Written for Wolfram Mathematica 11.0

Some abbreviations:

PFS = progression free survival, defined for this data as time for tumor volume to double (close to clinical criteria, where progression = 25% increase in longest dimension; with 25% increase in all dimensions implying approximately double volume)

Tumor types:
CM = cutaneous melanoma (but referred to in code as 'Melanoma' rather than an abbreviation)
NSCLC = non-small cell lung cancer
PDAC = pancreatic ductal adenocarcinoma
CRC = colorectal carcinoma
BRCA = breast cancer
GC = gastric cancer

Objective response criteria:
PD = progressive disease
SD = stable disease
PR = partial response
CR = complete response

Importing PDX curve metrics, from Gao *et al* (2015), Nature Medicine

```
Clear["Global`*"]
```

```
PDXclinicaltrialresponses = Import[NotebookDirectory[] <> "PDX-CT curve metrics.xlsx", "XLSX"][[1]];
```

An illustration of the data format:
Our analysis is primarily concerned with 'TimeToDouble', indicating the duration of Progression Free Survival (PFS)

```
PDXclinicaltrialresponses[[1 ;; 8]] // TableForm
```

Model	Treatment	Treatment target	Treatment type	BestResponse
X-007	BGJ398	FGFR	single	396.5
X-007	BKM120	PIK3CA,PIK3CB,PIK3CG,PIK3CD,panPI3K	single	189.1
X-007	BYL719	PIK3CA	single	303.7
X-007	BYL719 + HSP990	PIK3CA,HSP90	combo	-12.7
X-007	BYL719 + LJM716	PIK3CA,ERBB3,ERBB3,PIK3CA	combo	47.9
X-007	CLR457	PIK3CA,PIK3CB,PIK3CG,PIK3CD,panPI3K	single	25.
X-007	HDM201	MDM2	single	330.8

```
ModelNames = {"Cutaneous melanoma", "Non-small cell lung cancer",
   "Pancreatic ductal adenocarcinoma", "Colorectal carcinoma", "Breast cancer",
   "Gastric cancer"};
```

```
AllModels = Sort[Intersection[PDXclinicaltrialresponses[[2 ;;, 1]]]]
```

```
{X-007, X-010, X-011, X-015, X-017, X-020, X-023, X-024, X-025, X-027, X-028, X-029, X-031, X-034,
 X-035, X-037, X-038, X-039, X-050, X-055, X-056, X-057, X-064, X-065, X-067, X-074, X-075,
 X-077, X-078, X-080, X-084, X-089, X-090, X-091, X-0933, X-096, X-097, X-098, X-0988, X-099,
 X-0991, X-0992, X-1004, X-1008, X-101, X-102, X-1027, X-105, X-1055, X-1119, X-114, X-1156,
 X-1167, X-1172, X-1173, X-118, X-1189, X-119, X-1199, X-1210, X-1228, X-1234, X-1256, X-127,
 X-1270, X-128, X-1286, X-1289, X-129, X-1290, X-1298, X-1303, X-131, X-1310, X-1317, X-1323,
 X-1329, X-1333, X-1349, X-135, X-136, X-1362, X-137, X-1371, X-138, X-1383, X-1402, X-1407,
 X-141, X-142, X-144, X-1441, X-1442, X-1443, X-146, X-1468, X-1479, X-1499, X-1500, X-152,
 X-1536, X-1538, X-154, X-158, X-1586, X-160, X-1600, X-161, X-162, X-1631, X-165, X-1655,
 X-1658, X-166, X-1683, X-169, X-171, X-1725, X-177, X-1787, X-1795, X-1823, X-1828, X-1832,
 X-1834, X-1835, X-1855, X-1869, X-1870, X-1906, X-1916, X-1921, X-1934, X-1948, X-1959, X-1979,
 X-1980, X-1993, X-2017, X-2026, X-2042, X-2043, X-20508, X-20689, X-2081, X-20810, X-2082,
 X-2088, X-2094, X-2127, X-2145, X-21617, X-2163, X-2182, X-2195, X-2220, X-2239, X-2283,
 X-2306, X-2339, X-2344, X-2353, X-2374, X-2403, X-2428, X-2470, X-2483, X-2484, X-2487, X-2514,
 X-2524, X-2538, X-2564, X-2573, X-2602, X-2613, X-2633, X-2640, X-2659, X-2684, X-2700,
 X-2723, X-2753, X-2761, X-2780, X-2822, X-2838, X-2846, X-2861, X-2921, X-2992, X-2997,
 X-3028, X-3029, X-3038, X-3052, X-3077, X-3078, X-3093, X-3127, X-3201, X-3205, X-3209,
 X-3211, X-3224, X-3237, X-3267, X-3268, X-3298, X-3450, X-3453, X-3468, X-3483, X-3486, X-3503,
 X-3671, X-3676, X-3684, X-3697, X-3746, X-3773, X-3782, X-3792, X-3800, X-3816, X-3843,
 X-3846, X-3851, X-3873, X-3880, X-3898, X-3947, X-3990, X-4015, X-4018, X-4087, X-4145,
 X-4157, X-4215, X-4226, X-4316, X-4339, X-4347, X-4377, X-4378, X-4426, X-4439, X-4455,
 X-4530, X-4538, X-4567, X-4644, X-4649, X-4668, X-4676, X-4819, X-4824, X-4832, X-4849,
 X-4888, X-4927, X-4949, X-5189, X-5205, X-5238, X-5249, X-5254, X-5267, X-5355, X-5405,
 X-5421, X-5438, X-5446, X-5494, X-5495, X-5502, X-5536, X-5541, X-5578, X-5975, X-6047}
```

```
AllTreatments = Sort[Intersection[PDXclinicaltrialresponses[[2 ;;, 2]]]]
```

```
{5FU, abraxane, abraxane + gemcitabine, BGJ398, binimetinib, binimetinib-3.5mpk,
 BKM120, BKM120 + binimetinib, BKM120 + encorafenib, BKM120 + LDE225, BKM120 + LJC049,
 BYL719, BYL719 + binimetinib, BYL719 + cetuximab, BYL719 + cetuximab + encorafenib,
 BYL719 + encorafenib, BYL719 + HSP990, BYL719 + LEE011, BYL719 + LGH447, BYL719 + LJM716,
 cetuximab, cetuximab + encorafenib, CGM097, CKX620, CLR457, dacarbazine, encorafenib,
 encorafenib + binimetinib, erlotinib, everolimus, figitumumab", figitumumab" + binimetinib,
 gemcitabine-50mpk, HDM201, HSP990, INC280, INC280 + trastuzumab, INC424,
 INC424 + binimetinib, LCL161 + paclitaxel, LDE225, LDK378, LEE011, LEE011 + binimetinib,
 LEE011 + encorafenib, LEE011 + everolimus, LFA102, LFW527 + binimetinib,
 LFW527 + everolimus, LGH447, LGW813, LJC049, LJM716, LJM716 + trastuzumab, LKA136,
 LLM871, paclitaxel, tamoxifen, TAS266, trametinib, trastuzumab, untreated, WNT974}
```

annotation of tumors types was prepared from a different portion of the Supplementary Materials of Gao et al. Nature Medicine

```
ModelsAndTumorTypes = Import[NotebookDirectory[] <> "Tumor types of models.csv", "CSV"];
```

```
CutaneousMelanomaModels = Select[ModelsAndTumorTypes, #[[2]] == "CM" &][[All, 1]];
% // Length
NSCLCModels = Select[ModelsAndTumorTypes, #[[2]] == "NSCLC" &][[All, 1]];
% // Length
PDACModels = Select[ModelsAndTumorTypes, #[[2]] == "PDAC" &][[All, 1]];
% // Length
ColorectalModels = Select[ModelsAndTumorTypes, #[[2]] == "CRC" &][[All, 1]];
% // Length
BreastModels = Select[ModelsAndTumorTypes, #[[2]] == "BRCA" &][[All, 1]];
% // Length
GastricModels = Select[ModelsAndTumorTypes, #[[2]] == "GC" &][[All, 1]];
% // Length
```

33

36

43

58

43

64

Focusing analysis on PDX models tested against many therapies
(referred to in code as 'well covered models')

```
WellCoveredModelClasses = Import[NotebookDirectory[] <> "Well covered models.csv"];
WellCoveredModels = WellCoveredModelClasses[[All, 1]];

CutaneousMelanomaModels = Select[WellCoveredModelClasses, #[[2]] == "CM" &][[All, 1]];
% // Length
NSCLCModels = Select[WellCoveredModelClasses, #[[2]] == "NSCLC" &][[All, 1]];
% // Length
PDACModels = Select[WellCoveredModelClasses, #[[2]] == "PDAC" &][[All, 1]];
% // Length
ColorectalModels = Select[WellCoveredModelClasses, #[[2]] == "CRC" &][[All, 1]];
% // Length
BreastModels = Select[WellCoveredModelClasses, #[[2]] == "BRCA" &][[All, 1]];
% // Length
GastricModels = Select[WellCoveredModelClasses, #[[2]] == "GC" &][[All, 1]];
% // Length
```

33

29

41

42

39

46

```
AllModelGroups = {CutaneousMelanomaModels, NSCLCModels, PDACModels, ColorectalModels,
    BreastModels, GastricModels};

MonotherapiesByGroup = Table[
    Intersection[
     Select[PDXclinicaltrialresponses,
       And[MemberQ[AllModelGroups[[i]], #[[1]]], #[[4]] == "single", #[[2]] ≠ "untreated"] &][[All, 2]]],
    {i, 1, Length[AllModelGroups]}];
CombinationTherapiesByGroup = Table[
    Intersection[
     Select[PDXclinicaltrialresponses,
       And[MemberQ[AllModelGroups[[i]], #[[1]]], #[[4]] == "combo", #[[2]] ≠ "untreated"] &][[All, 2]]],
    {i, 1, Length[AllModelGroups]}];

(* removing "untreated" from the list of treatments *)
AllTreatmentsExcludingUntreated = Complement[AllTreatments, {"untreated"}];
```

Plotting a 'treatment matrix' - PDX models by treatments

```
(* assigning a number to each tumor type,
for purpose of coloring a 'treatment matrix' (matrix of therapies tested on PDX models) *)
ModelToIndicationNumber[pdxmodel_] := Which[
  MemberQ[CutaneousMelanomaModels, pdxmodel],
  1,
  MemberQ[NSCLCModels, pdxmodel],
  2,
  MemberQ[PDACModels, pdxmodel],
  3,
  MemberQ[ColorectalModels, pdxmodel],
  4,
  MemberQ[BreastModels, pdxmodel],
  5,
  MemberQ[GastricModels, pdxmodel],
  6,
  True,
  -1]

(* computing the treatment matrix *)
ModelsTreatmentsMatrix =
  Table[
   If[
    Select[PDXclinicaltrialresponses,
      And[#[[1]] == AllModels[[models]], #[[2]] == AllTreatmentsExcludingUntreated[[treatments]]] &] == {},
    0, ModelToIndicationNumber[AllModels[[models]]], {models, 1, Length[AllModels]},
   {treatments, 1, Length[AllTreatmentsExcludingUntreated]}];

(* loading the clustering package *)
Needs["HierarchicalClustering`"]

(* Mathematica does not track object labels when performing hierarchical
 clustering. Therefore we attach a column of numbers that uniquely identify each
 PDX model in sequence, so that subsequently we can affix the proper PDX model
 labels to the clustered treatment matrix *)
ModelLabels = Range[Length[AllModels]] / 10000;
LabelledModelsTreatmentsMatrix = Prepend[ModelsTreatmentsMatrix^T, ModelLabels];
% // Dimensions
```

```
{63, 281}
```

```
(* Similarly, we attach a row of numbers that uniquely identify each treatment in sequence,
so that subsequently we can affix the proper treatment labels to the clustered
 treatment matrix *)
TreatmentsLabels = Prepend[Range[Length[AllTreatmentsExcludingUntreated]], 0] / 1000;
LabelledModelsTreatmentsMatrix = Prepend[LabelledModelsTreatmentsMatrix^T, TreatmentsLabels]^T;
% // Dimensions
```

```
{63, 282}
```

```
(* turning off an error message about ties. There are many 'ties' in this treatment
 matrix (PDX models receiving the same set of treatments;
  and treatments tested on the same sets of PDX models) *)
Off[Agglomerate::ties]
(* heirarchical clustering *)
ClusteredModelsTreatmentsMatrix =
  ClusterFlatten[Agglomerate[ClusterFlatten[Agglomerate[(LabelledModelsTreatmentsMatrix)]]^T]];

(* using our affixed row and column of numbers to correctly order the PDX and
 treatment labels in the clustered matrix *)
ClusteredModelSequence = AllModels[[ClusteredModelsTreatmentsMatrix^T[[1, 2 ;;]] * 10 000]];
ClusteredTreatmentSequence =
  AllTreatmentsExcludingUntreated[[ClusteredModelsTreatmentsMatrix^T[[2 ;;, 1]] * 1000]];
```

Plotting a matrix of PDX models versus treatments, with a spot at every intersection where a particular treatment was tested on a particular PDX model.

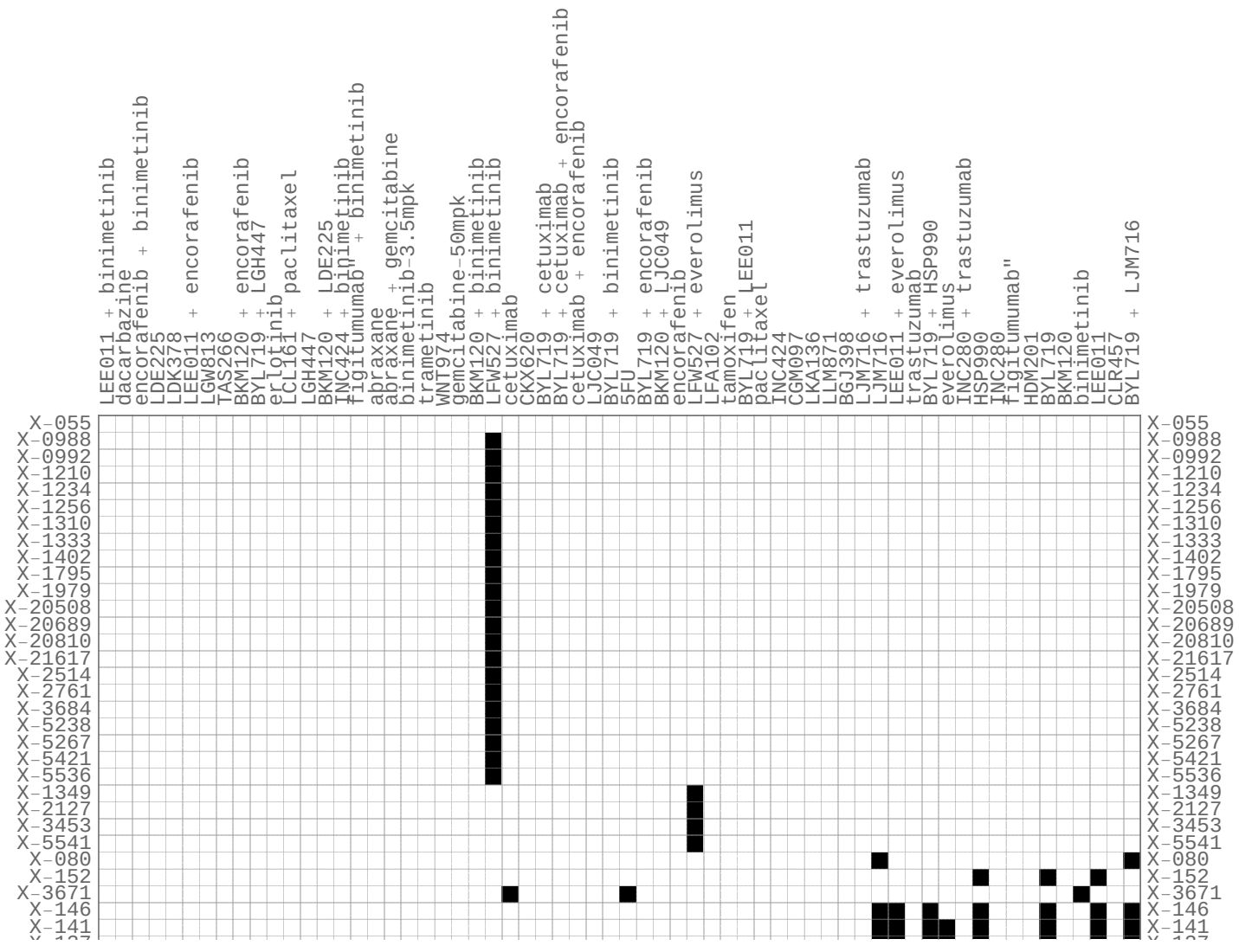
White indicates the treatment was *not* tested on that PDX model.

Red = well covered Melanoma PDX models
Green = well covered Non-Small Cell Lung Cancer (NSCLC) PDX models
Magenta = well covered Pancreatic Ductal Adenocarcinoma (PDAC) PDX models
Orange = well covered Colorectal cancer PDX models
Blue = well covered Breast cancer PDX models
Gray = well covered Gastric cancer PDX models

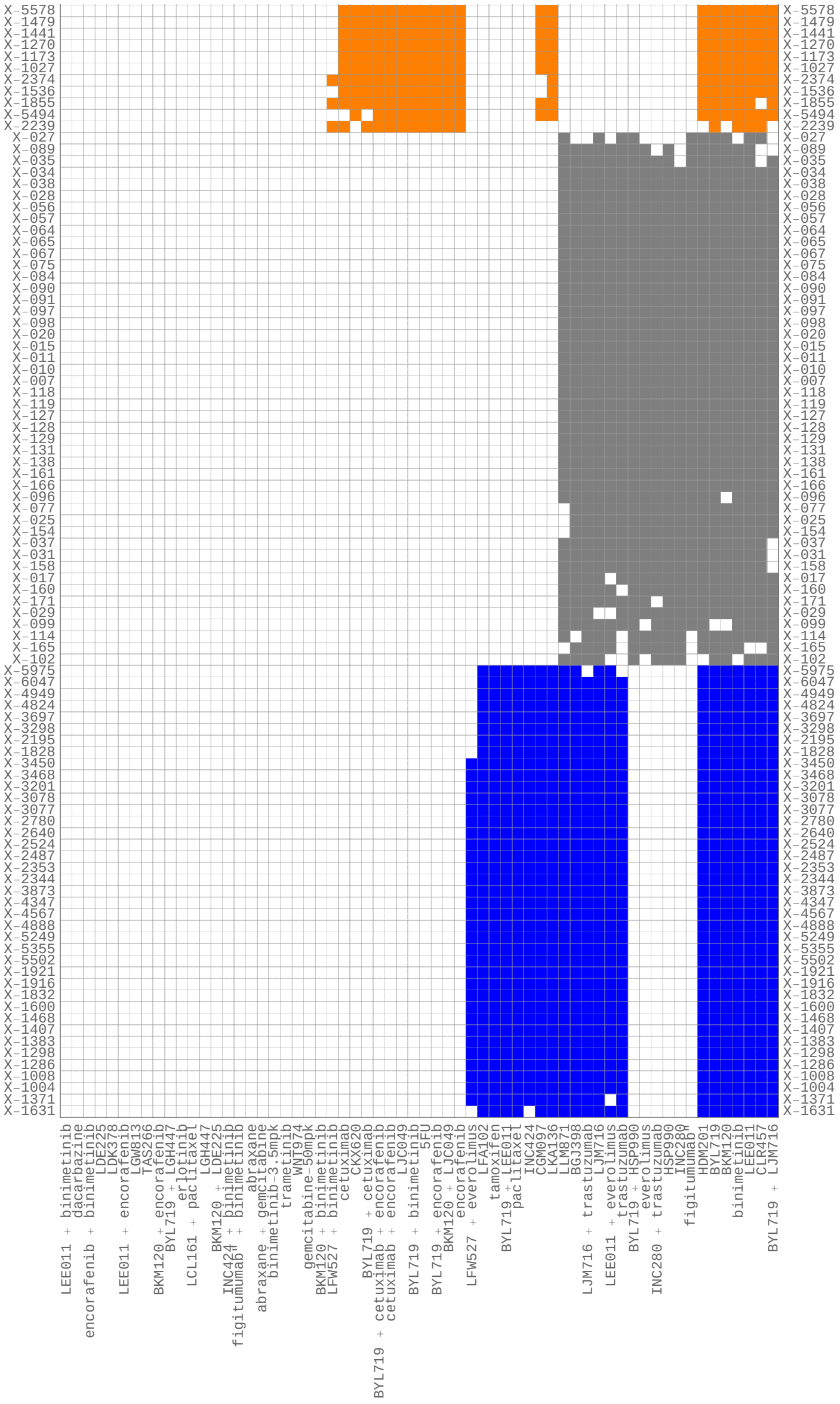
Black = models from a variety of tumor types that are deemed to be not 'well-covered' - they are tested in a very limited set of treatments and were considered unsuitable for analyses that compare how a single PDX model responds to a variety of different monotherapy and combination therapy treatments.

(note in the top row, PDX model X-055 is indeed part of the data set but was not tested with any form of treatment, only tested as 'untreated')

```
ModelsTreatmentsPlot = ArrayPlot[ClusteredModelsTreatmentsMatrix[[2 ;;, 2 ;;]],
  PlotRangePadding → None, Mesh → All, ImageSize → {{2400}, {2400}},
  MeshStyle → Directive[Thickness[0.0005], GrayLevel[0.6], Opacity[0.5]], Frame → True,
  FrameTicks →
   {{Table[{i, ClusteredModelSequence[[i]], {0, 0}}, {i, 1, Length[ClusteredModelSequence]}],
     Table[{i, ClusteredModelSequence[[i]], {0, 0}}, {i, 1, Length[ClusteredModelSequence]}]},
    {Table[{i, Rotate[ClusteredTreatmentSequence[[i]], π / 2], {0, 0}},
      {i, 1, Length[ClusteredTreatmentSequence]}],
     Table[{i, Rotate[ClusteredTreatmentSequence[[i]], π / 2], {0, 0}},
      {i, 1, Length[ClusteredTreatmentSequence]}]}},
  BaseStyle → {FontFamily → "Courier New", FontSize → 9},
  ColorRules → {0 → White, -1 → Black, 1 → Red, 2 → Darker[Green], 3 → Darker[Magenta],
    4 → Orange, 5 → Blue, 6 → Gray}]
```




X-137
X-136
X-135
X-105
X-101
X-078
X-074
X-050
X-039
X-024
X-023
X-142
X-144
X-177
X-162
X-169
X-2220
X-1538
X-1959
X-1317
X-4530
X-4538
X-4668
X-4832
X-4426
X-3880
X-3746
X-3676
X-3503
X-3486
X-3483
X-2602
X-4644
X-4455
X-4157
X-4339
X-3851
X-3773
X-4849
X-5189
X-3211
X-3127
X-2992
X-2921
X-2838
X-2753
X-2723
X-2700
X-2613
X-2306
X-2163
X-1906
X-1655
X-3029
X-1683
X-1442
X-1189
X-1658
X-1725
X-1787
X-1823
X-1834
X-1835
X-1869
X-1934
X-1980
X-1993
X-2017
X-2042
X-2082
X-2094
X-1586
X-1499
X-1323
X-1228
X-1172
X-1156
X-3237
X-3843
X-4819
X-2088
X-1870
X-3209
X-2043
X-1948
X-2564
X-3052
X-3268
X-3947
X-3990
X-4145
X-4226
X-4378
X-4439
X-4649
X-4676
X-4377
X-4215
X-3898
X-4927
X-3038
X-3028
X-2684
X-2997
X-4316
X-2633
X-3816
X-2339
X-3800
X-2428
X-4018
X-3846
X-1362
X-1199
X-2081
X-0991
X-1289
X-4015
X-5205
X-2470
X-2026
X-2283
X-3782
X-1303
X-1290
X-1329
X-1443
X-1500
X-1167
X-1119
X-1055
X-0933
X-2145
X-2182
X-2483
X-2573
X-2659
X-2861
X-3205
X-3792
X-4087
X-5254
X-5438
X-5446
X-5495
X-2846
X-2822
X-3093
X-3224
X-3267
X-2538
X-2484
X-2403
X-5405



```
Export[NotebookDirectory[] <> "Complete treatment matrix.pdf", ModelsTreatmentsPlot, "PDF"];
```

Creating figure that focuses on well-covered models.

```
CombinationsInClusteredTreatmentSequence =
  Select[ClusteredTreatmentSequence, StringCases[#, " + "] ≠ {} &];
MonotherapiesInClusteredTreatmentSequence =
  Select[ClusteredTreatmentSequence, StringCases[#, " + "] == {} &];
```

```
CombinationPositionsInClusteredTreatmentSequence =
  Table[Position[ClusteredTreatmentSequence, CombinationsInClusteredTreatmentSequence[[i]]][[1, 1]],
   {i, 1, Length[CombinationsInClusteredTreatmentSequence]}];
MonotherapyPositionsInClusteredTreatmentSequence =
  Table[Position[ClusteredTreatmentSequence, MonotherapiesInClusteredTreatmentSequence[[i]]][[
    1, 1]], {i, 1, Length[MonotherapiesInClusteredTreatmentSequence]}];

SeparatingMonoAndComboSequence =
  Join[MonotherapyPositionsInClusteredTreatmentSequence,
   CombinationPositionsInClusteredTreatmentSequence];

plotdata = ClusteredModelsTreatmentsMatrix[[2 ;;, 2 ;;]][[52 ;;, SeparatingMonoAndComboSequence]];

MonoPartOfPlot = plotdata[[All, 1 ;; 37]] /. {2 → 1, 3 → 1, 4 → 1, 5 → 1, 6 → 1};
ComboPartOfPlot = plotdata[[All, 38 ;;]] /. {1 → 2, 3 → 2, 4 → 2, 5 → 2, 6 → 2};
ReMergedPlotData = Join[MonoPartOfPlot^T, {Table[0, {230}]}, ComboPartOfPlot^T]^T;

PlotDataShiftingGastricToEnd = Join[
   ReMergedPlotData[[1 ;; 145, All]],
   ReMergedPlotData[[192 ;;, All]],
   ReMergedPlotData[[146 ;; 191, All]]
  ];

PaddingColumnOfZeros = {Table[0, {Length[PlotDataShiftingGastricToEnd^T]}]};

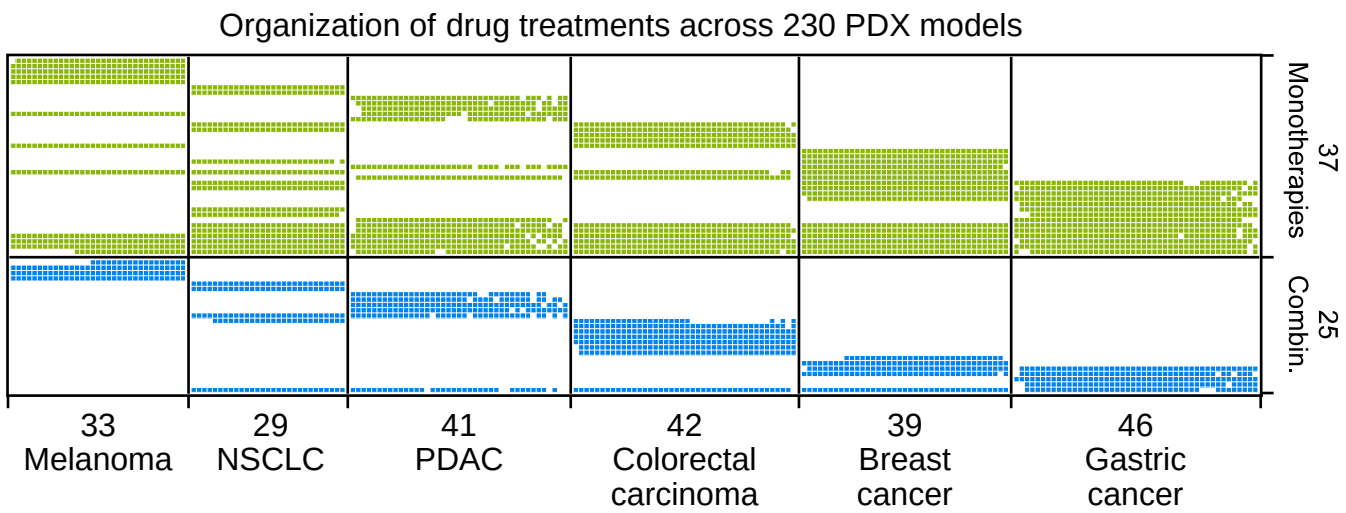
PlotDataShiftingGastricToEndWithPaddingBetweenTumorTypes =
  Join[PlotDataShiftingGastricToEnd[[1 ;; 33]], PaddingColumnOfZeros,
   PlotDataShiftingGastricToEnd[[33 + 1 ;; 33 + 29]], PaddingColumnOfZeros,
   PlotDataShiftingGastricToEnd[[33 + 29 + 1 ;; 33 + 29 + 41]], PaddingColumnOfZeros,
   PlotDataShiftingGastricToEnd[[33 + 29 + 41 + 1 ;; 33 + 29 + 41 + 42]], PaddingColumnOfZeros,
   PlotDataShiftingGastricToEnd[[33 + 29 + 41 + 42 + 1 ;; 33 + 29 + 41 + 42 + 39]],
   PaddingColumnOfZeros, PlotDataShiftingGastricToEnd[[
    33 + 29 + 41 + 42 + 39 + 1 ;; 33 + 29 + 41 + 42 + 39 + 46]]];
```

```
ModelsTreatmentsPlotWhiteGridLines =
  ArrayPlot[PlotDataShiftingGastricToEndWithPaddingBetweenTumorTypesᵀ,
   PlotRangePadding → {{0.6, 0.6}, {0.6, 0.6}}, Mesh → All, ImageSize → {{550}, {1000}},
   ImagePadding → {{100, 5}, {50, 25}},
   MeshStyle → Directive[AbsoluteThickness[0.3], White, Opacity[1]], Frame → True,
   FrameTicks →
    {{Join[Table[{i + 1 / 2, , {0, 0.01}}, {i, {0 - 0.6, 37.5, 63 + 0.6}}],
       {{37 / 2, Rotate["37\nMonotherapies", π / 2 * 0], {0, 0}},
        {(37.5 + 63) / 2, Rotate["25\nCombinations", π / 2 * 0], {0, 0}}}],
      Table[{i + 1 / 2, , {0, 0.00}}, {i, {0, 37.5, 63}}]},
     {Join[Table[{i + 1 / 2, , {0, 0.01}},
        {i, {-0.5, 33 + 0.5, 62 + 1.5, 103 + 2.5, 145 + 3.5, 184 + 4.5, 230 + 5.5}}],
       {{33 / 2, "33\nMelanoma", {0, 0}}, {1 + (33 + 63) / 2, "29\nNSCLC", {0, 0}},
        {2 + (62 + 103) / 2, "41\nPancreatic", {0, 0}}, {3 + (103 + 145) / 2, "42\nColorectal", {0, 0}},
        {4 + (145 + 184) / 2, "39\nBreast", {0, 0}}, {5 + (184 + 230) / 2, "46\nGastric", {0, 0}}}],
      Join[Table[{i + 1 / 2, , {0, 0.00}}, {i, {0, 33, 62, 103, 145, 184, 230}}],
       {{230 / 2, "Organization of drug treatments across 230 PDX models", {0, 0}}}]}},
   BaseStyle → {FontFamily → "Arial", FontSize → 12},
   FrameStyle -> Directive[AbsoluteThickness[1], GrayLevel[0.], Opacity[1]],
   ColorRules → {0 → White, -1 → Black, 1 → ColorData[3, 4], 2 → ColorData[3, 6]}];

ModelsTreatmentsPlotJustBlackGridLines =
  ArrayPlot[
   Table[0, {Dimensions[PlotDataShiftingGastricToEndWithPaddingBetweenTumorTypesᵀ][[1]]},
    {Dimensions[PlotDataShiftingGastricToEndWithPaddingBetweenTumorTypesᵀ][[2]]}],
   PlotRangePadding → {{0.6, 0.6}, {0.6, 0.6}},
   Mesh → {{37.5}, {33 + 0.5, 62 + 1.5, 103 + 2.5, 145 + 3.5, 184 + 4.5}}, ImageSize → {{550}, {1000}},
   ImagePadding → {{100, 5}, {50, 25}},
   MeshStyle → Directive[AbsoluteThickness[1], GrayLevel[0.], Opacity[1]], Frame → True,
   FrameTicks →
    {{Join[Table[{i + 1 / 2, , {0, 0.01}}, {i, {0 - 0.6, 37.5, 63 + 0.6}}],
       {{37 / 2, Rotate["37\nMonotherapies", π / 2 * 0], {0, 0}},
        {(37.5 + 63) / 2, Rotate["25\nCombinations", π / 2 * 0], {0, 0}}}],
      Table[{i + 1 / 2, , {0, 0.00}}, {i, {0, 37.5, 63}}]},
     {Join[Table[{i + 1 / 2, , {0, 0.01}},
        {i, {-0.5, 33 + 0.5, 62 + 1.5, 103 + 2.5, 145 + 3.5, 184 + 4.5, 230 + 5.5}}],
       {{33 / 2, "33\nMelanoma", {0, 0}}, {1 + (33 + 63) / 2, "29\nNSCLC", {0, 0}},
        {2 + (62 + 103) / 2, "41\nPancreatic", {0, 0}}, {3 + (103 + 145) / 2, "42\nColorectal", {0, 0}},
        {4 + (145 + 184) / 2, "39\nBreast", {0, 0}}, {5 + (184 + 230) / 2, "46\nGastric", {0, 0}}}],
      Join[Table[{i + 1 / 2, , {0, 0.00}}, {i, {0, 33, 62, 103, 145, 184, 230}}],
       {{230 / 2, "Organization of drug treatments across 230 PDX models", {0, 0}}}]}},
   BaseStyle → {FontFamily → "Arial", FontSize → 12},
   FrameStyle -> Directive[AbsoluteThickness[1], GrayLevel[0.], Opacity[1]],
   ColorRules → {0 → Directive[White, Opacity[0]], -1 → Directive[Black, Opacity[0]],
     1 → Directive[ColorData[3, 4], Opacity[0]], 2 → Directive[ColorData[3, 6], Opacity[0]]}];
```

```
TreatmentMatrixFigure = Show[ModelsTreatmentsPlotWhiteGridLines,
  ModelsTreatmentsPlotJustBlackGridLines, PlotRangePadding → {{0.6, 0.6}, {0.6, 0.6}},
  ImageSize → {{575}, {1000}}, ImagePadding → {{5, 100}, {100, 25}}, Frame → True,
  FrameTicks →
   {{Table[{i + 1 / 2, , {0, 0.00}}, {i, {0, 37.5, 63}}],
     Join[Table[{i + 1 / 2, , {0, 0.01}}, {i, {0 - 0.6, 25, 63}}],
      {{25 / 2, Rotate[Style["25\nCombin.", FontSize → 10, LineSpacing → {0, 13}], -π / 2], {0, 0}},
       {(25 + 63) / 2, Rotate[Style["37\nMonotherapies  ", FontSize → 10, LineSpacing → {0, 13}],
         -π / 2], {0, 0}}}]},
    {Join[Table[{i + 1 / 2, , {0, 0.01}}, {i, {-1, 33 + 0, 62 + 1, 103 + 2, 145 + 3, 184 + 4, 230 + 5}}],
      {{33 / 2, Rotate[Style["33\nMelanoma", LineSpacing → {0, 13}], 0], {0, 0}},
       {1 + (33 + 63) / 2, Rotate[Style["29\nNSCLC", LineSpacing → {0, 13}], 0], {0, 0}},
       {2 + (62 + 103) / 2, Rotate[Style["41\nPDAC", LineSpacing → {0, 13}], 0], {0, 0}},
       {3 + (103 + 145) / 2, Rotate[Style["42\nColorectal\ncarcinoma", LineSpacing → {0, 13}], 0],
        {0, 0}}, {4 + (145 + 184) / 2, Rotate[Style["39\nBreast\ncancer", LineSpacing → {0, 13}], 0],
        {0, 0}}, {5 + (184 + 230) / 2, Rotate[Style["46\nGastric\ncancer", LineSpacing → {0, 13}],
         0], {0, 0}}}], Join[Table[{i + 1 / 2, , {0, 0.00}}, {i, {0, 33, 62, 103, 145, 184, 230}}],
      {{230 / 2, Rotate["Organization of drug treatments across 230 PDX models", 0], {0, 0}}}]}},
  BaseStyle → {FontFamily → "Arial", FontSize → 12},
  FrameStyle -> Directive[AbsoluteThickness[1], GrayLevel[0.], Opacity[1]]]

Export[NotebookDirectory[] <> "Supplementary Figure S3B, Treatment matrix.pdf",
  TreatmentMatrixFigure, "PDF"];
```



