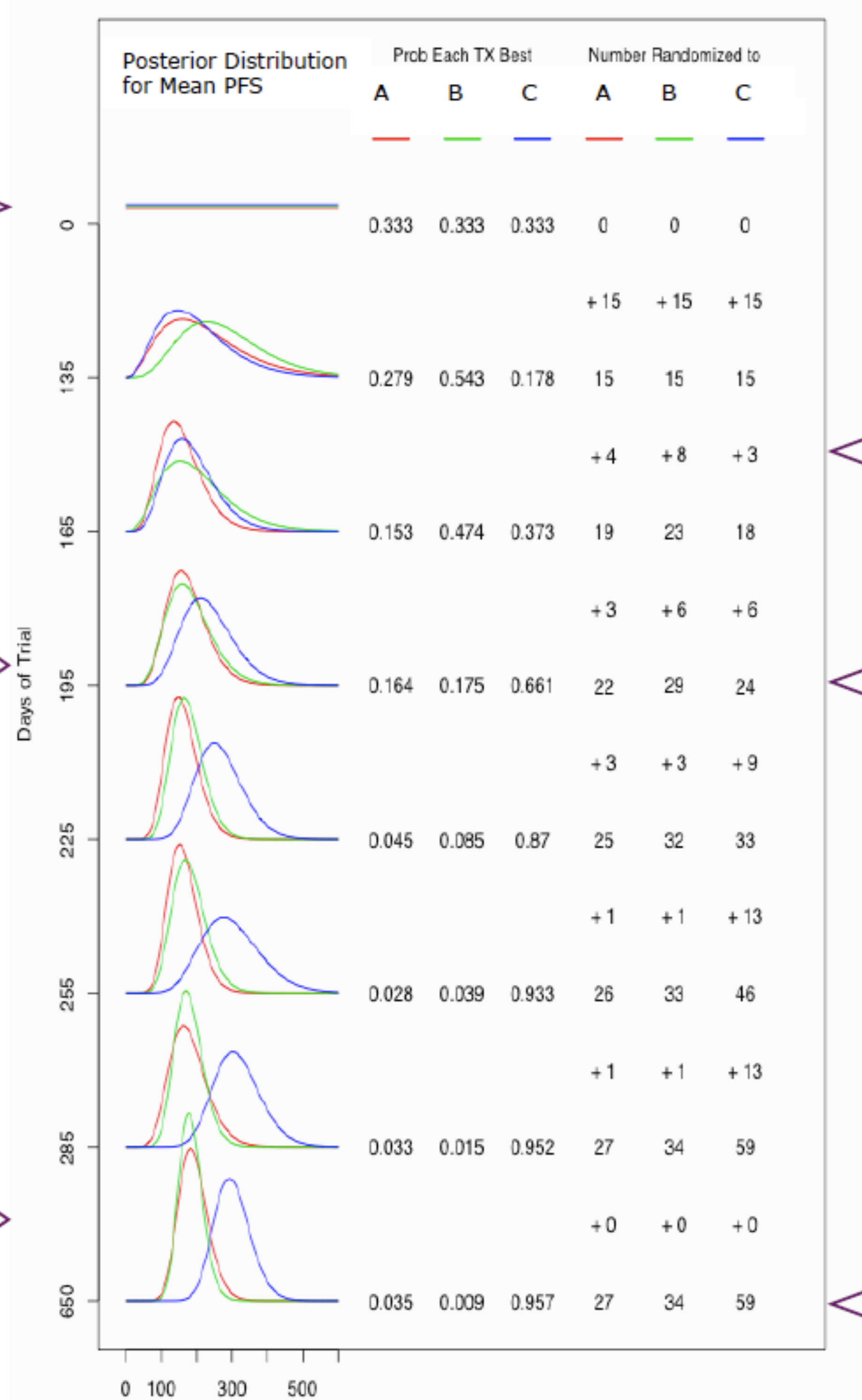
Subjects Per Group
0
20
40
60
80
100
0
0
0
0.008
0.002
0.99
Control
+q2w
+q1w


N = 150, Day = 709
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
PFS
Posterior Means
0
100
200
300
400
500
600
Mean PFS
Subjects Per Group
100
80
60
40
20
0
0.003
0
0.996
Control
+q2w
+q1w

"Flat" Prior
(Vague, Non-informative)

Interim
Posterior Distributions
& Posterior Probabilities

Final
Posterior Distributions
& Posterior Probabilities



n per block

Interim Ns

Final Ns

Output I Shared (Make it prettier)

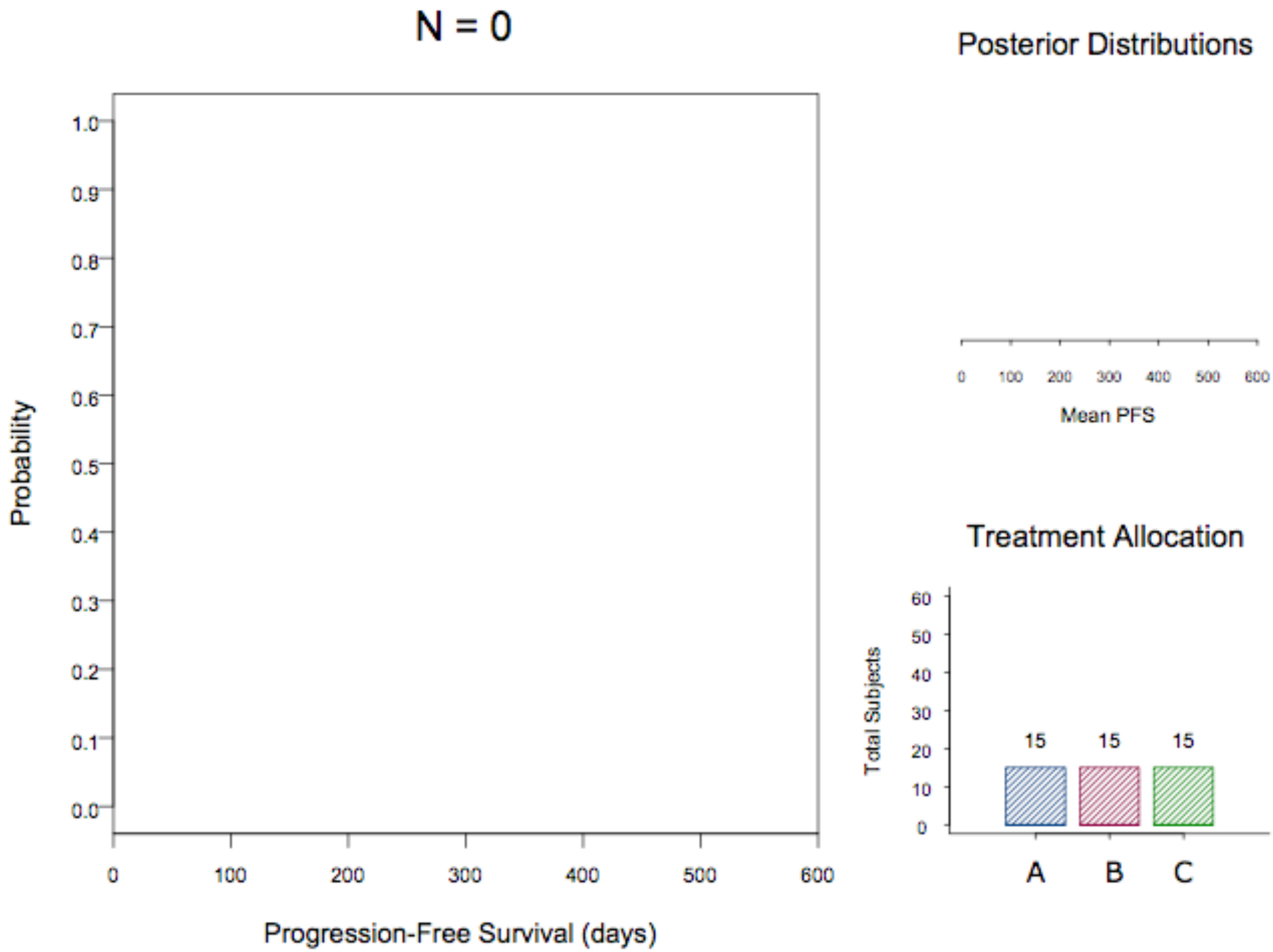
Treatment	Mean PFS	%Δ	Mean N	SD	Pr(Best)	Pr(Win)	Pr(Beat Control)
Control	303		59.7	25.3	0.343	0.000	-----
+q2w	303	No Δ	59.7	28.4	0.322	0.007	0.054
+q1w	303	No Δ	60.0	28.5	0.335	0.008	0.053
Fully Adaptive Trial			179.4	38.7	Pr(Stop for Success) = 0.071 Pr(Stop for Futility) = 0.117 Pr(Stop for Max N) = 0.813 Pr(Either Beats Control) = 0.090		

Treatment	Mean PFS	%Δ	Mean N	SD	Pr(Best)	Pr(Win)	Pr(Beat Control)
Control	303		34.0	14.2	0.001	0.000	-----
+q2w	455	+50%	56.9	27.0	0.099	0.002	0.462
+q1w	606	+100%	79.4	28.6	0.900	0.351	0.881
Fully Adaptive Trial			170.3	43.2	Pr(Stop for Success) = 0.345 Pr(Stop for Futility) = 0.004 Pr(Stop for Max N) = 0.650 Pr(Either Beats Control) = 0.907		

