

Scenario 2: tissue of interest (e.g. CRC) or disease indication of interest (e.g. KRAS mut CRC)

Step 1

Remove RMSE > 0.3 measurements for both libraries
Filter for lib1_RMSE ≤ 0.3 & lib2_RMSE ≤ 0.3

Display combo_max_effect across combinations 1

Step 2

yes, several combo-CL pairs

Are there combo-CL pairs with high efficiency?
Check combo_MaxE ≥ 0.5 1

no combo-CL pairs

In how many combinations?

one

Visualise ΔMaxE & synergy
in MatrixExplorer
(combination level) 2

Chosen tissue might not
contain relevant
combination responses

no

Are less pronounced combination
activity effects of interest?
e.g. combo_MaxE < 0.5

Step 3

several

Investigate synergy
Recommended metric¹:
Bliss_matrix 4

Compare combination with single
agent response
Use ΔMaxE to investigate
differential combination response 3

1

Rank models by
combination activity
Sort models by
combo_MaxE

Q: which combinations
have the biggest effect?

3

Compare combination with single
agent response
Use ΔMaxE to investigate
differential combination response

of CLs with pos. ΔMaxE for one of the drugs
of CLs with pos. ΔMaxE for both drugs

Q: which models have
the biggest effect?

of CLs with pos. ΔMaxE for one of the drugs
of CLs with pos. ΔMaxE for both drugs

Count # of models passing certain thresholds
and/or
Rank models by effect size for one or both of the above 5

Step 1

Quality control

Filter for RMSE ≤ 0.3 for both libraries
(at the moment: on libraries only)

Step 2

Determine whether there is any combination activity

Use combination MaxE

Step 3

Compare combination with single agent response

a) Use synergy scores

b) Use ΔMaxE for both libraries

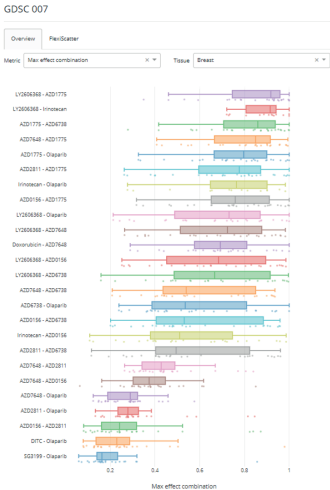
¹ Other synergy metrics are available and could be explored including metrics based on 3x3 windows.

1 Combination activity: plot Combo_MaxE across combinations

Use available plots in MatrixExplorer (Screen level), subset to tissue of interest

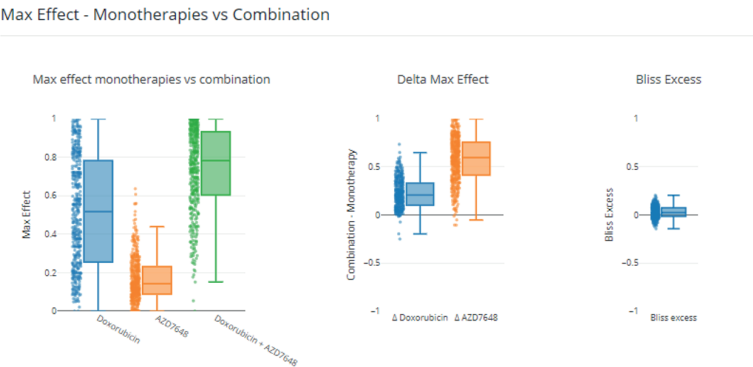
lib1 ID	lib1 Name	lib2 ID	lib2 Name	Cell lines screened	Combo MaxE ≥ 0.5
2430	AZD7648	2436	AZD1775	24	22
2431	LY2606368	2436	AZD1775	24	22
2436	AZD1775	2434	Olaparib	24	21
2436	AZD1775	2435	AZD6738	24	21
2429	AZD0156	2436	AZD1775	24	20

If a Combo_MaxE threshold is applied (here: ≥ 0.5), the number of cell lines per combo can be counted