Global comparison of monotherapy with combination therapy

```
(* A list of drug responses sorted by PDX model *)
ResponsesByModel = Table[Select[PDXclinicaltrialresponses, #[[1]] == WellCoveredModels[[model]] &],
   {model, 1, Length[WellCoveredModels]}];
(* A list of monotherapy responses sorted by PDX model;
specifically progression-free-survival (time without tumor volume doubling) *)
PerModelMonotherapyResponses =
  Table[
   Select[PDXclinicaltrialresponses,
     And[#[[1]] == WellCoveredModels[[model]], #[[4]] == "single", #[[2]] ≠ "untreated"] &][[All, 9]],
   {model, 1, Length[WellCoveredModels]}];
(* A list of combination responses sorted by PDX model;
specifically progression-free-survival (time without tumor volume doubling) *)
PerModelCombinationResponses =
  Table[
   Select[PDXclinicaltrialresponses,
     And[#[[1]] == WellCoveredModels[[model]], #[[4]] == "combo", #[[2]] ≠ "untreated"] &][[All, 9]],
   {model, 1, Length[WellCoveredModels]}];

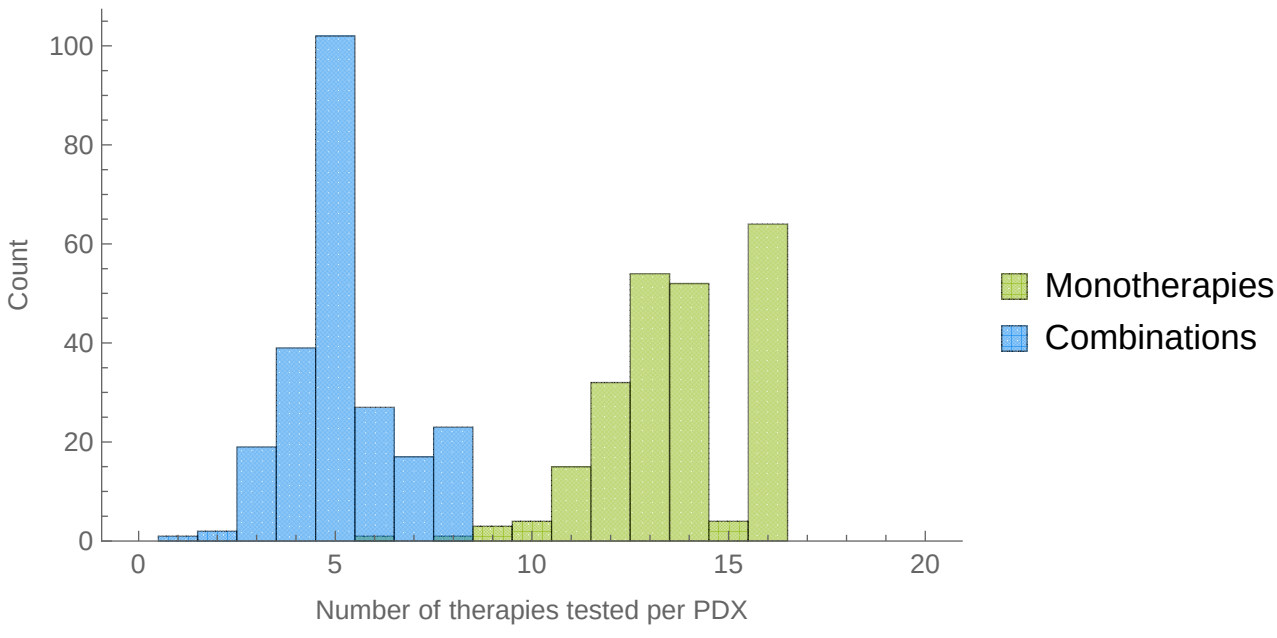
(* How many monotherapies are tested on each PDX model, on average? *)
AverageNumberOfMonotherapyTreatmentsPerModel =
 Mean[Map[Length, PerModelMonotherapyResponses]] // N

(* How many combination therapies are tested on each PDX model, on average? *)
AverageNumberOfCombinationTreatmentsPerModel =
 Mean[Map[Length, PerModelCombinationResponses]] // N
```

```
13.6696
```

```
5.18696
```

```
(* Histogram of the number of different monotherapies and combination therapies
 tested on each PDX model *)
Histogram[{
  Map[Length, PerModelMonotherapyResponses],
  Map[Length, PerModelCombinationResponses]
 }, {-0.5, 20.5, 1}, ChartLegends → {"Monotherapies", "Combinations"},
 ChartStyle → {ColorData[3, 4], ColorData[3, 6]}, Frame → {{True, False}, {True, False}},
 Axes → False, FrameLabel → {"Number of therapies tested per PDX", "Count"}]
```



```
(* Average PFS in response to monotherapy, for each PDX model *)
PerModelMeanMonoResponses = Map[Mean, PerModelMonotherapyResponses];
(* Average PFS in response to combination therapy, for each PDX model *)
PerModelMeanComboResponses = Map[Mean, PerModelCombinationResponses];

(* Best response to any monotherapy, for each PDX model *)
PerModelMaxMonoResponses = Map[Max, PerModelMonotherapyResponses];
(* Best response to any combination therapy, for each PDX model *)
PerModelMaxComboResponses = Map[Max, PerModelCombinationResponses];

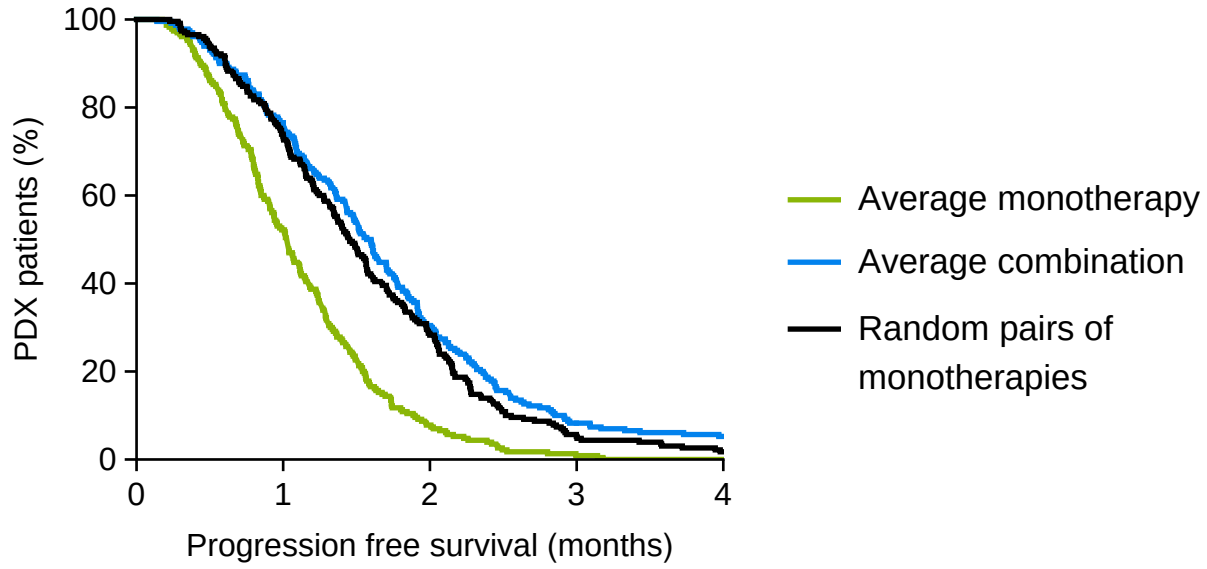
(* This function takes a list of drug responses (PFS times),
and provided that it is longer than 1, it randomly selects a pair of drugs,
and supposes that the response to the drug pair is the best one of the two
 responses. This is repeated 10000 times,
and the function's output is the average of this set. *)
AverageBestOfRandomlyChosenPairs[listofresponses_] :=
 Module[{NumberOfRandomPairs, IndividualBestResponses},
  If[listofresponses == {}, Return[{}]];
  If[Length[listofresponses] == 1, Return[listofresponses[[1]]]];
  NumberOfRandomPairs = 10000;
  IndividualBestResponses = Table[Max[RandomSample[listofresponses, 2]],
    {NumberOfRandomPairs}];
  Mean[IndividualBestResponses]
 ]

(* The above function is applied to each PDXs list of monotherapy responses *)
PerModelAverageBestOfRandomMonotherapyPairs =
  Map[AverageBestOfRandomlyChosenPairs, PerModelMonotherapyResponses];
```

```
(* This option allows figures with legends to be exported without legends without
 altering the figure size *)
SetOptions[$FrontEndSession, PrintingStyleEnvironment → "Working"]

(* Plot of progression free survival over all PDX models,
comparing their average monotherapy response, average combination response,
and average response to random pairs of monotherapies *)
AveragePFSPlot = Plot[{
    SurvivalFunction[EmpiricalDistribution[PerModelMeanMonoResponses]][x],
    SurvivalFunction[EmpiricalDistribution[PerModelMeanComboResponses]][x],
    SurvivalFunction[EmpiricalDistribution[PerModelAverageBestOfRandomMonotherapyPairs]][x]
   }
   , {x, 0, 5 * 61 / 2}, Exclusions → None, PlotRange → {{0, 4 * 61 / 2}, {0, 1}}, PlotPoints → 1000,
   Frame → {{True, False}, {True, False}}, BaseStyle → {FontFamily → "Arial", FontSize → 12},
   FrameStyle → Directive[Black, Thickness[Medium]],
   FrameTicks → {{Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}], None},
     {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 300, 61 / 2}], None}},
   PlotStyle → {Directive[ColorData[3, 4], AbsoluteThickness[2]],
     Directive[ColorData[3, 6], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]],
     Directive[ColorData[3, 8], AbsoluteThickness[2]]},
   FrameLabel → {"Progression free survival (months)", "PDX patients (%)"},
   ImageSize → {{1000}, {225}}, ImagePadding → {{50, 10}, {50, 10}},
   (*PlotLegends→
    Placed[Map[Style[#,FontSize→12]&,{"Average monotherapy","Average combination",
       "Random pairs of\nmonotherapies"}],{Scaled[{0.45,0.99}], {0, 1}}]*)
   PlotLegends → {"Average monotherapy", "Average combination", "Random pairs of\nmonotherapies"},
   AspectRatio → 3 / 4]

Export[NotebookDirectory[] <> "Figure 3A, PFS averages.pdf", AveragePFSPlot, "PDF"];
```



```
(* statistical comparisons by Log Rank Test *)
(* mono vs combo *)
LogRankTest[{PerModelMeanMonoResponses, PerModelMeanComboResponses}, "Equal", "PValueTable"]
(* mono vs random pairs of mono *)
LogRankTest[{PerModelAverageBestOfRandomMonotherapyPairs, PerModelMeanMonoResponses},
 "Equal", "PValueTable"]
(* random pairs of mono vs combo *)
LogRankTest[{PerModelAverageBestOfRandomMonotherapyPairs, PerModelMeanComboResponses},
 "Equal", "PValueTable"]
```

	P-Value
Log-Rank	3.36765×10^{-16}

	P-Value
Log-Rank	3.81192×10^{-12}

	P-Value
Log-Rank	0.053795

```
(* statistical comparisons by Mann Whitney Test *)
(* mono vs combo *)
MannWhitneyTest[{PerModelMeanMonoResponses, PerModelMeanComboResponses}, 0, "PValueTable"]
(* mono vs random pairs of mono *)
MannWhitneyTest[{PerModelAverageBestOfRandomMonotherapyPairs, PerModelMeanMonoResponses},
 0, "PValueTable"]
(* random pairs of mono vs combo *)
MannWhitneyTest[{PerModelAverageBestOfRandomMonotherapyPairs, PerModelMeanComboResponses},
 0, "PValueTable"]
```

	P-Value
Mann-Whitney	2.79107×10^{-13}

	P-Value
Mann-Whitney	1.17367×10^{-10}

	P-Value
Mann-Whitney	0.243249

```
(* Cox proportional hazards model *)
myeventdata =
  EventData[Join[PerModelMeanComboResponses, PerModelAverageBestOfRandomMonotherapyPairs],
   Table[0,
    {Length[Join[PerModelMeanComboResponses, PerModelAverageBestOfRandomMonotherapyPairs]]}]];
descriptors = Join[Table["actual combinations", {Length[PerModelMeanComboResponses]}],
   Table["random monotherapy pairs", {Length[PerModelAverageBestOfRandomMonotherapyPairs]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[random monotherapy pairs]	0.182453	0.0947374	1.20016	3.709	1	0.0541197

```
{{0.996776, 1.44504}}
```

Analysis within each tumor type

```
(* data for each tumor type are extracted from previous data structures by tracking
 the positions (row numbers) corresponding to each tumor type *)
CutaneousMelanomaModelPositions =
  Table[Position[WellCoveredModels, CutaneousMelanomaModels[[i]][[1, 1]],
    {i, 1, Length[CutaneousMelanomaModels]}];
NSCLSModelPositions = Table[Position[WellCoveredModels, NSCLCModels[[i]][[1, 1]],
    {i, 1, Length[NSCLCModels]}];
PDACModelPositions = Table[Position[WellCoveredModels, PDACModels[[i]][[1, 1]],
    {i, 1, Length[PDACModels]}];
ColorectalModelPositions = Table[Position[WellCoveredModels, ColorectalModels[[i]][[1, 1]],
    {i, 1, Length[ColorectalModels]}];
BreastModelPositions = Table[Position[WellCoveredModels, BreastModels[[i]][[1, 1]],
    {i, 1, Length[BreastModels]}];
GastricModelPositions = Table[Position[WellCoveredModels, GastricModels[[i]][[1, 1]],
    {i, 1, Length[GastricModels]}];

(* random pairs of monotherapies are significantly better than monotherapies in
 every tumor type *)
LogRankTest[{PerModelMeanMonoResponses[[CutaneousMelanomaModelPositions]],
  PerModelAverageBestOfRandomMonotherapyPairs[[CutaneousMelanomaModelPositions]]}]
LogRankTest[{PerModelMeanMonoResponses[[NSCLSModelPositions]],
  PerModelAverageBestOfRandomMonotherapyPairs[[NSCLSModelPositions]]}]
LogRankTest[{PerModelMeanMonoResponses[[PDACModelPositions]],
  PerModelAverageBestOfRandomMonotherapyPairs[[PDACModelPositions]]}]
LogRankTest[{PerModelMeanMonoResponses[[ColorectalModelPositions]],
  PerModelAverageBestOfRandomMonotherapyPairs[[ColorectalModelPositions]]}]
LogRankTest[{PerModelMeanMonoResponses[[BreastModelPositions]],
  PerModelAverageBestOfRandomMonotherapyPairs[[BreastModelPositions]]}]
LogRankTest[{PerModelMeanMonoResponses[[GastricModelPositions]],
  PerModelAverageBestOfRandomMonotherapyPairs[[GastricModelPositions]]}]
```

```
0.0365319

0.0327313

0.000204455

0.00030352

0.000311849

0.00134281
```

```
(* random pairs of monotherapies are statistically indistinguishable from observed
 combinations in every tumor type but melanoma,
and gastric cancer (where tested combinations are inferior) *)
LogRankTest[{PerModelMeanComboResponses[[CutaneousMelanomaModelPositions]],
  PerModelAverageBestOfRandomMonotherapyPairs[[CutaneousMelanomaModelPositions]]}]
LogRankTest[{PerModelMeanComboResponses[[NSCLSModelPositions]],
  PerModelAverageBestOfRandomMonotherapyPairs[[NSCLSModelPositions]]}]
LogRankTest[{PerModelMeanComboResponses[[PDACModelPositions]],
  PerModelAverageBestOfRandomMonotherapyPairs[[PDACModelPositions]]}]
LogRankTest[{PerModelMeanComboResponses[[ColorectalModelPositions]],
  PerModelAverageBestOfRandomMonotherapyPairs[[ColorectalModelPositions]]}]
LogRankTest[{PerModelMeanComboResponses[[BreastModelPositions]],
  PerModelAverageBestOfRandomMonotherapyPairs[[BreastModelPositions]]}]
LogRankTest[{PerModelMeanComboResponses[[GastricModelPositions]],
  PerModelAverageBestOfRandomMonotherapyPairs[[GastricModelPositions]]}]
```

```
0.0000109687

0.727885

0.280283

0.402728

0.199405

0.00119502
```

Cox proportional hazards model, comparing observed effects of combinations with random pairs of monotherapies (under assumption of independent drug action), in each tumor type

```
(* Melanoma *)
modelpositions = CutaneousMelanomaModelPositions;
myeventdata =
  EventData[Join[PerModelMeanComboResponses[[modelpositions]],
    PerModelAverageBestOfRandomMonotherapyPairs[[modelpositions]],
   Table[0,
    {Length[Join[PerModelMeanComboResponses[[modelpositions]],
       PerModelAverageBestOfRandomMonotherapyPairs[[modelpositions]]]}]];
descriptors =
  Join[Table["tested combinations", {Length[PerModelMeanComboResponses[[modelpositions]]}],
   Table["random monotherapy pairs",
    {Length[PerModelAverageBestOfRandomMonotherapyPairs[[modelpositions]]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[tested combinations]	−1.18506	0.2821	0.305726	17.6472	1	0.0000265901

```
{{0.175877, 0.531444}}
```

```
(* NSCLC *)
modelpositions = NSCLSModelPositions;
myeventdata =
  EventData[Join[PerModelMeanComboResponses[[modelpositions]],
    PerModelAverageBestOfRandomMonotherapyPairs[[modelpositions]]],
   Table[0,
    {Length[Join[PerModelMeanComboResponses[[modelpositions]],
       PerModelAverageBestOfRandomMonotherapyPairs[[modelpositions]]]}]];
descriptors =
  Join[Table["tested combinations", {Length[PerModelMeanComboResponses[[modelpositions]]}],
   Table["random monotherapy pairs",
    {Length[PerModelAverageBestOfRandomMonotherapyPairs[[modelpositions]]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[tested combinations]	−0.09255	0.266087	0.911604	0.120978	1	0.727976

```
{{0.541144, 1.53568}}
```

```
(* PDAC *)
modelpositions = PDACModelPositions;
myeventdata =
  EventData[Join[PerModelMeanComboResponses[[modelpositions]],
    PerModelAverageBestOfRandomMonotherapyPairs[[modelpositions]]],
   Table[0,
    {Length[Join[PerModelMeanComboResponses[[modelpositions]],
       PerModelAverageBestOfRandomMonotherapyPairs[[modelpositions]]]}]];
descriptors =
  Join[Table["tested combinations", {Length[PerModelMeanComboResponses[[modelpositions]]}],
   Table["random monotherapy pairs",
    {Length[PerModelAverageBestOfRandomMonotherapyPairs[[modelpositions]]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[tested combinations]	−0.241101	0.223825	0.785763	1.16032	1	0.281399

```
{{0.506723, 1.21846}}
```

```
(* CRC *)
modelpositions = ColorectalModelPositions;
myeventdata =
  EventData[Join[PerModelMeanComboResponses[[modelpositions]],
    PerModelAverageBestOfRandomMonotherapyPairs[[modelpositions]]],
   Table[0,
    {Length[Join[PerModelMeanComboResponses[[modelpositions]],
       PerModelAverageBestOfRandomMonotherapyPairs[[modelpositions]]]}]];
descriptors =
  Join[Table["tested combinations", {Length[PerModelMeanComboResponses[[modelpositions]]}],
   Table["random monotherapy pairs",
    {Length[PerModelAverageBestOfRandomMonotherapyPairs[[modelpositions]]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[tested combinations]	0.184954	0.221348	1.20316	0.698194	1	0.403391

```
{{0.779673, 1.85668}}
```

```
(* Breast *)
modelpositions = BreastModelPositions;
myeventdata =
  EventData[Join[PerModelMeanComboResponses[[modelpositions]],
    PerModelAverageBestOfRandomMonotherapyPairs[[modelpositions]]],
   Table[0,
    {Length[Join[PerModelMeanComboResponses[[modelpositions]],
       PerModelAverageBestOfRandomMonotherapyPairs[[modelpositions]]]}]];
descriptors =
  Join[Table["tested combinations", {Length[PerModelMeanComboResponses[[modelpositions]]}],
   Table["random monotherapy pairs",
    {Length[PerModelAverageBestOfRandomMonotherapyPairs[[modelpositions]]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[tested combinations]	−0.295699	0.231237	0.744011	1.63526	1	0.200977

```
{{0.472879, 1.1706}}
```

```
(* Gastric *)
modelpositions = GastricModelPositions;
myeventdata =
  EventData[Join[PerModelMeanComboResponses[[modelpositions]],
    PerModelAverageBestOfRandomMonotherapyPairs[[modelpositions]]],
   Table[0,
    {Length[Join[PerModelMeanComboResponses[[modelpositions]],
       PerModelAverageBestOfRandomMonotherapyPairs[[modelpositions]]]}]];
descriptors =
  Join[Table["tested combinations", {Length[PerModelMeanComboResponses[[modelpositions]]}],
   Table["random monotherapy pairs",
    {Length[PerModelAverageBestOfRandomMonotherapyPairs[[modelpositions]]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

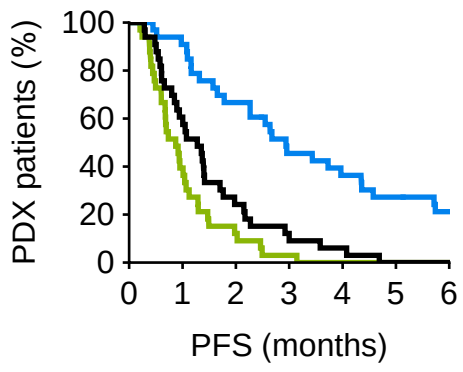
	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[tested combinations]	0.707044	0.222359	2.02799	10.1107	1	0.00147409

```
{{1.31157, 3.13573}}
```

Repeating Figure 3B for each tumor subtype

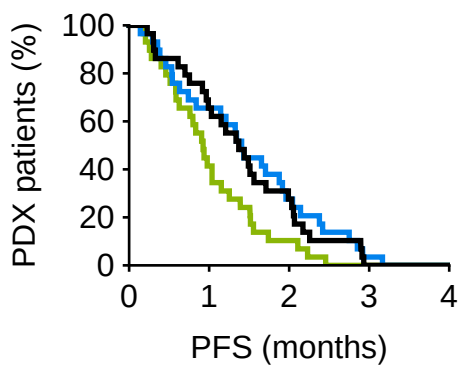
```
Plot[{
  SurvivalFunction[EmpiricalDistribution[
     PerModelMeanMonoResponses[[CutaneousMelanomaModelPositions]]]][x],
  SurvivalFunction[EmpiricalDistribution[
     PerModelMeanComboResponses[[CutaneousMelanomaModelPositions]]]][x],
  SurvivalFunction[EmpiricalDistribution[
     PerModelAverageBestOfRandomMonotherapyPairs[[CutaneousMelanomaModelPositions]]]][x]
 }
 , {x, 0, 7 * 61 / 2}, Exclusions → None, PlotRange → {{0, 6 * 61 / 2}, {0, 1}}, PlotPoints → 1000,
 Frame → {{True, False}, {True, False}}, BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {{Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}], None},
   {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 300, 61 / 2}], None}},
 PlotStyle → {Directive[ColorData[3, 4], AbsoluteThickness[2]],
   Directive[ColorData[3, 6], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]],
   Directive[ColorData[3, 8], AbsoluteThickness[2]]},
 FrameLabel → {"PFS (months)", "PDX patients (%)"}, ImageSize → {{1000}, {160}},
 ImagePadding → {{60, 10}, {60, 10}},
 (*PlotLegends→
  Placed[Map[Style[#,FontSize→12]&,{"Average monotherapy","Average combination",
     "Random pairs of\nmonotherapies"}],{Scaled[{0.45,0.99}], {0, 1}}],*)AspectRatio → 3 / 4]

Export[NotebookDirectory[] <> "Supplementary Figure S4B, Melanoma PFS.pdf", %, "PDF"];
```



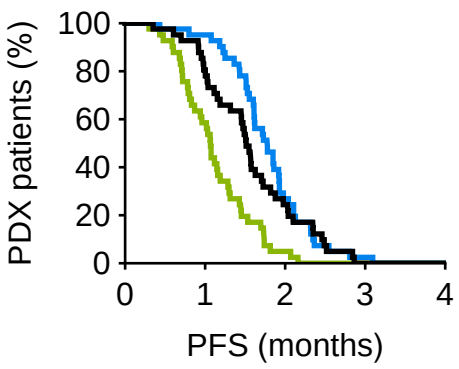
```
Plot[{
  SurvivalFunction[EmpiricalDistribution[PerModelMeanMonoResponses[[NSCLSModelPositions]]]][x],
  SurvivalFunction[EmpiricalDistribution[PerModelMeanComboResponses[[NSCLSModelPositions]]]][x],
  SurvivalFunction[EmpiricalDistribution[
     PerModelAverageBestOfRandomMonotherapyPairs[[NSCLSModelPositions]]]][x]
 }
 , {x, 0, 5 * 61 / 2}, Exclusions → None, PlotRange → {{0, 4 * 61 / 2}, {0, 1}}, PlotPoints → 1000,
 Frame → {{True, False}, {True, False}}, BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {{Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}], None},
   {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 300, 61 / 2}], None}},
 PlotStyle → {Directive[ColorData[3, 4], AbsoluteThickness[2]],
   Directive[ColorData[3, 6], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]],
   Directive[ColorData[3, 8], AbsoluteThickness[2]]},
 FrameLabel → {"PFS (months)", "PDX patients (%)"}, ImageSize → {{1000}, {160}},
 ImagePadding → {{60, 10}, {60, 10}},
 (*PlotLegends→
  Placed[Map[Style[#,FontSize→12]&,{"Average monotherapy","Average combination",
    "Random pairs of\nmonotherapies"}],{Scaled[{0.45,0.99}], {0, 1}}], *)AspectRatio → 3 / 4]

Export[NotebookDirectory[] <> "Supplementary Figure S4B, NSCLC PFS.pdf", %, "PDF"];
```



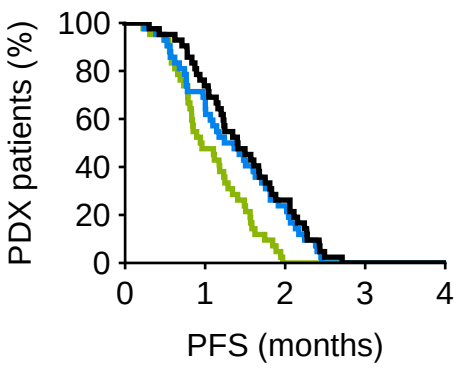
```
Plot[{
  SurvivalFunction[EmpiricalDistribution[PerModelMeanMonoResponses[[PDACModelPositions]]]][x],
  SurvivalFunction[EmpiricalDistribution[PerModelMeanComboResponses[[PDACModelPositions]]]][x],
  SurvivalFunction[EmpiricalDistribution[
     PerModelAverageBestOfRandomMonotherapyPairs[[PDACModelPositions]]]][x]
 }
 , {x, 0, 5 * 61 / 2}, Exclusions → None, PlotRange → {{0, 4 * 61 / 2}, {0, 1}}, PlotPoints → 1000,
 Frame → {{True, False}, {True, False}}, BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {{Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}], None},
   {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 300, 61 / 2}], None}},
 PlotStyle → {Directive[ColorData[3, 4], AbsoluteThickness[2]],
   Directive[ColorData[3, 6], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]],
   Directive[ColorData[3, 8], AbsoluteThickness[2]]},
 FrameLabel → {"PFS (months)", "PDX patients (%)"}, ImageSize → {{1000}, {160}},
 ImagePadding → {{60, 10}, {60, 10}},
 (*PlotLegends→
  Placed[Map[Style[#,FontSize→12]&,{"Average monotherapy","Average combination",
    "Random pairs of\nmonotherapies"}],{Scaled[{0.45,0.99}], {0, 1}}], *)AspectRatio → 3 / 4]

Export[NotebookDirectory[] <> "Supplementary Figure S4B, PDAC PFS.pdf", %, "PDF"];
```



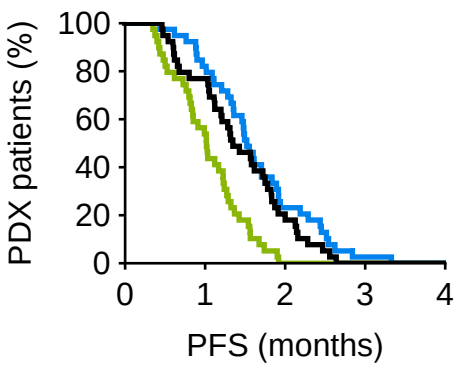
```
Plot[{
  SurvivalFunction[EmpiricalDistribution[PerModelMeanMonoResponses[[ColorectalModelPositions]]][
   x],
  SurvivalFunction[EmpiricalDistribution[
     PerModelMeanComboResponses[[ColorectalModelPositions]]][x],
  SurvivalFunction[EmpiricalDistribution[
     PerModelAverageBestOfRandomMonotherapyPairs[[ColorectalModelPositions]]][x]
 }
 , {x, 0, 5 * 61 / 2}, Exclusions → None, PlotRange → {{0, 4 * 61 / 2}, {0, 1}}, PlotPoints → 1000,
 Frame → {{True, False}, {True, False}}, BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {{Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}], None},
   {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 300, 61 / 2}], None}},
 PlotStyle → {Directive[ColorData[3, 4], AbsoluteThickness[2]],
   Directive[ColorData[3, 6], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]],
   Directive[ColorData[3, 8], AbsoluteThickness[2]]},
 FrameLabel → {"PFS (months)", "PDX patients (%)"}, ImageSize → {{1000}, {160}},
 ImagePadding → {{60, 10}, {60, 10}},
 (*PlotLegends→
  Placed[Map[Style[#,FontSize→12]&,{"Average monotherapy","Average combination",
     "Random pairs of\nmonotherapies"}],{Scaled[{0.45,0.99}], {0, 1}}], *)AspectRatio → 3 / 4]

Export[NotebookDirectory[] <> "Supplementary Figure S4B, CRC PFS.pdf", %, "PDF"];
```



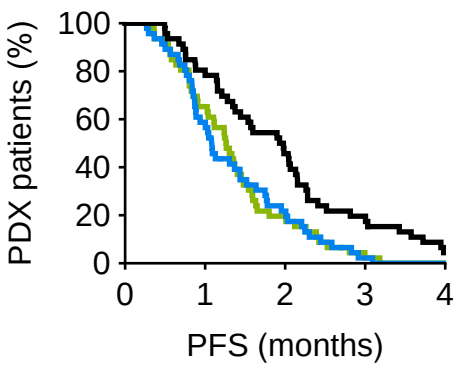
```
Plot[{
  SurvivalFunction[EmpiricalDistribution[PerModelMeanMonoResponses[[BreastModelPositions]]][x],
  SurvivalFunction[EmpiricalDistribution[PerModelMeanComboResponses[[BreastModelPositions]]][
   x],
  SurvivalFunction[EmpiricalDistribution[
     PerModelAverageBestOfRandomMonotherapyPairs[[BreastModelPositions]]][x]
 }
 , {x, 0, 5 * 61 / 2}, Exclusions → None, PlotRange → {{0, 4 * 61 / 2}, {0, 1}}, PlotPoints → 1000,
 Frame → {{True, False}, {True, False}}, BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {{Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}], None},
   {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 300, 61 / 2}], None}},
 PlotStyle → {Directive[ColorData[3, 4], AbsoluteThickness[2]],
   Directive[ColorData[3, 6], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]],
   Directive[ColorData[3, 8], AbsoluteThickness[2]]},
 FrameLabel → {"PFS (months)", "PDX patients (%)"}, ImageSize → {{1000}, {160}},
 ImagePadding → {{60, 10}, {60, 10}},
 (*PlotLegends→
   Placed[Map[Style[#,FontSize→12]&,{"Average monotherapy","Average combination",
     "Random pairs of\nmonotherapies"}],{Scaled[{0.45,0.99}], {0, 1}}], *)AspectRatio → 3 / 4]

Export[NotebookDirectory[] <> "Supplementary Figure S4B, Breast PFS.pdf", %, "PDF"];
```



```
Plot[{
  SurvivalFunction[EmpiricalDistribution[PerModelMeanMonoResponses[[GastricModelPositions]]][x],
  SurvivalFunction[EmpiricalDistribution[PerModelMeanComboResponses[[GastricModelPositions]]][
   x],
  SurvivalFunction[EmpiricalDistribution[
     PerModelAverageBestOfRandomMonotherapyPairs[[GastricModelPositions]]][x]
 }
 , {x, 0, 5 * 61 / 2}, Exclusions → None, PlotRange → {{0, 4 * 61 / 2}, {0, 1}}, PlotPoints → 1000,
 Frame → {{True, False}, {True, False}}, BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {{Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}], None},
   {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 300, 61 / 2}], None}},
 PlotStyle → {Directive[ColorData[3, 4], AbsoluteThickness[2]],
   Directive[ColorData[3, 6], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]],
   Directive[ColorData[3, 8], AbsoluteThickness[2]]},
 FrameLabel → {"PFS (months)", "PDX patients (%)"}, ImageSize → {{1000}, {160}},
 ImagePadding → {{60, 10}, {60, 10}},
 (*PlotLegends→
   Placed[Map[Style[#,FontSize→12]&,{"Average monotherapy","Average combination",
     "Random pairs of\nmonotherapies"}],{Scaled[{0.45,0.99}], {0, 1}}], *)AspectRatio → 3 / 4]

Export[NotebookDirectory[] <> "Supplementary Figure S4B, Gastric PFS.pdf", %, "PDF"];
```

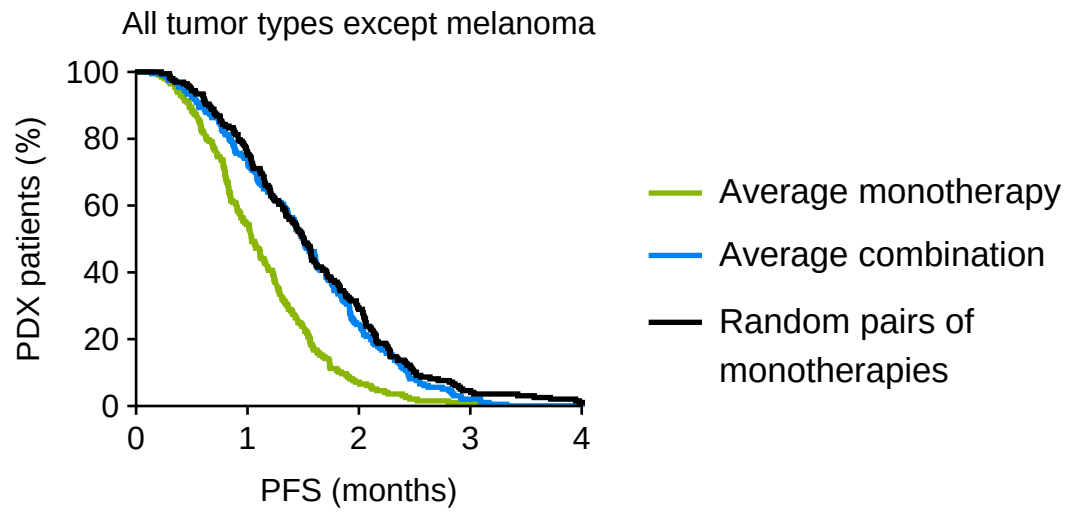


Repeating Figure 3B in all PDX models excepting melanoma (where combinations show genuine 'synergy', defined in this analysis as superior response to independent drug action - see Supplementary Figure S4D)
n=197 non-melanoma PDXs

```
AllPositionsExceptingMelanoma = Join[NSCLSModelPositions, PDACModelPositions,
   ColorectalModelPositions, BreastModelPositions, GastricModelPositions];
Length[%]

Plot[{
  SurvivalFunction[EmpiricalDistribution[
     PerModelMeanMonoResponses[[AllPositionsExceptingMelanoma]]][x],
  SurvivalFunction[EmpiricalDistribution[
     PerModelMeanComboResponses[[AllPositionsExceptingMelanoma]]][x],
  SurvivalFunction[EmpiricalDistribution[
     PerModelAverageBestOfRandomMonotherapyPairs[[AllPositionsExceptingMelanoma]]][x]
 }
 , {x, 0, 5 * 61 / 2}, Exclusions → None, PlotRange → {{0, 4 * 61 / 2}, {0, 1}}, PlotPoints → 1000,
 Frame → {{True, False}, {True, False}}, BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {{Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}], None},
   {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 300, 61 / 2}], None}},
 PlotStyle → {Directive[ColorData[3, 4], AbsoluteThickness[2]],
   Directive[ColorData[3, 6], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]],
   Directive[ColorData[3, 8], AbsoluteThickness[2]]},
 FrameLabel → {"PFS (months)", "PDX patients (%)"}, ImageSize → {{1000}, {210}},
 ImagePadding → {{60, 10}, {60, 10}},
 PlotLegends → {"Average monotherapy", "Average combination", "Random pairs of\nmonotherapies"},
 AspectRatio → 3 / 4, PlotLabel → Style["All tumor types except melanoma", FontSize → 12, Black]]
```

197



```
(* Cox proportional hazards model,
comparing observed effects of combinations to random pairs of monotherapies
 (under the assumption of independent drug action), in all PDX models excepting melanoma *)
myeventdata =
  EventData[Join[PerModelMeanComboResponses[[AllPositionsExceptingMelanoma]],
    PerModelAverageBestOfRandomMonotherapyPairs[[AllPositionsExceptingMelanoma]]],
   Table[0,
    {Length[Join[PerModelMeanComboResponses[[AllPositionsExceptingMelanoma]],
       PerModelAverageBestOfRandomMonotherapyPairs[[AllPositionsExceptingMelanoma]]]}]];
descriptors =
  Join[Table["tested combinations",
    {Length[PerModelMeanComboResponses[[AllPositionsExceptingMelanoma]]}],
   Table["random pairs of monotherapies",
    {Length[PerModelAverageBestOfRandomMonotherapyPairs[[AllPositionsExceptingMelanoma]]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

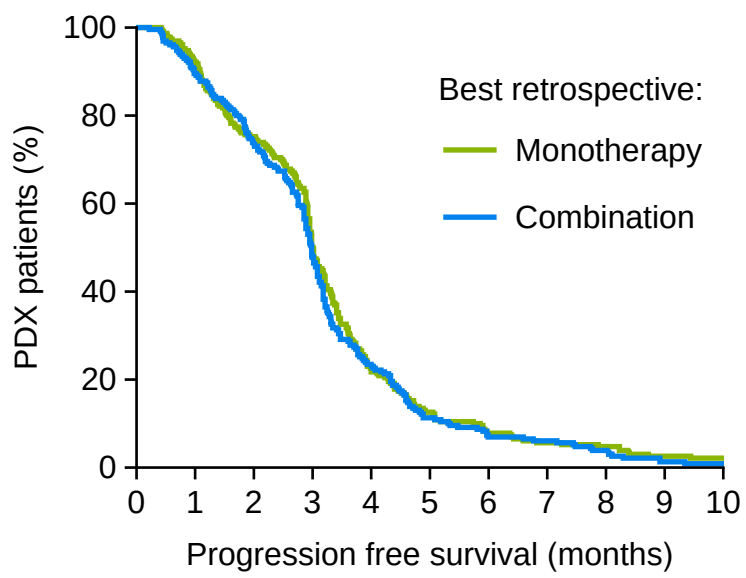
	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[tested combinations]	0.125161	0.102052	1.13333	1.50416	1	0.220032

```
{{0.927876, 1.38428}}
```

Comparing each PDXs longest PFS observed with any monotherapy and with any combination

```
BestResponsesPlot = Plot[{
    SurvivalFunction[EmpiricalDistribution[PerModelMaxMonoResponses]][x],
    SurvivalFunction[EmpiricalDistribution[PerModelMaxComboResponses]][x]
   }
   , {x, 0, 10 * 61 / 2}, Exclusions → None, PlotRange → {{0, 10 * 61 / 2}, {0, 1}},
   PlotPoints → 1000, Frame → {{True, False}, {True, False}},
   BaseStyle → {FontFamily → "Arial", FontSize → 12},
   FrameStyle → Directive[Black, Thickness[Medium]],
   FrameTicks → {{Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}], None},
     {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 330, 61 / 2}], None}},
   PlotStyle → {Directive[ColorData[3, 4], AbsoluteThickness[2]],
     Directive[ColorData[3, 6], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]],
     Directive[ColorData[3, 8], AbsoluteThickness[2]]},
   FrameLabel → {"Progression free survival (months)", "PDX patients (%)"},
   ImageSize → {{1000}, {225}}, ImagePadding → {{50, 10}, {50, 10}},
   PlotLegends → Placed[Map[Style[#, FontSize → 12] &, {"Monotherapy", "Combination"}],
     {Scaled[{0.5, 0.8}], {0, 1}}], AspectRatio → 3 / 4,
   Epilog → {Black, Text[Style["Best retrospective:", FontSize → 12], Scaled[{0.515, 0.81}],
      {-1, -1}]}]

Export[NotebookDirectory[] <> "Figure 3C, best monotherapy and best combination responses.pdf",
   BestResponsesPlot, "PDF"];
```




```
(* Cox proportional hazards model does not detect a significant difference in
 relative risk between 'best retrospective monotherapy' and 'best retrospective
 combination' *)
myeventdata = EventData[Join[PerModelMaxMonoResponses, PerModelMaxComboResponses],
    Table[0, {Length[Join[PerModelMaxMonoResponses, PerModelMaxComboResponses]]}]];
descriptors = Join[Table["best monotherapy per PDX", {Length[PerModelMaxMonoResponses]}],
    Table["best combination per PDX", {Length[PerModelMaxComboResponses]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
    NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[best monotherapy per PDX]	−0.0470808	0.0936047	0.95401	0.252984	1	0.614982

```
{{0.794103, 1.14612}}
```

Comparing each PDXs longest PFS observed with any monotherapy and with any combination,
but focusing only on matching sets of drugs (drugs tested in the same tumor type both as

a monotherapy and as a part of a combination)

First, for each tumor type, selecting monotherapies that are contained within a combination tested on that same tumor type

```
MonotherapiesWithinCombinationsPerGroup =
  Map[Intersection, Map[Flatten, Map[StringSplit[#, " + "] &, CombinationTherapiesByGroup, {2}],
     {1}], {1}] /. {"gemcitabine" → "gemcitabine-50mpk"} ;
 (*need to adjust gemcitabine name because dosage was written its name as a monotherapy
 name but not in the combination name *)

(* this data structure is a table of length 6, one entry per tumor type *)
MonotherapiesWithinCombinationsPerGroup // TableForm
```

binimetinib	BKM120	encorafenib	LEE011			
binimetinib	BKM120	BYL719	LCL161	LFW527	LGH447	LJM
abraxane	binimetinib	BKM120	BYL719	figitumumab"	gemcitabine-50mpk	INC
binimetinib	BKM120	BYL719	cetuximab	encorafenib	LFW527	LJC
BYL719	everolimus	LEE011	LFW527	LJM716	trastuzumab	
BYL719	everolimus	HSP990	INC280	LEE011	LJM716	tra

```
(* In total there are 42 drug-by-tumor type trials of monotherapies,
that were also tested in a combination *)
Flatten[MonotherapiesWithinCombinationsPerGroup] // Length
```

42

```
(* Taking the best monotherapy response per PDX model;
this is conducted on a per-tumor-
 type basis since different therapies were tested on different tumor types *)
BestMonotherapyResponsesFromCombinationIngredientsMelanoma =
  Table[
   Sort[Select[PDXclinicaltrialresponses,
      And[#[[1]] == CutaneousMelanomaModels[[i]],
        MemberQ[MonotherapiesWithinCombinationsPerGroup[[1]], #[[2]]], #[[4]] == "single"] &],
     #1[[9]] > #2[[9]] &][[1]], {i, 1, Length[CutaneousMelanomaModels]}];

BestMonotherapyResponsesFromCombinationIngredientsNSCLC =
  Table[
   Sort[Select[PDXclinicaltrialresponses,
      And[#[[1]] == NSCLCModels[[i]], MemberQ[MonotherapiesWithinCombinationsPerGroup[[2]], #[[2]]],
        #[[4]] == "single"] &], #1[[9]] > #2[[9]] &][[1]], {i, 1, Length[NSCLCModels]}];