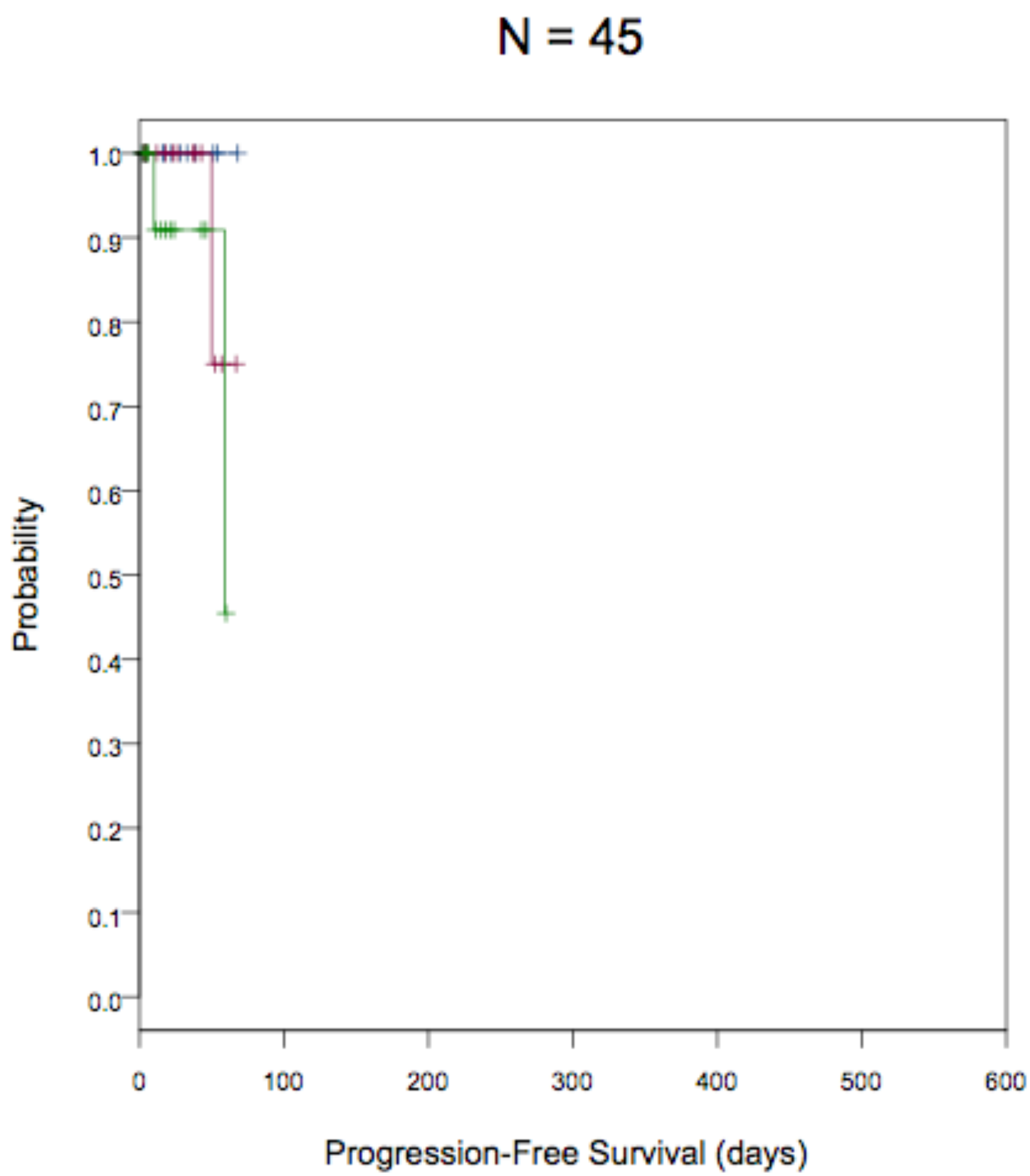
The trial is over!

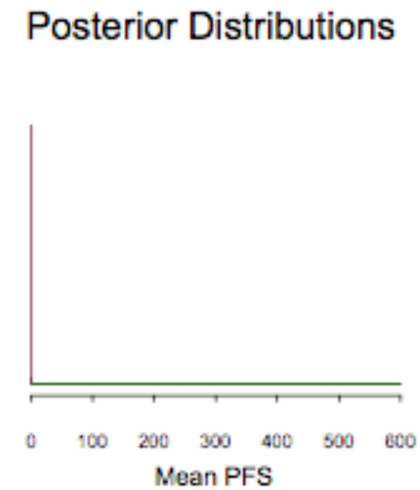
This is how it really went.

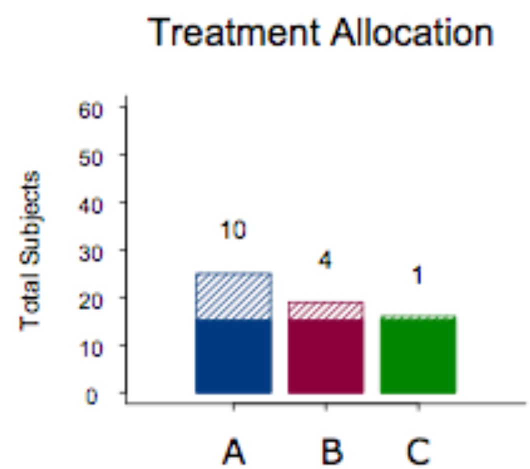
Feb 11, 2008


N = 0
Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
100
200
300
400
500
600
Progression-Free Survival (days)
Posterior Distributions
0
100
200
300
400
500
600
Mean PFS
Treatment Allocation
Total Subjects
60
50
40
30
20
10
0
15
15
15
A
B
C

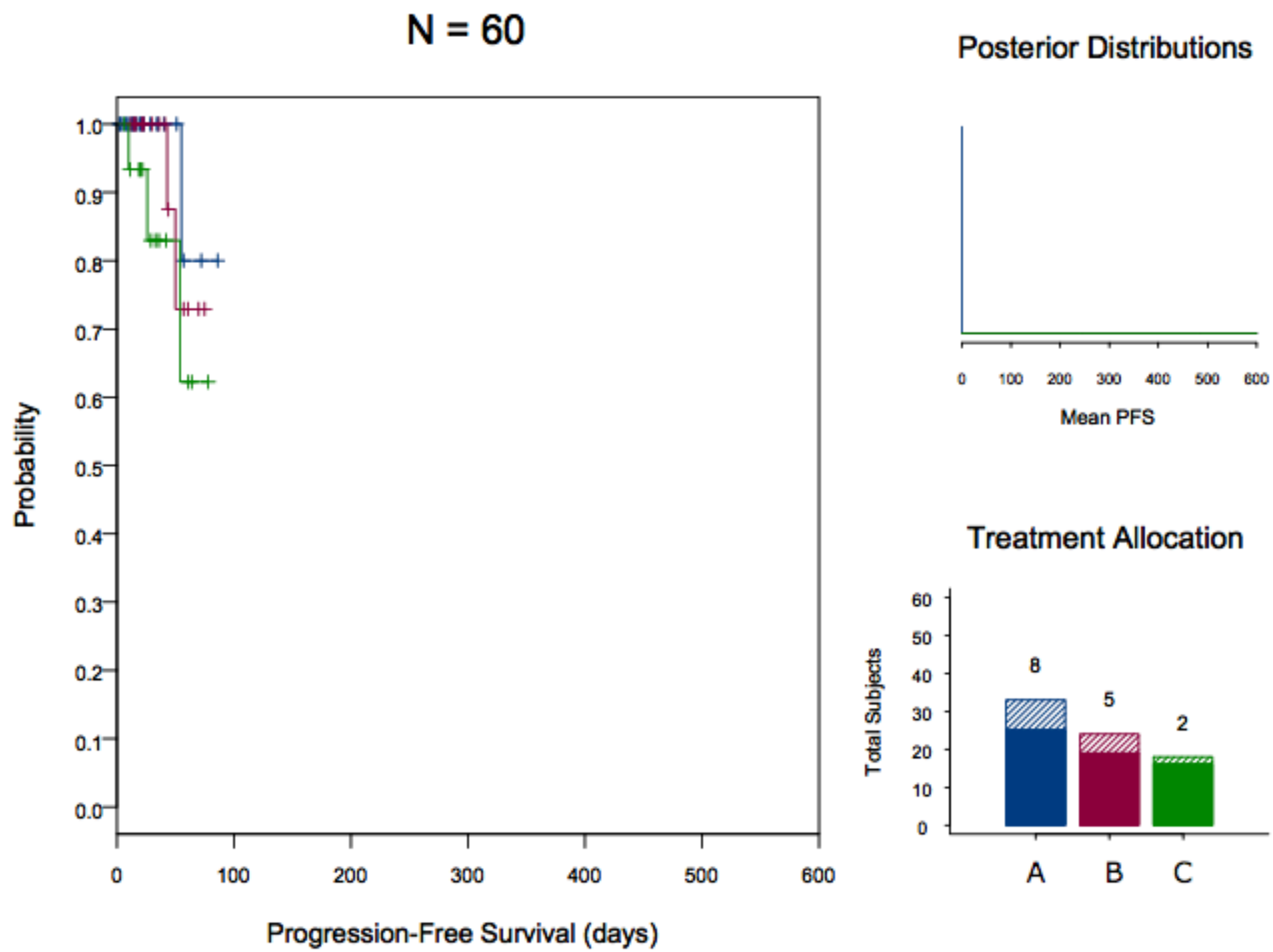
Apr 18, 2008, Expected @ Day 135; Actual Day 67



