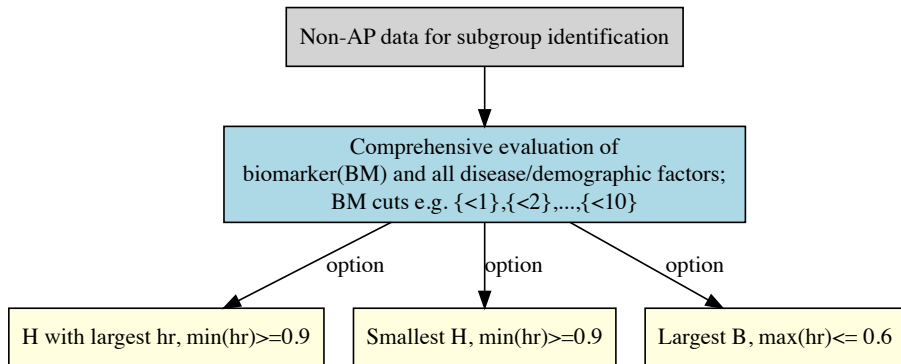# MRCT Consistency Evaluation

Larry Leon, Masashi Shimura, Xiaojing Cui, Kenichi Takahashi, Shuping Jiang, and William Wang
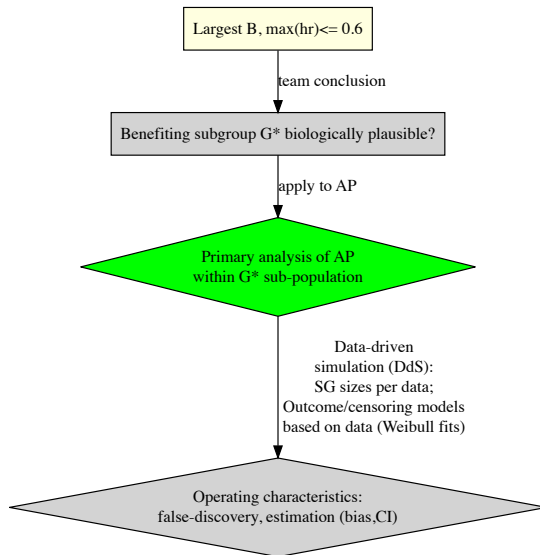
Overview: Exploratory Subgroup Identification Analyses

- Despite global trial success, AP consistency can be challenging (for many reasons);
  - A subgroup (SG) may exist with *stronger* benefit
  - Can potentially be identified based on non-AP data
- If **benefit** in identified SG translates to AP
  - May enable consistency determination
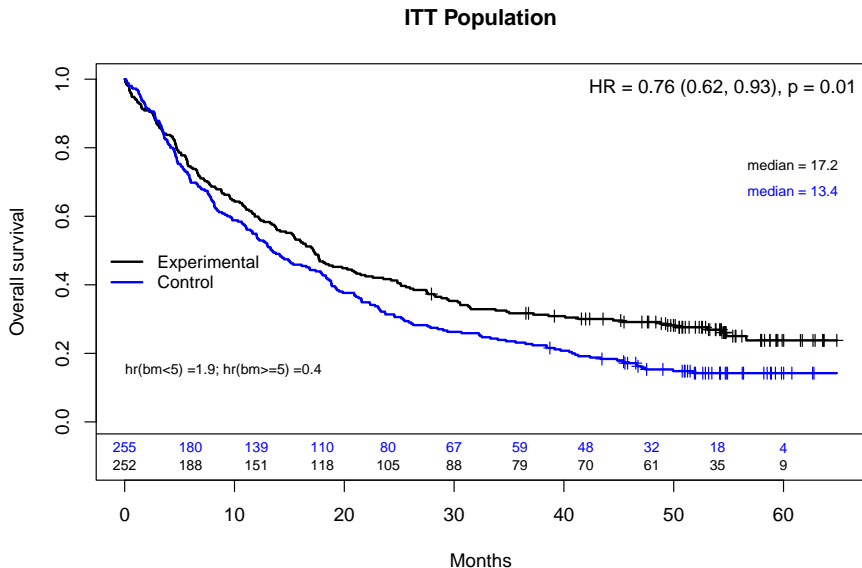- We describe an analysis paradigm and proof-of-concept *simulation*

Analysis Flowchart

Non-AP data for subgroup identification

Comprehensive evaluation of
biomarker(BM) and all disease/demographic factors;
BM cuts e.g. {<1},{<2},...,{<10}

option   option   option

H with largest hr, min(hr)>=0.9   Smallest H, min(hr)>=0.9   Largest B, max(hr)<= 0.6

ITT Population

HR = 0.76 (0.62, 0.93), p = 0.01

median = 17.2
median = 13.4

Overall survival

— Experimental
— Control

hr(bm<5) =1.9; hr(bm>=5) =0.4

| 255 | 180 | 139 | 110 | 80 | 67 | 59 | 48 | 32 | 18 | 4 |
| 252 | 188 | 151 | 118 | 105 | 88 | 79 | 70 | 61 | 35 | 9 |