BestMonotherapyResponsesFromCombinationIngredientsPDAC =
  Table[
   Sort[Select[PDXclinicaltrialresponses,
      And[#[[1]] == PDACModels[[i]], MemberQ[MonotherapiesWithinCombinationsPerGroup[[3]], #[[2]]],
        #[[4]] == "single"] &], #1[[9]] > #2[[9]] &][[1]], {i, 1, Length[PDACModels]}];

BestMonotherapyResponsesFromCombinationIngredientsCRC =
  Table[
   Sort[Select[PDXclinicaltrialresponses,
      And[#[[1]] == ColorectalModels[[i]], MemberQ[MonotherapiesWithinCombinationsPerGroup[[4]],
         #[[2]]], #[[4]] == "single"] &], #1[[9]] > #2[[9]] &][[1]], {i, 1, Length[ColorectalModels]}];

BestMonotherapyResponsesFromCombinationIngredientsBreast =
  Table[
   Sort[Select[PDXclinicaltrialresponses,
      And[#[[1]] == BreastModels[[i]], MemberQ[MonotherapiesWithinCombinationsPerGroup[[5]], #[[2]]],
        #[[4]] == "single"] &], #1[[9]] > #2[[9]] &][[1]], {i, 1, Length[BreastModels]}];

BestMonotherapyResponsesFromCombinationIngredientsGastric =
  Table[
   Sort[Select[PDXclinicaltrialresponses,
      And[#[[1]] == GastricModels[[i]], MemberQ[MonotherapiesWithinCombinationsPerGroup[[6]], #[[2]]],
        #[[4]] == "single"] &], #1[[9]] > #2[[9]] &][[1]], {i, 1, Length[GastricModels]}];

(* merging results from different tumor types *)
AllBestMonotherapyResponsesFromCombinationIngredients =
  Join[BestMonotherapyResponsesFromCombinationIngredientsMelanoma,
   BestMonotherapyResponsesFromCombinationIngredientsNSCLC,
   BestMonotherapyResponsesFromCombinationIngredientsPDAC,
   BestMonotherapyResponsesFromCombinationIngredientsCRC,
   BestMonotherapyResponsesFromCombinationIngredientsBreast,
   BestMonotherapyResponsesFromCombinationIngredientsGastric];
```

For each tumor type, selecting combinations where both constituents were tested as monotherapies on that same tumor type

```
CombinationIngredientsByGroup =
  Map[StringSplit[#, " + "] &, CombinationTherapiesByGroup, {2}] /.
   {"gemcitabine" → "gemcitabine-50mpk"};
CombinationIngredientsBothTestedAsMonotherapiesByGroup =
  Table[Select[CombinationIngredientsByGroup[[i]],
     And[MemberQ[MonotherapiesByGroup[[i]], #[[1]]], MemberQ[MonotherapiesByGroup[[i]], #[[2]]]] &],
    {i, 1, 6}] /. {"gemcitabine-50mpk" → "gemcitabine"};
CombinationsBothTestedAsMonotherapiesByGroup =
  Table[Map[#[[1]] <> " + " <> #[[2]] &, CombinationIngredientsBothTestedAsMonotherapiesByGroup[[i]]],
   {i, 1, 6, 1}];

(* this data structure is a table of length 6, one entry per tumor type *)
CombinationsBothTestedAsMonotherapiesByGroup // TableForm
```

BKM120 + encorafenib	encorafenib + binimetinib	LEE011 + binimetinib	LEE011 + enc
BKM120 + binimetinib	BYL719 + LGH447		
abraxane + gemcitabine	BKM120 + binimetinib	figitumumab" + binimetinib	INC424 + bin
BKM120 + LJC049	BYL719 + binimetinib	BYL719 + cetuximab	BYL719 + cet
BYL719 + LEE011	BYL719 + LJM716	LJM716 + trastuzumab	
BYL719 + HSP990	BYL719 + LJM716	INC280 + trastuzumab	LEE011 + eve

```
(* In total there are 24 drug-by-tumor type trials of combinations,
where both parts of the combination were also tested as monotherapies *)
Flatten[CombinationsBothTestedAsMonotherapiesByGroup] // Length
```

```
24
```

```
(* Taking the best combination response per PDX model;
this is conducted on a per-tumor-
 type basis since different therapies were tested on different tumor types *)
BestCombinationFromThoseTestedAsMonotherapiesMelanoma =
  Table[
   Sort[Select[PDXclinicaltrialresponses,
      And[#[[1]] == CutaneousMelanomaModels[[i]],
        MemberQ[CombinationsBothTestedAsMonotherapiesByGroup[[1]], #[[2]]], #[[4]] == "combo"] &],
     #1[[9]] > #2[[9]] &][[1]], {i, 1, Length[CutaneousMelanomaModels]}];

BestCombinationFromThoseTestedAsMonotherapiesNSCLC =
  Table[
   Sort[Select[PDXclinicaltrialresponses,
      And[#[[1]] == NSCLCModels[[i]], MemberQ[CombinationsBothTestedAsMonotherapiesByGroup[[2]],
        #[[2]]], #[[4]] == "combo"] &], #1[[9]] > #2[[9]] &][[1]], {i, 1, Length[NSCLCModels]}];

BestCombinationFromThoseTestedAsMonotherapiesPDAC =
  Table[
   Sort[Select[PDXclinicaltrialresponses,
      And[#[[1]] == PDACModels[[i]], MemberQ[CombinationsBothTestedAsMonotherapiesByGroup[[3]], #[[2]]],
        #[[4]] == "combo"] &], #1[[9]] > #2[[9]] &][[1]], {i, 1, Length[PDACModels]}];

BestCombinationFromThoseTestedAsMonotherapiesCRC =
  Table[
   Sort[Select[PDXclinicaltrialresponses,
      And[#[[1]] == ColorectalModels[[i]], MemberQ[CombinationsBothTestedAsMonotherapiesByGroup[[4]],
        #[[2]]], #[[4]] == "combo"] &], #1[[9]] > #2[[9]] &][[1]], {i, 1, Length[ColorectalModels]}];

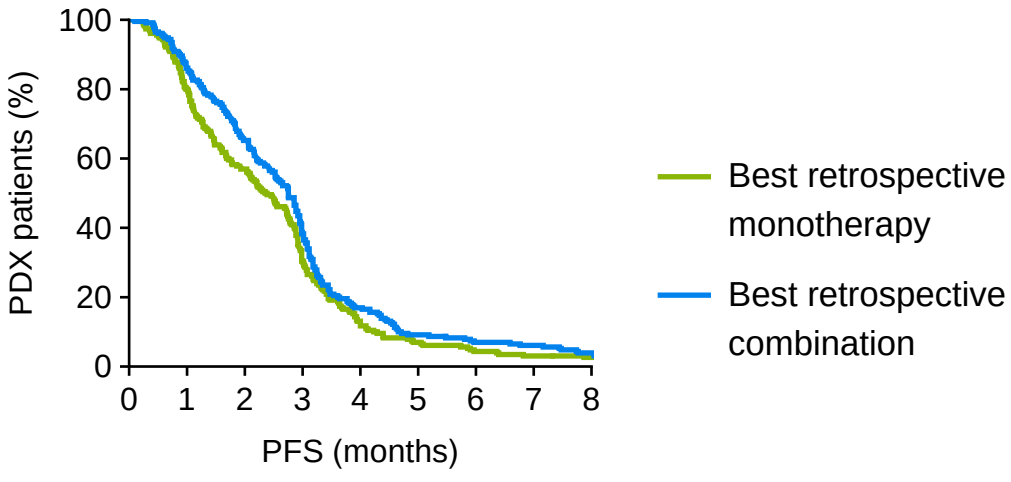
BestCombinationFromThoseTestedAsMonotherapiesBreast =
  Table[
   Sort[Select[PDXclinicaltrialresponses,
      And[#[[1]] == BreastModels[[i]], MemberQ[CombinationsBothTestedAsMonotherapiesByGroup[[5]],
        #[[2]]], #[[4]] == "combo"] &], #1[[9]] > #2[[9]] &][[1]], {i, 1, Length[BreastModels]}];

BestCombinationFromThoseTestedAsMonotherapiesGastric =
  Table[
   Sort[Select[PDXclinicaltrialresponses,
      And[#[[1]] == GastricModels[[i]], MemberQ[CombinationsBothTestedAsMonotherapiesByGroup[[6]],
        #[[2]]], #[[4]] == "combo"] &], #1[[9]] > #2[[9]] &][[1]], {i, 1, Length[GastricModels]}];

(* merging results from different tumor types *)
AllBestCombinationResponsesFromThoseTestedAsMonotherapies =
  Join[BestCombinationFromThoseTestedAsMonotherapiesMelanoma,
   BestCombinationFromThoseTestedAsMonotherapiesNSCLC,
   BestCombinationFromThoseTestedAsMonotherapiesPDAC,
   BestCombinationFromThoseTestedAsMonotherapiesCRC,
   BestCombinationFromThoseTestedAsMonotherapiesBreast,
   BestCombinationFromThoseTestedAsMonotherapiesGastric];
```

```
BestResponsesPlotOverlappingDrugs = Plot[{
    SurvivalFunction[EmpiricalDistribution[
       AllBestMonotherapyResponsesFromCombinationIngredients[[All, 9]]]][x],
    SurvivalFunction[EmpiricalDistribution[
       AllBestCombinationResponsesFromThoseTestedAsMonotherapies[[All, 9]]]][x]
   }
   , {x, 0, 10 * 61 / 2}, Exclusions → None, PlotRange → {{0, 8 * 61 / 2}, {0, 1}}, PlotPoints → 1000,
   Frame → {{True, False}, {True, False}}, BaseStyle → {FontFamily → "Arial", FontSize → 12},
   FrameStyle → Directive[Black, Thickness[Medium]],
   FrameTicks → {{Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}], None},
     {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 330, 61 / 2}], None}},
   PlotStyle → {Directive[ColorData[3, 4], AbsoluteThickness[2]],
     Directive[ColorData[3, 6], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]],
     Directive[ColorData[3, 8], AbsoluteThickness[2]]},
   FrameLabel → {"PFS (months)", "PDX patients (%)"}, ImageSize → {{1000}, {200}},
   ImagePadding → {{60, 10}, {60, 10}},
   PlotLegends → {"Best retrospective\nmonotherapy", "Best retrospective\ncombination"},
   AspectRatio → 3 / 4]
```

```
Export[NotebookDirectory[] <>
    "Supplementary Figure S4C, best mono and best combo, only overlapping drugs,
      all tumor types.pdf", BestResponsesPlotOverlappingDrugs, "PDF"];
```



Cox proportional hazards model identifies a borderline-significant advantage (p = 0.065) to combination therapy

```
(* calculating relative risk between 'best retrospective monotherapy' and 'best
 retrospective combination' *)
myeventdata =
  EventData[Join[AllBestMonotherapyResponsesFromCombinationIngredients[All, 9],
    AllBestCombinationResponsesFromThoseTestedAsMonotherapies[All, 9]],
   Table[0,
    {Length[Join[AllBestMonotherapyResponsesFromCombinationIngredients[All, 9],
       AllBestCombinationResponsesFromThoseTestedAsMonotherapies[All, 9]]]}]];
descriptors =
  Join[Table["best retrospective monotherapy",
    {Length[AllBestMonotherapyResponsesFromCombinationIngredients[All, 9]]}],
   Table["best retrospective combination",
    {Length[AllBestCombinationResponsesFromThoseTestedAsMonotherapies[All]]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[best retrospective monotherapy]	0.17268	0.0936243	1.18849	3.40177	1	0.0651265

```
{{0.989238, 1.42786}}
```

```
(* same analysis as above but altering labels to see relative risk of combination
 compared to monotherapy (instead of monotherapy compared to combination) *)
myeventdata =
  EventData[Join[AllBestMonotherapyResponsesFromCombinationIngredients[All, 9],
    AllBestCombinationResponsesFromThoseTestedAsMonotherapies[All, 9]],
   Table[0,
    {Length[Join[AllBestMonotherapyResponsesFromCombinationIngredients[All, 9],
       AllBestCombinationResponsesFromThoseTestedAsMonotherapies[All, 9]]]}]];
descriptors =
  Join[Table["best retrospective monotherapy",
    {Length[AllBestMonotherapyResponsesFromCombinationIngredients[All, 9]]}],
   Table["combination (best retrospective)",
    {Length[AllBestCombinationResponsesFromThoseTestedAsMonotherapies[All]]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[combination (best retrospective)]	−0.17268	0.0936243	0.841407	3.40177	1	0.0651265

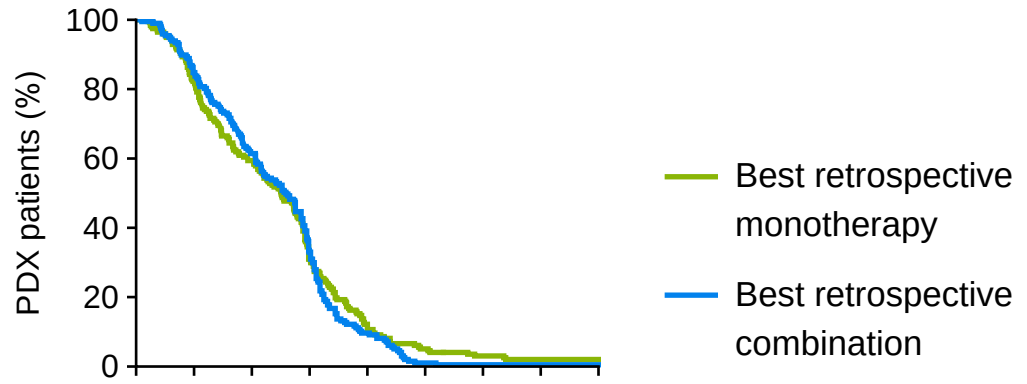
```
{{0.700347, 1.01088}}
```

This small advantage of combinations is due to synergistic combinations in melanoma: analyzing all tumor types other than melanoma, there is no statistical difference between best monotherapy and best combination responses

```
(* selecting the data corresponding to all tumor types other than melanoma *)
AllModelPositionsButMelanoma = Complement[Range[230], CutaneousMelanomaModelPositions];

Plot[{
  SurvivalFunction[EmpiricalDistribution[
     AllBestMonotherapyResponsesFromCombinationIngredients[[AllModelPositionsButMelanoma, 9]]][
   x],
  SurvivalFunction[EmpiricalDistribution[
     AllBestCombinationResponsesFromThoseTestedAsMonotherapies[[AllModelPositionsButMelanoma,
      9]]][x]
 }
 , {x, 0, 10 * 61 / 2}, Exclusions → None, PlotRange → {{0, 8 * 61 / 2}, {0, 1}}, PlotPoints → 1000,
 Frame → {{True, False}, {True, False}}, BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {{Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}], None},
   {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 330, 61 / 2}], None}},
 PlotStyle → {Directive[ColorData[3, 4], AbsoluteThickness[2]],
   Directive[ColorData[3, 6], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]],
   Directive[ColorData[3, 8], AbsoluteThickness[2]]},
 FrameLabel → {"PFS (months)", "PDX patients (%)"}, ImageSize → {{1000}, {200}},
 ImagePadding → {{60, 10}, {60, 10}},
 PlotLegends → {"Best retrospective\nmonotherapy", "Best retrospective\ncombination"},
 AspectRatio → 3 / 4]

Export[NotebookDirectory[] <>
   "Supplementary Figure S4C, best mono and best combo, only overlapping drugs,
     excluding melanoma.pdf", %, "PDF"];
```



```
(* Cox Proportional Hazards model does not detect a significant difference in relative risk *)
myeventdata =
  EventData[Join[AllBestMonotherapyResponsesFromCombinationIngredients[
     AllModelPositionsButMelanoma, 9],
    AllBestCombinationResponsesFromThoseTestedAsMonotherapies[AllModelPositionsButMelanoma, 9]],
   Table[0,
    {Length[Join[AllBestMonotherapyResponsesFromCombinationIngredients[
        AllModelPositionsButMelanoma, 9],
       AllBestCombinationResponsesFromThoseTestedAsMonotherapies[AllModelPositionsButMelanoma,
        9]]]}]];
descriptors =
  Join[Table["best retrospective monotherapy",
    {Length[AllBestMonotherapyResponsesFromCombinationIngredients[AllModelPositionsButMelanoma,
       9]]}], Table["combination (best retrospective)",
    {Length[AllBestCombinationResponsesFromThoseTestedAsMonotherapies[
       AllModelPositionsButMelanoma]]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[combination (best retrospective)]	0.0814431	0.102044	1.08485	0.636988	1	0.424803

```
{{0.888199, 1.32504}}
```

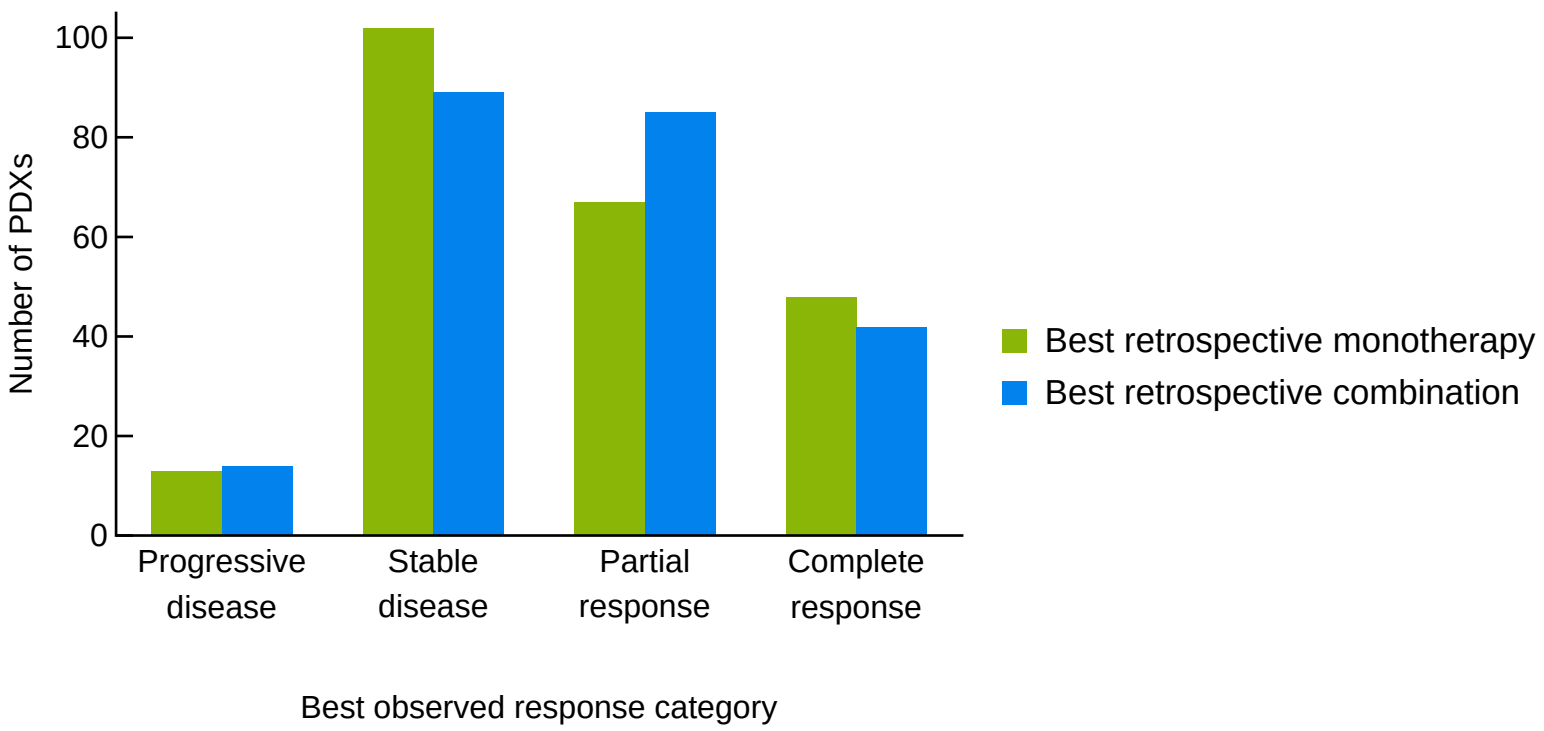
Analyzing best retrospective monotherapy or combination responses in terms of response criteria;
PD = progressive disease
SD = stable disease
PR = partial response
CR = complete response
(See Gao et al. Nature Medicine for additional information)

```
(* this function takes a list of response classifications,
and returns the 'best' or 'strongest' response *)
BestResponseOfSet[listofresponsetypes_] := Module[{},
  InitialResponse = Map[StringTake[#, 2] &, listofresponsetypes];
  ReponsesAsNumbers = InitialResponse /. {"CR" → 3, "PR" → 2, "SD" → 1, "PD" → 0};
  BestResponseAsNumber = Max[ReponsesAsNumbers];
  BestResponseType = (BestResponseAsNumber /. {3 → "CR", 2 → "PR", 1 → "SD", 0 → "PD"})
 ]

(* best response criteria per PDX model, to any monotherapy or to any combination *)
BestMonotherapyResponseCriteriaPerModel =
  Table[BestResponseOfSet[
    Select[ResponsesByModel[[model]], And[#[[4]] == "single", #[[2]] ≠ "untreated"] &][[All, -1]]],
   {model, 1, Length[ResponsesByModel]}];
BestCombinationResponseCriteriaPerModel =
  Table[BestResponseOfSet[Select[ResponsesByModel[[model]], #[[4]] == "combo" &][[All, -1]]],
   {model, 1, Length[ResponsesByModel]}];
```

```
(* How frequent are different response criteria? *)
FractionsOfResponseCriteriaWithPersonalizedMonotherapy =
  Table[Length[Select[BestMonotherapyResponseCriteriaPerModel, # == category &]],
   {category, {"PD", "SD", "PR", "CR"}}];
FractionsOfResponseCriteriaWithPersonalizedCombination =
  Table[Length[Select[BestCombinationResponseCriteriaPerModel, # == category &]],
   {category, {"PD", "SD", "PR", "CR"}}];

BarChart[
 {FractionsOfResponseCriteriaWithPersonalizedMonotherapy,
   FractionsOfResponseCriteriaWithPersonalizedCombination}^T,
 ChartStyle → {Directive[EdgeForm[None], ColorData[3, 4]],
   Directive[EdgeForm[None], ColorData[3, 6]]}, BarSpacing → {0., 1}, Axes → False,
 Frame → {{True, False}, {True, False}}, FrameStyle → Directive[Black, Thickness[Medium]],
 PlotRange → {{0.5, 12.5}, {0, 105}},
 FrameTicks → {{Table[{i, i, {0.02, 0}}, {i, 0, 100, 20}], None},
   {{{2, "Progressive\ndisease", {0, 0}}, {5, "Stable\ndisease", {0, 0}},
     {8, "Partial\nresponse", {0, 0}}, {11, "Complete\nresponse", {0, 0}}}, None}},
 PlotRangePadding → None, BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameLabel → {"\nBest observed response category", "Number of PDXs"},
 ChartLegends → {"Best retrospective monotherapy", "Best retrospective combination"}]
```



Chi-squared test rejects the hypothesis that the response distributions for monotherapies and for combinations are from different distributions: (p = 0.3)

```
(* loading a hypothesis-testing package *)
Needs["HypothesisTesting`"]

expectedValues[rc_List] := Module[{rowTotals, colTotals, grandTotal},
  colTotals := Total[rc];
  rowTotals := Total[Transpose[rc]];
  grandTotal := Total[rowTotals];
  Outer[Times, rowTotals, colTotals] / grandTotal
 ]

chiSquare[data_List] := Module[{ev},
  ev = expectedValues[data];
  Total[((data - ev)^2) / ev, 2]
 ]

MyChiSquare =
 chiSquare[{FractionsOfResponseCriteriaWithPersonalizedMonotherapy,
    FractionsOfResponseCriteriaWithPersonalizedCombination}] // N

degreesOfFreedom[rc_List] := Times @@ (Dimensions[rc] - 1)

MyDegreesofFreedom =
 degreesOfFreedom[{FractionsOfResponseCriteriaWithPersonalizedMonotherapy,
   FractionsOfResponseCriteriaWithPersonalizedCombination}]

ChiSquarePValue[MyChiSquare, MyDegreesofFreedom]
```

```
3.45343

3

OneSidedPValue → 0.326852
```

Is there a benefit to 'personalized' or 'precision' therapy, compared to 'one-size-fits-all' therapy?

This is first addressed in terms of Progression Free Survival

```
(* creating a list of all therapies, be they monotherapies or combinations,
that were tested in each tumor type *)
AllTherapiesByGroup =
  Table[Join[MonotherapiesByGroup[[indication]], CombinationTherapiesByGroup[[indication]]],
   {indication, 1, 6}];
```

```
(* calculating median PFS for each posible treatment,
calculated over all PDXs of a tumor type that were tested with that treatment. Note
 that the treatment matrix (Figure 3A) has a few gaps within blocks,
meaning that median PFS is by necessity calculated from only those xenografts that
 were tested with a particular treatment,
and so not every treatment's median PFS is calculated from the very same set of xenografts. *)
MedianPFSByTherapyByIndication =
  Table[
   Sort[Table[{AllTherapiesByGroup[[indication, therapy]],
      Median[Select[PDXclinicaltrialresponses,
         And[MemberQ[AllModelGroups[[indication]], #[[1]]],
           #[[2]] == AllTherapiesByGroup[[indication, therapy]] &]][[All, 9]]]},
     {therapy, 1, Length[AllTherapiesByGroup[[indication]]]}], #1[[2]] > #2[[2]] &],
   {indication, 1, 6}];

(* this data has 6 rows,
one for each tumor type
 (in sequence: Melanoma, NSCLC, PDAC, Colorectal cancer, Breast cancer, Gastric cancer). Within
 each row are treatments and their median PFS (in days),
ranked from longest to shortest median PFS *)
Print["Melanoma"]
Grid[Prepend[MedianPFSByTherapyByIndication[[1]], {"TREATMENT", "MEDIAN PFS"}], Frame → All]

Print["NSCLC"]
Grid[Prepend[MedianPFSByTherapyByIndication[[2]], {"TREATMENT", "MEDIAN PFS"}], Frame → All]

Print["PDAC"]
Grid[Prepend[MedianPFSByTherapyByIndication[[3]], {"TREATMENT", "MEDIAN PFS"}], Frame → All]

Print["Colorectal"]
Grid[Prepend[MedianPFSByTherapyByIndication[[4]], {"TREATMENT", "MEDIAN PFS"}], Frame → All]

Print["Breast"]
Grid[Prepend[MedianPFSByTherapyByIndication[[5]], {"TREATMENT", "MEDIAN PFS"}], Frame → All]

Print["Gastric"]
Grid[Prepend[MedianPFSByTherapyByIndication[[6]], {"TREATMENT", "MEDIAN PFS"}],
 Frame → All]
```

Melanoma

TREATMENT	MEDIAN PFS
LEE011 + binimetinib	171.5
LEE011 + encorafenib	96.4074
BKM120 + encorafenib	58.589
encorafenib + binimetinib	58.
binimetinib	34.6222
CLR457	27.6621
LEE011	24.
BKM120	18.9308
encorafenib	16.5159
CGM097	15.8727
TAS266	15.3563
dacarbazine	15.
LDK378	13.
LGW813	11.8934
WNT974	10.5143
LDE225	9.64861

NSCLC

TREATMENT	MEDIAN PFS
BKM120 + binimetinib	48.2917
LCL161 + paclitaxel	44.867
binimetinib	44.
CKX620	39.2113
LFW527 + binimetinib	33.8852
BYL719 + LGH447	29.4859
BYL719	29.199
BKM120	27.9278
LEE011	21.4219
CLR457	20.6389
HSP990	20.5444
erlotinib	17.7047
BYL719 + LJM716	17.2947
paclitaxel	16.4066
cetuximab	12.2685
BGJ398	12.0114
HDM201	11.5531
LLM871	11.2514
LGH447	10.5014
INC280	9.81207
CGM097	9.3506

PDAC

TREATMENT	MEDIAN PFS
BKM120 + binimetinib	81.
abraxane + gemcitabine	69.
INC424 + binimetinib	57.9896
gemcitabine–50mpk	56.6557
trametinib	49.598
BKM120 + LDE225	49.
BYL719 + LJM716	45.
binimetinib	42.5
BYL719	31.4752
CLR457	31.3492
BKM120	29.9033
INC424	21.375
figitumumab" + binimetinib	18.6923
HDM201	18.
binimetinib–3.5mpk	17.9727
figitumumab"	14.6985
LEE011	14.3836
abraxane	13.3648
WNT974	13.
LKA136	12.8324

Colorectal

TREATMENT	MEDIAN PFS
BYL719 + binimetinib	80.5
BYL719 + LJM716	41.5856
CKX620	39.
CLR457	35.025
BKM120	33.672
5FU	33.
LFW527 + binimetinib	32.
BYL719 + cetuximab	30.9429
LEE011	29.8579
binimetinib	29.
BYL719 + encorafenib	27.2993
BYL719	26.8373
cetuximab + encorafenib	25.5769
BYL719 + cetuximab + encorafenib	23.7784
BKM120 + LJC049	20.6329
HDM201	20.
cetuximab	19.7589
CGM097	18.6156
encorafenib	16.0112
LKA136	15.8476
LJC049	10.9904

Breast

TREATMENT	MEDIAN PFS
LEE011 + everolimus	65.
LFW527 + everolimus	47.9
BYL719 + LEE011	44.8907
BKM120	42.1975
paclitaxel	39.8904
CLR457	39.6854
BYL719 + LJM716	39.2308
binimetinib	33.
BYL719	32.3291
LEE011	29.2333
LLM871	26.2441
LJM716 + trastuzumab	22.7896
INC424	20.3782
LJM716	19.9209
BGJ398	19.4676
HDM201	17.6364
trastuzumab	16.3251
LKA136	16.2286
tamoxifen	14.6181
LFA102	14.6137
CGM097	13.2736

Gastric

TREATMENT	MEDIAN PFS
BYL719	38.
LEE011 + everolimus	36.8115
BKM120	33.8184
BYL719 + LJM716	33.
everolimus	33.
BYL719 + HSP990	31.5
LEE011	31.
binimetinib	30.9378
CLR457	30.
HDM201	20.2509
LJM716 + trastuzumab	20.2435
INC280 + trastuzumab	19.8238
LLM871	18.5009
trastuzumab	18.1769
HSP990	17.8971
BGJ398	17.6537
INC280	17.3916
LJM716	17.3281
figitumumab"	14.8645

```
(* a comparison between the best "one-size-fits-all" therapy and personalized
 therapy is necessarily limited to those xenografts that were tested with the
 aforementioned best therapy. Here we calculate a list of PDX models eligible for
 such a comparison *)
ModelsPerIndicationReceivingBestTherapy =
  Table[Select[PDXclinicaltrialresponses,
     And[MemberQ[AllModelGroups[[indication]], #[[1]]],
       #[[2]] == MedianPFSByTherapyByIndication[[indication, 1, 1]] &], {indication, 1, 6, 1}][[
   All, All, 1]];
(* 208 PDX models out of 230 'well-
 covered' PDX models in total are eligible for this analysis *)
Length[Flatten[ModelsPerIndicationReceivingBestTherapy]]
```

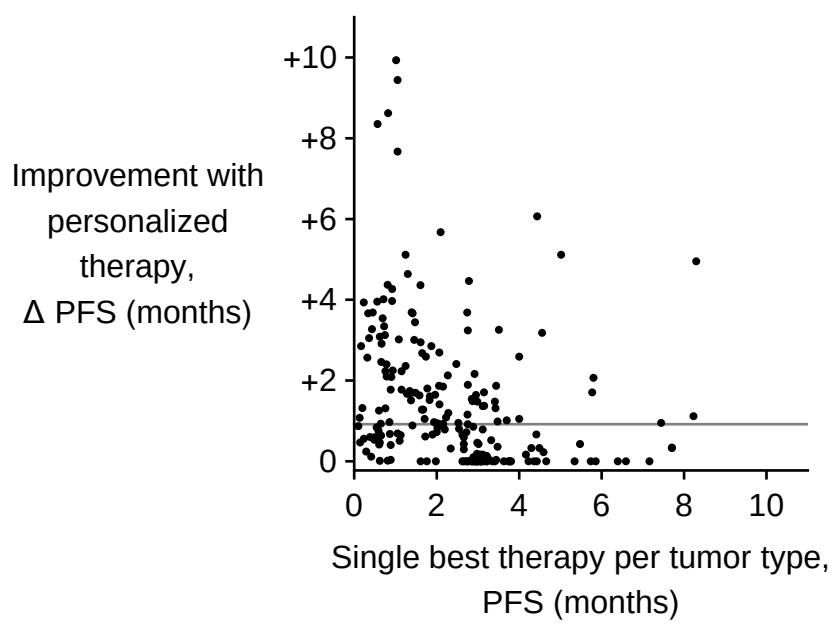
```
208
```

```
(* within this set of 208 PDX models,
finding their PFS on the single best therapy per tumor type *)
PFSPerIndicationOnBestTherapy =
  Table[
   Table[
    Select[PDXclinicaltrialresponses,
      And[#[[1]] == ModelsPerIndicationReceivingBestTherapy[[indication, model]],
        #[[2]] == MedianPFSByTherapyByIndication[[indication, 1, 1]] &][[1, 9]],
     {model, 1, Length[ModelsPerIndicationReceivingBestTherapy[[indication]]]}],
   {indication, 1, 6}];

(* For each individual PDX, what is the longest PFS acheived by any tested treatment? *)
OtherBestPFSPerIndication =
  Table[
   Table[
    Max[Select[PDXclinicaltrialresponses,
       And[#[[1]] == ModelsPerIndicationReceivingBestTherapy[[indication, model]]] &][[All, 9]]],
     {model, 1, Length[ModelsPerIndicationReceivingBestTherapy[[indication]]]}],
   {indication, 1, 6}];
```

```
(* on the horizontal axis is PFS in months (30.5 days per month) with the single
 best therapy per tumor type,
and on the vertical axis is how much better they are observed to respond with any other therapy.
   Points with a vertical coordinate of zero are those that respond better to the best-
 overall therapy than to any other.
   A horizontal line is drawn at 4 weeks.
*)
ListPlot[
 {Flatten[PFSPerIndicationOnBestTherapy],
   Flatten[OtherBestPFSPerIndication] - Flatten[PFSPerIndicationOnBestTherapy]}^T,
 AspectRatio → 1, PlotRange → {{0, 30.5 * 11}, {-7, 30.5 * 11}},
 (*Prolog→{GrayLevel[0.5],Dashing[{0.04,0.025}],Thickness[Medium],Line[{{0,0},{400,400}}],
   (*Line[{{0,0+14},{400,400+14}}]*)},*)
 Prolog → {GrayLevel[0.5], Dashing[None], Thickness[Medium], Line[{{0, 28}, {400, 28}}]},
 PlotRangePadding → None, Frame → {{True, False}, {True, False}},
 FrameStyle → Directive[Black, Thickness[Medium]],
 BaseStyle → {FontFamily → "Arial", FontSize → 12}, Axes → False,
 FrameTicks →
  {{Table[{i, If[i == 0, 0, "+" <> ToString[i / (61 / 2)]]}, {0, 0.02}}, {i, 0, 400, 61}], None},
   {Table[{i, i / (61 / 2)}, {0, 0.02}}, {i, 0, 400, 61}], None}},
 PlotStyle → Directive[Black, AbsolutePointSize[3]],
 FrameLabel → {"Single best therapy per tumor type,\nPFS (months)",
   Rotate["Improvement with\npersonalized\ntherapy,\nΔ PFS (months)", -π / 2]},
 ImagePadding → {{150, 20}, {70, 10}}, ImageSize → {{1000}, {250}}]

Export[NotebookDirectory[] <> "Supplementary Figure S3A, Benefit of personalized therapy.pdf",
  %, "PDF"];
```



How many tumors have a sizeable benefit to ‘precision’ therapy? This is defined here as having a more durable response to the retrospectively chosen best personal treatment, as compared to the best overall therapy for that tumor type.

```
DifferencesBetweenOneSizeFitsAllAndPersonalizedPFS =
  Flatten[PFSPerIndicationOnBestTherapy] - Flatten[OtherBestPFSPerIndication];
```

```
Print[
 "Percentage of tumors that are ideally treated by the overall best treatment per
   tumor type (not more than four weeks benefit with any other treatment)"]
100 * Length[Select[DifferencesBetweenOneSizeFitsAllAndPersonalizedPFS, # >= -28 &]] /
   Length[DifferencesBetweenOneSizeFitsAllAndPersonalizedPFS] // N

Print[
 "Percentage of tumors that survive at least four weeks longer on some treatment
   other than the overall best treatment per tumor type"]
100 * Length[Select[DifferencesBetweenOneSizeFitsAllAndPersonalizedPFS, # < -28 &]] /
   Length[DifferencesBetweenOneSizeFitsAllAndPersonalizedPFS] // N
```

```
Percentage of tumors that are ideally treated by the overall best
  treatment per tumor type (not more than four weeks benefit with any other treatment)

49.0385

Percentage of tumors that survive at least four weeks
  longer on some treatment other than the overall best treatment per tumor type

50.9615
```

How large is this benefit on average?

```
Print[
 "What is the typical benefit of personalized therapy compared to the overall best
   therapy per indication? (for tumors with at least 4 weeks benefit on some
   treatment other than overall best treatment per tumor type)"]
Print[
 ToString[Round[-Mean[Select[DifferencesBetweenOneSizeFitsAllAndPersonalizedPFS, # < -28 &]]]] <>
  " days"]

Print[
 "≈ " <>
  ToString[Round[-Mean[Select[DifferencesBetweenOneSizeFitsAllAndPersonalizedPFS, # < -28 &]] /
     7]] <> " weeks"]
```

```
What is the typical benefit of personalized therapy compared
  to the overall best therapy per indication? (for tumors with at least 4 weeks
  benefit on some treatment other than overall best treatment per tumor type)

82 days

≈ 12 weeks
```