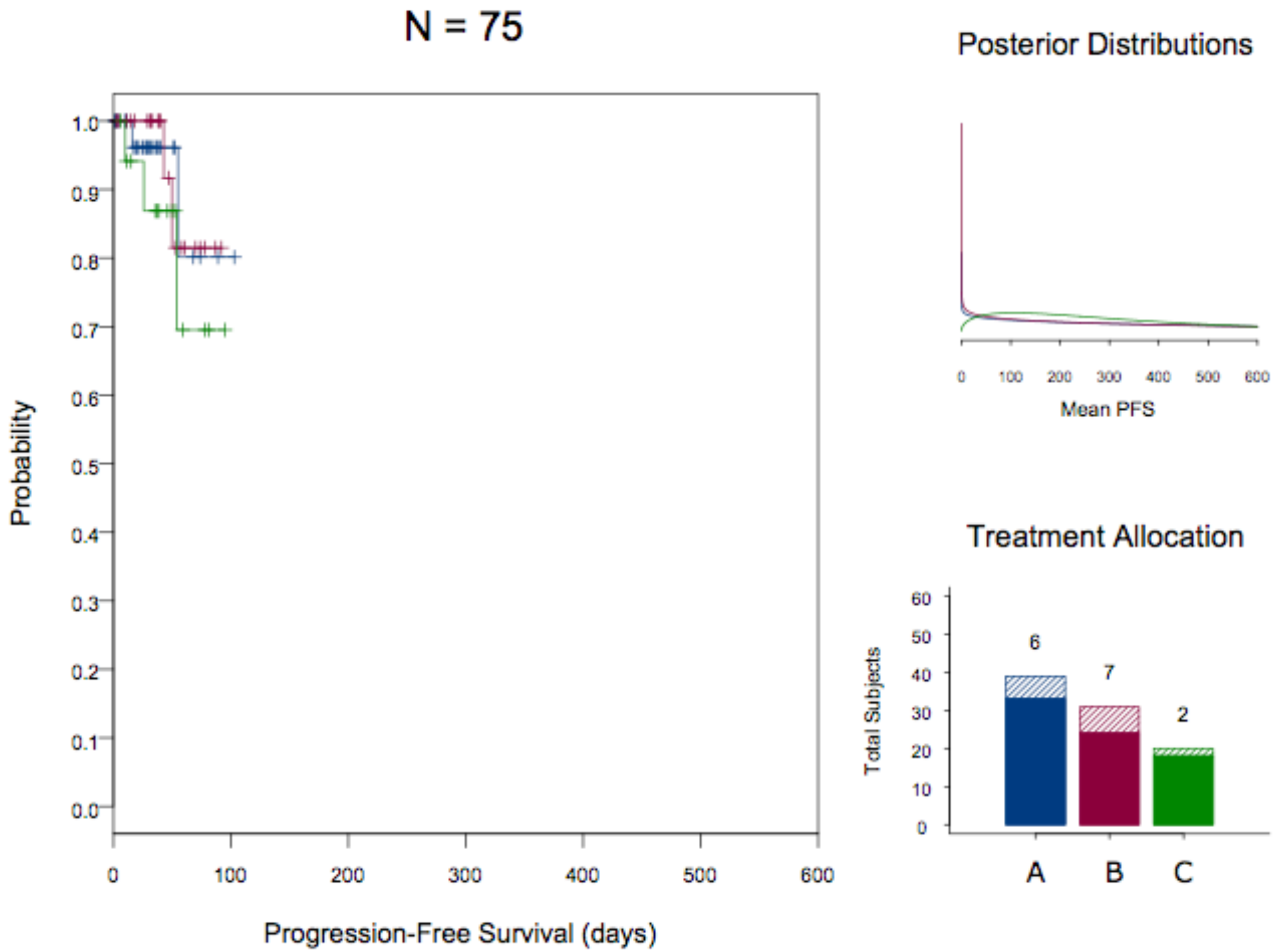




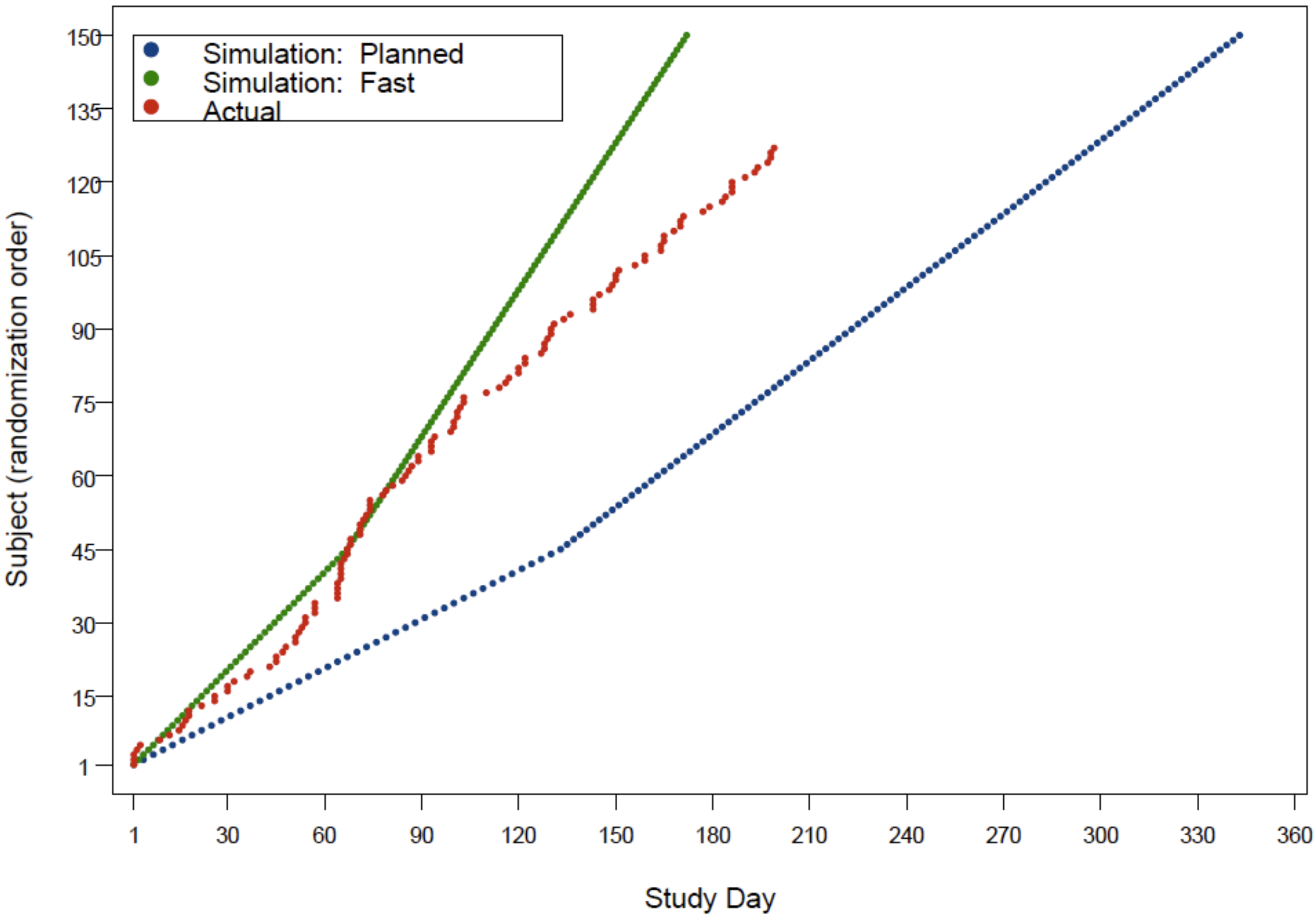
May 8, 2008, Expected @ Day 165; Day 87



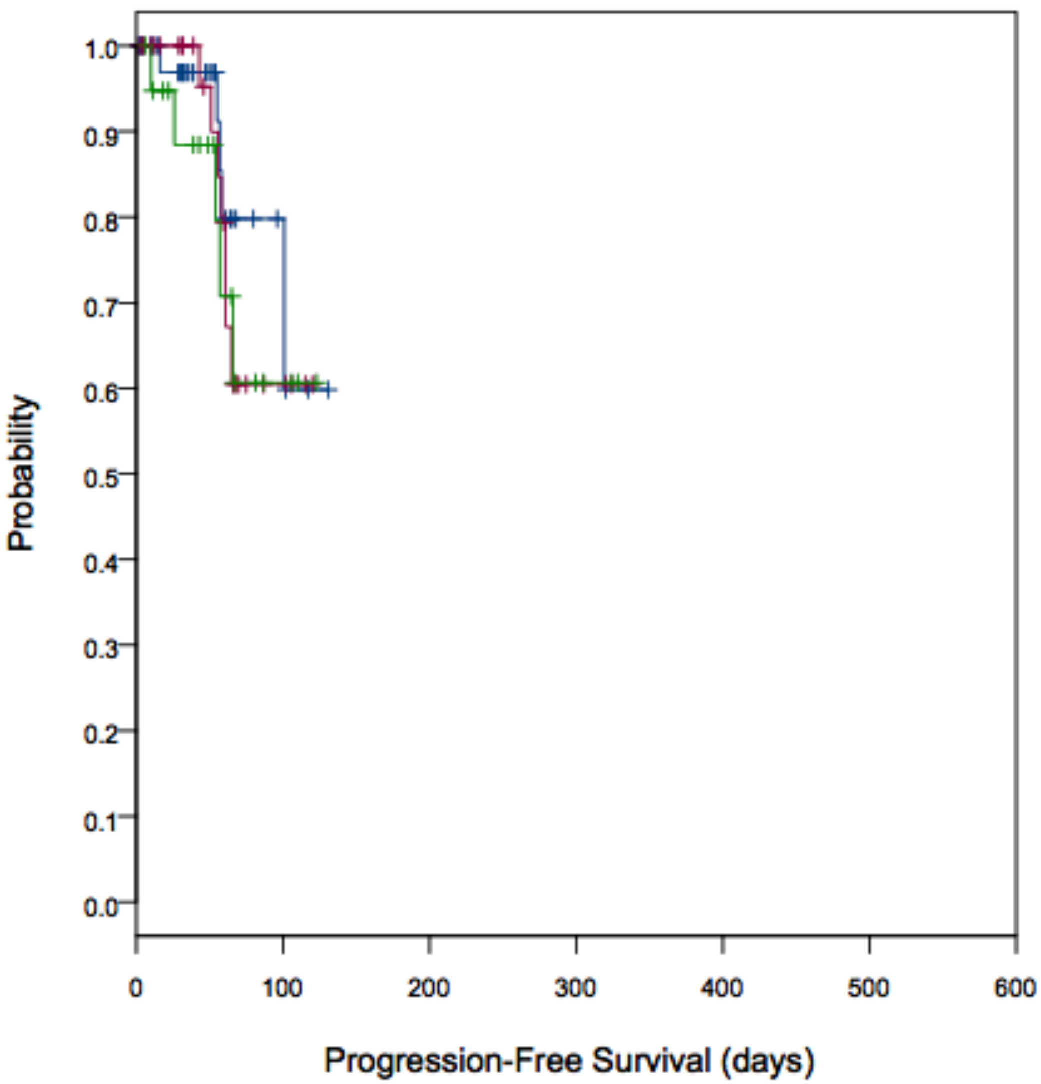
May 27, 2008, Expected @ Day 195; Day 106