0   10   20   30   40   50   60

Months

Kaplan-Meier Non-AP and AP Populations

Non–AP Population

HR = 0.68 (0.55, 0.84), p = <0.001

Experimental
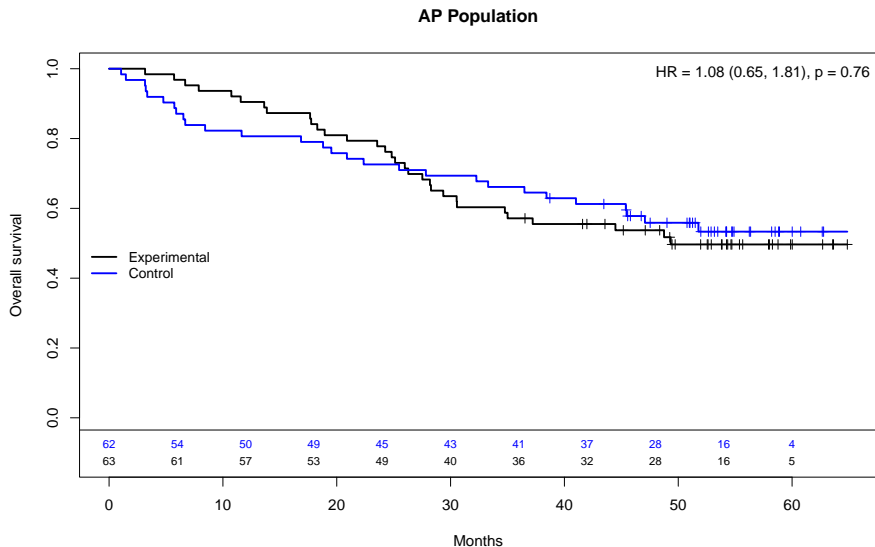Control

AP Population

HR = 1.08 (0.65, 1.81), p = 0.76
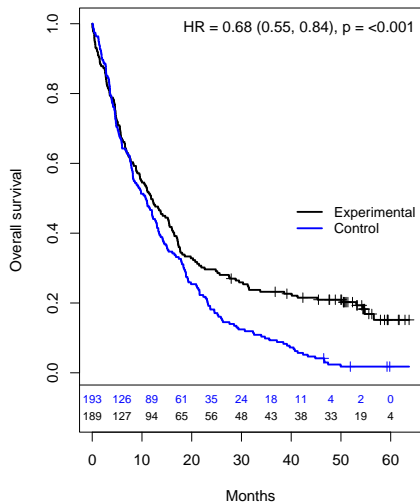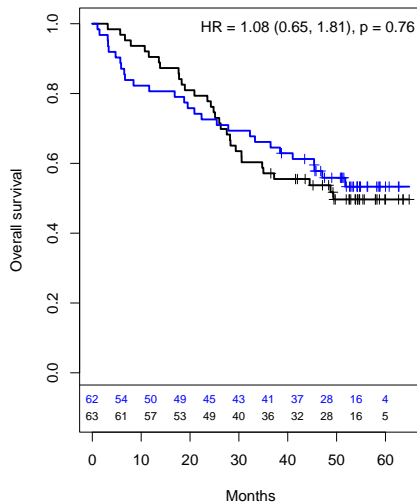
Example: Biomarker Subgroups Identified (non-AP)

Subgroups formed by single-factors
maxk=1

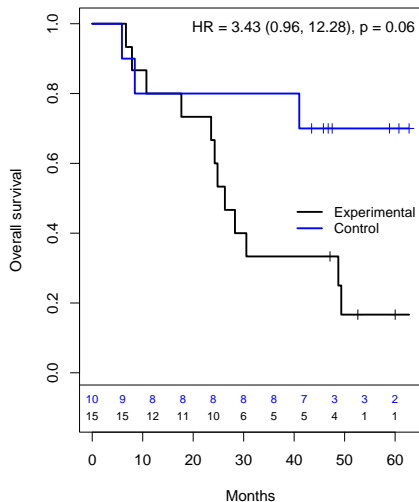| M.1	N	E	hr	Pcons
{biomarker < 2}	95	94	1.655311	0.998000
{biomarker < 3}	135	134	1.584584	1.000000
{biomarker < 4}	148	147	1.643559	1.000000
{biomarker < 5}	149	148	1.658330	1.000000
{biomarker < 6}	219	218	1.570647	1.000000
{biomarker < 7}	235	233	1.563982	1.000000
{biomarker < 8}	238	236	1.537168	1.000000
{biomarker < 10}	241	239	1.456963	1.000000

AP Population

HR = 1.08 (0.65, 1.81), p = 0.76

Overall survival

Experimental
Control

62	54	50	49	45	43	41	37	28	16	4
63	61	57	53	49	40	36	32	28	16	5

Months

AP by biomarker low-vs-high (<2, $>=2$)