In PDX data, what benefit from multi-drug combinations is expected by independent action?

```
MedianPFSByMonotherapyByIndication =
  Table[
   Sort[Table[{MonotherapiesByGroup[[indication, therapy]],
      Median[Select[PDXclinicaltrialresponses,
         And[MemberQ[AllModelGroups[[indication]], #[[1]]],
           #[[2]] == MonotherapiesByGroup[[indication, therapy]] &][[All, 9]]]},
     {therapy, 1, Length[MonotherapiesByGroup[[indication]]]}], #1[[2]] > #2[[2]] &],
   {indication, 1, 6}];

MedianPFSByMonotherapyByIndication[[1, 1]]
```

```
{binimetinib, 34.6222}
```

```
ResponsesPerIndicationOnBestOneDrug =
  Table[
   Select[PDXclinicaltrialresponses,
     And[MemberQ[AllModelGroups[[tumortype]], #[[1]]],
       #[[2]] == MedianPFSByMonotherapyByIndication[[tumortype, 1, 1]] &][[All, 9]],
    {tumortype, 1, 6}];

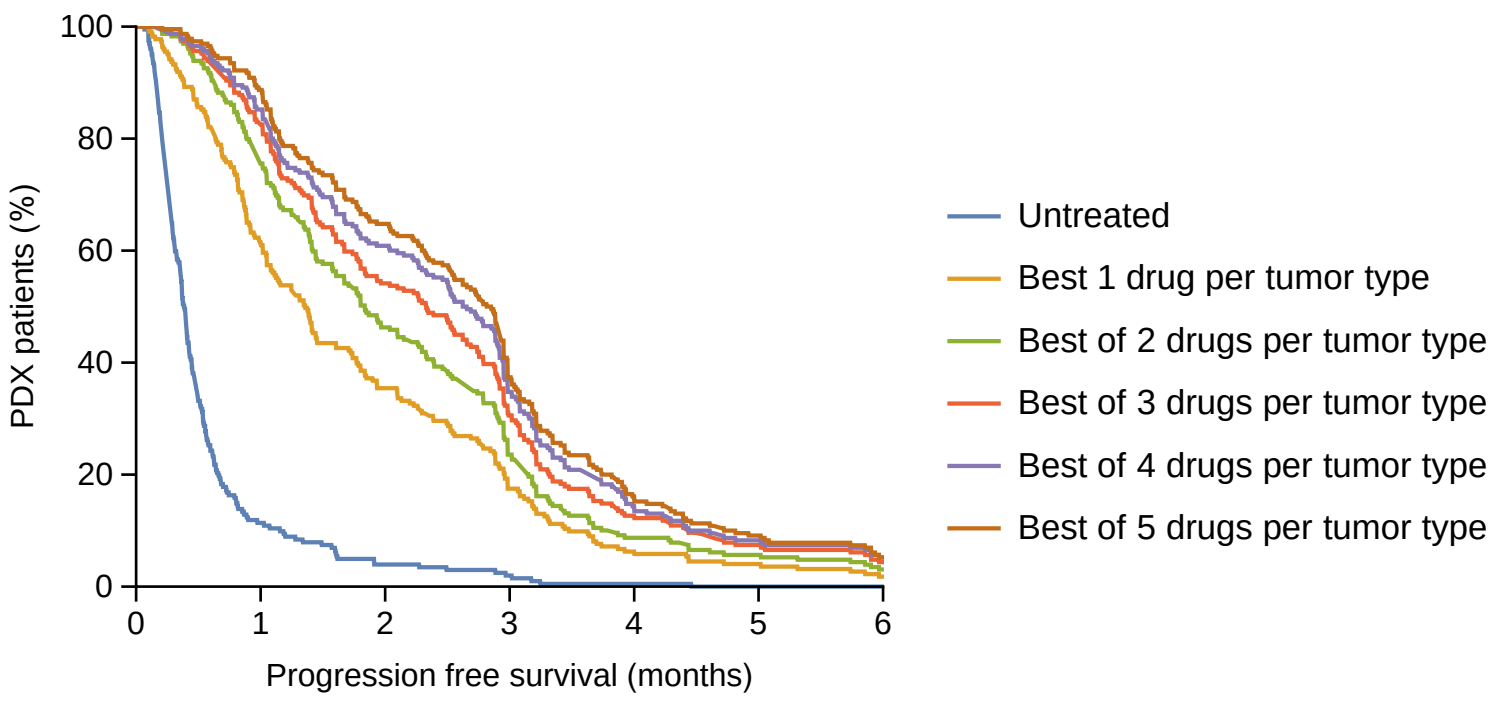
(* this function takes a specific PDX model and a specific drug,
and returns the measured PFS when that drug was tested on that PDX,
or returns 'Null' if no such test exists in the data *)
FindTumorsResponseToDrug[PDXmodel_, drug_] := Module[{},
  (* search for a specific PDX model's response to a specific drug *)
  selection = Select[PDXclinicaltrialresponses, And[#[[1]] == PDXmodel, #[[2]] == drug] &];
  (* if no data found, return nothing *)
  If[selection == {}, Return[]];
  (* if data found, return the 9th column, which is TimeToDouble, i.e,
  duration of progression free survival *)
  selection[[1, 9]]
 ]

(* this function takes a specific PDX model and a list of drug,
and returns the best PFS observed in that PDX model from any drug in the specified
 list of drugs. This function returns 'Null' if none of the specified drugs were
 tested on that PDX. *)
FindTumorsBestResponseToDrugList[PDXmodel_, druglist_] := Module[{},
  ListOfResponses = Table[FindTumorsResponseToDrug[PDXmodel, drug], {drug, druglist}];
  (* select all cases where the drug was actually tested on the PDX
   (i.e, the entry is not 'Null'). This is acheived by testing if each entry is a number,
  using the 'NumberQ' function *)
  MeasuredResponses = Select[ListOfResponses, NumberQ[#] &];
  (* if there is no data, return Null *)
  If[MeasuredResponses == {}, Return[]];
  (* if data is found, return the longest measured PFS *)
  Max[MeasuredResponses]
 ]

(* this function takes a particular tumor type
 (as a number from 1 to 6; from melanoma to gastric cancer), and a list of drugs,
and returns a list over PDX models of each PDXs best observed response to any drug
 in the specified list *)
BestResponsesInTumorTypeToDrugList[tumortype_, druglist_] := Module[{},
  ListOfAllResponses =
   Table[FindTumorsBestResponseToDrugList[AllModelGroups[[tumortype, tumornumber]], druglist],
    {tumornumber, 1, Length[AllModelGroups[[tumortype]]]}];
  (* when a particular PDX model was not tested in any of the specified drugs,
  there is an entry of 'Null'. In the next step we select all cases where a xenograft
   was tested on at least one drug in the list,
  by selecting entries which are not 'Null'. This is acheived by testing if each
   entry is a number, using the 'NumberQ' function *)
  Select[ListOfAllResponses, NumberQ[#] &]
 ]
```

```
(* responses when untreated *)
ResponsesWhenUntreated =
  Flatten[Table[BestResponsesInTumorTypeToDrugList[tumortype, {"untreated"}],
    {tumortype, 1, 6}]];
(* Responses for each PDX when treated with the best monotherapy for that tumor type,
according to its median PFS *)
ResponsesOnBestOneDrugPerTumorType =
  Flatten[Table[BestResponsesInTumorTypeToDrugList[tumortype,
     {MedianPFSByMonotherapyByIndication[[tumortype, 1, 1]]}], {tumortype, 1, 6}]];
(* Best responses for each PDX when treated with either of the top two monotherapies
 for that tumor type, according to their median PFS *)
ResponsesOnBestTwoDrugsPerTumorType =
  Flatten[Table[BestResponsesInTumorTypeToDrugList[tumortype,
     {MedianPFSByMonotherapyByIndication[[tumortype, 1, 1]],
      MedianPFSByMonotherapyByIndication[[tumortype, 2, 1]]}], {tumortype, 1, 6}]];
(* Best responses for each PDX when treated with either of the top three monotherapies
 for that tumor type, according to their median PFS *)
ResponsesOnBestThreeDrugsPerTumorType =
  Flatten[Table[BestResponsesInTumorTypeToDrugList[tumortype,
     {MedianPFSByMonotherapyByIndication[[tumortype, 1, 1]],
      MedianPFSByMonotherapyByIndication[[tumortype, 2, 1]],
      MedianPFSByMonotherapyByIndication[[tumortype, 3, 1]]}], {tumortype, 1, 6}]];
(* Best responses for each PDX when treated with either of the top four monotherapies
 for that tumor type, according to their median PFS *)
ResponsesOnBestFourDrugsPerTumorType =
  Flatten[Table[BestResponsesInTumorTypeToDrugList[tumortype,
     {MedianPFSByMonotherapyByIndication[[tumortype, 1, 1]],
      MedianPFSByMonotherapyByIndication[[tumortype, 2, 1]],
      MedianPFSByMonotherapyByIndication[[tumortype, 3, 1]],
      MedianPFSByMonotherapyByIndication[[tumortype, 4, 1]]}], {tumortype, 1, 6}]];
(* Best responses for each PDX when treated with either of the top five monotherapies
 for that tumor type, according to their median PFS *)
ResponsesOnBestFiveDrugsPerTumorType =
  Flatten[Table[BestResponsesInTumorTypeToDrugList[tumortype,
     {MedianPFSByMonotherapyByIndication[[tumortype, 1, 1]],
      MedianPFSByMonotherapyByIndication[[tumortype, 2, 1]],
      MedianPFSByMonotherapyByIndication[[tumortype, 3, 1]],
      MedianPFSByMonotherapyByIndication[[tumortype, 4, 1]],
      MedianPFSByMonotherapyByIndication[[tumortype, 5, 1]]}], {tumortype, 1, 6}]];
```

```
Plot[{
  SurvivalFunction[EmpiricalDistribution[ResponsesWhenUntreated]][t],
  SurvivalFunction[EmpiricalDistribution[ResponsesOnBestOneDrugPerTumorType]][t],
  SurvivalFunction[EmpiricalDistribution[ResponsesOnBestTwoDrugsPerTumorType]][t],
  SurvivalFunction[EmpiricalDistribution[ResponsesOnBestThreeDrugsPerTumorType]][t],
  SurvivalFunction[EmpiricalDistribution[ResponsesOnBestFourDrugsPerTumorType]][t],
  SurvivalFunction[EmpiricalDistribution[ResponsesOnBestFiveDrugsPerTumorType]][t]
 }, {t, 0, 7 * 30.5}, Exclusions → None, PlotRange → {{0, 6 * 30.5}, {0, 1}},
 PlotRangePadding → None, PlotPoints → 50, Frame → {{True, False}, {True, False}},
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {{Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}], None},
   {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 330, 61 / 2}], None}},
 FrameLabel → {"Progression free survival (months)", "PDX patients (%)"},
 ImageSize → {{1000}, {280}}, ImagePadding → {{60, 10}, {60, 10}}, AspectRatio → 3 / 4,
 PlotLegends → {"Untreated", "Best 1 drug per tumor type", "Best of 2 drugs per tumor type",
   "Best of 3 drugs per tumor type", "Best of 4 drugs per tumor type",
   "Best of 5 drugs per tumor type"}]
```




```
(* hazard ratio by Cox Model, best 1 drug versus untreated *)
myeventdata = EventData[Join[ResponsesWhenUntreated, ResponsesOnBestOneDrugPerTumorType],
   Table[0, {Length[Join[ResponsesWhenUntreated, ResponsesOnBestOneDrugPerTumorType]]}]];
descriptors = Join[Table["no treatment", {Length[ResponsesWhenUntreated]}],
   Table["top 1 drug", {Length[ResponsesOnBestOneDrugPerTumorType]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
Best1DrugRelativeRisk = MyModelFit["RelativeRisk"][[1]]
Best1DrugRiskInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1]]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[top 1 drug]	−1.29351	0.105813	0.274306	149.439	1	2.29914×10^{-34}

```
0.274306
```

```
{0.222929, 0.337522}
```

```
(* hazard ratio by Cox Model, best 2 drugs versus best 1 drug *)
myeventdata =
  EventData[Join[ResponsesOnBestOneDrugPerTumorType, ResponsesOnBestTwoDrugsPerTumorType],
   Table[0,
    {Length[Join[ResponsesOnBestOneDrugPerTumorType, ResponsesOnBestTwoDrugsPerTumorType]]}]];
descriptors = Join[Table["top 1 drug", {Length[ResponsesOnBestOneDrugPerTumorType]}],
   Table["top 2 drugs", {Length[ResponsesOnBestTwoDrugsPerTumorType]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
Best2DrugsRelativeRisk = MyModelFit["RelativeRisk"][[1]]
Best2DrugsRiskInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1]]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[top 2 drugs]	−0.237587	0.0943027	0.788528	6.34743	1	0.0117551

```
0.788528
```

```
{0.655461, 0.94861}
```

```
(* hazard ratio by Cox Model, best 3 drugs versus best 2 drugs *)
myeventdata =
  EventData[Join[ResponsesOnBestTwoDrugsPerTumorType, ResponsesOnBestThreeDrugsPerTumorType],
   Table[0,
    {Length[Join[ResponsesOnBestTwoDrugsPerTumorType,
       ResponsesOnBestThreeDrugsPerTumorType]]}]];
descriptors = Join[Table["top 2 drugs", {Length[ResponsesOnBestTwoDrugsPerTumorType]}],
   Table["top 3 drugs", {Length[ResponsesOnBestThreeDrugsPerTumorType]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
Best3DrugsRelativeRisk = MyModelFit["RelativeRisk"][[1]]
Best3DrugsRiskInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1]]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[top 3 drugs]	−0.172433	0.0936413	0.841615	3.39081	1	0.0655608

```
0.841615
```

```
{0.700496, 1.01116}
```

```
(* hazard ratio by Cox Model, best 4 drugs versus best 3 drugs *)
myeventdata =
  EventData[Join[ResponsesOnBestThreeDrugsPerTumorType, ResponsesOnBestFourDrugsPerTumorType],
   Table[0,
    {Length[Join[ResponsesOnBestThreeDrugsPerTumorType,
       ResponsesOnBestFourDrugsPerTumorType]]}]];
descriptors = Join[Table["top 3 drugs", {Length[ResponsesOnBestThreeDrugsPerTumorType]}],
   Table["top 4 drugs", {Length[ResponsesOnBestFourDrugsPerTumorType]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
Best4DrugsRelativeRisk = MyModelFit["RelativeRisk"][[1]]
Best4DrugsRiskInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1]]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[top 4 drugs]	−0.101175	0.0934094	0.903775	1.17318	1	0.27875

```
0.903775
```

```
{0.752576, 1.08535}
```

```
(* hazard ratio by Cox Model, best 5 drugs versus best 4 drugs *)
myeventdata =
  EventData[Join[ResponsesOnBestFourDrugsPerTumorType, ResponsesOnBestFiveDrugsPerTumorType],
   Table[0,
    {Length[Join[ResponsesOnBestFourDrugsPerTumorType,
       ResponsesOnBestFiveDrugsPerTumorType]]}]];
descriptors = Join[Table["top 4 drugs", {Length[ResponsesOnBestFourDrugsPerTumorType]}],
   Table["top 5 drugs", {Length[ResponsesOnBestFiveDrugsPerTumorType]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
Best5DrugsRelativeRisk = MyModelFit["RelativeRisk"][[1]]
Best5DrugsRiskInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1]]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[top 5 drugs]	−0.0622574	0.0932634	0.939641	0.445614	1	0.504425

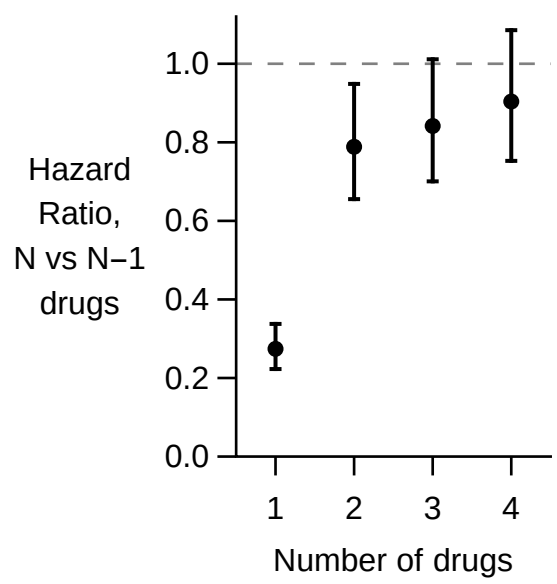
```
0.939641
```

```
{0.782665, 1.1281}
```

```
(* loading package *)
Needs["ErrorBarPlots`"]
```

```
ErrorListPlot[{
  {{1, Best1DrugRelativeRisk},
   ErrorBar[{Best1DrugRiskInterval[[2]] - Best1DrugRelativeRisk,
     Best1DrugRiskInterval[[1]] - Best1DrugRelativeRisk}]},
  {{2, Best2DrugsRelativeRisk},
   ErrorBar[{Best2DrugsRiskInterval[[2]] - Best2DrugsRelativeRisk,
     Best2DrugsRiskInterval[[1]] - Best2DrugsRelativeRisk}]},
  {{3, Best3DrugsRelativeRisk},
   ErrorBar[{Best3DrugsRiskInterval[[2]] - Best3DrugsRelativeRisk,
     Best3DrugsRiskInterval[[1]] - Best3DrugsRelativeRisk}]},
  {{4, Best4DrugsRelativeRisk},
   ErrorBar[{Best4DrugsRiskInterval[[2]] - Best4DrugsRelativeRisk,
     Best4DrugsRiskInterval[[1]] - Best4DrugsRelativeRisk}]}
 }, PlotRange → {{0.5, 4.5}, {0, 1.12}}, Frame → {{True, False}, {True, False}},
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {{Table[{i, NumberForm[i, {2, 1}], {0, 0.06}}, {i, 0, 1.2, 0.2}], None},
   {Table[{i, i, {0, 0.06}}, {i, 1, 5, 1}], None}},
 FrameLabel → {"Number of drugs", Rotate["Hazard\nRatio,\nN vs N-1\ndrugs", -π / 2]},
 ImageSize → {{1000}, {225}}, ImagePadding → {{90, 10}, {50, 10}}, AspectRatio → 1.4,
 Prolog → {Thickness[Medium], Dashing[{0.05, 0.05}], Gray, Line[{{0.5, 1}, {5.5, 1}}]},
 PlotStyle → Directive[Black, AbsolutePointSize[6], AbsoluteThickness[1.5]]]

Export[NotebookDirectory[] <>
   "Figure 3D, Hazard ratios of multidrug combinations in PDX data.pdf", %, "PDF"];
```



Is there a benefit to 'personalized' or 'precision' therapy, compared to 'one-size-fits-all' therapy?

This is next addressed in terms of response criteria:

PD = progressive disease

SD = stable disease

PR = partial response

CR = complete response

```
(* what is each PDXs response criteria when treated with the best overall treatment
 per tumor type? *)
ResponseCriteriaPerIndicationOnBestTherapy =
  Table[
   Table[
    Select[PDXclinicaltrialresponses,
      And[#[[1]] == ModelsPerIndicationReceivingBestTherapy[[indication, model]],
        #[[2]] == MedianPFSByTherapyByIndication[[indication, 1, 1]] &][[1, -1]],
     {model, 1, Length[ModelsPerIndicationReceivingBestTherapy[[indication]]]}],
   {indication, 1, 6}];

(* a list of all response criteria acheived by each PDX model *)
AllResponseCriteriaPerModelPerIndication =
  Table[
   Table[
    Select[PDXclinicaltrialresponses,
      And[#[[1]] == ModelsPerIndicationReceivingBestTherapy[[indication, model]]] &][[All, -1]],
     {model, 1, Length[ModelsPerIndicationReceivingBestTherapy[[indication]]]}],
   {indication, 1, 6}];

(* this function takes a list of observed response criteria and returns the
 strongest / best response *)
BestResponseOfSet[listofresponsetypes_] := Module[{},
  InitialResponse = Map[StringTake[#, 2] &, listofresponsetypes];
  ReponsesAsNumbers = InitialResponse /. {"CR" → 3, "PR" → 2, "SD" → 1, "PD" → 0};
  BestResponseAsNumber = Max[ReponsesAsNumbers];
  BestResponseType = (BestResponseAsNumber /. {3 → "CR", 2 → "PR", 1 → "SD", 0 → "PD"})
 ]

(* what is the best response observed with any treatment for each PDX model? *)
BestResponseCriteriaPerModelPerIndication =
  Map[BestResponseOfSet, AllResponseCriteriaPerModelPerIndication, {2}];

(* Responses are tabulated in Gao et al, Nature Medicine, with sub-classifications,
like SD --> PD (initially stable, later progressing) and SD -->
 --> PD (initially stable, much later progressing). Here we take just the first
    two characters to determine the 'major' or initial response criteria *)
MajorResponseCategoryPerIndicationOnBestTherapy =
  Map[StringTake[#, 2] &, ResponseCriteriaPerIndicationOnBestTherapy, {2}];

(* How many steps in response criteria is the benefit of personalized therapy? *)
NumberOfmRECISTcriteriaDifferentBetweenBestResponseAndBestTherapy =
  (MajorResponseCategoryPerIndicationOnBestTherapy /. {"PD" → 0, "SD" → 1, "PR" → 2, "CR" → 3}) -
   (BestResponseCriteriaPerModelPerIndication /. {"PD" → 0, "SD" → 1, "PR" → 2, "CR" → 3});
```

```
(* Given a list of responses,
returns a table with the fraction of responses in each criteria (PD, SD, PR, CR) *)
HowManyResponses[listofresponses_] := Module[{},
  FirstTwoCharacters = Map[StringTake[#, 2] &, listofresponses];
  NumberOfConditions = Length[listofresponses];
  FractionOfProgressiveDisease = Length[Select[FirstTwoCharacters, # == "PD" &]] /
    NumberOfConditions;
  FractionOfStableDisease = Length[Select[FirstTwoCharacters, # == "SD" &]] / NumberOfConditions;
  FractionOfPartialResponses = Length[Select[FirstTwoCharacters, # == "PR" &]] /
    NumberOfConditions;
  FractionOfCompleteResponses = Length[Select[FirstTwoCharacters, # == "CR" &]] /
    NumberOfConditions;

  {FractionOfProgressiveDisease, FractionOfStableDisease, FractionOfPartialResponses,
   FractionOfCompleteResponses}
 ]
```

The rate of partial or complete response is 2.2× higher with 'personalized' therapy than with 'one-size-fits-all' therapy, and the rate of complete response is 5.8× higher:

```
Print[
 "Summing over all PDXs from all indications; what is the response rate (%) with
   the single best therapy per indication?"]
{{"Progressive Disease", "Stable Disease", "Partial Response", "Complete Response"},
   Round[100 * HowManyResponses[Flatten[MajorResponseCategoryPerIndicationOnBestTherapy]],
    0.1]} // N // TableForm
```

```
Summing over all PDXs from all indications; what
  is the response rate (%) with the single best therapy per indication?
```

Progressive Disease	Stable Disease	Partial Response	Complete Response
21.6	47.6	25.5	5.3

```
Print[
 "Summing over all PDXs from all indications; what is the best response (%) acheivable
   with 'personalized' therapy?"]
{{"Progressive Disease", "Stable Disease", "Partial Response", "Complete Response"},
   Round[100 * HowManyResponses[Flatten[BestResponseCriteriaPerModelPerIndication]], 0.1]} // N //
 TableForm
```

```
Summing over all PDXs from all indications;
  what is the best response (%) acheivable with 'personalized' therapy?
```

Progressive Disease	Stable Disease	Partial Response	Complete Response
1.9	26.4	40.9	30.8

Plotting response rate for monotherapies, combination therapies, and random pairs of monotherapies (according to independent drug action)

```
(* A list of drug responses sorted by PDX model *)
ResponsesByModel = Table[Select[PDXclinicaltrialresponses, #[[1]] == WellCoveredModels[[model]] &],
   {model, 1, Length[WellCoveredModels]}];
```

```
(* A list of response criteria produced by each monotherapy in each tumor type
 (this is a table with an entry for each tumor type,
  which then contains lists of responses for each treatment) *)
PerMonotherapyByGroupResponseTypes =
  Table[
   Table[
    Select[PDXclinicaltrialresponses,
      And[MemberQ[AllModelGroups[[indication]], #[[1]]],
        #[[2]] == MonotherapiesByGroup[[indication, TherapiesWithinIndication]] &][[All, 11]],
    {TherapiesWithinIndication, 1, Length[MonotherapiesByGroup[[indication]]]}],
   {indication, 1, Length[AllModelGroups]}];

(* A list of response criteria produced by each combination therapy in each tumor
 type (this is a table with an entry for each tumor type,
  which then contains lists of responses for each treatment) *)
PerCombinationByGroupResponseTypes =
  Table[
   Table[
    Select[PDXclinicaltrialresponses,
      And[MemberQ[AllModelGroups[[indication]], #[[1]]],
        #[[2]] == CombinationTherapiesByGroup[[indication, TherapiesWithinIndication]] &][[All, 11]],
    {TherapiesWithinIndication, 1, Length[CombinationTherapiesByGroup[[indication]]]}],
   {indication, 1, Length[AllModelGroups]}];

(* this function converts a string of response type into an integer, for 1=responding,
0 = not responding,
"CR" = complete response = 1,
"PR" = partial response = 1,
"SD" = stable disease = 1,
"PD" = progressive disease = 0  *)
ResponseOrNot[responsetype_] := If[
  Or[StringTake[responsetype, 2] == "CR", StringTake[responsetype, 2] == "PR",
   StringTake[responsetype, 2] == "SD"], 1, 0]

(* this function takes a list of drug response criteria and reports what fraction
 counted as a 'response' (SD, PR, or CR) *)
ResponseRate[listofresponsetypes_] := Mean[Map[ResponseOrNot, listofresponsetypes]]

(* this function takes a list of observed response criteria and returns the
 strongest / best response *)
BestResponseOfSet[listofresponsetypes_] := Module[{},
  InitialResponse = Map[StringTake[#, 2] &, listofresponsetypes];
  ReponsesAsNumbers = InitialResponse /. {"CR" → 3, "PR" → 2, "SD" → 1, "PD" → 0};
  BestResponseAsNumber = Max[ReponsesAsNumbers];
  BestResponseType = (BestResponseAsNumber /. {3 → "CR", 2 → "PR", 1 → "SD", 0 → "PD"})
 ]
```

```
(* a list of response rates for each monotherapy in each tumor type *)
MonotherapyByGroupResponseRates =
  Table[
   Table[ResponseRate[PerMonotherapyByGroupResponseTypes[[indication,
      TherapiesWithinIndication]]],
    {TherapiesWithinIndication, 1, Length[MonotherapiesByGroup[[indication]]]}],
   {indication, 1, Length[AllModelGroups]}];

(* a list of response rates for each combination therapy in each tumor type *)
CombinationByGroupResponseRates =
  Table[
   Table[ResponseRate[PerCombinationByGroupResponseTypes[[indication,
      TherapiesWithinIndication]]],
    {TherapiesWithinIndication, 1, Length[CombinationTherapiesByGroup[[indication]]]}],
   {indication, 1, Length[AllModelGroups]}];

(* this function takes a tumor type
 (numbered 1 to 6; melanoma, NSCLC, PDAC, CRC, breast, gastric) and two named monotherapies,
and computes the response rate of the hypothetical combination according to independent
 drug action: each individual tumor's response is the better one of its two observed
  responses *)
ResponseRateFromRandomMonotherapyPair[therapy1_, therapy2_, tumortype_] := Module[{},
  Therapy1Responses = Select[PDXclinicaltrialresponses,
    And[MemberQ[AllModelGroups[[tumortype]], #[[1]]], #[[2]] == therapy1] &];
  Therapy2Responses = Select[PDXclinicaltrialresponses,
    And[MemberQ[AllModelGroups[[tumortype]], #[[1]]], #[[2]] == therapy2] &];
  (* For any two monotherapies,
  response rate is necessarily calculated over the PDX models that were tested with
   both therapies *)
  ModelsInIntersection = Intersection[Therapy1Responses[[All, 1]], Therapy2Responses[[All, 1]]];

  Therapy1ResponsesInIntersection =
   Table[Select[Therapy1Responses, #[[1]] == ModelsInIntersection[[model]] &][[1]],
    {model, 1, Length[ModelsInIntersection]}];
  Therapy2ResponsesInIntersection =
   Table[Select[Therapy2Responses, #[[1]] == ModelsInIntersection[[model]] &][[1]],
    {model, 1, Length[ModelsInIntersection]}];

  BestResponsesPerPDX =
   Table[BestResponseOfSet[{Therapy1ResponsesInIntersection[[model, 11]],
      Therapy2ResponsesInIntersection[[model, 11]]}], {model, 1, Length[ModelsInIntersection]}];

  ResponseRate[BestResponsesPerPDX]
 ]

(* this function takes a tumor type (by number, from 1 to 6, as above),
randomly selects two monotherapies from those tested on that tumor type,
and calls the above function to compute the response rate to the hypothetical combination *)
ResponseRateFromOneRandomMonotherapyPair[tumortype_] := Module[{},
  randompair = RandomSample[MonotherapiesByGroup[[tumortype]], 2];
  ResponseRateFromRandomMonotherapyPair[randompair[[1]], randompair[[2]], tumortype]
 ]
```

Different numbers of combination therapies were applied to the different disease indications :

```
Map[Length, CombinationTherapiesByGroup]
```

```
{4, 5, 6, 8, 5, 5}
```

For a fair comparison between the tested combinations and hypothetical combinations of

random pairs of monotherapies, generate random pairs of monotherapies in abundance proportional to the number of combinations tested per disease indication. Otherwise, the comparison could be biased by some tumor types having systematically higher or lower response rates than others.

```
NumberOfRandomPairsToCreatePerIndication = 100 * Map[Length, CombinationTherapiesByGroup]
```

```
{400, 500, 600, 800, 500, 500}
```

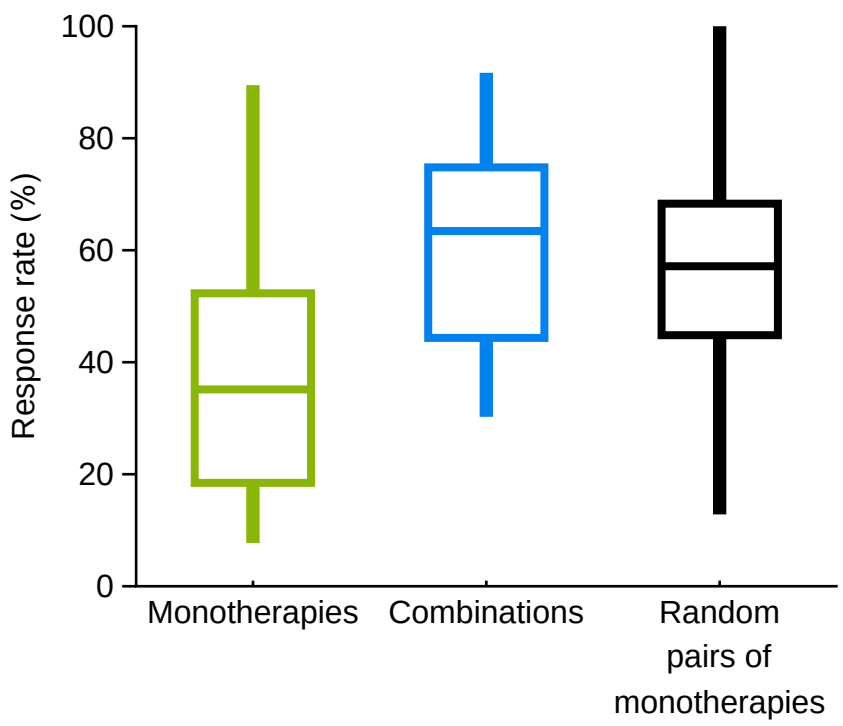
```
(* how many possible combinations are there for each tumor
 type? (list of length 6; one entry per tumor type *)
Map[(Length[#] * (Length[#] - 1) / 2) &, MonotherapiesByGroup]
```

```
{66, 120, 91, 78, 120, 91}
```

Computing response rates for hundreds of random pairs of monotherapies per tumor type; in abundance proportional to the number of combinations tested in each tumor type, as explained above.
Note, this step is time-consuming.

```
(* computing response rates for hundreds of random pairs of monotherapies per tumor type;
in abundance proportional to the number of combinations tested in each tumor type,
as explained above *)
ResponseRatesPerGroupFromRandomMonotherapyPairs =
  Table[Table[ResponseRateFromOneRandomMonotherapyPair[tumortype],
     {NumberOfRandomPairsToCreatePerIndication[[tumortype]]}],
    {tumortype, 1, Length[AllModelGroups]}] // N;
```

```
(* plotting response rates with box-whisker plot *)
ResponseRatePlot = Show[
  BoxWhiskerChart[{Flatten[MonotherapyByGroupResponseRates] // N, {-1}, {-1}},
   {"Median", {"MedianMarker", 1, Directive[ColorData[3, 4], AbsoluteThickness[3]]},
    {"Whiskers", Directive[ColorData[3, 4], AbsoluteThickness[5], CapForm["Butt"]]},
    {"Fences", 0, Opacity[0]}}, PlotRange → {{0.5, 3.5}, {0, 1}}, PlotRangePadding → None,
   ChartStyle → {Directive[White, EdgeForm[Directive[ColorData[3, 4], AbsoluteThickness[3]]]],
     Directive[ColorData[3, 6]], Directive[Black]},
   ChartLabels → {"Monotherapies", "Combinations", "Random\npairs of\nmonotherapies"},
   Frame → {{True, False}, {True, False}}, Axes → False,
   FrameStyle → Directive[Black, Thickness[Medium]],
   BaseStyle → {FontFamily → "Arial", FontSize → 12}, FrameLabel → {, "Response rate (%)"},
   FrameTicks → {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {None, None}},
   AspectRatio → 4 / 5, ImageSize → {{1000}, {280}}, ImagePadding → {{60, 10}, {60, 10}}]
  ,
  BoxWhiskerChart[{{-1}, Flatten[CombinationByGroupResponseRates] // N, {-1}},
   {"Median", {"MedianMarker", 1, Directive[ColorData[3, 6], AbsoluteThickness[3]]},
    {"Whiskers", Directive[ColorData[3, 6], AbsoluteThickness[5], CapForm["Butt"]]},
    {"Fences", 0, Opacity[0]}}, PlotRange → {{0.5, 3.5}, {0, 1}}, PlotRangePadding → None,
   ChartStyle → {Directive[ColorData[3, 4]],
     Directive[White, EdgeForm[Directive[ColorData[3, 6], AbsoluteThickness[3]]]],
     Directive[Black]},
   ChartLabels → {"Monotherapies", "Combinations", "Random pairs of\nmonotherapies"},
   Frame → {{True, False}, {True, False}}, Axes → False,
   FrameStyle → Directive[Black, Thickness[Medium]],
   BaseStyle → {FontFamily → "Arial", FontSize → 12}, FrameLabel → {, "Response rate (%)"},
   FrameTicks → {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {None, None}},
   AspectRatio → 4 / 5, ImageSize → {{1000}, {280}}, ImagePadding → {{60, 10}, {60, 10}}]
  ,
  BoxWhiskerChart[{{-1}, {-1}, Flatten[ResponseRatesPerGroupFromRandomMonotherapyPairs]},
   {"Median", {"MedianMarker", 1, Directive[Black, AbsoluteThickness[3]]},
    {"Whiskers", Directive[Black, AbsoluteThickness[5], CapForm["Butt"]]},
    {"Fences", 0, Opacity[0]}}, PlotRange → {{0.5, 3.5}, {0, 1}}, PlotRangePadding → None,
   ChartStyle → {Directive[ColorData[3, 4]], Directive[ColorData[3, 6]],
     Directive[White, EdgeForm[Directive[Black, AbsoluteThickness[3]]]]},
   ChartLabels → {"Monotherapies", "Combinations", "Random pairs of\nmonotherapies"},
   Frame → {{True, False}, {True, False}}, Axes → False,
   FrameStyle → Directive[Black, Thickness[Medium]],
   BaseStyle → {FontFamily → "Arial", FontSize → 12}, FrameLabel → {, "Response rate (%)"},
   FrameTicks → {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {None, None}},
   AspectRatio → 4 / 5, ImageSize → {{1000}, {280}}, ImagePadding → {{60, 10}, {60, 10}}]
]
```



Statistical tests for differences in response rates by Kolomorov-Smirnov tests

```
(* monotherapies vs combinations *)
KolmogorovSmirnovTest[Flatten[MonotherapyByGroupResponseRates],
 Flatten[CombinationByGroupResponseRates], "PValueTable"]
```

```
(* random pairs of monotherapies vs combinations *)
KolmogorovSmirnovTest[Flatten[ResponseRatesPerGroupFromRandomMonotherapyPairs],
 Flatten[CombinationByGroupResponseRates], "PValueTable"]
```

```
(* monotherapies vs random pairs of monotherapies *)
KolmogorovSmirnovTest[Flatten[ResponseRatesPerGroupFromRandomMonotherapyPairs],
 Flatten[MonotherapyByGroupResponseRates], "PValueTable"]
```

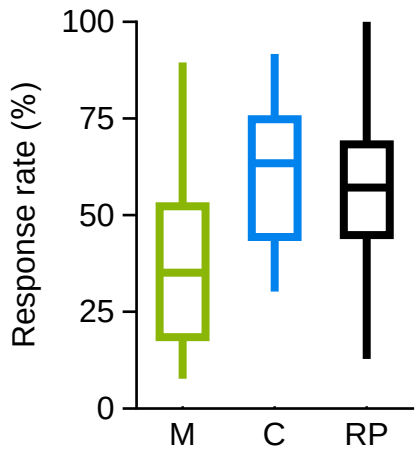
	P-Value
Kolmogorov-Smirnov	6.42957×10^{-6}

	P-Value
Kolmogorov-Smirnov	0.3436

	P-Value
Kolmogorov-Smirnov	9.37028×10^{-14}

Plot of response rates sized for publication:

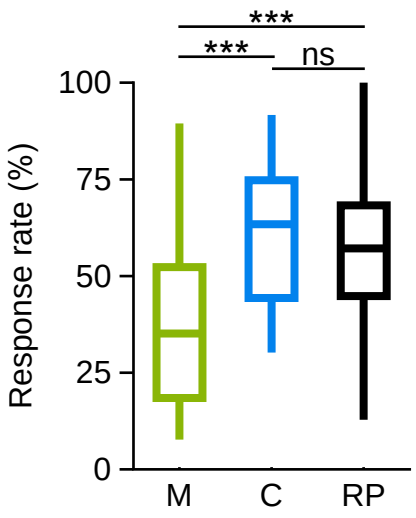
```
ResponseRatePlot = Show[
  BoxWhiskerChart[{Flatten[MonotherapyByGroupResponseRates] // N, {-1}, {-1}},
   {"Median", {"MedianMarker", 1, Directive[ColorData[3, 4], AbsoluteThickness[3]]},
    {"Whiskers", Directive[ColorData[3, 4], AbsoluteThickness[3], CapForm["Butt"]]},
    {"Fences", 0, Opacity[0]}}, PlotRange → {{0.5, 3.5}, {0, 1}}, PlotRangePadding → None,
   ChartStyle → {Directive[White, EdgeForm[Directive[ColorData[3, 4], AbsoluteThickness[3]]]],
     Directive[ColorData[3, 6]], Directive[Black]}, ChartLabels → {"M", "C", "RP"},
   Frame → {{True, False}, {True, False}}, Axes → False,
   FrameStyle → Directive[Black, Thickness[Medium]],
   BaseStyle → {FontFamily → "Arial", FontSize → 12}, FrameLabel → {, "Response rate (%)"},
   FrameTicks → {{Table[{i, 100 * i, {0, 0.05}}, {i, 0, 1, 1 / 4}], None}, {None, None}},
   AspectRatio → 1.4, ImageSize → {{1000}, {225}}, ImagePadding → {{50, 10}, {50, 30}}]
  ,
  BoxWhiskerChart[{{-1}, Flatten[CombinationByGroupResponseRates] // N, {-1}},
   {"Median", {"MedianMarker", 1, Directive[ColorData[3, 6], AbsoluteThickness[3]]},
    {"Whiskers", Directive[ColorData[3, 6], AbsoluteThickness[3], CapForm["Butt"]]},
    {"Fences", 0, Opacity[0]}}, PlotRange → {{0.5, 3.5}, {0, 1}}, PlotRangePadding → None,
   ChartStyle → {Directive[ColorData[3, 4]],
     Directive[White, EdgeForm[Directive[ColorData[3, 6], AbsoluteThickness[3]]]],
     Directive[Black]},
   ChartLabels → {"Monotherapies", "Combinations", "Random pairs of\nmonotherapies"},
   Frame → {{True, False}, {True, False}}, Axes → False,
   FrameStyle → Directive[Black, Thickness[Medium]],
   BaseStyle → {FontFamily → "Arial", FontSize → 12}, FrameLabel → {, "Response rate (%)"},
   FrameTicks → {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {None, None}},
   AspectRatio → 1.4, ImageSize → {{1000}, {225}}, ImagePadding → {{50, 10}, {50, 30}}]
  ,
  BoxWhiskerChart[{{-1}, {-1}, Flatten[ResponseRatesPerGroupFromRandomMonotherapyPairs]},
   {"Median", {"MedianMarker", 1, Directive[Black, AbsoluteThickness[3]]},
    {"Whiskers", Directive[Black, AbsoluteThickness[3], CapForm["Butt"]]},
    {"Fences", 0, Opacity[0]}}, PlotRange → {{0.5, 3.5}, {0, 1}}, PlotRangePadding → None,
   ChartStyle → {Directive[ColorData[3, 4]], Directive[ColorData[3, 6]],
     Directive[White, EdgeForm[Directive[Black, AbsoluteThickness[3]]]]},
   ChartLabels → {"Monotherapies", "Combinations", "Random pairs of\nmonotherapies"},
   Frame → {{True, False}, {True, False}}, Axes → False,
   FrameStyle → Directive[Black, Thickness[Medium]],
   BaseStyle → {FontFamily → "Arial", FontSize → 12}, FrameLabel → {, "Response rate (%)"},
   FrameTicks → {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {None, None}},
   AspectRatio → 1.4, ImageSize → {{1000}, {225}}, ImagePadding → {{50, 10}, {50, 30}}]
  ]
```



```
line1pos = 0.368;
line2pos = 0.446;
line3pos = 0.521;
line1h = 0.37 + 0.035;
line2h = 0.36 + 0.035;
line3h = 0.395 + 0.035;

ResponseComposite =
 Show[Graphics[{Inset[ResponseRatePlot, {0.4, 0.2}, Automatic, 1]} ~Join~
    {Black, Opacity[1], FontSize → 12, FontFamily → "Arial", Thickness[Medium],
     Line[{{line1pos, line1h}, {line2pos, line1h}}],
     Line[{{line2pos, line2h}, {line3pos, line2h}}],
     Line[{{line1pos, line3h}, {line3pos, line3h}}],
     Text["***", {line1pos / 2 + line2pos / 2, line1h}, {0, -0.7}],
     Text["***", {line1pos / 2 + line3pos / 2, line3h}, {0, -0.7}],
     Text["ns", {line2pos / 2 + line3pos / 2, line2h}, {0, -0.8}]} ~Join~
    {Opacity[0.1], White, EdgeForm[None]} ~Join~
    Flatten[Table[{Opacity[0.1 + i * 10], Rectangle[{0.65, 0.43 + i}, {0.7, 0.5}]},
      {i, 0, 0.06, 0.003}]], PlotRange → {{0.2, 0.7}, {0, 0.5}}], ImageSize → {{1000}, {225}}]

Export[NotebookDirectory[] <> "Figure 3B, response rates.pdf", ResponseComposite, "PDF"];
```



Evaluating the effect of random monotherapy pairs in context of animal-to-animal variability.

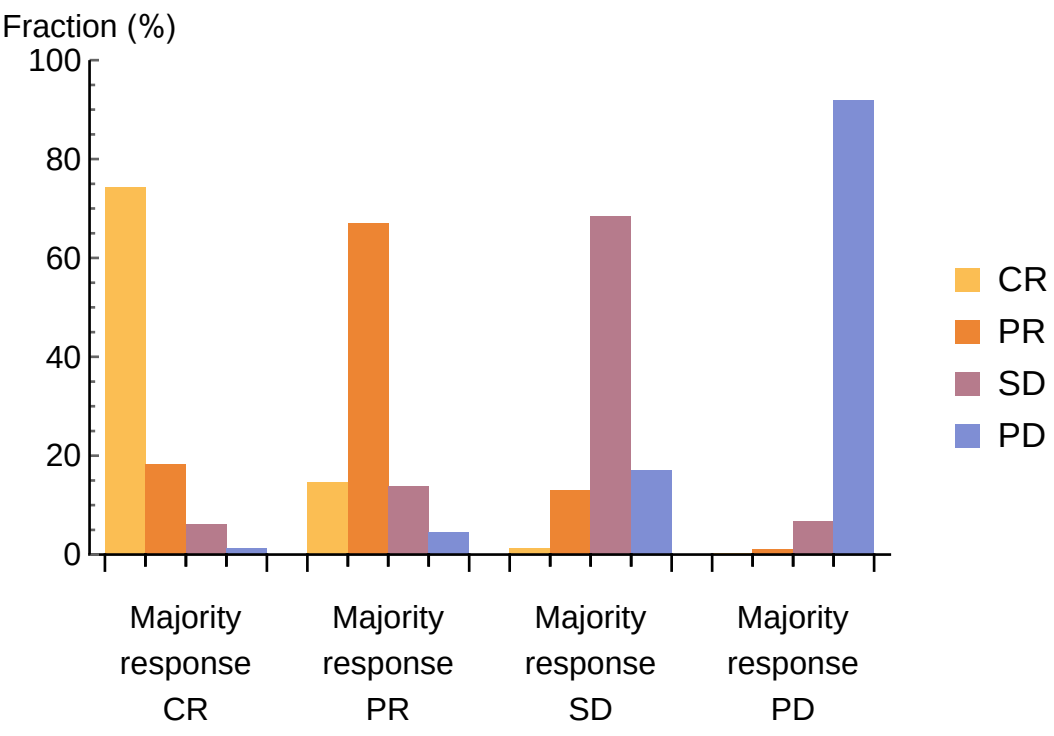
A degree of animal-to-animal variability was reported by Gao *et al*. Nature Medicine (Figure 2a of that article) on the basis of 440 treatment models (meaning a specific treatment applied to a specific PDX) that were repeated on average in 5 different mice each, for a total of over 2000 drug-treated animals. Each treatment model was classified according to its 'majority' response criteria (which response was most commonly observed across the repeats). Figure 2a of Gao *et al* shows the fraction of times that each response criteria was observed within treatment models belonging to each majority response criteria (i.e, how often did an individual animal vary from other replicates of the same treatment model?). For example, treatment models that were most often a complete response (CR) were only CR in 74% of individual animals, being PR in 18% of animals and SD in 6% of animals.
This data was extracted from the published figure by digital image analysis.

Here we use this data as an error model for Gao *et al*'s PDX drug trials, and compute the expected benefit of repeating each drug trial twice and choosing the best observed response from two replicates. If this provides a significant improvement in response then

our analysis of the benefits of random pairs of monotherapies may be no more than the benefit of random experimental repeats.