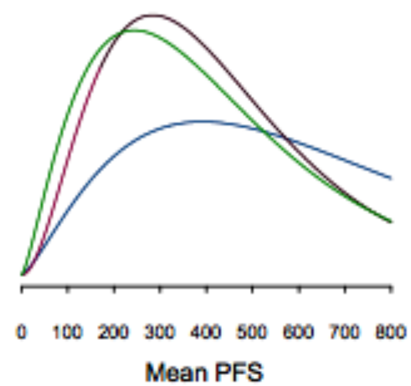
Accrual Rate



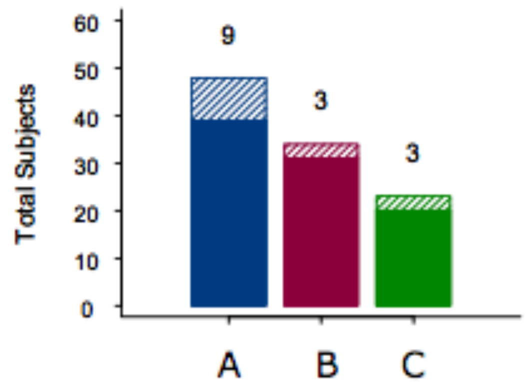
N = 90



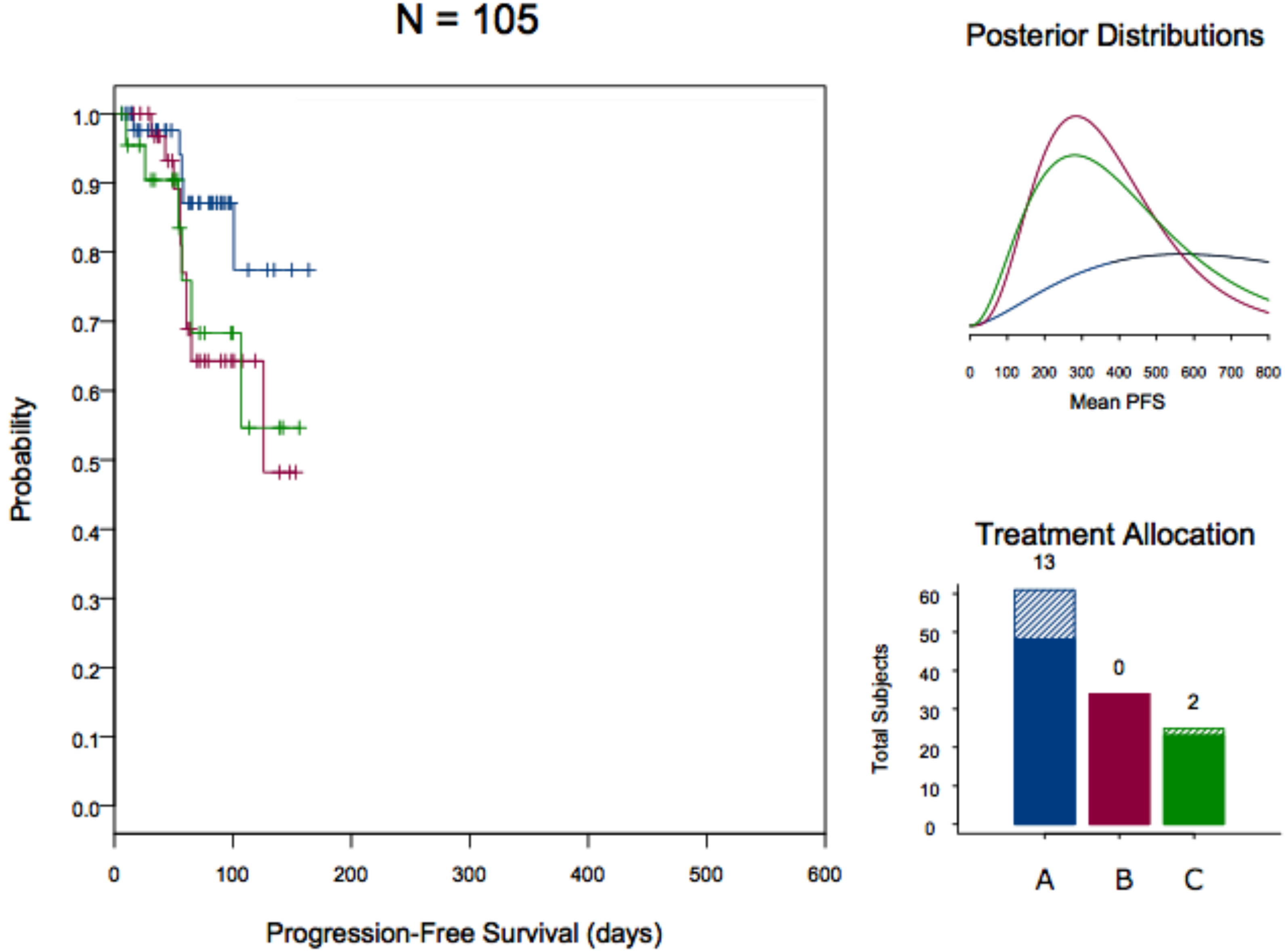
Posterior Distributions

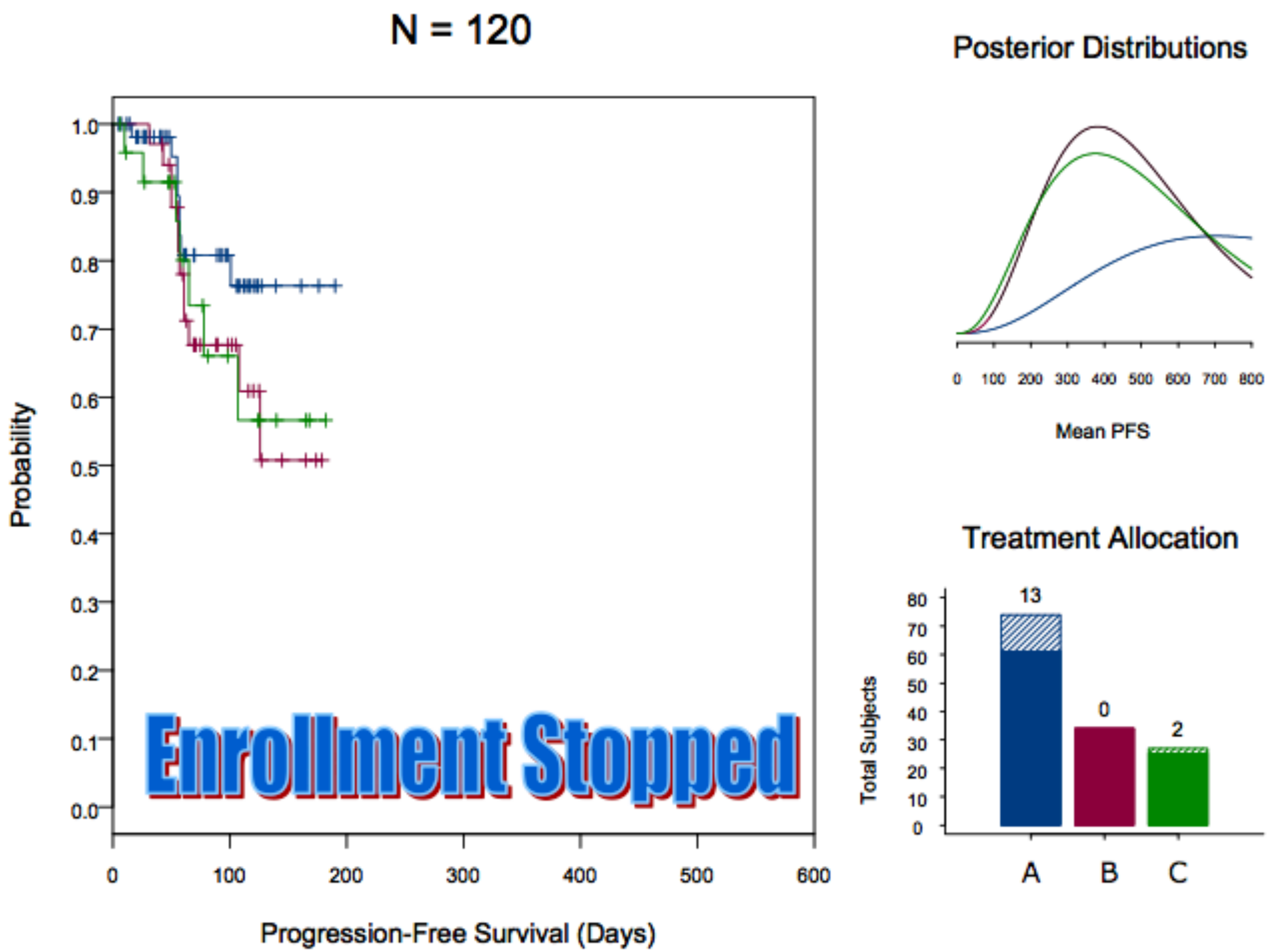


Treatment Allocation

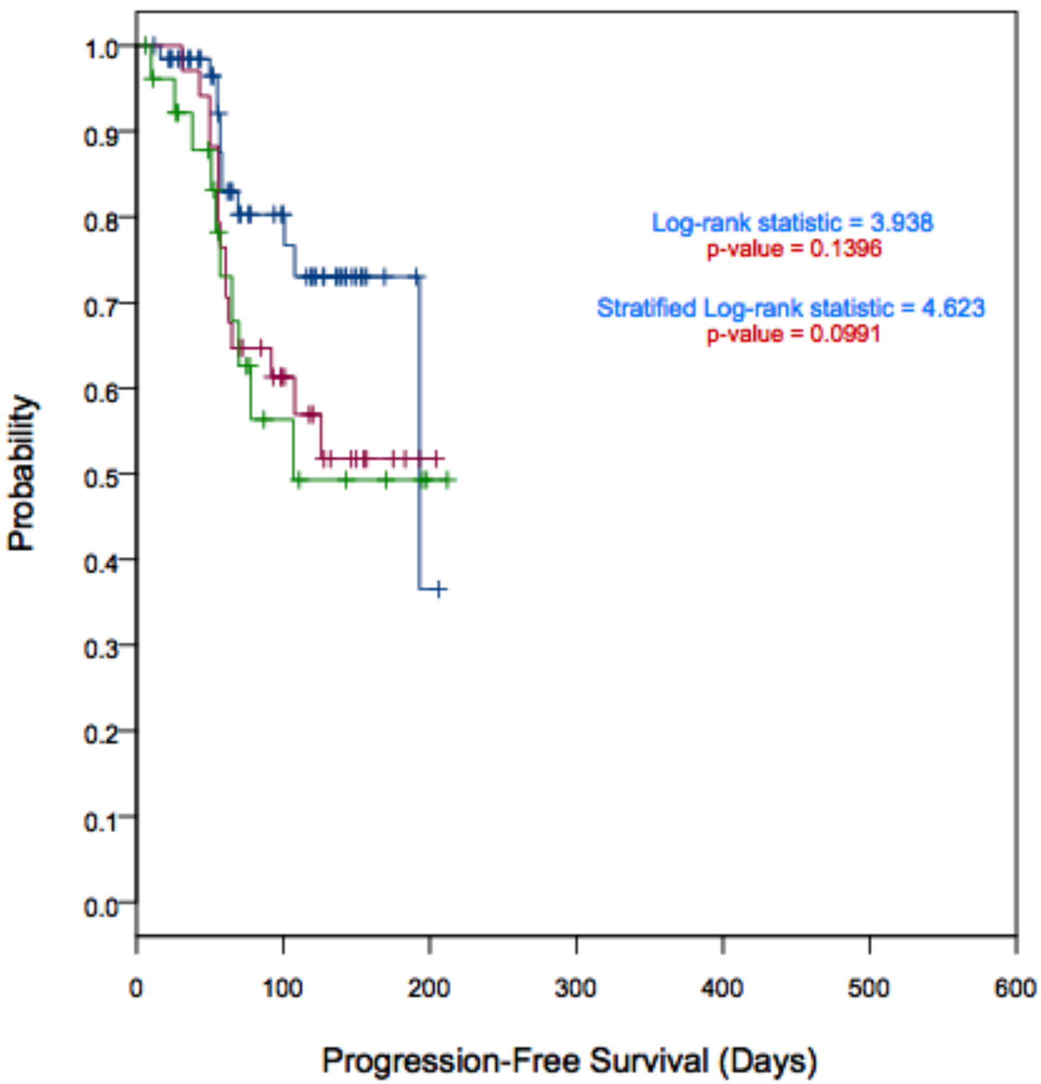


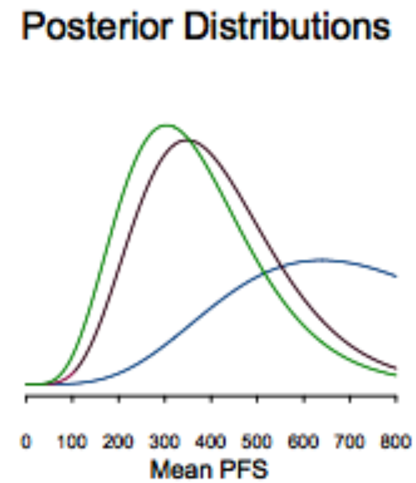
N = 105

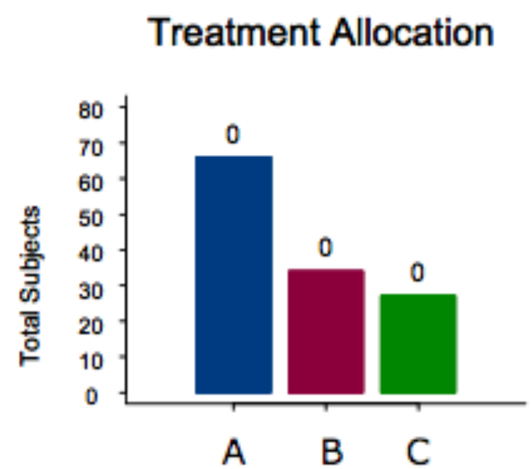

Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
100
200
300
400
500
600
Progression-Free Survival (days)
Posterior Distributions
0
100
200
300
400
500
600
700
800
Mean PFS
Treatment Allocation
Total Subjects
0
10
20
30
40
50
60
13
0
2
A
B
C