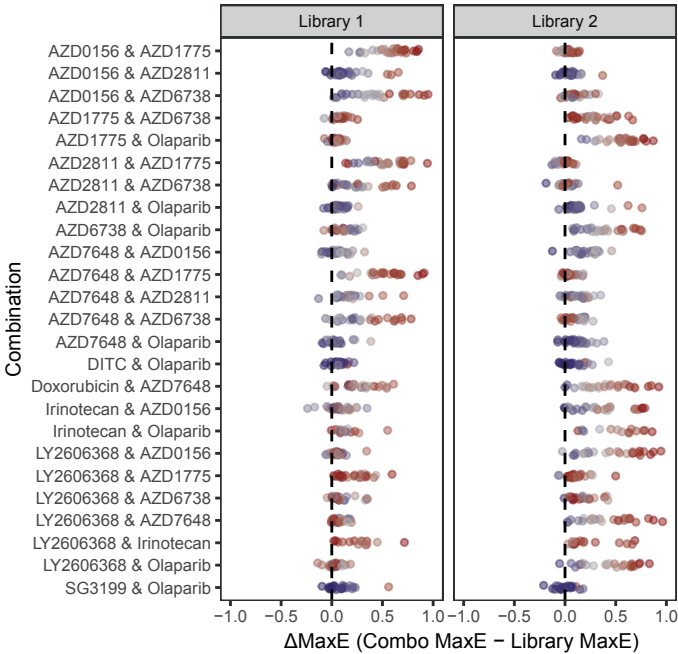
2 Visualise MaxE, Δ MaxE & synergy of chosen combination

Use available plots in MatrixExplorer (Combination level)



3 Compare combination with single agent response: Δ MaxE across combinations

To visualise across combinations & by Δ MaxE: plot individually



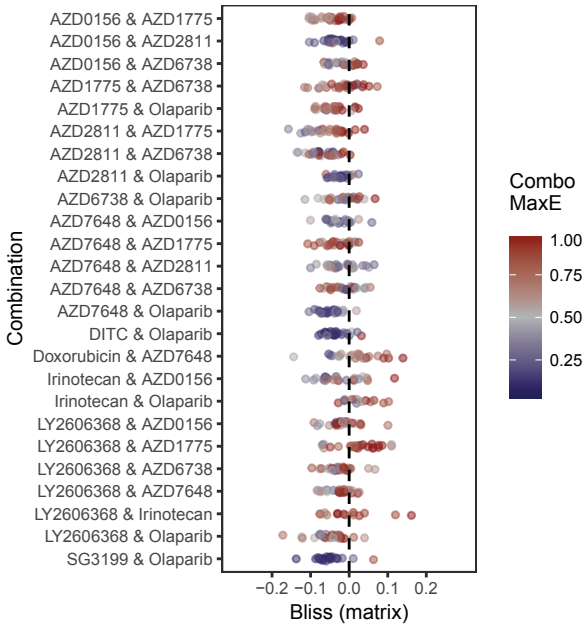
Observations:

- Neg. Δ MaxE are rare (combination is often better than the single agent)
- As expected, large Δ MaxE and Combo MaxE seem to be correlated

4 Investigate synergy

Use available synergy plots in MatrixExplorer (Screen level)

To implement filters or colour Combo_MaxE: plot individually



5 Count # of models passing certain thresholds

Thresholds used here:

1) Combo_MaxE ≥ 0.5 , 2) Positive Δ MaxE lib1, 3) Positive Δ MaxE lib2, 4) Positive Bliss (window, synergy only)

Combination	Cell lines	Combo MaxE ≥ 0.5	Pos Δ MaxE Lib1	Pos Δ MaxE Lib2	Pos Bliss	Pass.all Both Δ MaxE	Pass.all One Δ MaxE
LY2606368 & AZD1775	24	22	24	22	19	19	19
Doxorubicin & AZD7648	24	19	23	23	17	17	17
AZD0156 & AZD6738	24	10	24	20	8	8	8

Example of top 3 combinations (sorted by # of cell lines passing all filters (green))