```
AnimalToAnimalVariabilityMatrix =
  Import[NotebookDirectory[] <> "Animal to animal consistency probability matrix.csv", "CSV"];

(* Reproducing Figure 2A of Gao et al, Nature Medicine *)
BarChart[100 * AnimalToAnimalVariabilityMatrix[[2 ;;, 2 ;;]], PlotRange → {0, 100},
 PlotRangePadding → None, BarSpacing → {0, 1}, ChartStyle → EdgeForm[None],
 ChartLegends → {"CR", "PR", "SD", "PD"},
 ChartLabels →
  {{"Majority\nresponse\nCR", "Majority\nresponse\nPR", "Majority\nresponse\nSD",
    "Majority\nresponse\nPD"}, {, , ,}}, ImagePadding → {{50, 10}, {70, 30}},
 AxesLabel → {"", "Fraction (%)"}, AxesStyle → Directive[Black, Thickness[Medium]],
 BaseStyle → {FontFamily → "Arial", FontSize → 12}]
```




```
(* this function takes a response criteria,
and applies the 'error model' – it samples from the animal-to-
 animal variability data so that there is a chance of obtaining a different response,
consistent with observed probabilities of variation *)
SampleResponseInDifferentAnimal[responsecategory_] := Module[{},
  (* which row of probabilities in the ConsistencyMatrix should we look up? *)
  AppropriateRow = Which[
    responsecategory == "CR", 2,
    responsecategory == "PR", 3,
    responsecategory == "SD", 4,
    responsecategory == "PD", 5
   ];

  RandomizedResponseInDifferentAnimal =
   RandomChoice[AnimalToAnimalVariabilityMatrix[[AppropriateRow, 2 ;;]] ->
     {"CR", "PR", "SD", "PD"}]
 ]

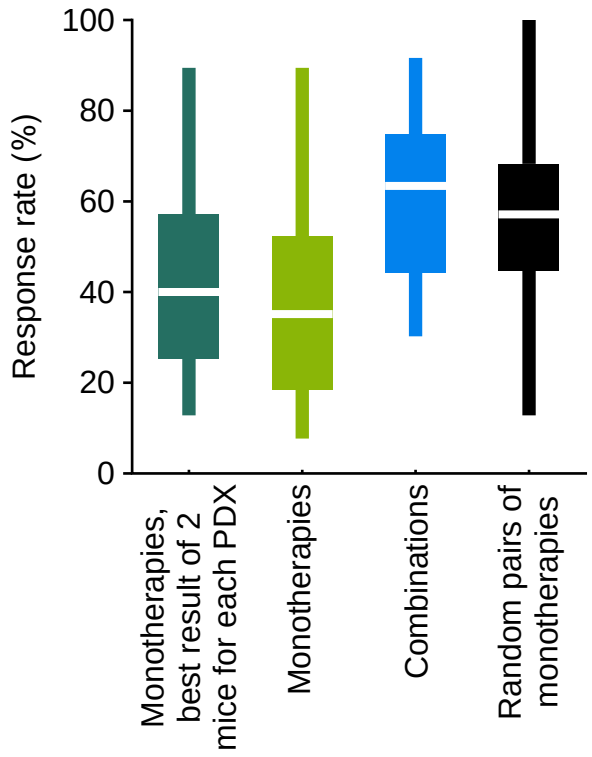
(* this function takes a list of response criteria,
and applies the error model to each response in the list *)
SimulatedAnimalToAnimalVariability[listofresponses_] := Module[{},
  (* take just the first two characters (CR, PR, SD, PD) to look at major response categories,
  which is what the animal-to-animal consistency data addresses *)
  ListOfMajorResponses = Map[StringTake[#, 2] &, listofresponses];
  Map[SampleResponseInDifferentAnimal, ListOfMajorResponses]
 ]
```

```
(* this function takes a list of response criteria
 (representing different tumors receiving a treatment),
uses the above function to apply the error model,
and then selects for each individual tumor the best of the two responses *)
BestResponsesPerPDXFromRealAnimalAndSimulatedSecondAnimalWithVariability[listofresponses_] :=
 Module[{},
  ListOfMajorResponses = Map[StringTake[#, 2] &, listofresponses];
  SecondAnimalMajorResponses = SimulatedAnimalToAnimalVariability[ListOfMajorResponses];

  Table[BestResponseOfSet[{ListOfMajorResponses[[pdx]], SecondAnimalMajorResponses[[pdx]]}],
   {pdx, 1, Length[ListOfMajorResponses]}]
 ]

(* a list of response rates computed according to the error model,
where every observed response has a chance to be superior on account of animal-to-
 animal variability *)
MonotherapyByGroupResponseRatesFromActualAnimalAndSimulatedSecondAnimal =
  Table[
   Table[ResponseRate[BestResponsesPerPDXFromRealAnimalAndSimulatedSecondAnimalWithVariability[
     PerMonotherapyByGroupResponseTypes[[indication, TherapiesWithinIndication]]]],
    {TherapiesWithinIndication, 1, Length[MonotherapiesByGroup[[indication]]]}],
  {indication, 1, Length[AllModelGroups]}];
```

```
ResponseRatePlot = Show[
  BoxWhiskerChart[{{-1}, Flatten[MonotherapyByGroupResponseRates] // N, {-1}, {-1}},
   {"Median", {"MedianMarker", 1, Directive[White, AbsoluteThickness[3]]},
    {"Whiskers", Directive[ColorData[3, 4], AbsoluteThickness[5], CapForm["Butt"]]},
    {"Fences", 0, Opacity[0]}}, PlotRange → {{0.5, 4.5}, {0, 1}}, PlotRangePadding → None,
   ChartStyle → {Directive[ColorData[3, 5]], Directive[ColorData[3, 4]],
     Directive[ColorData[3, 6]], Directive[Black]},
   ChartLabels →
    {Rotate[Style["Monotherapies,\nbest result of 2\nmice for each PDX", LineSpacing → {0, 14}],
      π / 2], Rotate["Monotherapies", π / 2], Rotate["Combinations", π / 2],
     Rotate[Style["Random pairs of\nmonotherapies", LineSpacing → {0, 14}], π / 2]},
   Frame → {{True, False}, {True, False}}, Axes → False,
   FrameStyle → Directive[Black, Thickness[Medium]],
   BaseStyle → {FontFamily → "Arial", FontSize → 12}, FrameLabel → {, "Response rate (%)"},
   FrameTicks → {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {None, None}},
   AspectRatio → 1, ImageSize → {{1000}, {300}}, ImagePadding → {{60, 10}, {120, 10}}]
  ,
  BoxWhiskerChart[{{-1}, {-1}, Flatten[CombinationByGroupResponseRates] // N, {-1}},
   {"Median", {"MedianMarker", 1, Directive[White, AbsoluteThickness[3]]},
    {"Whiskers", Directive[ColorData[3, 6], AbsoluteThickness[5], CapForm["Butt"]]},
    {"Fences", 0, Opacity[0]}}, PlotRange → {{0.5, 4.5}, {0, 1}}, PlotRangePadding → None,
   ChartStyle → {Directive[ColorData[3, 5]], Directive[ColorData[3, 4]],
     Directive[ColorData[3, 6]], Directive[Black]}, Frame → {{True, False}, {True, False}},
   Axes → False, FrameStyle → Directive[Black, Thickness[Medium]],
   BaseStyle → {FontFamily → "Arial", FontSize → 12}, FrameLabel → {, "Response rate (%)"},
   FrameTicks → {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {None, None}},
   AspectRatio → 1, ImageSize → {{1000}, {300}}, ImagePadding → {{60, 10}, {120, 10}}]
  ,
  BoxWhiskerChart[{{-1}, {-1}, {-1}, Flatten[ResponseRatesPerGroupFromRandomMonotherapyPairs]},
   {"Median", {"MedianMarker", 1, Directive[White, AbsoluteThickness[3]]},
    {"Whiskers", Directive[Black, AbsoluteThickness[5], CapForm["Butt"]]},
    {"Fences", 0, Opacity[0]}}, PlotRange → {{0.5, 4.5}, {0, 1}}, PlotRangePadding → None,
   ChartStyle → {Directive[ColorData[3, 5]], Directive[ColorData[3, 4]],
     Directive[ColorData[3, 6]], Directive[Black]}, Frame → {{True, False}, {True, False}},
   Axes → False, FrameStyle → Directive[Black, Thickness[Medium]],
   BaseStyle → {FontFamily → "Arial", FontSize → 12}, FrameLabel → {, "Response rate (%)"},
   FrameTicks → {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {None, None}},
   AspectRatio → 1, ImageSize → {{1000}, {300}}, ImagePadding → {{60, 10}, {120, 10}}]
  ,
  BoxWhiskerChart[
   {Flatten[MonotherapyByGroupResponseRatesFromActualAnimalAndSimulatedSecondAnimal],
    {-1}, {-1}, {-1}}, {"Median", {"MedianMarker", 1, Directive[White, AbsoluteThickness[3]]},
    {"Whiskers", Directive[ColorData[3, 5], AbsoluteThickness[5], CapForm["Butt"]]},
    {"Fences", 0, Opacity[0]}}, PlotRange → {{0.5, 4.5}, {0, 1}}, PlotRangePadding → None,
   ChartStyle → {Directive[ColorData[3, 5]], Directive[ColorData[3, 4]],
     Directive[ColorData[3, 6]], Directive[Black]}, Frame → {{True, False}, {True, False}},
   Axes → False, FrameStyle → Directive[Black, Thickness[Medium]],
   BaseStyle → {FontFamily → "Arial", FontSize → 12}, FrameLabel → {, "Response rate (%)"},
   FrameTicks → {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {None, None}},
   AspectRatio → 1, ImageSize → {{1000}, {300}}, ImagePadding → {{60, 10}, {120, 10}}]
  ]
```




```
Export[NotebookDirectory[] <>
   "Supplementary Figure S4A, response rates with simulated animal variability.pdf",
   ResponseRatePlot, "PDF"];
```

Kolomorov-Smirnov test shows no statistically significant difference in response rate between observed monotherapies and applying the error model to observed monotherapies, simulating the effect of taking the best result of 2 mice for each PDX-treatment.

```
(* monotherapies vs monotherapies, best of 2 animals *)
KolmogorovSmirnovTest[Flatten[MonotherapyByGroupResponseRates],
 Flatten[MonotherapyByGroupResponseRatesFromActualAnimalAndSimulatedSecondAnimal],
 "PValueTable"]
```

	P-Value
Kolmogorov-Smirnov	0.189235

Analysis of combinations that surpass independent drug action

```
(* converting drug codes to names *)
NameSubstitutions = {"LEE011" → "Ribociclib", "BKM120" → "Buparlisib", "BYL719" → "Alpelisib",
   "encorafenib" → "Encorafenib", "binimetinib" → "Binimetinib"};
```

The first of four combinations in Melanoma that surpass independent drug action

```
DrugA = "BKM120"
DrugB = "encorafenib"
```

```
BKM120
```

```
encorafenib
```

```
DrugAresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[CutaneousMelanomaModels, #[[1]]],
      #[[2]] == DrugA] &];
% // Length

DrugBresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[CutaneousMelanomaModels, #[[1]]],
      #[[2]] == DrugB] &];
% // Length

Combinationresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[CutaneousMelanomaModels, #[[1]]],
      #[[2]] == DrugA <> " + " <> DrugB] &];
% // Length
```

```
33
```

```
33
```

```
33
```

```
ModelsInIntersection = Intersection[Combinationresponses[[All, 1]], DrugAresponses[[All, 1]],
  DrugBresponses[[All, 1]]]
```

```
{X-1655, X-1906, X-2163, X-2306, X-2602, X-2613, X-2700, X-2723, X-2753, X-2838, X-2921,
 X-2992, X-3127, X-3211, X-3483, X-3486, X-3503, X-3676, X-3746, X-3773, X-3851, X-3880,
 X-4157, X-4339, X-4426, X-4455, X-4530, X-4538, X-4644, X-4668, X-4832, X-4849, X-5189}
```

```
DrugAresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #[[1]]],
      #[[2]] == DrugA] &];

DrugBresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #[[1]]],
      #[[2]] == DrugB] &];

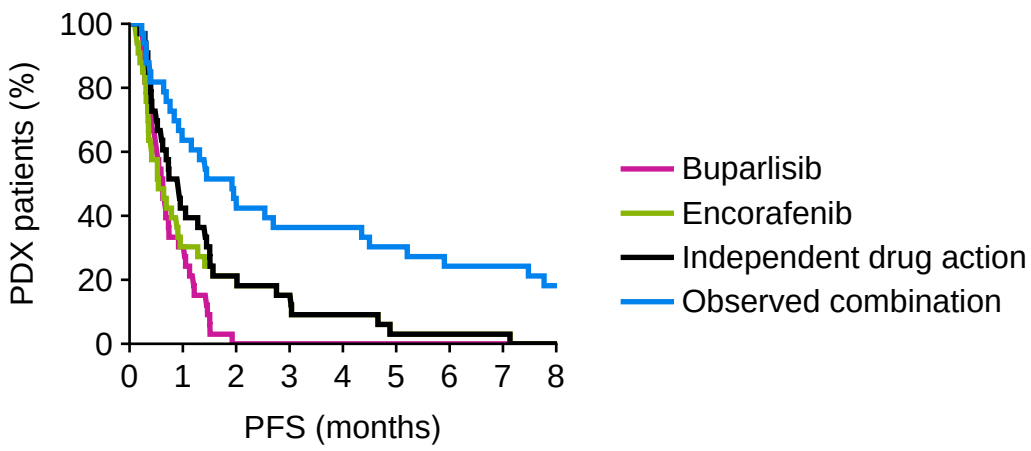
CombinationresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #[[1]]],
      #[[2]] == DrugA <> " + " <> DrugB] &];

(* computing the expected effect of 'independent drug action' by assigning each
 xenograft the more durable response observed with either monotherapy *)
BestOfMonotherapiesIntersection =
  Map[Max, {DrugAresponsesIntersection[[All, 9]], DrugBresponsesIntersection[[All, 9]]}^T];

DoublingFreeSurvival[ClinicalTrialResponses_] :=
 SurvivalFunction[EmpiricalDistribution[ClinicalTrialResponses[[All, 9]]]]
```

```
Plot[{
  DoublingFreeSurvival[DrugAresponsesIntersection][x],
  DoublingFreeSurvival[DrugBresponsesIntersection][x],
  SurvivalFunction[EmpiricalDistribution[BestOfMonotherapiesIntersection]][x],
  DoublingFreeSurvival[CombinationresponsesIntersection][x]
 }, {x, 0, 6 * 61}, PlotRange → {{0, 4 * 61}, {0, 1}}, PlotPoints → 500, Exclusions → None,
 PlotStyle → {Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[2]],
   Directive[ColorData[3, 4], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]],
   Directive[ColorData[3, 6], AbsoluteThickness[2]]},
 BaseStyle → {FontFamily → "Arial", FontSize → 12}, Frame → {{True, False}, {True, False}},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameLabel → {"PFS (months)", "PDX patients (%)"},
 FrameTicks → {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 12 * 61 / 2, 61 / 2}],
   Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}]},
 PlotLegends →
  LineLegend[({DrugA, DrugB, "Independent drug action", "Observed combination"} /.
     NameSubstitutions), Spacings → {0.25, 0.3}, LegendMarkerSize → {20, 12},
   LabelStyle → {FontSize → 12}], ImagePadding → {{50, 10}, {50, 10}}, ImageSize → {{1000}, {180}},
 AspectRatio → 3 / 4]

Export[NotebookDirectory[] <> "Supplementary Figure S4D, " <> DrugA <> "  " <> DrugB <>
   " Melanoma PFS.pdf", %, "PDF"];
```



statistics of observed vs independent drug action

```
(* log rank test *)
LogRankTest[{BestOfMonotherapiesIntersection, CombinationresponsesIntersection[[All, 9]]},
 0, "PValueTable"]
```

	P-Value
Log-Rank	0.00294866

```
(* hazard ratio by Cox Model *)
myeventdata =
  EventData[Join[BestOfMonotherapiesIntersection, CombinationresponsesIntersection[[All, 9]]],
   Table[0,
    {Length[Join[BestOfMonotherapiesIntersection,
       CombinationresponsesIntersection[[All, 9]]]}]];
descriptors = Join[Table["independent", {Length[BestOfMonotherapiesIntersection]}],
   Table["observed", {Length[BestOfMonotherapiesIntersection]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[observed]	−0.795195	0.274206	0.451493	8.40995	1	0.00373173

```
{{0.263783, 0.77278}}
```

statistics of observed vs best monotherapy

```
(* log rank test *)
LogRankTest[{DrugBresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]},
 0, "PValueTable"]
```

	P-Value
Log-Rank	0.000590032

```
(* hazard ratio by Cox Model *)
myeventdata =
  EventData[Join[DrugBresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]],
   Table[0,
    {Length[Join[DrugAresponsesIntersection[[All, 9]],
       CombinationresponsesIntersection[[All, 9]]]]}]];
descriptors = Join[Table["independent", {Length[DrugAresponsesIntersection[[All, 9]]]}],
   Table["observed", {Length[BestOfMonotherapiesIntersection]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[observed]	−0.909419	0.273059	0.402758	11.0921	1	0.000866951

```
{{0.235839, 0.687817}}
```

The second of four combinations in Melanoma that surpass independent drug action

The statistical significance of this combination of RAF and MEK inhibitors is borderline when evaluated in all melanoma PDXs, but is highly significant in BRAF V600-mutant PDX models.

First, in all melanomas:

```
DrugA = "encorafenib"
DrugB = "binimetinib"
```

```
encorafenib
```

```
binimetinib
```

```
DrugAresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[CutaneousMelanomaModels, #[[1]]],
      #[[2]] == DrugA] &];
% // Length

DrugBresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[CutaneousMelanomaModels, #[[1]]],
      #[[2]] == DrugB] &];
% // Length

Combinationresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[CutaneousMelanomaModels, #[[1]]],
      #[[2]] == DrugA <> " + " <> DrugB] &];
% // Length
```

```
33
```

```
33
```

```
33
```

```
ModelsInIntersection = Intersection[Combinationresponses⟦All, 1⟧, DrugAresponses⟦All, 1⟧,
  DrugBresponses⟦All, 1⟧]
```

```
{X-1655, X-1906, X-2163, X-2306, X-2602, X-2613, X-2700, X-2723, X-2753, X-2838, X-2921,
 X-2992, X-3127, X-3211, X-3483, X-3486, X-3503, X-3676, X-3746, X-3773, X-3851, X-3880,
 X-4157, X-4339, X-4426, X-4455, X-4530, X-4538, X-4644, X-4668, X-4832, X-4849, X-5189}
```

```
DrugAresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #⟦1⟧],
      #⟦2⟧ == DrugA] &];

DrugBresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #⟦1⟧],
      #⟦2⟧ == DrugB] &];

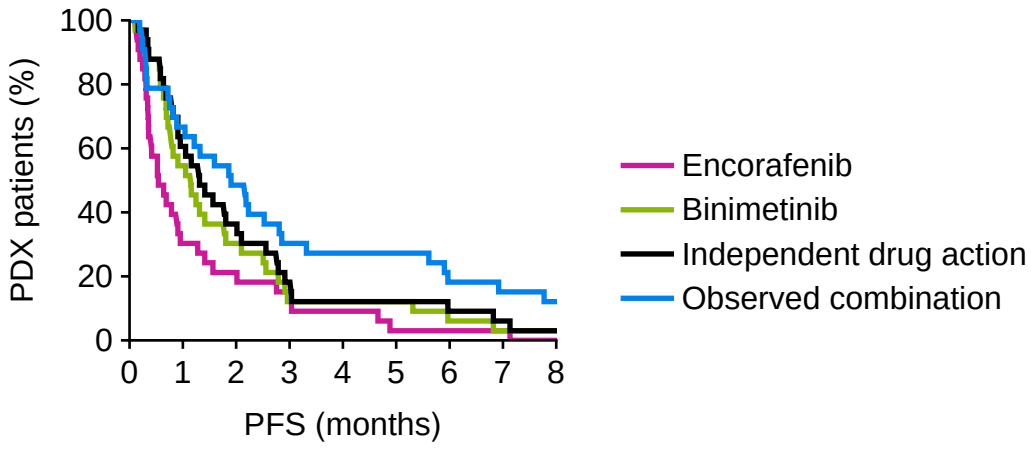
CombinationresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #⟦1⟧],
      #⟦2⟧ == DrugA <> " + " <> DrugB] &];

BestOfMonotherapiesIntersection =
  Map[Max, {DrugAresponsesIntersection⟦All, 9⟧, DrugBresponsesIntersection⟦All, 9⟧}ᵀ];

DoublingFreeSurvival[ClinicalTrialResponses_] :=
 SurvivalFunction[EmpiricalDistribution[ClinicalTrialResponses⟦All, 9⟧]]

Plot[{
  DoublingFreeSurvival[DrugAresponsesIntersection][x],
  DoublingFreeSurvival[DrugBresponsesIntersection][x],
  SurvivalFunction[EmpiricalDistribution[BestOfMonotherapiesIntersection]][x],
  DoublingFreeSurvival[CombinationresponsesIntersection][x]
 }, {x, 0, 6 * 61}, PlotRange → {{0, 4 * 61}, {0, 1}}, PlotPoints → 500, Exclusions → None,
 PlotStyle → {Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[2]],
   Directive[ColorData[3, 4], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]],
   Directive[ColorData[3, 6], AbsoluteThickness[2]]},
 BaseStyle → {FontFamily → "Arial", FontSize → 12}, Frame → {{True, False}, {True, False}},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameLabel → {"PFS (months)", "PDX patients (%)"},
 FrameTicks → {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 12 * 61 / 2, 61 / 2}],
   Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}]},
 PlotLegends →
  LineLegend[({DrugA, DrugB, "Independent drug action", "Observed combination"} /.
    NameSubstitutions), Spacings → {0.25, 0.3}, LegendMarkerSize → {20, 12},
   LabelStyle → {FontSize → 12}], ImagePadding → {{50, 10}, {50, 10}}, ImageSize → {{1000}, {180}},
 AspectRatio → 3 / 4]
```

```
Export[NotebookDirectory[] <> "Supplementary Figure S4D, " <> DrugA <> "  " <> DrugB <>
   " Melanoma PFS.pdf", %, "PDF"];
```



statistics of observed vs independent drug action

```
(* log rank test *)
LogRankTest[{BestOfMonotherapiesIntersection, CombinationresponsesIntersection[[All, 9]]},
 0, "PValueTable"]
```

	P-Value
Log-Rank	0.1421

```
(* hazard ratio by Cox Model *)
myeventdata =
  EventData[Join[BestOfMonotherapiesIntersection, CombinationresponsesIntersection[[All, 9]]],
   Table[0,
    {Length[Join[BestOfMonotherapiesIntersection,
       CombinationresponsesIntersection[[All, 9]]]}]];
descriptors = Join[Table["independent", {Length[BestOfMonotherapiesIntersection]}],
   Table["observed", {Length[BestOfMonotherapiesIntersection]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[observed]	−0.374122	0.256607	0.687893	2.12564	1	0.144852

```
{{0.416003, 1.13748}}
```

statistics of observed vs best monotherapy

```
(* log rank test *)
LogRankTest[{DrugBresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]},
 0, "PValueTable"]
```

	P-Value
Log-Rank	0.0586054

```
(* hazard ratio by Cox Model *)
myeventdata =
  EventData[Join[DrugBresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]],
   Table[0,
    {Length[Join[DrugAresponsesIntersection[[All, 9]],
       CombinationresponsesIntersection[[All, 9]]]}]];
descriptors = Join[Table["independent", {Length[DrugAresponsesIntersection[[All, 9]]}],
   Table["observed", {Length[BestOfMonotherapiesIntersection]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[observed]	−0.482204	0.257616	0.617421	3.50361	1	0.0612353

```
{{0.372647, 1.02297}}
```

Next, in BRAF-V600E melanomas:

```
(* Melanoma responses to RAF inhibition by encorafenib *)
RAFresponses = Select[PDXclinicaltrialresponses,
   And[MemberQ[CutaneousMelanomaModels, #[[1]]], #[[2]] == "encorafenib"] &];
(* Melanoma responses to MEK inhibition by binimetinib *)
MEKresponses = Select[PDXclinicaltrialresponses,
   And[MemberQ[CutaneousMelanomaModels, #[[1]]], #[[2]] == "binimetinib"] &];
(* which PDX models were tested with both RAF and MEK inhibition? *)
RAFMEKIntersection = Intersection[MEKresponses[[All, 1]], RAFresponses[[All, 1]]];
(* importing a table of all BRAF mutations in PDX models. This is a subset of the
 mutation data in the Supplementary Materials of Gao et al. Nature Medicine *)
BRAFmutations = Import[NotebookDirectory[] <> "BRAF mutations.csv", "CSV"];

(* identifying PDX models that were tested with both RAF and MEK inhibition,
and which contains BRAF V600 mutations *)
Off[StringTake::strse]
RAKMEKIntersectionWithBRAFV600mutations =
  Select[BRAFmutations[[2 ;;]],
   And[MemberQ[RAFMEKIntersection, #[[1]]], StringTake[#[[5]], 4] == "V600"] &];
% // TableForm
```

X-1906	BRAF	673	MutKnownFunctional	V600E,0.798
X-2602	BRAF	673	MutKnownFunctional	V600E,0.625
X-2613	BRAF	673	MutKnownFunctional	V600E,0.792
X-2723	BRAF	673	MutKnownFunctional	V600E,0.786
X-3211	BRAF	673	MutKnownFunctional	V600K,0.585
X-3483	BRAF	673	MutKnownFunctional	V600E,0.893
X-3676	BRAF	673	MutKnownFunctional	V600E,0.510
X-3746	BRAF	673	MutKnownFunctional	V600E,0.467
X-4530	BRAF	673	MutKnownFunctional	V600E,0.266
X-4538	BRAF	673	MutKnownFunctional	V600E,0.485
X-4644	BRAF	673	MutKnownFunctional	V600E,0.719
X-4668	BRAF	673	MutKnownFunctional	V600E,0.855
X-4849	BRAF	673	MutKnownFunctional	V600E,0.646

```
DrugAresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[RAKMEKIntersectionWithBRAFV600mutations[[All, 1]], #[[1]]],
      #[[2]] == DrugA] &];

DrugBresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[RAKMEKIntersectionWithBRAFV600mutations[[All, 1]], #[[1]]],
      #[[2]] == DrugB] &];

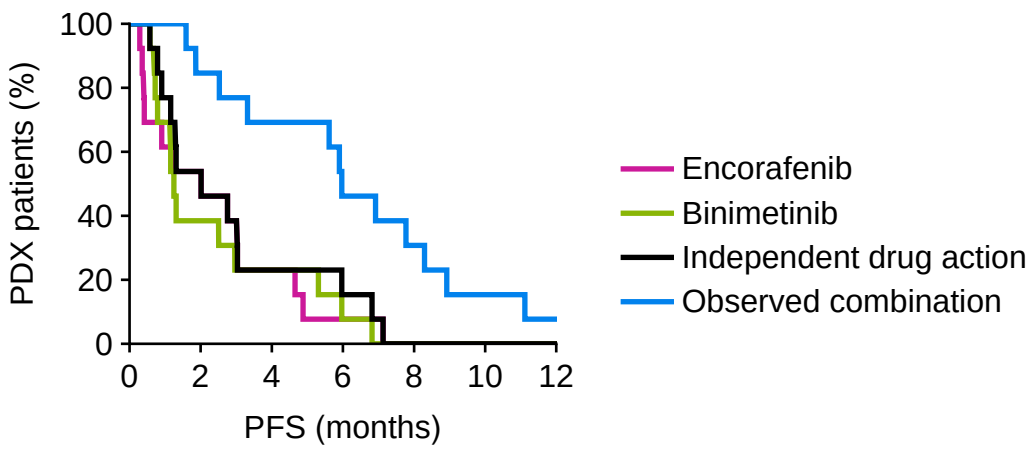
CombinationresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[RAKMEKIntersectionWithBRAFV600mutations[[All, 1]], #[[1]]],
      #[[2]] == DrugA <> " + " <> DrugB] &];

BestOfMonotherapiesIntersection =
  Map[Max, {DrugAresponsesIntersection[[All, 9]], DrugBresponsesIntersection[[All, 9]]}^T];

DoublingFreeSurvival[ClinicalTrialResponses_] :=
 SurvivalFunction[EmpiricalDistribution[ClinicalTrialResponses[[All, 9]]]]
```

```
Plot[{
  DoublingFreeSurvival[DrugAresponsesIntersection][x],
  DoublingFreeSurvival[DrugBresponsesIntersection][x],
  SurvivalFunction[EmpiricalDistribution[BestOfMonotherapiesIntersection]][x],
  DoublingFreeSurvival[CombinationresponsesIntersection][x]
 }, {x, 0, 6 * 61}, PlotRange → {{0, 6 * 61}, {0, 1}}, PlotPoints → 500, Exclusions → None,
 PlotStyle → {Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[2]],
   Directive[ColorData[3, 4], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]],
   Directive[ColorData[3, 6], AbsoluteThickness[2]]},
 BaseStyle → {FontFamily → "Arial", FontSize → 12}, Frame → {{True, False}, {True, False}},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameLabel → {"PFS (months)", "PDX patients (%)"},
 FrameTicks → {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 12 * 61 / 2, 61}],
   Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}]},
 PlotLegends →
  LineLegend[({DrugA, DrugB, "Independent drug action", "Observed combination"} /.
     NameSubstitutions), Spacings → {0.25, 0.3}, LegendMarkerSize → {20, 12},
   LabelStyle → {FontSize → 12}], ImagePadding → {{50, 10}, {50, 10}}, ImageSize → {{1000}, {180}},
 AspectRatio → 3 / 4]

Export[NotebookDirectory[] <> "Supplementary Figure S4D, " <> DrugA <> "  " <> DrugB <>
   " BRAF-mut Melanoma PFS.pdf", %, "PDF"];
```



statistics of observed vs independent drug action

```
(* log rank test *)
LogRankTest[{BestOfMonotherapiesIntersection, CombinationresponsesIntersection[[All, 9]]},
 0, "PValueTable"]
```

	P-Value
Log-Rank	0.00462779

```
(* hazard ratio by Cox Model *)
myeventdata =
  EventData[Join[BestOfMonotherapiesIntersection, CombinationresponsesIntersection[[All, 9]]],
   Table[0,
    {Length[Join[BestOfMonotherapiesIntersection,
       CombinationresponsesIntersection[[All, 9]]]}]];
descriptors = Join[Table["independent", {Length[BestOfMonotherapiesIntersection]}],
   Table["observed", {Length[BestOfMonotherapiesIntersection]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[observed]	−1.22854	0.460506	0.292718	7.11724	1	0.00763459

```
{{0.118704, 0.721827}}
```

statistics of observed vs best monotherapy

```
(* log rank test *)
LogRankTest[{DrugBresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]},
 0, "PValueTable"]
```

	P-Value
Log-Rank	0.00073289

```
(* hazard ratio by Cox Model *)
myeventdata =
  EventData[Join[DrugBresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]],
   Table[0,
    {Length[Join[DrugAresponsesIntersection[[All, 9]],
       CombinationresponsesIntersection[[All, 9]]]]}]];
descriptors = Join[Table["independent", {Length[DrugAresponsesIntersection[[All, 9]]]}],
   Table["observed", {Length[BestOfMonotherapiesIntersection]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[observed]	−1.49362	0.480773	0.224559	9.65154	1	0.00189193

```
{{0.0875177, 0.576191}}
```

The third of four combinations in Melanoma that surpass independent drug action

```
DrugA = "LEE011"
DrugB = "binimetinib"
```

```
LEE011
```

```
binimetinib
```

```
DrugAresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[CutaneousMelanomaModels, #[[1]]],
      #[[2]] == DrugA] &];
% // Length

DrugBresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[CutaneousMelanomaModels, #[[1]]],
      #[[2]] == DrugB] &];
% // Length

Combinationresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[CutaneousMelanomaModels, #[[1]]],
      #[[2]] == DrugA <> " + " <> DrugB] &];
% // Length
```

```
33
```

```
33
```

```
18
```

```
ModelsInIntersection = Intersection[Combinationresponses[[All, 1]], DrugAresponses[[All, 1]],
  DrugBresponses[[All, 1]]]
```

```
{X-1655, X-1906, X-2163, X-2306, X-2613, X-2700, X-2723, X-2753,
 X-2838, X-2921, X-2992, X-3127, X-3211, X-3773, X-3851, X-4339, X-4849, X-5189}
```

```
DrugAresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #[[1]]],
      #[[2]] == DrugA] &];

DrugBresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #[[1]]],
      #[[2]] == DrugB] &];

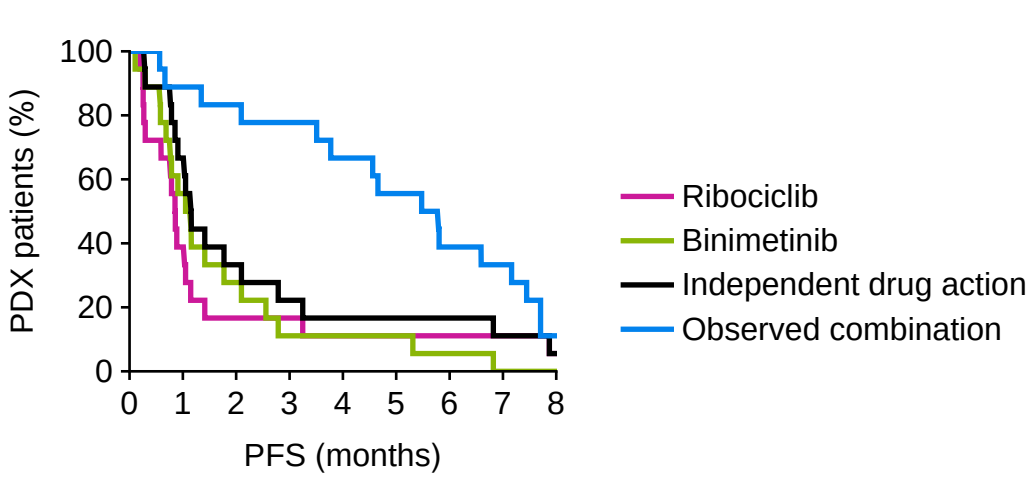
CombinationresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #[[1]]],
      #[[2]] == DrugA <> " + " <> DrugB] &];

BestOfMonotherapiesIntersection =
  Map[Max, {DrugAresponsesIntersection[[All, 9]], DrugBresponsesIntersection[[All, 9]]}^T];

DoublingFreeSurvival[ClinicalTrialResponses_] :=
 SurvivalFunction[EmpiricalDistribution[ClinicalTrialResponses[[All, 9]]]]

Plot[{
  DoublingFreeSurvival[DrugAresponsesIntersection][x],
  DoublingFreeSurvival[DrugBresponsesIntersection][x],
  SurvivalFunction[EmpiricalDistribution[BestOfMonotherapiesIntersection]][x],
  DoublingFreeSurvival[CombinationresponsesIntersection][x]
 }, {x, 0, 6 * 61}, PlotRange → {{0, 4 * 61}, {0, 1}}, PlotPoints → 500, Exclusions → None,
 PlotStyle → {Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[2]],
   Directive[ColorData[3, 4], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]],
   Directive[ColorData[3, 6], AbsoluteThickness[2]]},
 BaseStyle → {FontFamily → "Arial", FontSize → 12}, Frame → {{True, False}, {True, False}},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameLabel → {"PFS (months)", "PDX patients (%)"},
 FrameTicks → {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 12 * 61 / 2, 61 / 2}],
   Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}]},
 PlotLegends →
  LineLegend[({DrugA, DrugB, "Independent drug action", "Observed combination"} /.
     NameSubstitutions), Spacings → {0.25, 0.3}, LegendMarkerSize → {20, 12},
   LabelStyle → {FontSize → 12}], ImagePadding → {{50, 10}, {50, 10}}, ImageSize → {{1000}, {180}},
 AspectRatio → 3 / 4]

Export[NotebookDirectory[] <> "Supplementary Figure S4D, " <> DrugA <> "  " <> DrugB <>
   " Melanoma PFS.pdf", %, "PDF"];
```



statistics of observed vs independent drug action

```
(* log rank test *)
LogRankTest[{BestOfMonotherapiesIntersection, CombinationresponsesIntersection[[All, 9]]},
 0, "PValueTable"]
```

	P-Value
Log-Rank	0.033766