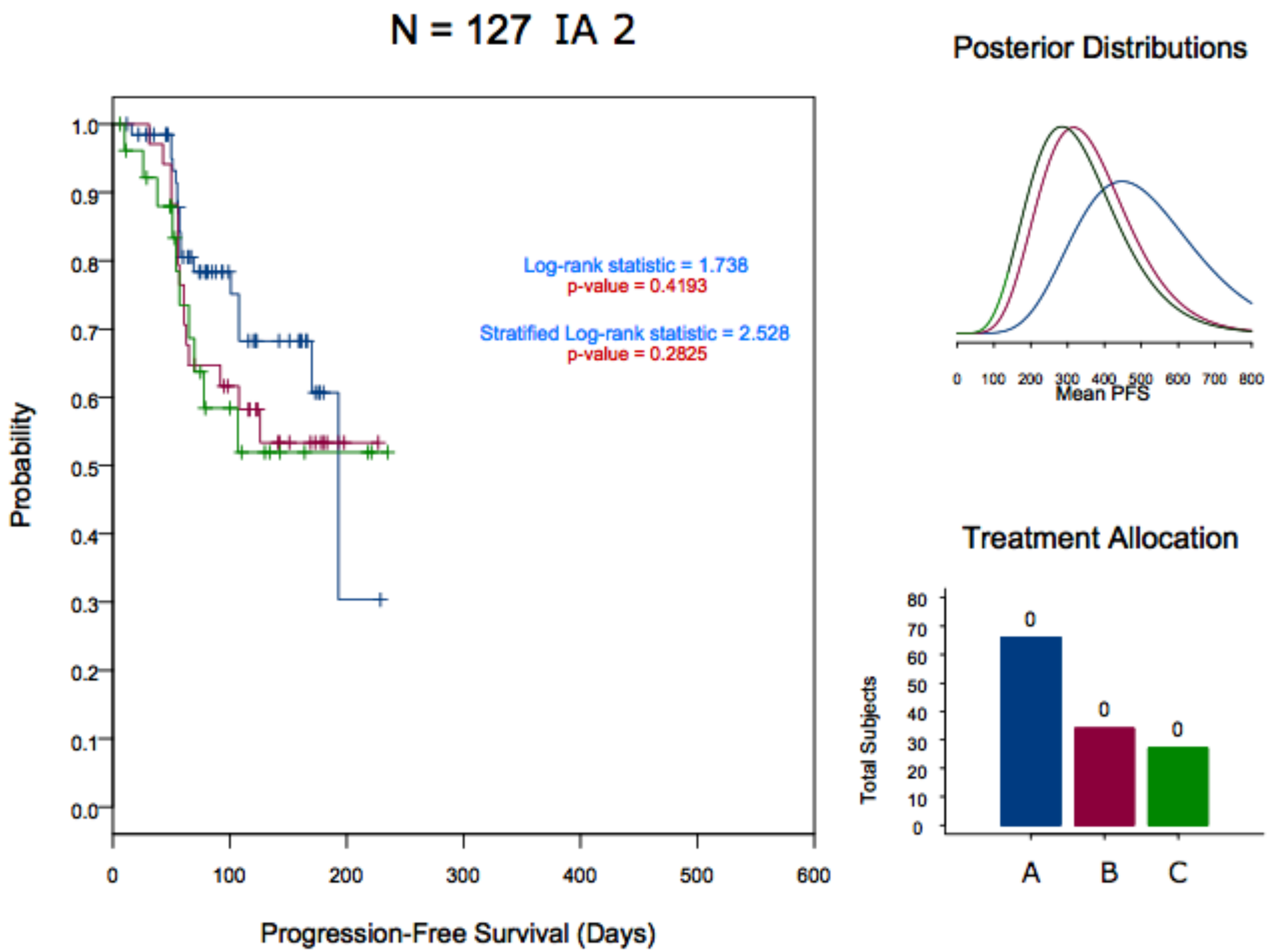

N = 120
Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
100
200
300
400
500
600
Progression-Free Survival (Days)
Enrollment Stopped
Posterior Distributions
0 100 200 300 400 500 600 700 800
Mean PFS
Treatment Allocation
Total Subjects
80
70
60
50
40
30
20
10
0
13
0
2
A
B
C

N = 127 IA 1

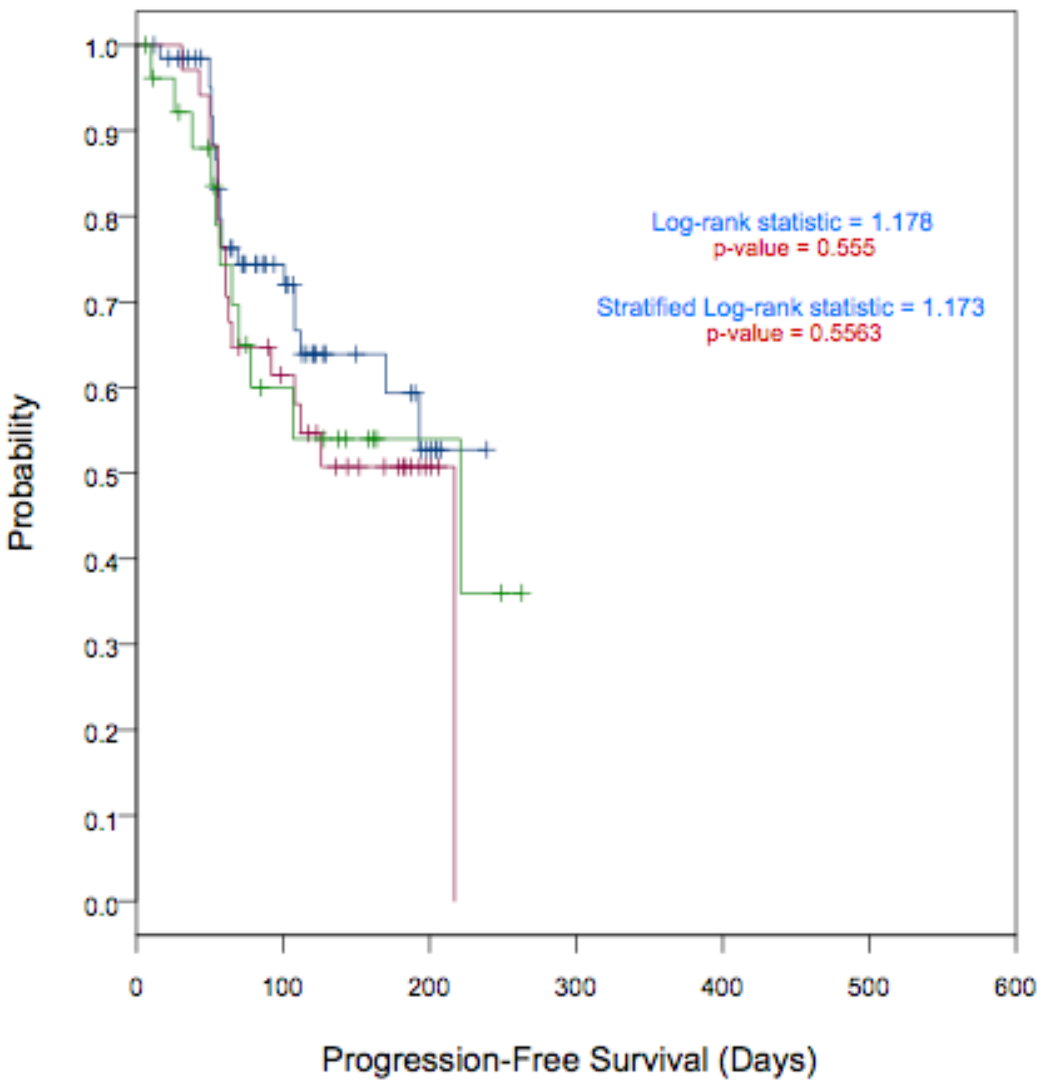

Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
100
200
300
400
500
600
Progression-Free Survival (Days)
Log-rank statistic = 3.938
p-value = 0.1396
Stratified Log-rank statistic = 4.623
p-value = 0.0991


Posterior Distributions
0
100
200
300
400
500
600
700
800
Mean PFS

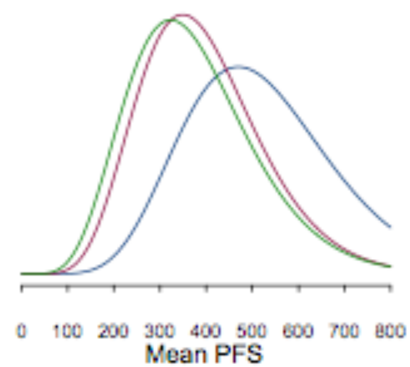

Treatment Allocation
Total Subjects
80
70
60
50
40
30
20
10
0
0
0
0
A
B
C


N = 127 IA 2
Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
100
200
300
400
500
600
Progression-Free Survival (Days)
Log-rank statistic = 1.738
p-value = 0.4193
Stratified Log-rank statistic = 2.528
p-value = 0.2825
Posterior Distributions
0 100 200 300 400 500 600 700 800
Mean PFS
Treatment Allocation
Total Subjects
80
70
60
50
40
30
20
10
0
0
0
0
A
B
C