```
(* hazard ratio by Cox Model *)
myeventdata =
  EventData[Join[BestOfMonotherapiesIntersection, CombinationresponsesIntersection[[All, 9]]],
   Table[0,
    {Length[Join[BestOfMonotherapiesIntersection,
       CombinationresponsesIntersection[[All, 9]]]}]];
descriptors = Join[Table["independent", {Length[BestOfMonotherapiesIntersection]}],
   Table["observed", {Length[BestOfMonotherapiesIntersection]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[observed]	−0.719445	0.347267	0.487022	4.2921	1	0.0382899

```
{{0.246578, 0.961928}}
```

statistics of observed vs monotherapy A

```
(* log rank test *)
LogRankTest[{DrugBresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]},
 0, "PValueTable"]
```

	P-Value
Log-Rank	0.0000987661

```
(* hazard ratio by Cox Model *)
myeventdata =
  EventData[Join[DrugBresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]],
   Table[0,
    {Length[Join[DrugAresponsesIntersection[[All, 9]],
       CombinationresponsesIntersection[[All, 9]]]}]];
descriptors = Join[Table["independent", {Length[DrugAresponsesIntersection[[All, 9]]]}],
   Table["observed", {Length[BestOfMonotherapiesIntersection]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[observed]	−1.45808	0.397738	0.232682	13.439	1	0.000246443

```
{{0.106711, 0.507363}}
```

statistics of observed vs monotherapy B

```
(* log rank test *)
LogRankTest[{DrugAresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]},
 0, "PValueTable"]
```

	P-Value
Log-Rank	0.00743595

```
(* hazard ratio by Cox Model *)
myeventdata =
  EventData[Join[DrugAresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]],
   Table[0,
    {Length[Join[DrugAresponsesIntersection[[All, 9]],
       CombinationresponsesIntersection[[All, 9]]]}]];
descriptors = Join[Table["independent", {Length[DrugAresponsesIntersection[[All, 9]]}],
   Table["observed", {Length[BestOfMonotherapiesIntersection]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[observed]	−0.914328	0.353316	0.400786	6.69695	1	0.0096578

```
{{0.200525, 0.801043}}
```

The last of four combinations in Melanoma that surpass independent drug action

```
DrugA = "LEE011"
DrugB = "encorafenib"
```

```
LEE011
```

```
encorafenib
```

```
DrugAresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[CutaneousMelanomaModels, #[[1]]],
      #[[2]] == DrugA] &];
% // Length
```

```
DrugBresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[CutaneousMelanomaModels, #[[1]]],
      #[[2]] == DrugB] &];
% // Length
```

```
Combinationresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[CutaneousMelanomaModels, #[[1]]],
      #[[2]] == DrugA <> " + " <> DrugB] &];
% // Length
```

```
33
```

```
33
```

```
33
```

```
ModelsInIntersection = Intersection[Combinationresponses[[All, 1]], DrugAresponses[[All, 1]],
  DrugBresponses[[All, 1]]]
```

```
{X-1655, X-1906, X-2163, X-2306, X-2602, X-2613, X-2700, X-2723, X-2753, X-2838, X-2921,
 X-2992, X-3127, X-3211, X-3483, X-3486, X-3503, X-3676, X-3746, X-3773, X-3851, X-3880,
 X-4157, X-4339, X-4426, X-4455, X-4530, X-4538, X-4644, X-4668, X-4832, X-4849, X-5189}
```

```
DrugAresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #[[1]]],
      #[[2]] == DrugA] &];

DrugBresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #[[1]]],
      #[[2]] == DrugB] &];

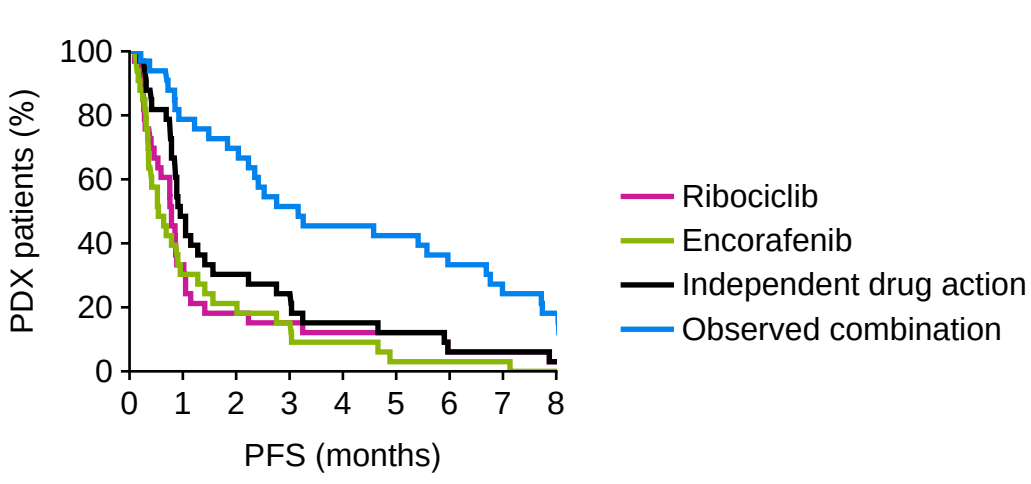
CombinationresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #[[1]]],
      #[[2]] == DrugA <> " + " <> DrugB] &];

BestOfMonotherapiesIntersection =
  Map[Max, {DrugAresponsesIntersection[[All, 9]], DrugBresponsesIntersection[[All, 9]]}^T];

DoublingFreeSurvival[ClinicalTrialResponses_] :=
 SurvivalFunction[EmpiricalDistribution[ClinicalTrialResponses[[All, 9]]]]

Plot[{
  DoublingFreeSurvival[DrugAresponsesIntersection][x],
  DoublingFreeSurvival[DrugBresponsesIntersection][x],
  SurvivalFunction[EmpiricalDistribution[BestOfMonotherapiesIntersection]][x],
  DoublingFreeSurvival[CombinationresponsesIntersection][x]
 }, {x, 0, 6 * 61}, PlotRange → {{0, 4 * 61}, {0, 1}}, PlotPoints → 500, Exclusions → None,
 PlotStyle → {Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[2]],
   Directive[ColorData[3, 4], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]],
   Directive[ColorData[3, 6], AbsoluteThickness[2]]},
 BaseStyle → {FontFamily → "Arial", FontSize → 12}, Frame → {{True, False}, {True, False}},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameLabel → {"PFS (months)", "PDX patients (%)"},
 FrameTicks → {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 12 * 61 / 2, 61 / 2}],
   Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}]},
 PlotLegends →
  LineLegend[({DrugA, DrugB, "Independent drug action", "Observed combination"} /.
     NameSubstitutions), Spacings → {0.25, 0.3}, LegendMarkerSize → {20, 12},
   LabelStyle → {FontSize → 12}], ImagePadding → {{50, 10}, {50, 10}}, ImageSize → {{1000}, {180}},
 AspectRatio → 3 / 4]

Export[NotebookDirectory[] <> "Supplementary Figure S4D, " <> DrugA <> "  " <> DrugB <>
   " Melanoma PFS.pdf", %, "PDF"];
```



statistics of observed vs independent drug action

```
(* log rank test *)
LogRankTest[{BestOfMonotherapiesIntersection, CombinationresponsesIntersection[[All, 9]]},
 0, "PValueTable"]
```

	P-Value
Log-Rank	0.00218542

```
(* hazard ratio by Cox Model *)
myeventdata =
  EventData[Join[BestOfMonotherapiesIntersection, CombinationresponsesIntersection[[All, 9]]],
   Table[0,
    {Length[Join[BestOfMonotherapiesIntersection,
       CombinationresponsesIntersection[[All, 9]]]}]];
descriptors = Join[Table["independent", {Length[BestOfMonotherapiesIntersection]}],
   Table["observed", {Length[BestOfMonotherapiesIntersection]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[observed]	−0.769931	0.257448	0.463045	8.94388	1	0.00278401

```
{{0.279565, 0.766943}}
```

statistics of observed vs monotherapy A

```
(* log rank test *)
LogRankTest[{DrugAresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]},
 0, "PValueTable"]
```

	P-Value
Log-Rank	0.000156086

```
(* hazard ratio by Cox Model *)
myeventdata =
  EventData[Join[DrugAresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]],
   Table[0,
    {Length[Join[DrugAresponsesIntersection[[All, 9]],
       CombinationresponsesIntersection[[All, 9]]]}]];
descriptors = Join[Table["independent", {Length[DrugAresponsesIntersection[[All, 9]]}],
   Table["observed", {Length[BestOfMonotherapiesIntersection]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[observed]	−0.943861	0.258181	0.389123	13.3649	1	0.000256371

```
{{0.234597, 0.645432}}
```

statistics of observed vs monotherapy B

```
(* log rank test *)
LogRankTest[{DrugBresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]},
 0, "PValueTable"]
```

	P-Value
Log-Rank	1.30452×10^{-6}

```
(* hazard ratio by Cox Model *)
myeventdata =
  EventData[Join[DrugBresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]],
   Table[0,
    {Length[Join[DrugAresponsesIntersection[[All, 9]],
       CombinationresponsesIntersection[[All, 9]]]}]];
descriptors = Join[Table["independent", {Length[DrugAresponsesIntersection[[All, 9]]}],
   Table["observed", {Length[BestOfMonotherapiesIntersection]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[observed]	−1.28526	0.280173	0.276578	21.0441	1	4.48842×10^{-6}

```
{{0.159711, 0.478963}}
```

One combination in colorectal carcinoma surpasses independent drug action

In this case the statistical significance is borderline when the observed effect of the combination is compared to the expectation of independent drug action, but strong when compared to the observed monotherapy.

```
DrugA = "BYL719"
DrugB = "binimetinib"
```

```
BYL719
```

```
binimetinib
```

```
DrugAresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[ColorectalModels, #[[1]]],
      #[[2]] == DrugA] &];
% // Length
```

```
DrugBresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[ColorectalModels, #[[1]]],
      #[[2]] == DrugB] &];
% // Length
```

```
Combinationresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[ColorectalModels, #[[1]]],
      #[[2]] == DrugA <> " + " <> DrugB] &];
% // Length
```

```
42
```

```
42
```

```
42
```

```
ModelsInIntersection = Intersection[CombinationresponsesIntersection[[All, 1]], DrugAresponses[[All, 1]],
  DrugBresponses[[All, 1]]]
```

```
{X-0933, X-1027, X-1055, X-1119, X-1167, X-1173, X-1270, X-1290, X-1303, X-1329,
 X-1441, X-1443, X-1479, X-1500, X-1536, X-1855, X-2145, X-2182, X-2239, X-2374, X-2403,
 X-2483, X-2484, X-2538, X-2573, X-2659, X-2822, X-2846, X-2861, X-3093, X-3205, X-3224,
 X-3267, X-3792, X-4087, X-5254, X-5405, X-5438, X-5446, X-5494, X-5495, X-5578}
```

```
DrugAresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #[[1]]],
      #[[2]] == DrugA] &];

DrugBresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #[[1]]],
      #[[2]] == DrugB] &];

CombinationresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #[[1]]],
      #[[2]] == DrugA <> " + " <> DrugB] &];

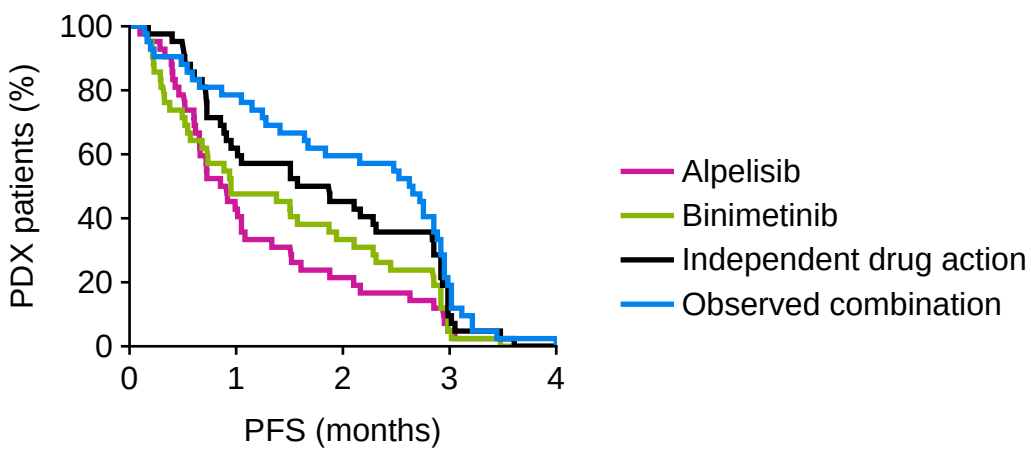
UntreatedIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #[[1]]],
      #[[2]] == "untreated"] &];

BestOfMonotherapiesIntersection =
  Map[Max, {DrugAresponsesIntersection[[All, 9]], DrugBresponsesIntersection[[All, 9]]}^T];

DoublingFreeSurvival[ClinicalTrialResponses_] :=
 SurvivalFunction[EmpiricalDistribution[ClinicalTrialResponses[[All, 9]]]]

Plot[{
  DoublingFreeSurvival[DrugAresponsesIntersection][x],
  DoublingFreeSurvival[DrugBresponsesIntersection][x],
  SurvivalFunction[EmpiricalDistribution[BestOfMonotherapiesIntersection]][x],
  DoublingFreeSurvival[CombinationresponsesIntersection][x]
 }, {x, 0, 3 * 61}, PlotRange → {{0, 2 * 61}, {0, 1}}, PlotPoints → 500, Exclusions → None,
 PlotStyle → {Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[2]],
   Directive[ColorData[3, 4], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]],
   Directive[ColorData[3, 6], AbsoluteThickness[2]]},
 BaseStyle → {FontFamily → "Arial", FontSize → 12}, Frame → {{True, False}, {True, False}},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameLabel → {"PFS (months)", "PDX patients (%)"},
 FrameTicks → {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 12 * 61 / 2, 61 / 2}],
   Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}]},
 PlotLegends →
  LineLegend[({DrugA, DrugB, "Independent drug action", "Observed combination"} /.
     NameSubstitutions), Spacings → {0.25, 0.3}, LegendMarkerSize → {20, 12},
   LabelStyle → {FontSize → 12}], ImagePadding → {{50, 10}, {50, 10}}, ImageSize → {{1000}, {180}},
 AspectRatio → 3 / 4]

Export[NotebookDirectory[] <> "Supplementary Figure S4D, " <> DrugA <> " " <> DrugB <>
   " Colorectal PFS.pdf", %, "PDF"];
```



statistics of observed vs independent drug action

```
(* log rank test *)
LogRankTest[{BestOfMonotherapiesIntersection, CombinationresponsesIntersection[[All, 9]]},
 0, "PValueTable"]
```

	P-Value
Log-Rank	0.291487

```
(* hazard ratio by Cox Model *)
myeventdata =
  EventData[Join[BestOfMonotherapiesIntersection, CombinationresponsesIntersection[[All, 9]]],
   Table[0,
    {Length[Join[BestOfMonotherapiesIntersection,
       CombinationresponsesIntersection[[All, 9]]]}]];
descriptors = Join[Table["independent", {Length[BestOfMonotherapiesIntersection]}],
   Table["observed", {Length[BestOfMonotherapiesIntersection]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[observed]	−0.226504	0.220959	0.797316	1.05082	1	0.305318

```
{{0.517071, 1.22945}}
```

statistics of observed vs monotherapy A

```
(* log rank test *)
LogRankTest[{DrugAresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]},
 0, "PValueTable"]
```

	P-Value
Log-Rank	0.00127719

```
(* hazard ratio by Cox Model *)
myeventdata =
  EventData[Join[DrugAresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]],
   Table[0,
    {Length[Join[DrugAresponsesIntersection[[All, 9]],
       CombinationresponsesIntersection[[All, 9]]]}]];
descriptors = Join[Table["independent", {Length[DrugAresponsesIntersection[[All, 9]]}],
   Table["observed", {Length[BestOfMonotherapiesIntersection]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[observed]	−0.704014	0.225433	0.494596	9.75281	1	0.00179049

```
{{0.317952, 0.769377}}
```

statistics of observed vs monotherapy B

```
(* log rank test *)
LogRankTest[{DrugBresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]},
 0, "PValueTable"]
```

	P-Value
Log-Rank	0.0154652

```
(* hazard ratio by Cox Model *)
myeventdata =
  EventData[Join[DrugBresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]],
   Table[0,
    {Length[Join[DrugAresponsesIntersection[[All, 9]],
       CombinationresponsesIntersection[[All, 9]]]}]];
descriptors = Join[Table["independent", {Length[DrugAresponsesIntersection[[All, 9]]}],
   Table["observed", {Length[BestOfMonotherapiesIntersection]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[observed]	−0.522057	0.223145	0.593299	5.47344	1	0.0193076

```
{{0.383118, 0.918788}}
```

One combination in PDAC surpasses independent drug action

```
DrugA = "BKM120"
DrugB = "binimetinib"
```

```
BKM120
```

```
binimetinib
```

```
DrugAresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[PDACModels, #[[1]]],
      #[[2]] == DrugA] &];
% // Length
```

```
DrugBresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[PDACModels, #[[1]]],
      #[[2]] == DrugB] &];
% // Length
```

```
Combinationresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[PDACModels, #[[1]]],
      #[[2]] == DrugA <> " + " <> DrugB] &];
% // Length
```

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38
```

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38
```

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36
```

```
ModelsInIntersection = Intersection[CombinationresponsesIntersection[[All, 1]], DrugAresponses[[All, 1]],
   DrugBresponses[[All, 1]]]
```

```
{X-1199, X-1362, X-1948, X-2026, X-2043, X-2081, X-2339, X-2428, X-2564, X-2633, X-2684,
 X-2997, X-3028, X-3038, X-3052, X-3209, X-3268, X-3800, X-3816, X-3846, X-3898, X-3947,
 X-3990, X-4018, X-4145, X-4226, X-4377, X-4378, X-4439, X-4649, X-4676, X-4927, X-5205}
```

```
DrugAresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #[[1]]],
      #[[2]] == DrugA] &];

DrugBresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #[[1]]],
      #[[2]] == DrugB] &];

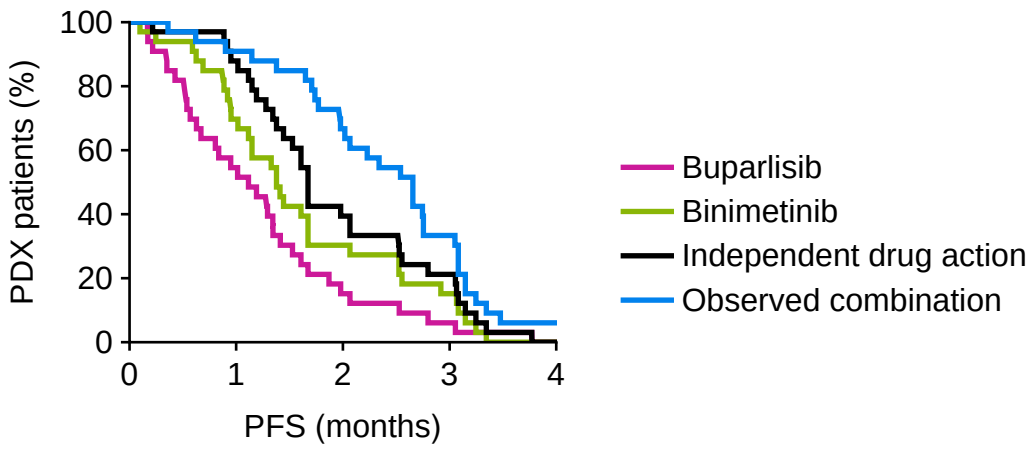
CombinationresponsesIntersection = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInIntersection, #[[1]]],
      #[[2]] == DrugA <> " + " <> DrugB] &];

BestOfMonotherapiesIntersection =
  Map[Max, {DrugAresponsesIntersection[[All, 9]], DrugBresponsesIntersection[[All, 9]]}^T];

DoublingFreeSurvival[ClinicalTrialResponses_] :=
 SurvivalFunction[EmpiricalDistribution[ClinicalTrialResponses[[All, 9]]]]

Plot[{
  DoublingFreeSurvival[DrugAresponsesIntersection][x],
  DoublingFreeSurvival[DrugBresponsesIntersection][x],
  SurvivalFunction[EmpiricalDistribution[BestOfMonotherapiesIntersection]][x],
  DoublingFreeSurvival[CombinationresponsesIntersection][x]
 }, {x, 0, 3 * 61}, PlotRange → {{0, 2 * 61}, {0, 1}}, PlotPoints → 500, Exclusions → None,
 PlotStyle → {Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[2]],
   Directive[ColorData[3, 4], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]],
   Directive[ColorData[3, 6], AbsoluteThickness[2]]},
 BaseStyle → {FontFamily → "Arial", FontSize → 12}, Frame → {{True, False}, {True, False}},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameLabel → {"PFS (months)", "PDX patients (%)"},
 FrameTicks → {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 12 * 61 / 2, 61 / 2}],
   Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}]},
 PlotLegends →
  LineLegend[({DrugA, DrugB, "Independent drug action", "Observed combination"} /.
     NameSubstitutions), Spacings → {0.25, 0.3}, LegendMarkerSize → {20, 12},
   LabelStyle → {FontSize → 12}], ImagePadding → {{50, 10}, {50, 10}}, ImageSize → {{1000}, {180}},
 AspectRatio → 3 / 4]

Export[NotebookDirectory[] <> "Supplementary Figure S4D, " <> DrugA <> "  " <> DrugB <>
   " Pancreatic PFS.pdf", %, "PDF"];
```



statistics of observed vs independent drug action

```
(* log rank test *)
LogRankTest[{BestOfMonotherapiesIntersection, CombinationresponsesIntersection[[All, 9]]},
 0, "PValueTable"]
```

	P-Value
Log-Rank	0.043589

```
(* hazard ratio by Cox Model *)
myeventdata =
  EventData[Join[BestOfMonotherapiesIntersection, CombinationresponsesIntersection[[All, 9]]],
   Table[0,
    {Length[Join[BestOfMonotherapiesIntersection,
       CombinationresponsesIntersection[[All, 9]]]}]];
descriptors = Join[Table["independent", {Length[BestOfMonotherapiesIntersection]}],
   Table["observed", {Length[BestOfMonotherapiesIntersection]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[observed]	−0.492165	0.252002	0.611302	3.81428	1	0.0508173

```
{{0.373036, 1.00175}}
```

statistics of observed vs monotherapy A

```
(* log rank test *)
LogRankTest[{DrugAresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]},
 0, "PValueTable"]
```

	P-Value
Log-Rank	0.000010988

```
(* hazard ratio by Cox Model *)
myeventdata =
  EventData[Join[DrugAresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]],
   Table[0,
    {Length[Join[DrugAresponsesIntersection[[All, 9]],
       CombinationresponsesIntersection[[All, 9]]]}]];
descriptors = Join[Table["independent", {Length[DrugAresponsesIntersection[[All, 9]]}],
   Table["observed", {Length[BestOfMonotherapiesIntersection]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[observed]	−1.10073	0.261973	0.332627	17.6543	1	0.000026491

```
{{0.199052, 0.555839}}
```

statistics of observed vs monotherapy B

```
(* log rank test *)
LogRankTest[{DrugBresponsesIntersection[[All, 9]], CombinationresponsesIntersection[[All, 9]]},
 0, "PValueTable"]
```

	P-Value
Log-Rank	0.00298922

```
(* hazard ratio by Cox Model *)
myeventdata =
  EventData[Join[DrugBresponsesIntersection[All, 9], CombinationresponsesIntersection[All, 9]],
   Table[0,
    {Length[Join[DrugAresponsesIntersection[All, 9],
       CombinationresponsesIntersection[All, 9]]}]];
descriptors = Join[Table["independent", {Length[DrugAresponsesIntersection[All, 9]]}],
   Table["observed", {Length[BestOfMonotherapiesIntersection]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[observed]	−0.726859	0.255916	0.483425	8.06689	1	0.00450815

```
{{0.292747, 0.798298}}
```

Which monotherapies are 'active', that is, significantly improve survival relative to no treatment?

This is determined by applying the Cox proportional hazards model, comparing PFS of each monotherapy to PFS in xenografts of the same tumor type that were untreated.

```
(* PFS times in each tumor type when untreated *)
MelanomaUntreatedResponses =
  Select[PDXclinicaltrialresponses,
   And[MemberQ[CutaneousMelanomaModels, #[[1]]], #[[2]] == "untreated"] &];
NSCLCUntreatedResponses = Select[PDXclinicaltrialresponses,
   And[MemberQ[NSCLCModels, #[[1]]], #[[2]] == "untreated"] &];
PDACUntreatedResponses = Select[PDXclinicaltrialresponses,
   And[MemberQ[PDACModels, #[[1]]], #[[2]] == "untreated"] &];
CRCUntreatedResponses = Select[PDXclinicaltrialresponses,
   And[MemberQ[ColorectalModels, #[[1]]], #[[2]] == "untreated"] &];
BreastUntreatedResponses = Select[PDXclinicaltrialresponses,
   And[MemberQ[BreastModels, #[[1]]], #[[2]] == "untreated"] &];
GastricUntreatedResponses = Select[PDXclinicaltrialresponses,
   And[MemberQ[GastricModels, #[[1]]], #[[2]] == "untreated"] &];

(* this function takes two lists of PFS times (treated and untreated) and computes
 the hazard ratio by Cox Model *)
CoxModelRisk[DrugResponses_, UntreatedResponses_] := Module[{},
  myeventdata = EventData[Join[DrugResponses, UntreatedResponses],
    Table[0, {Length[Join[DrugResponses, UntreatedResponses]]}]];
  descriptors = Join[Table["treated", {Length[DrugResponses]}],
    Table["no treatment", {Length[UntreatedResponses]}]];
  MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
    NominalVariables → treatment];
  RiskInterval = MyModelFit["RelativeRiskConfidenceIntervals"];
  MyModelFit["ParameterTable"]
 ]
```

```
(* melanoma *)
MelanomaTreatmentHazards =
  Table[{i, MonotherapiesByGroup[[1, i]],
    CoxModelRisk[
     Select[PDXclinicaltrialresponses,
       And[MemberQ[CutaneousMelanomaModels, #[[1]]], #[[2]] == MonotherapiesByGroup[[1, i]] &][
      All, 9]], MelanomaUntreatedResponses[[All, 9]]]}, {i, 1, Length[MonotherapiesByGroup[[1]]]}];

MelanomaTreatmentHazardsPValues =
  {MelanomaTreatmentHazards[[All, 1]], MelanomaTreatmentHazards[[All, 2]],
    MelanomaTreatmentHazards[[All, 3, 1, 1, 2, 4]], MelanomaTreatmentHazards[[All, 3, 1, 1, 2, 7]]}^T;
Export[NotebookDirectory[] <> "Melanoma monotherapy hazards.csv",
  Prepend[MelanomaTreatmentHazardsPValues,
   {"Treatment number", "Drug name", "Relative risk", "P-value, cox model"}], "CSV"];

MelanomaTreatmentHazards // TableForm
```

1	binimetinib		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−2.10628	0.340246	0.12169	38.3219	1	5.99861×10^{-10}
2	BKM120		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−1.27802	0.27887	0.278588	21.0026	1	4.58662×10^{-6}
3	CGM097		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−1.00265	0.269044	0.366905	13.8885	1	0.000193979
4	CLR457		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−1.5901	0.347878	0.203905	20.8928	1	4.85723×10^{-6}
5	dacarbazine		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−1.16221	0.283093	0.312794	16.8543	1	0.0000403615
6	encorafenib		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−1.21726	0.287914	0.296039	17.8749	1	0.0000235913
7	LDE225		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.565511	0.254296	0.56807	4.94542	1	0.02616
8	LDK378		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.694773	0.261454	0.499188	7.06148	1	0.00787589
9	LEE011		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−1.42719	0.292648	0.239982	23.7834	1	1.0781×10^{-6}
10	LGW813		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.858191	0.270429	0.423928	10.0708	1	0.00150641
11	TAS266		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.946571	0.275296	0.38807	11.8224	1	0.000585221
12	WNT974		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.617704	0.256913	0.539181	5.78081	1	0.0162021

```
(* NSCLC *)
NSCLCTreatmentHazards =
  Table[{i, MonotherapiesByGroup[[2, i]],
    CoxModelRisk[
     Select[PDXclinicaltrialresponses,
       And[MemberQ[NSCLCModels, #[[1]]], #[[2]] == MonotherapiesByGroup[[2, i]] &][[All, 9]],
     NSCLCUntreatedResponses[[All, 9]]]}, {i, 1, Length[MonotherapiesByGroup[[2]]]}];

NSCLCTreatmentHazardsPValues =
  {NSCLCTreatmentHazards[[All, 1]], NSCLCTreatmentHazards[[All, 2]],
    NSCLCTreatmentHazards[[All, 3, 1, 1, 2, 4]], NSCLCTreatmentHazards[[All, 3, 1, 1, 2, 7]]}^T;
Export[NotebookDirectory[] <> "NSCLC monotherapy hazards.csv",
  Prepend[NSCLCTreatmentHazardsPValues,
   {"Treatment number", "Drug name", "Relative risk", "P-value, cox model"}], "CSV"];

NSCLCTreatmentHazards // TableForm
```

			Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
1	BGJ398	treatment[treated]	−0.0684778	0.266913	0.933814	0.0658202	1	0.797523
2	binimetinib		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−1.35917	0.323019	0.256874	17.7049	1	0.0000257968
3	BKM120		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−1.09108	0.308473	0.335854	12.5106	1	0.000404654
4	BYL719		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.803651	0.283207	0.447691	8.05244	1	0.00454423
5	cetuximab		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.287151	0.271195	0.750398	1.12113	1	0.289674
6	CGM097		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.285101	0.275802	0.751938	1.06857	1	0.301269
7	CKX620		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−1.26007	0.30895	0.283634	16.6347	1	0.0000453149
8	CLR457		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.86216	0.285034	0.422249	9.1492	1	0.00248827
9	erlotinib		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.460806	0.275513	0.630775	2.79738	1	0.0944186
10	HDM201		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.30118	0.273095	0.739945	1.21625	1	0.270097
11	HSP990		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.579996	0.274924	0.5599	4.45065	1	0.0348879
12	INC280		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.168748	0.274334	0.844722	0.378371	1	0.538476
13	LEE011		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.762168	0.288615	0.466654	6.97371	1	0.00827159
14	LGH447		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.225641	0.265771	0.798004	0.720813	1	0.395877
15	LLM871		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.441107	0.275696	0.643324	2.55993	1	0.109603
16	paclitaxel		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.652435	0.288128	0.520776	5.12748	1	0.02355

```
(* PDAC *)
PDACTreatmentHazards =
  Table[{i, MonotherapiesByGroup[[3, i]],
    CoxModelRisk[
     Select[PDXclinicaltrialresponses,
       And[MemberQ[PDACModels, #[[1]]], #[[2]] == MonotherapiesByGroup[[3, i]] &][[All, 9]],
     PDACUntreatedResponses[[All, 9]]]}, {i, 1, Length[MonotherapiesByGroup[[3]]]}];

PDACTreatmentHazardsPValues =
  {PDACTreatmentHazards[[All, 1]], PDACTreatmentHazards[[All, 2]],
    PDACTreatmentHazards[[All, 3, 1, 1, 2, 4]], PDACTreatmentHazards[[All, 3, 1, 1, 2, 7]]}^T;
Export[NotebookDirectory[] <> "PDAC monotherapy hazards.csv",
  Prepend[PDACTreatmentHazardsPValues,
   {"Treatment number", "Drug name", "Relative risk", "P-value, cox model"}], "CSV"];

PDACTreatmentHazards // TableForm
```

1	abraxane		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	0.147659	0.235112	1.15912	0.394432	1	0.529979
2	binimetinib		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−1.4835	0.255431	0.226843	33.7306	1	6.32977×10^{-9}
3	binimetinib−3.5mpk		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.623669	0.251474	0.535974	6.15065	1	0.0131364
4	BKM120		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.896429	0.244858	0.408024	13.403	1	0.000251223
5	BYL719		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−1.1982	0.247489	0.301738	23.4393	1	1.28918×10^{-6}
6	CLR457		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−1.07466	0.244022	0.341414	19.3947	1	0.0000106302
7	figitumumab"		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.268031	0.23422	0.764884	1.30956	1	0.252475
8	gemcitabine−50mpk		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−1.45782	0.266643	0.232742	29.8917	1	4.56857×10^{-8}
9	HDM201		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.456934	0.237225	0.633222	3.7101	1	0.0540842
10	INC424		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.688202	0.238856	0.502478	8.30155	1	0.00396112
11	LEE011		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.518453	0.243805	0.595441	4.52202	1	0.0334613
12	LKA136		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.149673	0.231519	0.860989	0.41794	1	0.517967
13	trametinib		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−1.21992	0.255853	0.295254	22.7343	1	1.8602×10^{-6}
14	WNT974		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.15769	0.234154	0.854115	0.453528	1	0.500664

```
(* Colorectal *)
CRCTreatmentHazards =
  Table[{i, MonotherapiesByGroup[[4, i]],
    CoxModelRisk[
     Select[PDXclinicaltrialresponses,
       And[MemberQ[ColorectalModels, #[[1]]], #[[2]] == MonotherapiesByGroup[[4, i]] &][[All, 9]],
     CRCUntreatedResponses[[All, 9]]]}, {i, 1, Length[MonotherapiesByGroup[[4]]]}];

CRCTreatmentHazardsPValues =
  {CRCTreatmentHazards[[All, 1]], CRCTreatmentHazards[[All, 2]],
    CRCTreatmentHazards[[All, 3, 1, 1, 2, 4]], CRCTreatmentHazards[[All, 3, 1, 1, 2, 7]]}^T;
Export[NotebookDirectory[] <> "CRC monotherapy hazards.csv",
  Prepend[CRCTreatmentHazardsPValues,
   {"Treatment number", "Drug name", "Relative risk", "P-value, cox model"}], "CSV"];

CRCTreatmentHazards // TableForm
```

1	5FU		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.723893	0.225323	0.484861	10.3214	1	0.00131497
2	binimetinib		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.66484	0.22676	0.514356	8.59611	1	0.00336882
3	BKM120		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.70694	0.22709	0.493151	9.69101	1	0.00185171
4	BYL719		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.66063	0.222988	0.516526	8.77713	1	0.00305031
5	cetuximab		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.541784	0.227247	0.58171	5.68401	1	0.0171202
6	CGM097		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.170156	0.227263	0.843534	0.560577	1	0.454028
7	CKX620		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.994687	0.233217	0.369839	18.1908	1	0.0000199839
8	CLR457		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.933288	0.227151	0.393259	16.8812	1	0.0000397939
9	encorafenib		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	0.0205339	0.223582	1.02075	0.00843467	1	0.926825
10	HDM201		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.110487	0.228337	0.895398	0.234136	1	0.628474
11	LEE011		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.604441	0.226898	0.54638	7.09655	1	0.00772326
12	LJC049		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	0.242519	0.225003	1.27446	1.16176	1	0.281101
13	LKA136		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.0504631	0.224741	0.950789	0.0504175	1	0.822338

```
(* Breast *)
BreastTreatmentHazards =
  Table[{i, MonotherapiesByGroup[[5, i]],
    CoxModelRisk[
     Select[PDXclinicaltrialresponses,
       And[MemberQ[BreastModels, #[[1]]], #[[2]] == MonotherapiesByGroup[[5, i]] &][[All, 9]],
     BreastUntreatedResponses[[All, 9]]]}, {i, 1, Length[MonotherapiesByGroup[[5]]]}];

BreastTreatmentHazardsPValues =
  {BreastTreatmentHazards[[All, 1]], BreastTreatmentHazards[[All, 2]],
    BreastTreatmentHazards[[All, 3, 1, 1, 2, 4]], BreastTreatmentHazards[[All, 3, 1, 1, 2, 7]]}^T;
Export[NotebookDirectory[] <> "Breast monotherapy hazards.csv",
  Prepend[BreastTreatmentHazardsPValues,
   {"Treatment number", "Drug name", "Relative risk", "P-value, cox model"}], "CSV"];

BreastTreatmentHazards // TableForm
```

1	BGJ398		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.490923	0.230468	0.612061	4.53739	1	0.0331621
2	binimetinib		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.906032	0.24276	0.404125	13.9295	1	0.000189799
3	BKM120		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−1.24207	0.243766	0.288786	25.9625	1	3.4812×10^{-7}
4	BYL719		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.946767	0.242088	0.387993	15.2946	1	0.0000919777
5	CGM097		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.0129245	0.233108	0.987159	0.00307407	1	0.955784
6	CLR457		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−1.24131	0.244078	0.289005	25.8644	1	3.66261×10^{-7}
7	HDM201		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.414466	0.231197	0.660693	3.21377	1	0.0730209
8	INC424		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.433803	0.234531	0.64804	3.42124	1	0.0643626
9	LEE011		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.877965	0.237321	0.415628	13.6862	1	0.000216033
10	LFA102		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.275897	0.229694	0.758891	1.44276	1	0.229693
11	LJM716		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.581387	0.232	0.559122	6.27993	1	0.0122113
12	LKA136		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.142562	0.234311	0.867134	0.370185	1	0.542903
13	LLM871		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.918126	0.237205	0.399267	14.9816	1	0.000108566
14	paclitaxel		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−1.08015	0.242126	0.339545	19.9014	1	8.15407×10^{-6}
15	tamoxifen		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.231314	0.229865	0.793491	1.01264	1	0.314271
16	trastuzumab		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.25193	0.23124	0.777299	1.18695	1	0.275945

```
(* Gastric *)
GastricTreatmentHazards =
  Table[{i, MonotherapiesByGroup[[6, i]],
    CoxModelRisk[
     Select[PDXclinicaltrialresponses,
       And[MemberQ[GastricModels, #[[1]]], #[[2]] == MonotherapiesByGroup[[6, i]] &][[All, 9]],
     GastricUntreatedResponses[[All, 9]]]}, {i, 1, Length[MonotherapiesByGroup[[6]]]}];

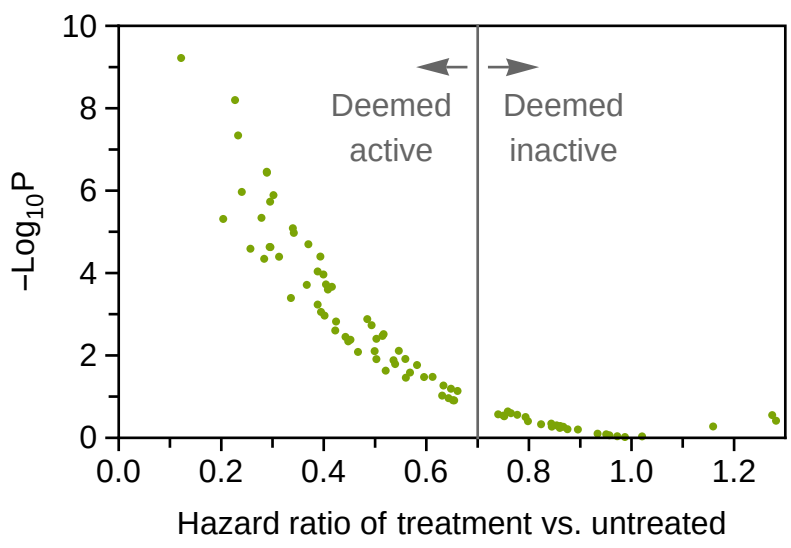
GastricTreatmentHazardsPValues =
  {GastricTreatmentHazards[[All, 1]], GastricTreatmentHazards[[All, 2]],
    GastricTreatmentHazards[[All, 3, 1, 1, 2, 4]], GastricTreatmentHazards[[All, 3, 1, 1, 2, 7]]}^T;
Export[NotebookDirectory[] <> "Gastric monotherapy hazards.csv",
  Prepend[GastricTreatmentHazardsPValues,
   {"Treatment number", "Drug name", "Relative risk", "P-value, cox model"}], "CSV"];

GastricTreatmentHazards // TableForm
```

1	BGJ398		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.424442	0.27594	0.654135	2.36596	1	0.124008
2	binimetinib		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.816005	0.279887	0.442195	8.50003	1	0.0035514
3	BKM120		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.93013	0.279726	0.394503	11.0566	1	0.000883743
4	BYL719		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−1.22277	0.289005	0.294413	17.901	1	0.0000232695
5	CLR457		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.793777	0.276999	0.452134	8.21186	1	0.00416175
6	everolimus		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.912679	0.279212	0.401447	10.6848	1	0.00108019
7	figitumumab"		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	0.248261	0.285972	1.28179	0.753651	1	0.385323
8	HDM201		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.150545	0.269618	0.860239	0.311771	1	0.576595
9	HSP990		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.193922	0.267681	0.823723	0.524827	1	0.46879
10	INC280		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.0441361	0.268939	0.956824	0.0269328	1	0.869643
11	LEE011		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.688222	0.274888	0.502469	6.26823	1	0.0122922
12	LJM716		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.133236	0.268148	0.875259	0.246884	1	0.619278
13	LLM871		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.427938	0.277274	0.651852	2.382	1	0.12274
14	trastuzumab		Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
		treatment[treated]	−0.0281482	0.273145	0.972244	0.0106198	1	0.917921

A natural gap presents itself in the distribution of hazard ratios, separating hazard ratios larger or smaller than 0.7; this position coincides with P-values greater or smaller than approximately 0.1.
We take this gap as a convenient distinction between monotherapies that we deem 'active' and or 'inactive'. We consider the slight lenience in P-value acceptable in light of modest numbers of xenografts tested with each therapy (as compared to human clinical trials) and because this distinction has little significance - it is only used for measuring the distribution of response correlations between 'active' agents (which is little different from response correlations between all agents).

```
ListPlot[Join[
  {MelanomaTreatmentHazardsPValues[[All, 3]], -Log[10, MelanomaTreatmentHazardsPValues[[All, 4]]]}^T,
  {NSCLCTreatmentHazardsPValues[[All, 3]], -Log[10, NSCLCTreatmentHazardsPValues[[All, 4]]]}^T,
  {PDACTreatmentHazardsPValues[[All, 3]], -Log[10, PDACTreatmentHazardsPValues[[All, 4]]]}^T,
  {CRCTreatmentHazardsPValues[[All, 3]], -Log[10, CRCTreatmentHazardsPValues[[All, 4]]]}^T,
  {BreastTreatmentHazardsPValues[[All, 3]], -Log[10, BreastTreatmentHazardsPValues[[All, 4]]]}^T,
  {GastricTreatmentHazardsPValues[[All, 3]], -Log[10, GastricTreatmentHazardsPValues[[All, 4]]]}^T
 ], PlotRange → {{0, 1.3}, {0, 10}}, Frame → True, Axes → False,
 FrameLabel → {"Hazard ratio of treatment vs. untreated", "-Log10P"},
 ImageSize → {{1000}, {200}}, FrameStyle → Directive[Black, Thickness[Medium]],
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 PlotStyle → Directive[AbsolutePointSize[3], Darker[ColorData[3, 4], 0.1]],
 FrameTicks →
  {{Join[Table[{i, i, {0, 0.02}}, {i, 0, 10, 2}], Table[{i, , {0, 0.015}}, {i, 1, 9, 2}]], None},
   {Join[Table[{i, NumberForm[i, {2, 1}], {0, 0.02}}, {i, 0, 2, 0.2}],
     Table[{i, , {0, 0.015}}, {i, 0.1, 2, 0.2}]], None}},
 Epilog → {GrayLevel[0.4], Thickness[Medium], Line[{{0.7, 0}, {0.7, 10}}], Arrowheads[0.05],
   Arrow[{{0.68, 9}, {0.58, 9}}], Arrow[{{0.72, 9}, {0.82, 9}}],
   Text["Deemed\nactive", {0.65, 8.5}, {1, 1}], Text["Deemed\ninactive", {0.75, 8.5}, {-1, 1}]}
]
```




```
(* designating lists of individually active agents, according to having hazard ratio ≤ 0.7,
which coincides with P-value by Cox Model of approximately <0.1 *)
MelanomaActiveAgents = Select[MelanomaTreatmentHazardsPValues, #[[3]] < 0.7 &][[All, 1]];
NSCLCActiveAgents = Select[NSCLCTreatmentHazardsPValues, #[[3]] < 0.7 &][[All, 1]];
PDACActiveAgents = Select[PDACTreatmentHazardsPValues, #[[3]] < 0.7 &][[All, 1]];
CRCActiveAgents = Select[CRCTreatmentHazardsPValues, #[[3]] < 0.7 &][[All, 1]];
BreastActiveAgents = Select[BreastTreatmentHazardsPValues, #[[3]] < 0.7 &][[All, 1]];
GastricActiveAgents = Select[GastricTreatmentHazardsPValues, #[[3]] < 0.7 &][[All, 1]];
```

Estimating the effect of hypothetical combinations under the assumption of independent drug action

```
(* from the above measurements of hazard ratios,
```

```
we note the most effective monotherapies per tumor type,
as evaluated by hazard ratio. These are used as a point of comparison to compute
 the hazard ratio of each hypothetical combination compared to the most effective
 monotherapy for each tumor type.
  Where multiple treatments appear similarly efficacious,
they are each used as a point of comparison,
with the final reported hazard ratio of a hypothetical combination always based on
 comparison against the most competitive observed monotherapy. *)
BestMonotherapiesPerTumorType = {{"binimetinib"}, {"binimetinib", "BKM120", "CKX620"},
   {"binimetinib", "gemcitabine-50mpk"}, {"CKX620", "CLR457"}, {"BKM120", "CLR457"}, {"BYL719"}};
(* note, to appropriately choose the drug(s) for comparison,
the 'modelnumber' variable (a number from 1 to 6) must be correctly defined before
 calling the function. *)

(* this function takes two drugs and a tumor type
 (specifying a list of PDX models,
  and the name of that tumor type for purpose of labeling a plot),
and computes the effect expected under the hypothetical combination with independent
 drug action, where each PDXs response to the combination is the best one of the
 two observed PFS times *)
IndependentActionPrediction[DrugA_, DrugB_, ModelSet_, ModelName_] :=
 Module[{(*DrugAresponses,DrugBresponses,ModelsInBothMonotherapies,
   DrugAresponsesInIntersection,DrugBresponsesInIntersection,UntreatedResponsesInIntersection,
   BestOfMonotherapyResponses*)},

  (* all responses to drug A in the set of PDX models *)
  DrugAresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelSet, #[[1]]],
      #[[2]] == DrugA] &];
  % // Length;

  (* all responses to drug B in the set of PDX models *)
  DrugBresponses = Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelSet, #[[1]]],
      #[[2]] == DrugB] &];
  % // Length;

  (* this function converts a set of PFS times to a survival distribution *)
  DoublingFreeSurvival[ClinicalTrialResponses_] :=
   SurvivalFunction[EmpiricalDistribution[ClinicalTrialResponses[[All, 9]]]];

(* this function computes a hazard ratio between two sets of responses;
intended here to compare the best observed monotherapy with the predicted effects
 of a hypothetical combination *)
HazardRatio[BestMonotherapyResponses_, PredictedCombinationResponses_] := Module[{},
  (* hazard ratio by Cox Model *)
  myeventdata = EventData[Join[BestMonotherapyResponses, PredictedCombinationResponses],
    Table[0, {Length[Join[BestMonotherapyResponses, PredictedCombinationResponses]]}]];
  descriptors = Join[Table["Observed monotherapy responses",
     {Length[BestMonotherapyResponses]}],
    Table["predicted combination", {Length[PredictedCombinationResponses]}]];
  MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
    NominalVariables → treatment];
  RelativeRisk = MyModelFit["RelativeRisk"][[1]];
  PValue = MyModelFit["ParameterTable"][[1, 1, 2, -1]];
  {RelativeRisk, PValue}
 ];
```

```
(* which PDX models were tested in both monotherapies? Only this intersecting
 set can be used for the comparison. *)
ModelsInBothMonotherapies = Intersection[DrugAresponses[[All, 1]], DrugBresponses[[All, 1]]];

(* don't attempt to calculate a survival curve when the number of intersecting
 models (treated with both drugA and drugB monotherapies) is fewer than this number. *)
MinimalNumberOfIntersectingModels = 10;
(* If too few PDXs are tested in both therapies, report this error message of all zeros. *)
If[Length[ModelsInBothMonotherapies] < MinimalNumberOfIntersectingModels,
 Return[{0, 0, 0, 0, 0}]];

(* responses to drug A in the intersecting set of PDX models *)
DrugAresponsesInIntersection = Sort[Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInBothMonotherapies, #[[1]]],
      #[[2]] == DrugA] &], #1[[1]] > #2[[1]] &];

(* responses to drug B in the intersecting set of PDX models *)
DrugBresponsesInIntersection = Sort[Select[PDXclinicaltrialresponses, And[
      MemberQ[ModelsInBothMonotherapies, #[[1]]],
      #[[2]] == DrugB] &], #1[[1]] > #2[[1]] &];

(* responses to no treatment in the intersecting set of PDX models *)
UntreatedResponsesInIntersection = Select[PDXclinicaltrialresponses, And[
     MemberQ[ModelsInBothMonotherapies, #[[1]]],
     #[[2]] == "untreated"] &];

(* responses to the best observed monotherapy for that tumor type in the intersecting
 set of PDX models. Because there are sometimes multiple drugs listed as candidate '
 best monotherapies', this is a list over different drugs. *)
BestMonotherapyForTumorTyperesponsesInIntersection = Table[
  Sort[Select[PDXclinicaltrialresponses, And[
       MemberQ[ModelsInBothMonotherapies, #[[1]]],
       #[[2]] == BestMonotherapiesPerTumorType[tumortype, BestMonotherapyIndex]] &],
    #1[[1]] > #2[[1]] &], {BestMonotherapyIndex, 1,
    Length[BestMonotherapiesPerTumorType[tumortype]]}];

(* this applies the principle of independent drug
 action: each PDX model's response is taken to be the stronger of its two observed
   responses to the two monotherapies *)
BestOfMonotherapyResponses =
 Table[ReplacePart[DrugAresponsesInIntersection[[i]],
   9 -> Max[{DrugAresponsesInIntersection[[i, 9]], DrugBresponsesInIntersection[[i, 9]]}]],
  {i, 1, Length[DrugAresponsesInIntersection]}];

(* computing the relative risk of the hypothetical combination versus the best
 observed monotherapies for that tumor type *)
RelativeRiskAndPValueAgainstBestMonotherapy =
 Sort[Table[HazardRatio[BestMonotherapyForTumorTyperesponsesInIntersection[
       BestMonotherapyIndex, All, 9]], BestOfMonotherapyResponses[[All, 9]]],
    {BestMonotherapyIndex, 1, Length[BestMonotherapyForTumorTyperesponsesInIntersection]}],
   #1[[1]] > #2[[1]] &][[1]];

(* Average PFS in each treatment condition *)
AverageUntreatedPFS = Mean[UntreatedResponsesInIntersection[[All, 9]]];
AverageDrugAPFS = Mean[DrugAresponsesInIntersection[[All, 9]]];
AverageDrugBPFS = Mean[DrugBresponsesInIntersection[[All, 9]]];
AveragePredictionPFS = Mean[BestOfMonotherapyResponses[[All, 9]]];
```

```
(* fold change in average PFS in comparison to no treatment,
and in comparison to the best of the two tested combination therapies. *)
ImprovementOverUntreated = AveragePredictionPFS / AverageUntreatedPFS;
ImprovementOverBestMonotherapy =
 AveragePredictionPFS / Max[{AverageDrugAPFS, AverageDrugBPFS}];

MinimalPredictedCombinationPlot = Plot[{
   DoublingFreeSurvival[UntreatedResponsesInIntersection][x],
   DoublingFreeSurvival[DrugAresponsesInIntersection][x],
   DoublingFreeSurvival[DrugBresponsesInIntersection][x],
   DoublingFreeSurvival[BestOfMonotherapyResponses][x]
  }, {x, 0, 200}, PlotRange → {{0, 120}, {0, 1}}, PlotPoints → 500, Exclusions → None,
  Frame → {{True, False}, {True, False}}, BaseStyle → {FontFamily → "Arial", FontSize → 12},
  FrameStyle → Directive[Black, Thickness[Medium]],
  PlotStyle → {Directive[GrayLevel[0.6], AbsoluteThickness[1.5]],
    Directive[ColorData[3, 2], AbsoluteThickness[2]],
    Directive[ColorData[3, 9], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]]},
  (*PlotLegends→{"Untreated",DrugA,DrugB,"Minimal prediction"},*)
  FrameLabel → {"Days", "Doubling-free survival"}, ImageSize -> {{250}, {250}},
   ImagePadding → {{50, 10}, {50, 10}}(*,PlotLabel→ModelName*),
   FrameTicks → {{Table[{i, NumberForm[N[i], {2, 1}], {0, 0.02}}, {i, 0, 1, 0.5}], None},
     {Table[{i, i, {0, 0.02}}, {i, 0, 120, 30}], None}}, AspectRatio → 3 / 4];

 (* computing correlation in drug response by Spearman's Rho Rank Correlation *)
 RankCorrelationBetweenAandBPFS = SpearmanRho[DrugAresponsesInIntersection[[All, 9]],
   DrugBresponsesInIntersection[[All, 9]]];

 {ImprovementOverUntreated, ImprovementOverBestMonotherapy, MinimalPredictedCombinationPlot,
  RankCorrelationBetweenAandBPFS, RelativeRiskAndPValueAgainstBestMonotherapy}
]
```

Examining the hypothetical combination of BYL719 (alpelisib) and LLM871 in gastric cancer xenografts

```
tumortype = 6;
drugAnumber = 4;
drugBnumber = 13;

BYL719LLM871Prediction =
  IndependentActionPrediction[MonotherapiesByGroup[[tumortype, drugAnumber]],
   MonotherapiesByGroup[[tumortype, drugBnumber]], AllModelGroups[[tumortype]],
   ModelNames[[tumortype]]];

Print[Style["untreated", Gray]]
Print[Style[MonotherapiesByGroup[[tumortype, drugAnumber]], ColorData[3, 2]]]
Print[Style[MonotherapiesByGroup[[tumortype, drugBnumber]], ColorData[3, 9]]]
Print[Style["hypothetical combination, according to independent action", Black]]
BYL719LLM871Prediction[[3]]

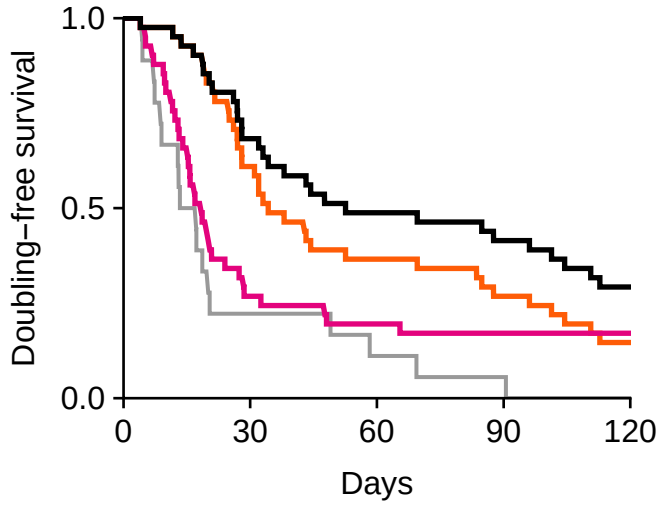
Print["Hazard ratio (predicted combination vs BYL719 alone) = " <>
  ToString[BYL719LLM871Prediction[[5, 1]]]]
Print["P-value = " <> ToString[BYL719LLM871Prediction[[5, 2]]]]
```

untreated

BYL719

LLM871

hypothetical combination, according to independent action



Hazard ratio (predicted combination vs BYL719 alone) = 0.64037

P−value = 0.0521545

Survival rates at 3 months :

```
Print["BYL719 PFS at 3 months = " <>
  ToString[Round[DoublingFreeSurvival[DrugAresponsesInIntersection][30.5 * 3] * 100]] <> "%"]
Print["LLM871 PFS at 3 months = " <>
  ToString[Round[DoublingFreeSurvival[DrugBresponsesInIntersection][30.5 * 3] * 100]] <> "%"]
Print["predicted combination PFS at 3 months = " <>
  ToString[Round[DoublingFreeSurvival[BestOfMonotherapyResponses][30.5 * 3] * 100]] <> "%"]
```

BYL719 PFS at 3 months = 27%

LLM871 PFS at 3 months = 17%

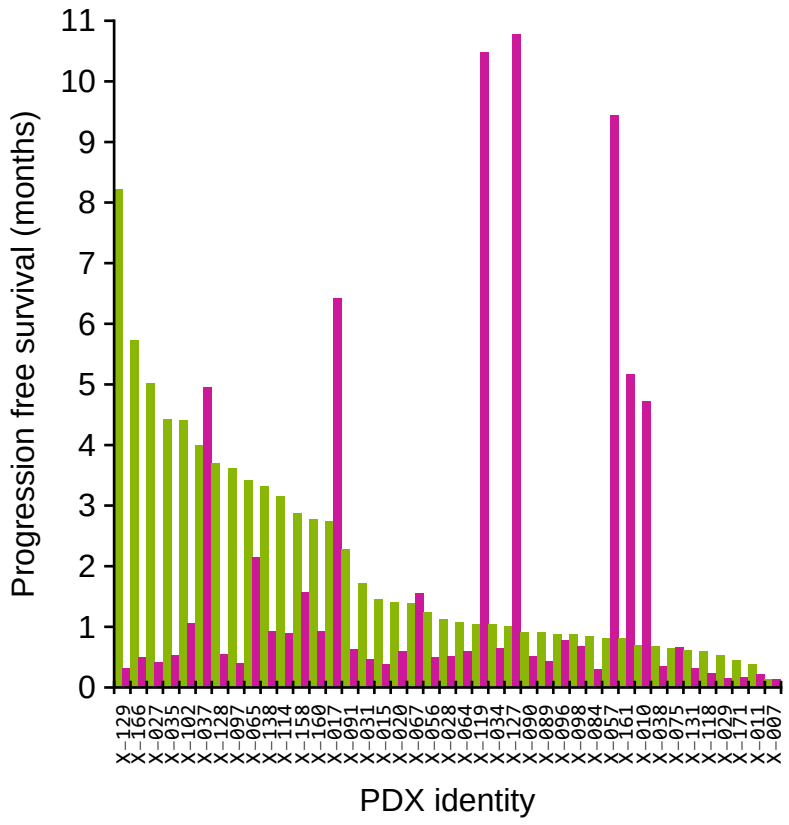
predicted combination PFS at 3 months = 41%

```
(* sorting drug responses and model names in order of best response to BYL719 *)
SortedResponses = Sort[{DrugAresponsesInIntersection[[All]], DrugBresponsesInIntersection[[All]]}^T,
    #1[[1, 9]] > #2[[1, 9]] &];
SortedModelNames = SortedResponses[[All, 1, 1]]
```

{X−129, X−166, X−027, X−035, X−102, X−037, X−128, X−097, X−065, X−138, X−114, X−158, X−160, X−017,
 X−091, X−031, X−015, X−020, X−067, X−056, X−028, X−064, X−119, X−034, X−127, X−090, X−089, X−096,
 X−098, X−084, X−057, X−161, X−010, X−038, X−075, X−131, X−118, X−029, X−171, X−011, X−007}

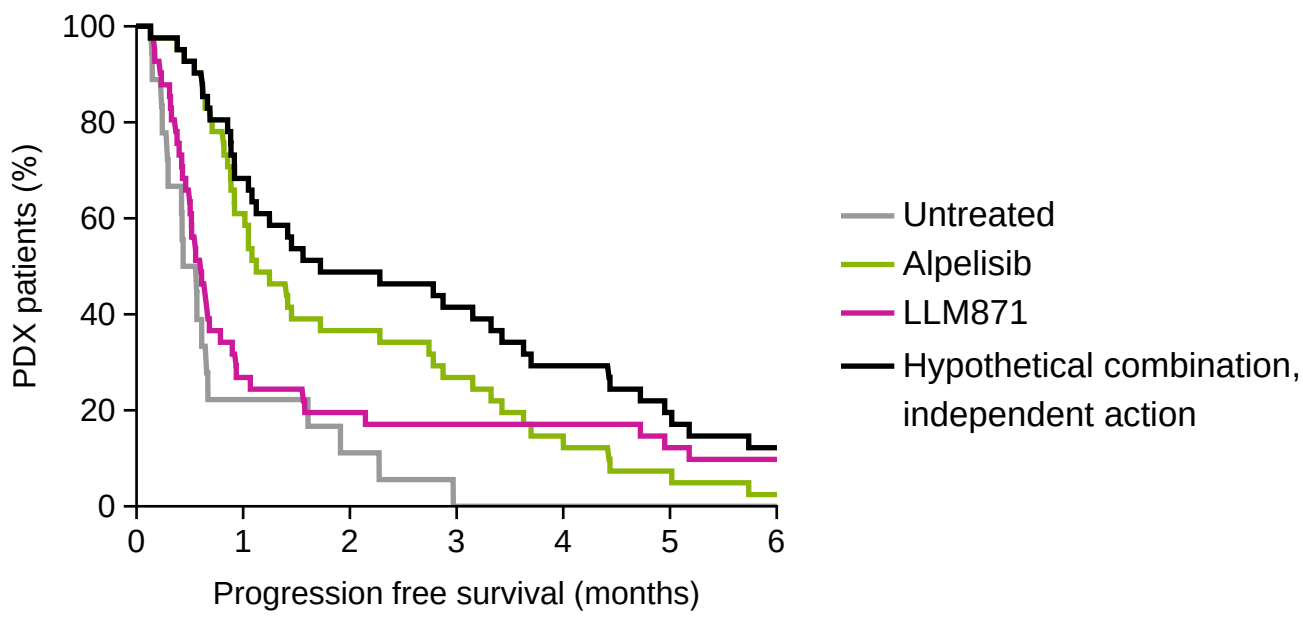
```
GastricExampleBarChartPlot = BarChart[{SortedResponses[[All, 1, 9]], SortedResponses[[All, 2, 9]]}^T,
  BarOrigin → Bottom, Axes → {False, False}, Frame → {{True, False}, {True, False}},
  FrameLabel → {"PDX identity", "Progression free survival (months)"},
  ChartStyle → {Directive[ColorData[3, 4], EdgeForm[None]],
    Directive[RGBColor[0.8, 0.1, 0.6], EdgeForm[None]]},
  BaseStyle → {FontFamily → "Arial", FontSize → 12},
  FrameStyle → Directive[Black, Thickness[Medium]],
  FrameTicks →
   Reverse[{Join[Table[{i, i / 61 * 2, {0, 0.015}}, {i, 0, 12 * 61 / 2, 61}],
      Table[{i, i / 61 * 2, {0, 0.015}}, {i, 61 / 2, 12 * 61 / 2, 61}]],
     Join[Table[{i, , {0.01, 0.01}}, {i, 0 + 1 / 2, 41 * 2 + 1 / 2, 2}],
      Table[{i, Rotate[Style[SortedModelNames[[(i + 1) / 2 - 1 / 4]], FontSize → 8,
          FontFamily → "Consolas"], π / 2], {0, 0}}, {i, 1 + 1 / 2, 41 * 2 + 1 / 2, 2}]]}],
  PlotRangePadding → None, PlotRange → Reverse[{{0, 11 * 61 / 2}, {1 / 2, 41 * 2 + 1 / 2}}],
  ImagePadding → {{60, 10}, {60, 10}}, ImageSize -> {{320}, {1000}}, AspectRatio → 1,
  BarSpacing → {0, 0}]

Export[NotebookDirectory[] <> "Figure 2B, PFS with BYL719 and LLM871.pdf",
 GastricExampleBarChartPlot, "PDF"];
```



```
GastricExampleSurvivalPlot = Plot[{
    DoublingFreeSurvival[UntreatedResponsesInIntersection][x],
    DoublingFreeSurvival[DrugAresponsesInIntersection][x],
    DoublingFreeSurvival[DrugBresponsesInIntersection][x],
    DoublingFreeSurvival[BestOfMonotherapyResponses][x]
   }, {x, 0, 200}, PlotRange → {{0, 6 * 61 / 2}, {0, 1}}, PlotPoints → 500, Exclusions → None,
   Frame → {{True, False}, {True, False}}, BaseStyle → {FontFamily → "Arial", FontSize → 12},
   FrameStyle → Directive[Black, Thickness[Medium]],
   PlotStyle → {Directive[GrayLevel[0.6], AbsoluteThickness[2]],
     Directive[ColorData[3, 4], AbsoluteThickness[2]],
     Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[2]],
     Directive[Black, AbsoluteThickness[2]]},
   (*PlotLegends→{"Untreated",DrugA,DrugB,"Minimal prediction"},*)
   FrameLabel → {"Progression free survival (months)", Rotate["PDX patients (%)", 0]},
   ImageSize -> {{1000}, {240}}, ImagePadding → {{50, 10}, {50, 10}}(*,PlotLabel→ModelName*),
   FrameTicks → {{Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}], None},
     {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 6 * 61 / 2, 61 / 2}], None}}, AspectRatio → 3 / 4,
   PlotLegends →
    LineLegend[{"Untreated", "Alpelisib", "LLM871",
      "Hypothetical combination,\nindependent action"}, Spacings → {0.25, 0.4},
    LegendMarkerSize → {20, 12}]]

Export[NotebookDirectory[] <> "Figure 2C, survival plot with BYL719 and LLM871.pdf",
  GastricExampleSurvivalPlot, "PDF"];
```



Predictions from drug pairs in each tumor type

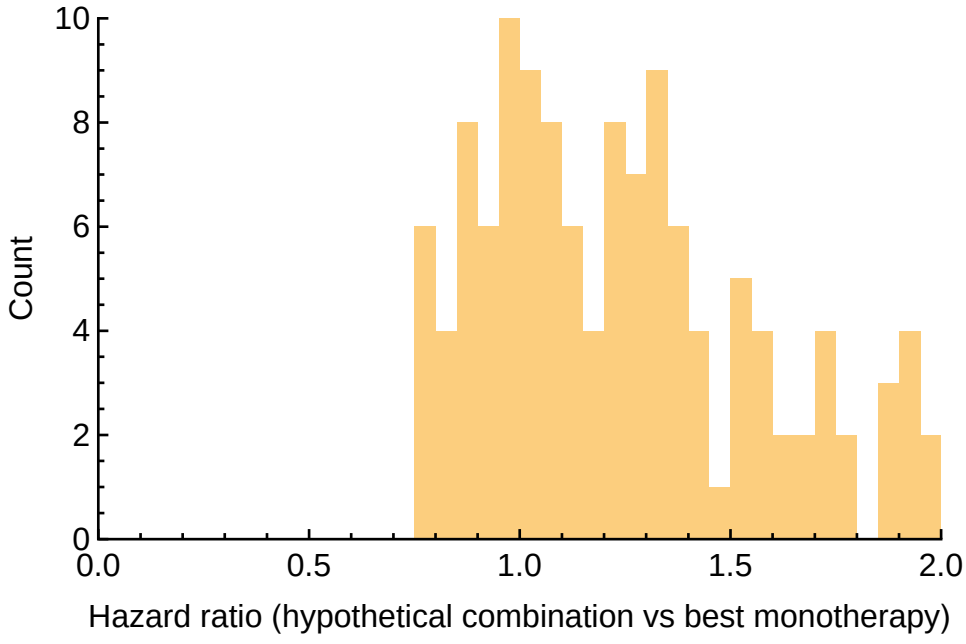
Note, this step is time-consuming

Testing all possible pairs of monotherapies in melanoma

```
tumortype = 1;
AllMelanomaPairs =
  Parallelize[Table[IndependentActionPrediction[MonotherapiesByGroup[[tumortype, i]],
     MonotherapiesByGroup[[tumortype, j]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]
    , {i, 1, Length[MonotherapiesByGroup[[tumortype]]]},
    {j, 1, Length[MonotherapiesByGroup[[tumortype]]]}]];
```

```
(* Response correlations between all agents *)
MelanomaResponseCorrelations =
  Flatten[Table[Table[AllMelanomaPairs[[i, j, 4]], {i, 1, j - 1}],
    {j, 2, Length[AllMelanomaPairs]}]];
(* Response correlations between active agents only *)
MelanomaResponseCorrelationsActiveAgentsOnly =
  Flatten[Table[Table[AllMelanomaPairs[[MelanomaActiveAgents, MelanomaActiveAgents]][[i, j, 4]],
     {i, 1, j - 1}],
    {j, 2, Length[AllMelanomaPairs[[MelanomaActiveAgents, MelanomaActiveAgents]]]}]];

(* histogram of hazard ratios *)
Histogram[Flatten[AllMelanomaPairs[[All, All, 5, 1]]], {0, 2, 0.05},
 Frame → {{True, False}, {True, False}},
 FrameLabel → {"Hazard ratio (hypothetical combination vs best monotherapy)", "Count"},
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]], PlotRangePadding → None,
 ChartStyle → EdgeForm[None]]
```



In melanoma, the best 'predicted combination' was among those experimentally tested and was the most effective observed combination in melanoma.
By independent action alone it is not expected to significantly improve on monotherapy (p=0.29); but it was observed to far surpass independent action (See Supplementary Figure S4D).

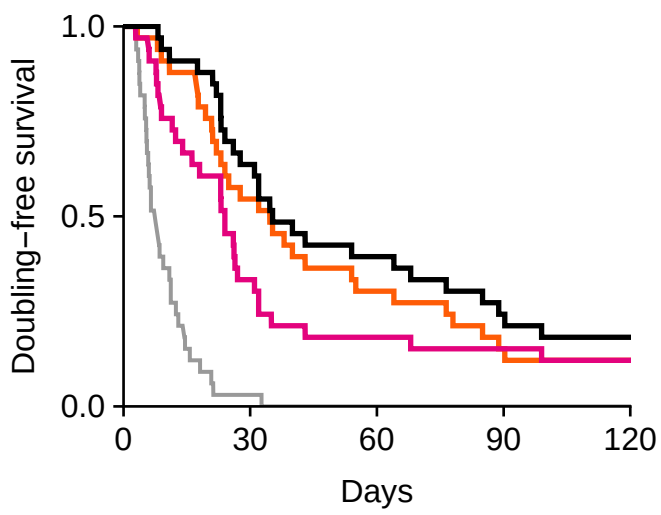
```
tumortype = 1;
MelanomaBestPrediction = Max[AllMelanomaPairs[[All, All, 1]]];
MelanomaBestPredictionPosition =
  Position[AllMelanomaPairs[[All, All, 1]], MelanomaBestPrediction][[1]];
MonotherapiesByGroup[[tumortype, MelanomaBestPredictionPosition[[1]]]]
MonotherapiesByGroup[[tumortype, MelanomaBestPredictionPosition[[2]]]]
Print["{Hazard ratio, P value} = "]
AllMelanomaPairs[[MelanomaBestPredictionPosition[[1]], MelanomaBestPredictionPosition[[2]], 5]]
AllMelanomaPairs[[MelanomaBestPredictionPosition[[1]], MelanomaBestPredictionPosition[[2]],
 3]]
```

```
binimetinib
```

```
LEE011
```

```
{Hazard ratio, P value} =
```

```
{0.766513, 0.28657}
```



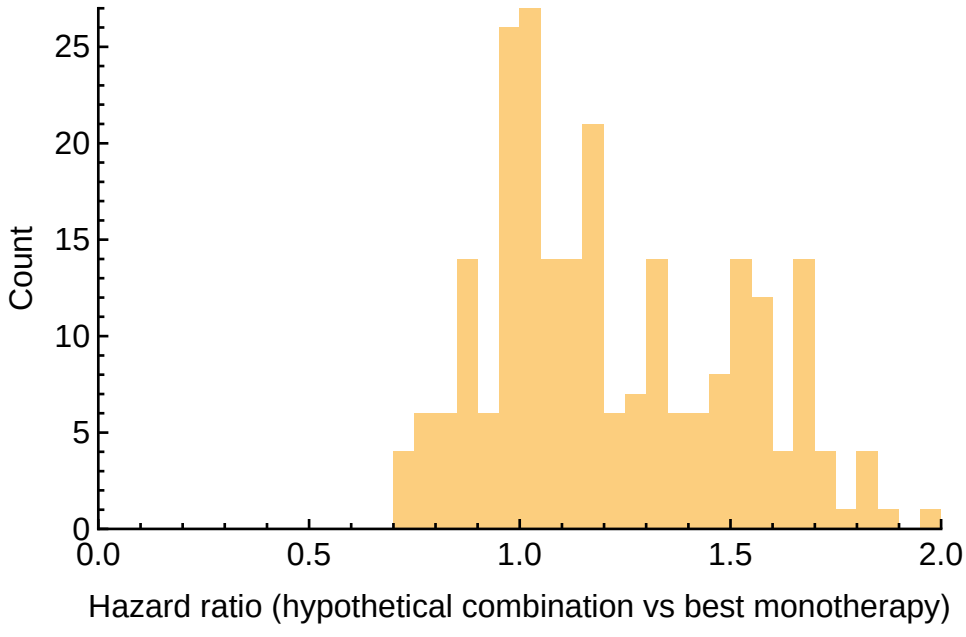
Testing all possible pairs of monotherapies in NSCLC

```
tumortype = 2;
```

```
AllNSCLCPairs =
  Parallelize[Table[IndependentActionPrediction[MonotherapiesByGroup[[tumortype, i]],
     MonotherapiesByGroup[[tumortype, j]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]
    , {i, 1, Length[MonotherapiesByGroup[[tumortype]]]},
    {j, 1, Length[MonotherapiesByGroup[[tumortype]]]}]];
```

```
(* Response correlations between all agents *)
NSCLCResponseCorrelations =
  Flatten[Table[Table[AllNSCLCPairs[[i, j, 4]], {i, 1, j - 1}], {j, 2, Length[AllNSCLCPairs]}]];
(* Response correlations between active agents only *)
NSCLCResponseCorrelationsActiveAgentsOnly =
  Flatten[Table[Table[AllNSCLCPairs[[NSCLCActiveAgents, NSCLCActiveAgents]][[i, j, 4]], {i, 1, j - 1}],
    {j, 2, Length[AllNSCLCPairs[[NSCLCActiveAgents, NSCLCActiveAgents]]]}]];

(* histogram of hazard ratios *)
Histogram[Flatten[AllNSCLCPairs[[All, All, 5, 1]]], {0, 2, 0.05},
 Frame → {{True, False}, {True, False}},
 FrameLabel → {"Hazard ratio (hypothetical combination vs best monotherapy)", "Count"},
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]], PlotRangePadding → None,
 ChartStyle → EdgeForm[None]]
```



In NSCLC, the best 'predicted combination' was among those experimentally tested and was the most effective observed combination in NSCLC (tied for efficacy with LFW527 + binimetinib).
Although, from independent action alone there was not a statistically significant expectation of benefit (p=0.23), and its observed effect was indeed not significantly superior to binimetinib monotherapy.

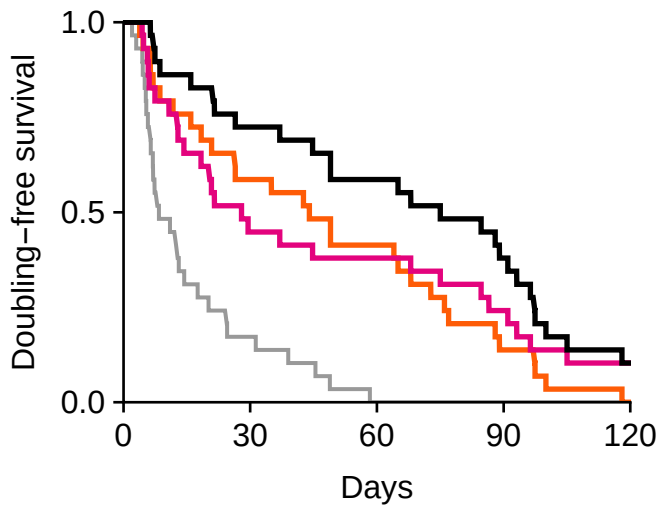
```
tumortype = 2;
NSCLCBestPrediction = Max[AllNSCLCPairs[[All, All, 1]]];
NSCLCBestPredictionPosition = Position[AllNSCLCPairs[[All, All, 1]], NSCLCBestPrediction][[1]];
MonotherapiesByGroup[[tumortype, NSCLCBestPredictionPosition[[1]]]
MonotherapiesByGroup[[tumortype, NSCLCBestPredictionPosition[[2]]]
Print["{Hazard ratio, P value} = "]
AllNSCLCPairs[[NSCLCBestPredictionPosition[[1]], NSCLCBestPredictionPosition[[2]], 5]]
AllNSCLCPairs[[NSCLCBestPredictionPosition[[1]], NSCLCBestPredictionPosition[[2]], 3]]
```

```
binimetinib

BKM120

{Hazard ratio, P value} =

{0.729869, 0.232704}
```



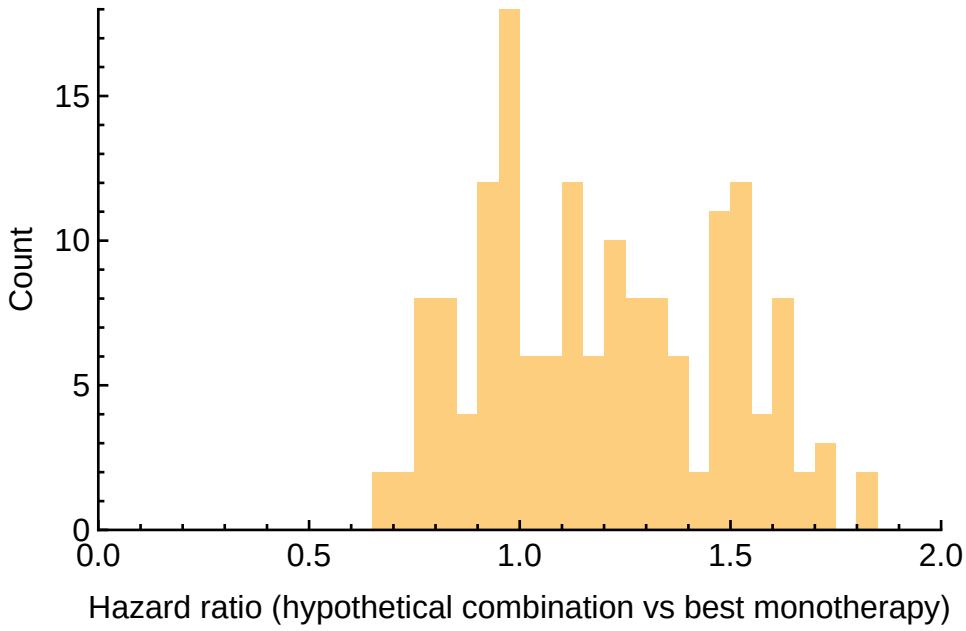
Testing all possible pairs of monotherapies in PDAC

```
tumortype = 3;

AllPDACPairs =
Table[IndependentActionPrediction[MonotherapiesByGroup[[tumortype, i]],
  MonotherapiesByGroup[[tumortype, j]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]
 , {i, 1, Length[MonotherapiesByGroup[[tumortype]]]},
 {j, 1, Length[MonotherapiesByGroup[[tumortype]]]}];
```

```
(* Response correlations between all agents *)
PDACResponseCorrelations =
  Flatten[Table[Table[AllPDACPairs[[i, j, 4]], {i, 1, j - 1}], {j, 2, Length[AllPDACPairs]}]];
(* Response correlations between active agents only *)
PDACResponseCorrelationsActiveAgentsOnly =
  Flatten[Table[Table[AllPDACPairs[[PDACActiveAgents, PDACActiveAgents]][[i, j, 4]], {i, 1, j - 1}],
    {j, 2, Length[AllPDACPairs[[PDACActiveAgents, PDACActiveAgents]]}]]];

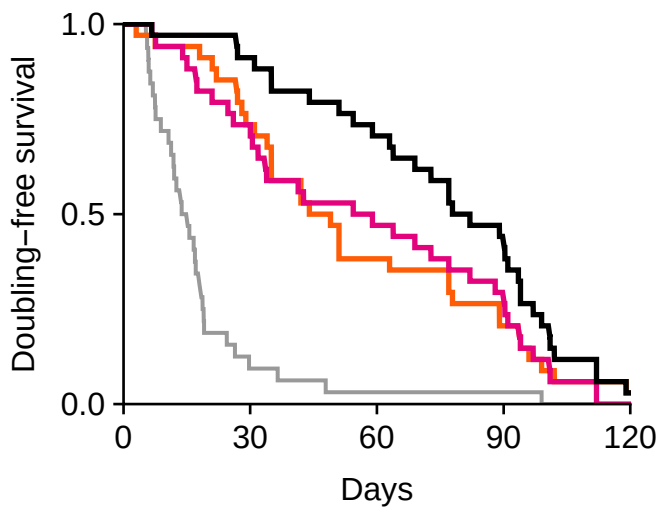
(* histogram of hazard ratios *)
Histogram[Flatten[AllPDACPairs[[All, All, 5, 1]]], {0, 2, 0.05},
 Frame → {{True, False}, {True, False}},
 FrameLabel → {"Hazard ratio (hypothetical combination vs best monotherapy)", "Count"},
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]], PlotRangePadding → None,
 ChartStyle → EdgeForm[None]]
```