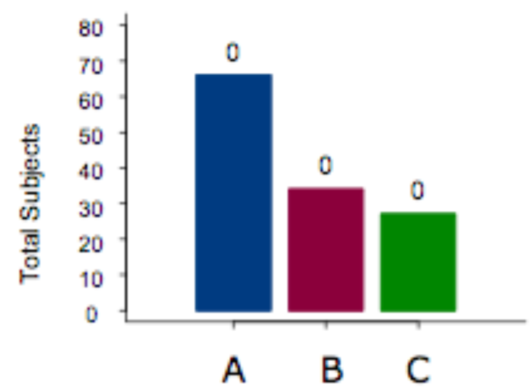
N = 127 IA 3



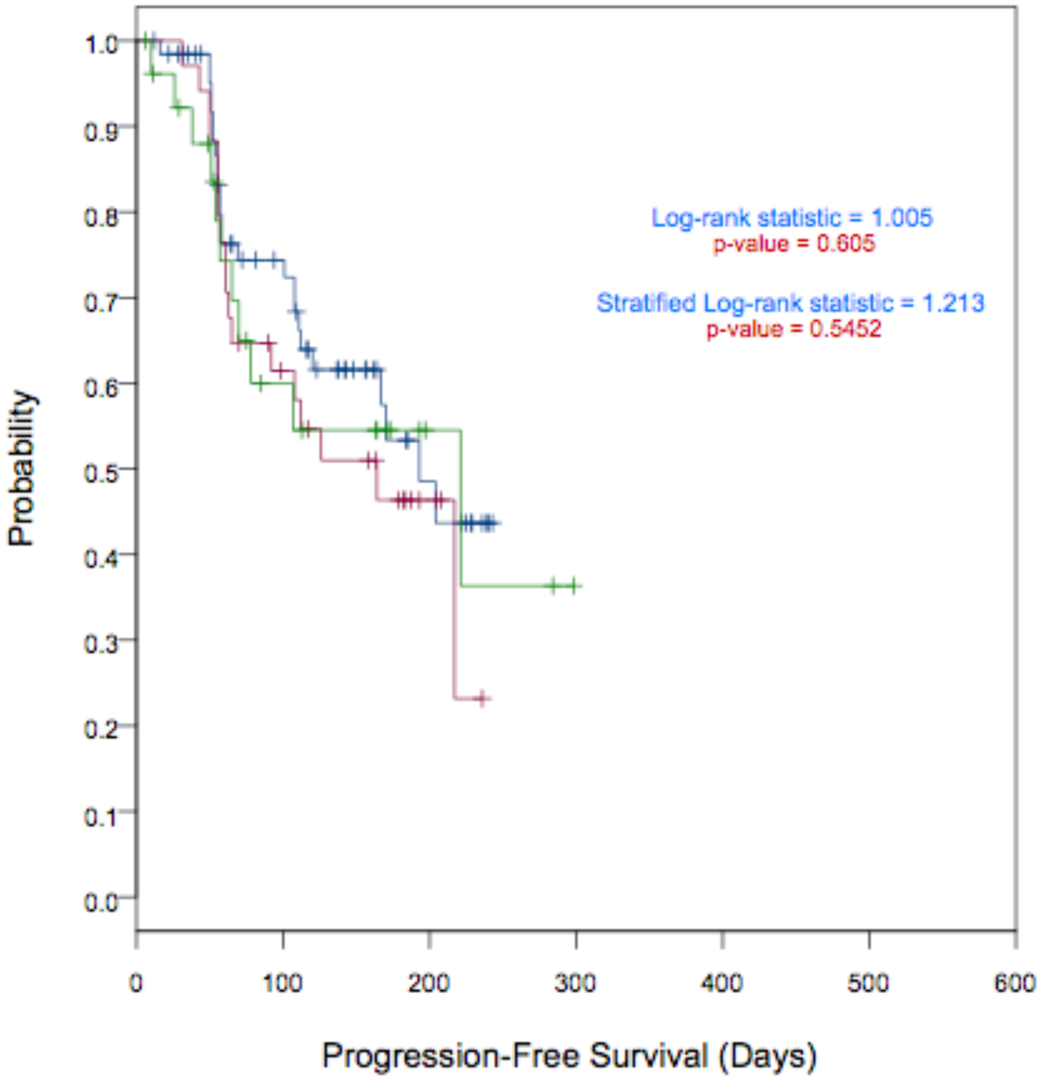
Posterior Distributions

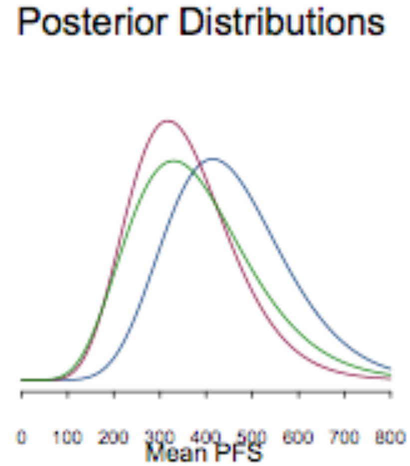


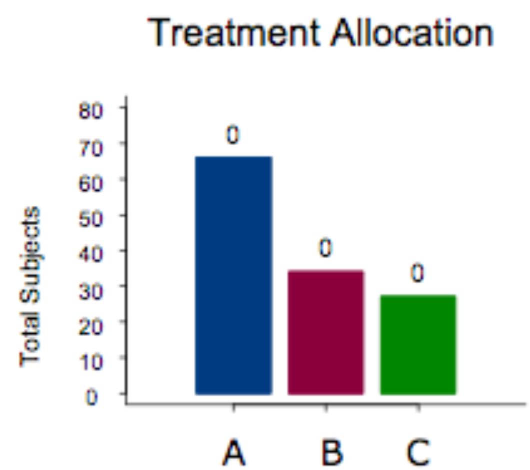
Treatment Allocation



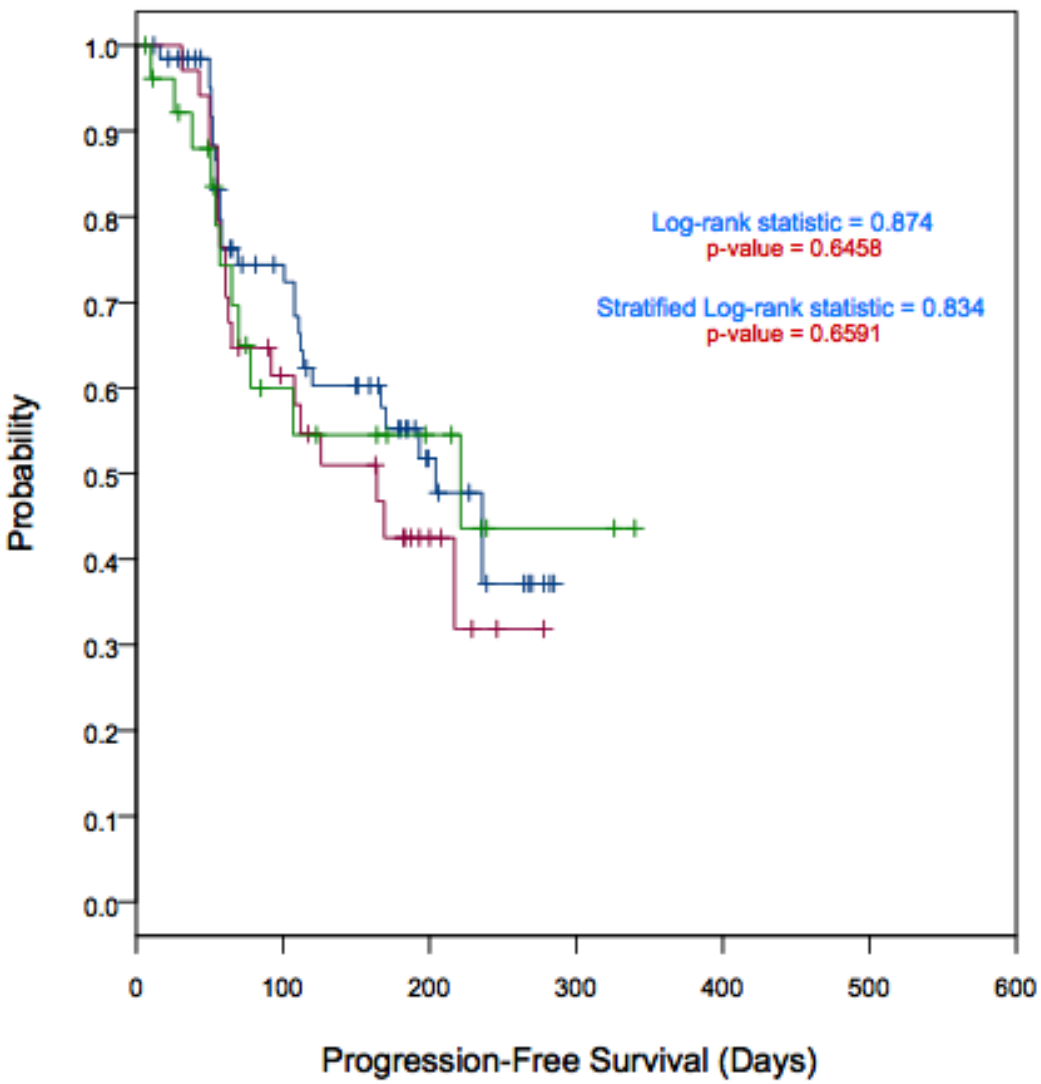
N = 127 IA 4


Log-rank statistic = 1.005
p-value = 0.605
Stratified Log-rank statistic = 1.213
p-value = 0.5452
Probability
Progression-Free Survival (Days)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
100
200
300
400
500
600

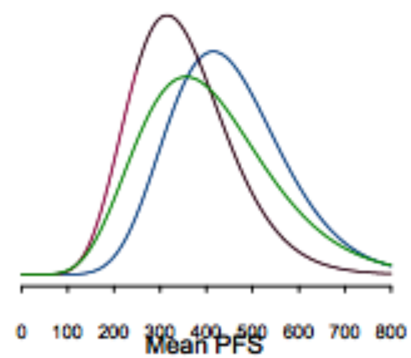

Posterior Distributions
Mean PFS
0
100
200
300
400
500
600
700
800


Treatment Allocation
Total Subjects
80
70
60
50
40
30
20
10
0
A
B
C

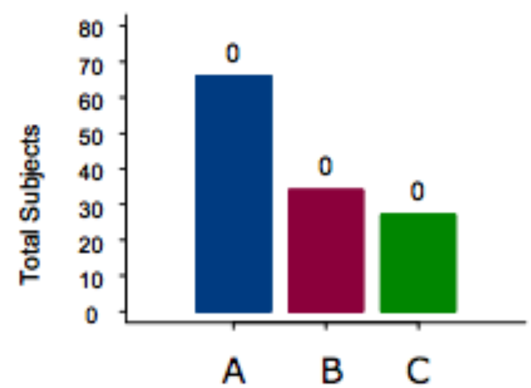
N = 127 IA 5



Posterior Distributions



Treatment Allocation



Lessons Learned

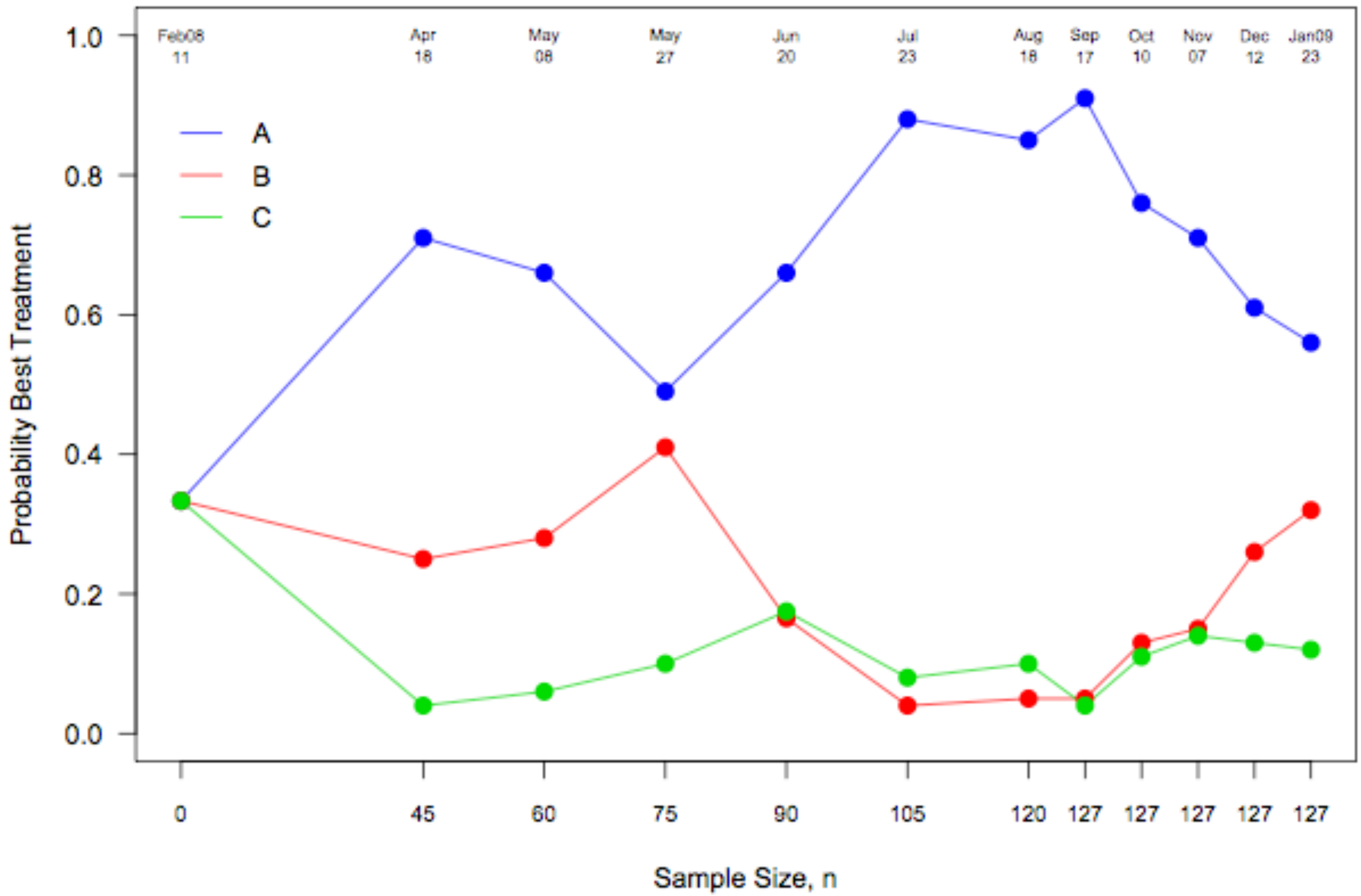
$$R_j = \frac{p_j^c}{p_1^c + p_2^c + p_3^c + \ldots + p_G^c}$$

R_j : randomization probability of treatment *j*

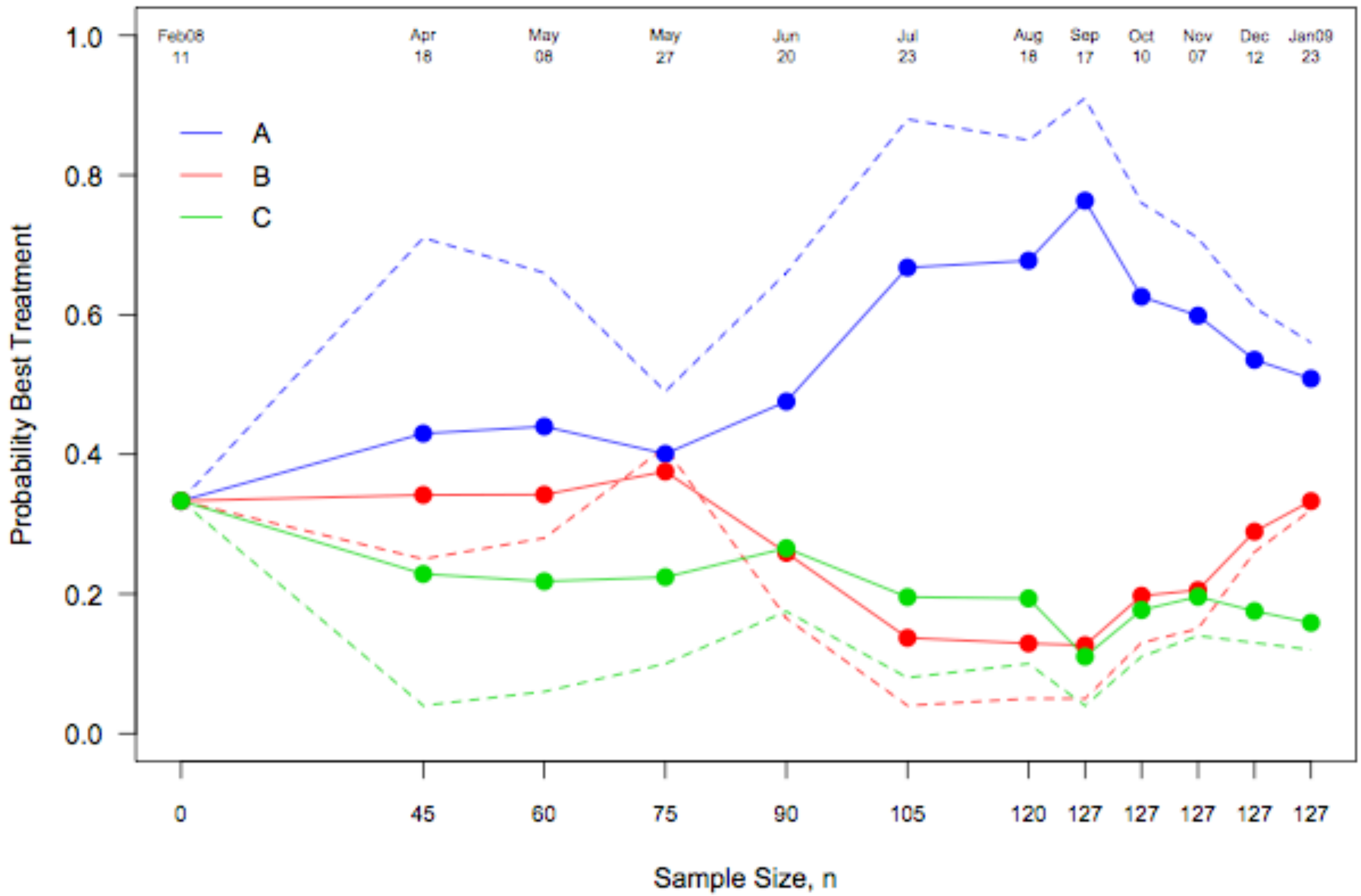
p_j: posterior probability treatment *j* is the best treatment.

- c = 0, equal randomization ($R_j = 1/G$)
- c = 1, proportional randomization ($R_j = p_j$)
- $c \geq 1$
  - more likely to favor 1 arm earlier in the trial, even when treatments are equal
  - more subjects likely assigned to the best treatment
- $c < 1$
  - randomization less likely to favor one arm earlier in the trial
  - fewer subjects likely assigned to best treatment
- c = n/N, trial begins with c = 0 and ends with c = 1

Randomization Assignments



Randomization using c = n/N



Summary