Best predicted combination in PDAC:

```
tumortype = 3;
PDACBestPrediction = Max[AllPDACPairs[[All, All, 1]]];
PDACBestPredictionPosition = Position[AllPDACPairs[[All, All, 1]], PDACBestPrediction][[1]];
MonotherapiesByGroup[[tumortype, PDACBestPredictionPosition[[1]]]]
MonotherapiesByGroup[[tumortype, PDACBestPredictionPosition[[2]]]]
Print["{Hazard ratio, P value} = "]
AllPDACPairs[[PDACBestPredictionPosition[[1]], PDACBestPredictionPosition[[2]], 5]]
AllPDACPairs[[PDACBestPredictionPosition[[1]], PDACBestPredictionPosition[[2]], 3]]
```

```
binimetinib
gemcitabine-50mpk
{Hazard ratio, P value} =
{0.654136, 0.0823313}
```



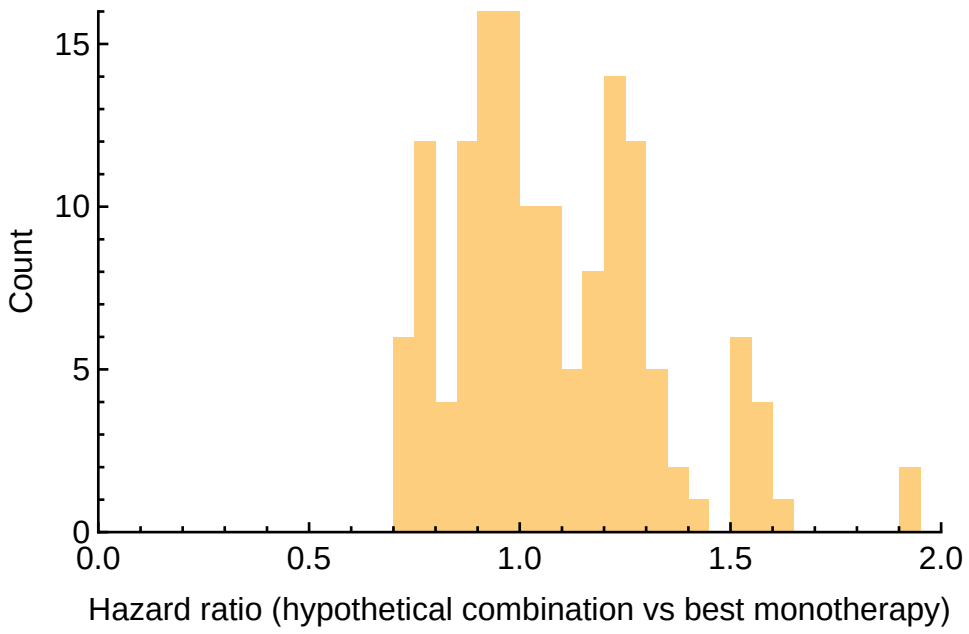
Testing all possible pairs of monotherapies in Colorectal carcinoma

```
tumortype = 4;

AllCRCPairs =
  Parallelize[Table[IndependentActionPrediction[MonotherapiesByGroup[[tumortype, i]],
     MonotherapiesByGroup[[tumortype, j]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]
    , {i, 1, Length[MonotherapiesByGroup[[tumortype]]]},
    {j, 1, Length[MonotherapiesByGroup[[tumortype]]]}]];

(* Response correlations between all agents *)
CRCResponseCorrelations =
  Flatten[Table[Table[AllCRCPairs[[i, j, 4]], {i, 1, j - 1}], {j, 2, Length[AllCRCPairs]}]];
(* Response correlations between active agents only *)
CRCResponseCorrelationsActiveAgentsOnly =
  Flatten[Table[Table[AllCRCPairs[[CRCActiveAgents, CRCActiveAgents]][[i, j, 4]], {i, 1, j - 1}],
    {j, 2, Length[AllCRCPairs[[CRCActiveAgents, CRCActiveAgents]]]}]];

(* histogram of hazard ratios *)
Histogram[Flatten[AllCRCPairs[[All, All, 5, 1]]], {0, 2, 0.05},
 Frame → {{True, False}, {True, False}},
 FrameLabel → {"Hazard ratio (hypothetical combination vs best monotherapy)", "Count"},
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]], PlotRangePadding → None,
 ChartStyle → EdgeForm[None]]
```



Best predicted combination in CRC:

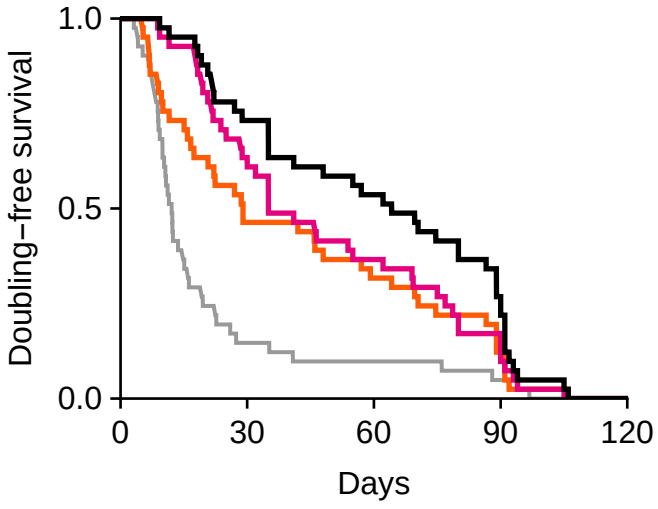
```
tumortype = 4;
CRCBestPrediction = Max[AllCRCPairs[[All, All, 1]]];
CRCBestPredictionPosition = Position[AllCRCPairs[[All, All, 1]], CRCBestPrediction][[1]];
MonotherapiesByGroup[[tumortype, CRCBestPredictionPosition[[1]]]]
MonotherapiesByGroup[[tumortype, CRCBestPredictionPosition[[2]]]]
Print["{Hazard ratio, P value} = "]
AllCRCPairs[[CRCBestPredictionPosition[[1]], CRCBestPredictionPosition[[2]], 5]]
AllCRCPairs[[CRCBestPredictionPosition[[1]], CRCBestPredictionPosition[[2]], 3]]
```

```
binimetinib
```

```
CLR457
```

```
{Hazard ratio, P value} =
```

```
{0.748279, 0.199989}
```



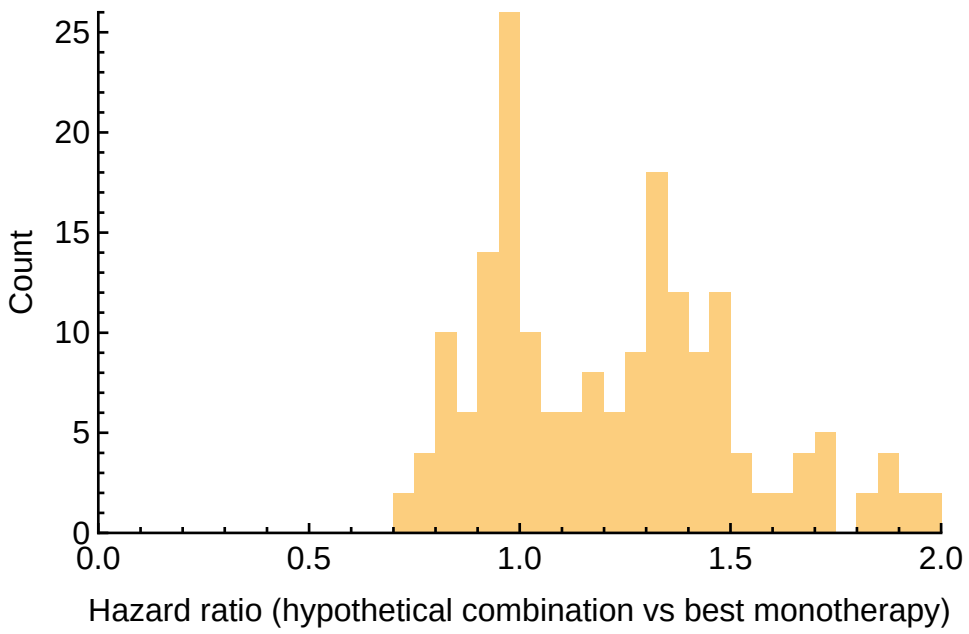
Testing all possible pairs of monotherapies in Breast cancer

```
tumortype = 5;

AllBCPairs =
  Parallelize[Table[IndependentActionPrediction[MonotherapiesByGroup[[tumortype, i]],
     MonotherapiesByGroup[[tumortype, j]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]
    , {i, 1, Length[MonotherapiesByGroup[[tumortype]]]},
    {j, 1, Length[MonotherapiesByGroup[[tumortype]]]}]];
```

```
(* Response correlations between all agents *)
BCResponseCorrelations =
  Flatten[Table[Table[AllBCPairs[[i, j, 4]], {i, 1, j - 1}], {j, 2, Length[AllBCPairs]}]];
(* Response correlations between active agents only *)
BCResponseCorrelationsActiveAgentsOnly =
  Flatten[Table[Table[AllBCPairs[[BreastActiveAgents, BreastActiveAgents]][[i, j, 4]], {i, 1, j - 1}],
    {j, 2, Length[AllBCPairs[[BreastActiveAgents, BreastActiveAgents]]]}]];

(* histogram of hazard ratios *)
Histogram[Flatten[AllBCPairs[[All, All, 5, 1]]], {0, 2, 0.05},
 Frame → {{True, False}, {True, False}},
 FrameLabel → {"Hazard ratio (hypothetical combination vs best monotherapy)", "Count"},
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]], PlotRangePadding → None,
 ChartStyle → EdgeForm[None]]
```



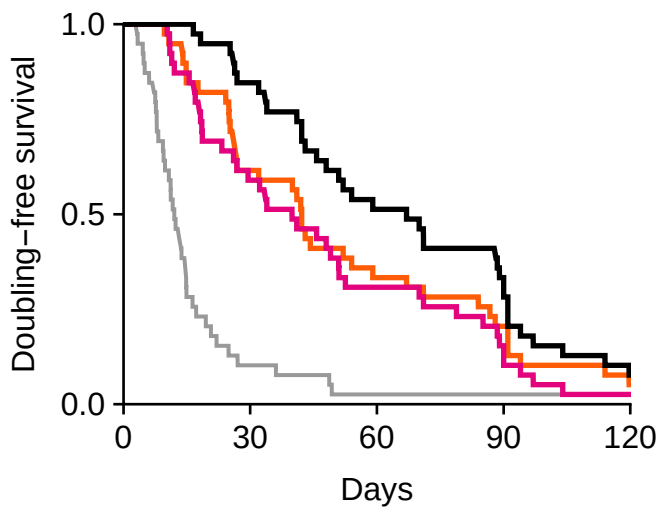

```
tumortype = 5;
BCBestPrediction = Max[AllBCPairs[[All, All, 1]]];
BCBestPredictionPosition = Position[AllBCPairs[[All, All, 1]], BCBestPrediction][[1]];
MonotherapiesByGroup[[tumortype, BCBestPredictionPosition[[1]]]]
MonotherapiesByGroup[[tumortype, BCBestPredictionPosition[[2]]]]
Print["{Hazard ratio, P value} = "]
AllBCPairs[[BCBestPredictionPosition[[1]], BCBestPredictionPosition[[2]], 5]]
AllBCPairs[[BCBestPredictionPosition[[1]], BCBestPredictionPosition[[2]], 3]]
```

```
BKM120

paclitaxel

{Hazard ratio, P value} =

{0.736309, 0.180824}
```



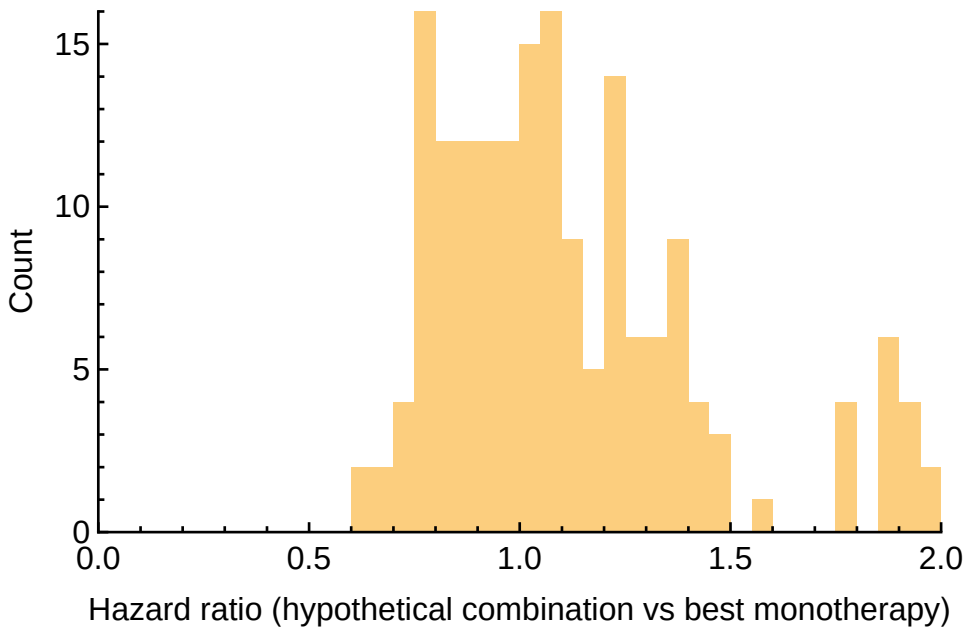
Testing all possible pairs of monotherapies in Gastric cancer

```
tumortype = 6;

AllGCPairs =
  Parallelize[Table[IndependentActionPrediction[MonotherapiesByGroup[[tumortype, i]],
     MonotherapiesByGroup[[tumortype, j]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]
    , {i, 1, Length[MonotherapiesByGroup[[tumortype]]]},
    {j, 1, Length[MonotherapiesByGroup[[tumortype]]]}]];

(* Response correlations between all agents *)
GCResponseCorrelations =
  Flatten[Table[Table[AllGCPairs[[i, j, 4]], {i, 1, j - 1}], {j, 2, Length[AllGCPairs]}]];
(* Response correlations between active agents only *)
GCResponseCorrelationsActiveAgentsOnly =
  Flatten[Table[Table[AllGCPairs[[GastricActiveAgents, GastricActiveAgents]][[i, j, 4]],
     {i, 1, j - 1}], {j, 2, Length[AllGCPairs[[GastricActiveAgents, GastricActiveAgents]]]}]];

(* histogram of hazard ratios *)
Histogram[Flatten[AllGCPairs[[All, All, 5, 1]]], {0, 2, 0.05},
 Frame → {{True, False}, {True, False}},
 FrameLabel → {"Hazard ratio (hypothetical combination vs best monotherapy)", "Count"},
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]], PlotRangePadding → None,
 ChartStyle → EdgeForm[None]]
```



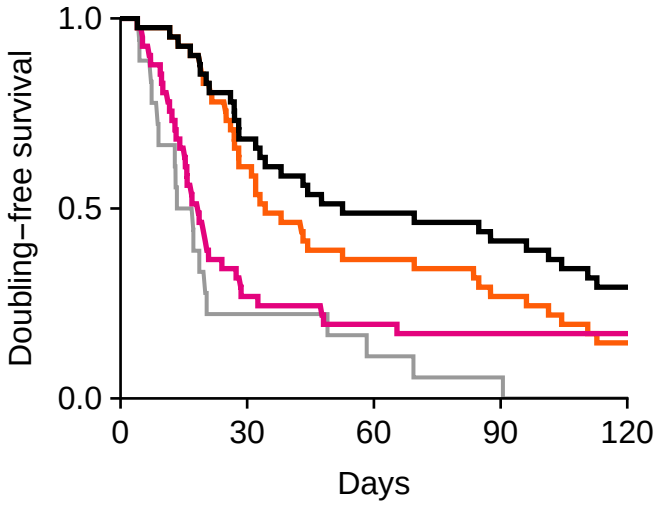
```
tumortype = 6;
GCBestPrediction = Max[AllGCPairs[[All, All, 1]]];
GCBestPredictionPosition = Position[AllGCPairs[[All, All, 1]], GCBestPrediction][[1]];
MonotherapiesByGroup[[tumortype, GCBestPredictionPosition[[1]]]]
MonotherapiesByGroup[[tumortype, GCBestPredictionPosition[[2]]]]
Print["{Hazard ratio, P value} = "]
AllGCPairs[[GCBestPredictionPosition[[1]], GCBestPredictionPosition[[2]], 5]]
AllGCPairs[[GCBestPredictionPosition[[1]], GCBestPredictionPosition[[2]], 3]]
```

BYL719

LLM871

{Hazard ratio, P value} =

{0.64037, 0.0521545}

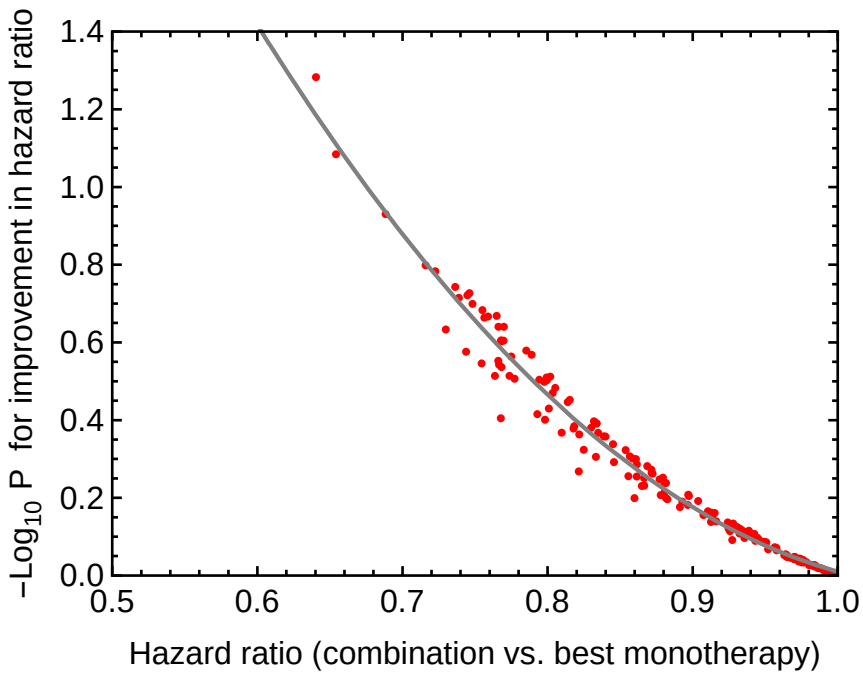


Plotting hazard ratios of all hypothetical combinations

```
MelanomaAllCombinationsHazardRatios =
  Flatten[Table[Table[{i, j, AllMelanomaPairs[[i, j, -1]]}, {i, 1, j - 1}],
    {j, 2, Length[AllMelanomaPairs]}], 1];
NSCLCAllCombinationsHazardRatios =
  Flatten[Table[Table[{i, j, AllNSCLCPairs[[i, j, -1]]}, {i, 1, j - 1}],
    {j, 2, Length[AllNSCLCPairs]}], 1];
PDACAllCombinationsHazardRatios =
  Flatten[Table[Table[{i, j, AllPDACPairs[[i, j, -1]]}, {i, 1, j - 1}], {j, 2, Length[AllPDACPairs]}],
   1];
CRCAllCombinationsHazardRatios =
  Flatten[Table[Table[{i, j, AllCRCPairs[[i, j, -1]]}, {i, 1, j - 1}], {j, 2, Length[AllCRCPairs]}],
   1];
BCAllCombinationsHazardRatios =
  Flatten[Table[Table[{i, j, AllBCPairs[[i, j, -1]]}, {i, 1, j - 1}], {j, 2, Length[AllBCPairs]}], 1];
GCAllCombinationsHazardRatios =
  Flatten[Table[Table[{i, j, AllGCPairs[[i, j, -1]]}, {i, 1, j - 1}], {j, 2, Length[AllGCPairs]}], 1];

AllCombinationsHazardRatios = Join[
   MelanomaAllCombinationsHazardRatios,
   NSCLCAllCombinationsHazardRatios,
   PDACAllCombinationsHazardRatios,
   CRCAllCombinationsHazardRatios,
   BCAllCombinationsHazardRatios,
   GCAllCombinationsHazardRatios
  ];
```

```
(* For each predicted combination,
the P-value for a significant improvement in hazard ratio (by Cox proportional hazards model)
  is closely related to the hazard ratio. We fit a function to this relationship,
in order to color the histogram of hazard ratio by the approximate P-
 value of the predictions in each 'bin' of hazard ratios *)
QuadraticFit =
  FindFit[
   Select[{AllCombinationsHazardRatios[[All, 3, 1]],
      -Log[10, AllCombinationsHazardRatios[[All, 3, 2]]]}^T, #[[1]] < 1 &], {a * x^2 + b * x + c},
   {a, b, c}, x];
Show[
 ListPlot[
  {AllCombinationsHazardRatios[[All, 3, 1]], -Log[10, AllCombinationsHazardRatios[[All, 3, 2]]]}^T,
  PlotRange → {{0.5, 1}, {0, 1.4}}, Frame → True,
  FrameLabel → {"Hazard ratio (combination vs. best monotherapy)",
    "-Log10 P  for improvement in hazard ratio"},
  PlotStyle → Directive[Red, AbsolutePointSize[3]],
  FrameStyle → Directive[Black, Thickness[Medium]],
  BaseStyle → {FontFamily → "Arial", FontSize → 12}, AspectRatio → 3 / 4,
  ImageSize → {{1000}, {250}}],
 Plot[(a * x^2 + b * x + c) /. QuadraticFit, {x, 0, 5}, PlotStyle → Gray]
]
```

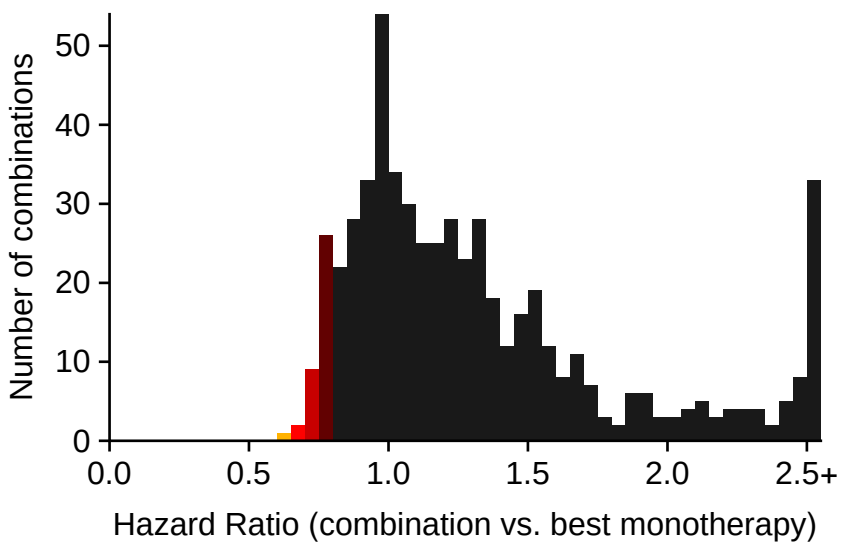


```
(* defining a custom color scale *)
Unprotect[ColorData];
ColorData["PValue"] =
  Function[x,
   Blend[Transpose[{{0, 0.025, 0.05, 0.1, 0.2, 0.275, 0.325, 1.0},
      {Blend[{Orange, Yellow}, 0.85], Blend[{Orange, Yellow}, 0.85], Blend[{Orange, Yellow}, 0.5],
       Red, Darker[Red, 0.3], Darker[Red, 0.6], GrayLevel[0.1], GrayLevel[0.1]}}], x]];
Protect[ColorData];

(* this function allows each bar in the histogram to be colored according to the P-
 value of the combinations in that bar *)
CustomChartElementFunction[{{xmin_, xmax_}, {ymin_, ymax_}}, ___] :=
 {ColorData["PValue"][
   If[xmax > 1, 1, 10^-((a * (xmin / 2 + xmax / 2)^2 + b * (xmin / 2 + xmax / 2) + c) /. QuadraticFit)]],
  Dynamic@EdgeForm[None], Rectangle[{xmin, ymin}, {xmax, ymax}, RoundingRadius → 0]}

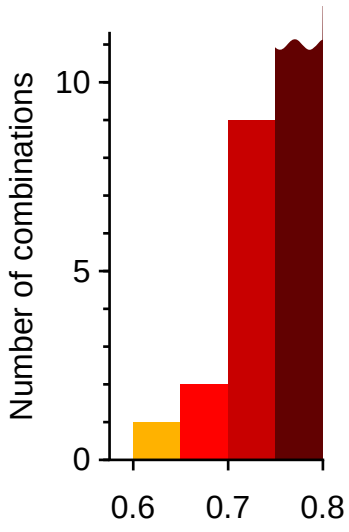
(* plotting a histogram of hazard ratios *)
HRHistogram = Histogram[Map[Min[{#, 2.5}] &, AllCombinationsHazardRatios[[All, 3, 1]]],
  {0.0, 2.55, 0.05}, PlotRange → {{0, 2.55}, {0, All}}, PlotRangePadding → None,
  Axes → False, Frame → {{True, False}, {True, False}},
  ChartElementFunction → CustomChartElementFunction,
  FrameStyle → Directive[Black, Thickness[Medium]],
  BaseStyle → {FontFamily → "Arial", FontSize → 12},
  FrameTicks → {Append[Table[{i, NumberForm[i, {2, 1}], {0, 0.015}}, {i, 0, 2, 0.5}],
     {2.5, "2.5+", {0, 0.015}}], Table[{i, i, {0, 0.015}}, {i, 0, 100, 10}]},
  FrameLabel → {"Hazard Ratio (combination vs. best monotherapy)", "Number of combinations"},
  ImagePadding → {{50, 10}, {50, 10}}, AspectRatio → 3 / 5, ImageSize → {{1000}, {220}}]

Export[NotebookDirectory[] <> "Figure 5A, Hazard ratio of predicted combinations.pdf",
  HRHistogram, "PDF"];
```



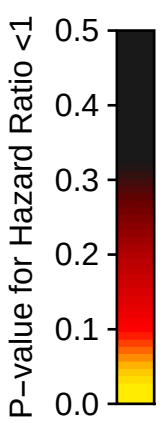
```
HRHistogramZoom = Histogram[Map[Min[{#, 2.5}] &, AllCombinationsHazardRatios[[All, 3, 1]]],
  {0.5, 1.0 - 4 * 0.05, 0.05}, PlotRange → {{0.575, 0.8}, {0, 11.3}}, PlotRangePadding → None,
  Axes → False, Frame → {{True, False}, {True, False}},
  ChartElementFunction → CustomChartElementFunction,
  FrameStyle → Directive[Black, Thickness[Medium]],
  BaseStyle → {FontFamily → "Arial", FontSize → 12},
  FrameTicks → {Table[{i, NumberForm[i, {2, 1}]}, {0, 0.05}}, {i, 0, 2, 0.1}],
    Join[Table[{i, i, {0, 0.05}}, {i, 0, 30, 5}], Table[{i, , {0, 0.03}}, {i, 0, 30, 1}]]},
  FrameLabel → {"", "Number of combinations"}, ImagePadding → {{50, 10}, {50, 10}},
  AspectRatio → 2, ImageSize → {{1000}, {220}},
  Epilog → (* this is a white sinusoid over the top of the highest bar to indicate
    that the vertical scale is truncated *)
   {White,
    Polygon[Append[Prepend[Table[{0.7 + θ / (6.4 π) * 0.1, 11 + 0.14 * Sin[θ]}, {θ, 0, 6.4 π, 0.2}],
       {0.7, 13}], {0.8, 13}]]}]

Export[NotebookDirectory[] <> "Figure 5A, zoomed.pdf", HRHistogramZoom, "PDF"];
```




```
(* color scale *)
HRHistogramColorScale =
 ContourPlot[y, {x, 0, 1}, {y, 0, 0.5}, ColorFunction → (ColorData["PValue"][#] &),
   ColorFunctionScaling → False, Contours → 50, ContourStyle → None, PlotRangePadding → None,
   AspectRatio → 10,
   FrameTicks → {{Table[{i, NumberForm[i, {2, 1}]}, {0, 0.25}}, {i, 0, 0.5, 0.1}], None},
     {None, None}}, FrameStyle → Directive[Black, Thickness[Medium]],
   BaseStyle → {FontFamily → "Arial", FontSize → 12}, ImagePadding → {{100, 5}, {10, 10}},
   ImageSize → {{500}, {160}}, FrameLabel → {, "P-value for Hazard Ratio <1"},
   PerformanceGoal → "Speed"] /.
  ({EdgeForm[], r_?(MemberQ[{RGBColor, Hue, CMYKColor, GrayLevel}, Head[#]] &), i___} :→
    {EdgeForm[r], r, i})

Export[NotebookDirectory[] <> "Figure 5A, color scale.pdf", HRHistogramColorScale, "PDF"];
```



If we call a P-value of 0.2 as a ‘trend towards significance’, then only 10 out of 566 possible combinations even trend towards significance.
This is ~2% of all possible combinations, or ~4% of all combinations of individually active

agents

```
PValueForTrendingToSignificance = 0.2;

NumberOfPossibleCombinationsOfActiveAgents =
  Length[MelanomaActiveAgents] * (Length[MelanomaActiveAgents] - 1) / 2 +
   Length[NSCLCActiveAgents] * (Length[NSCLCActiveAgents] - 1) / 2 +
   Length[PDACActiveAgents] * (Length[PDACActiveAgents] - 1) / 2 +
   Length[CRCActiveAgents] * (Length[CRCActiveAgents] - 1) / 2 +
   Length[BreastActiveAgents] * (Length[BreastActiveAgents] - 1) / 2 +
   Length[GastricActiveAgents] * (Length[GastricActiveAgents] - 1) / 2;

CombinationsWithHRpvaluezeropointtwo =
  Select[AllCombinationsHazardRatios[[All]],
   #[[3, 1]] ≤ 1 && #[[3, 2]] ≤ PValueForTrendingToSignificance &];

Print["Total number of hypothetical combinations = " <>
  ToString[Length[AllCombinationsHazardRatios]]]
Print["Number of hypothetical combinations of individually active agents = " <>
  ToString[NumberOfPossibleCombinationsOfActiveAgents]]
Print[
 "Number of hypothetical combinations that trend to significant improvement in
    hazard ratio = " <> ToString[Length[CombinationsWithHRpvaluezeropointtwo]]]

Print[
 "Percentage of all hypothetical combinations that trend to significant improvement
    in hazard ratio = " <>
  ToString[Length[CombinationsWithHRpvaluezeropointtwo] / Length[AllCombinationsHazardRatios] *
    100.]]
Print[
 "Percentage of all hypothetical combinations of individually active agents that
    trend to significant improvement in hazard ratio = " <>
  ToString[
   Length[CombinationsWithHRpvaluezeropointtwo] / NumberOfPossibleCombinationsOfActiveAgents *
    100.]]
```

```
Total number of hypothetical combinations = 566
Number of hypothetical combinations of individually active agents = 267
Number of hypothetical combinations that trend to significant improvement in hazard ratio = 10
Percentage of all hypothetical combinations
  that trend to significant improvement in hazard ratio = 1.76678
Percentage of all hypothetical combinations of individually
  active agents that trend to significant improvement in hazard ratio = 3.74532
```

Charts of predicted combinations (Figure 5B)

```
NameSubstitutions = {"LEE011" → "Ribociclib", "BKM120" → "Buparlisib", "BYL719" → "Alpelisib",
   "encorafenib" → "Encorafenib", "binimetinib" → "Binimetinib", "paclitaxel" → "Paclitaxel",
   "gemcitabine" → "Gemcitabine"};
```

PDAC

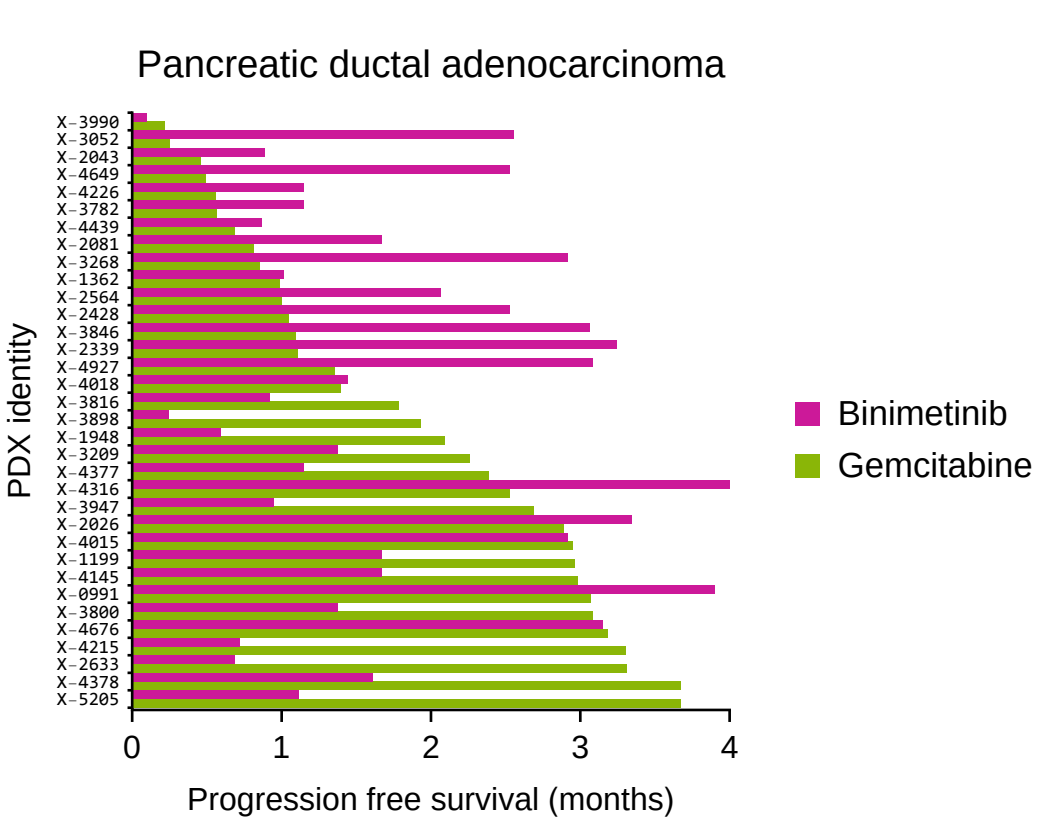
```
tumortype = 3;
ModelNames[[tumortype]]
i = 8;
j = 2;
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, i]],
   MonotherapiesByGroup[[tumortype, j]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]][[3]];

SortedResponses = Sort[{DrugAresponsesInIntersection[[All]], DrugBresponsesInIntersection[[All]]}^T,
   #1[[1, 9]] > #2[[1, 9]] &];
SortedModelNames = SortedResponses[[All, 1, 1]];

SetOptions[$FrontEndSession, PrintingStyleEnvironment → "Working"]

BarChart[{SortedResponses[[All, 1, 9]], SortedResponses[[All, 2, 9]]}^T, BarOrigin → Left,
 Axes → {False, False}, Frame → {{True, False}, {True, False}},
 FrameLabel → {"PDX identity", "Progression free survival (months)"},
 ChartStyle → {Directive[ColorData[3, 4], EdgeForm[None]],
   Directive[RGBColor[0.8, 0.1, 0.6], EdgeForm[None]]},
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 12 * 61 / 2, 61 / 2}],
   Join[Table[{i, , {0, 0.008}}, {i, 0 + 1 / 2, Length[SortedModelNames] * 2 + 1 / 2, 2}],
    Table[{i, Style[SortedModelNames[[i / 2 + 1 / 4]], FontSize → 7, FontFamily → "Consolas"], {0, 0}},
     {i, 1 + 1 / 2, Length[SortedModelNames] * 2 + 1 / 2, 2}]]}, PlotRangePadding → None,
 PlotRange → {{0, 4 * 61 / 2}, {1 / 4, Length[SortedModelNames] * 2 + 1 / 2}},
 ImagePadding → {{120, 10}, {50, 10}}, ImageSize -> {{1000}, {300}}, AspectRatio → 1,
 BarSpacing → {0, 0}, PlotLabel → Style[ModelNames[[tumortype]], Black],
 ChartLegends → {StringSplit[MonotherapiesByGroup[[tumortype, i]], "-50mpk"][[1]],
    StringSplit[MonotherapiesByGroup[[tumortype, j]], "-50mpk"][[1]]} /. NameSubstitutions
  (*,
 Epilog→{Black,Text[Style["ρ = "<>ToString[RankCorrelation],FontSize→12],
    Scaled[{0.98,0.98}],{1,1}]}*)]

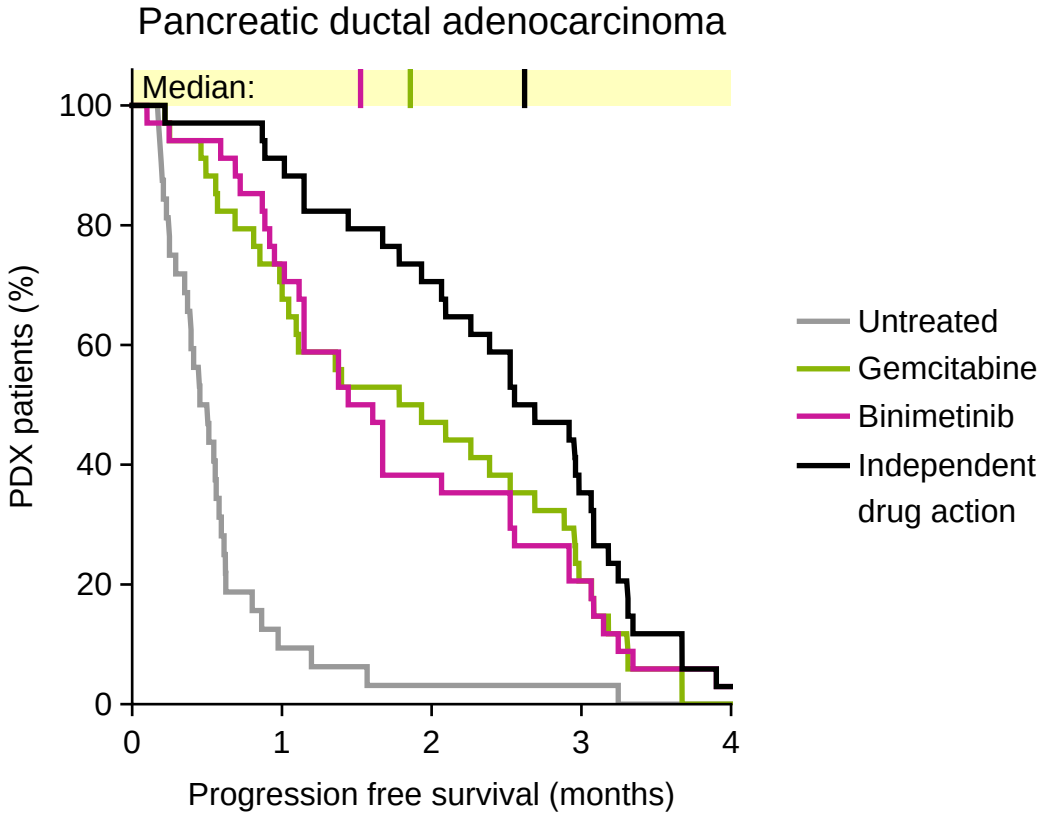
Export[NotebookDirectory[] <> "Figure 5B," <> ModelNames[[tumortype]] <>
   " best prediction barchart.pdf", %, "PDF"];
```



```
MedianA = Median[SortedResponses[[All, 1, 9]]];
MedianB = Median[SortedResponses[[All, 2, 9]]];
MedianIndependent = Median[BestOfMonotherapyResponses[[All, 9]]];

Plot[{SurvivalFunction[EmpiricalDistribution[UntreatedResponsesInIntersection[[All, 9]]]][x],
  SurvivalFunction[EmpiricalDistribution[SortedResponses[[All, 1, 9]]]][x],
  SurvivalFunction[EmpiricalDistribution[SortedResponses[[All, 2, 9]]]][x],
  SurvivalFunction[EmpiricalDistribution[BestOfMonotherapyResponses[[All, 9]]]][x]},
 {x, 0, 4 * 30.5}, Exclusions → None, PlotPoints → 500, Axes → {False, False},
 Frame → {{True, False}, {True, False}},
 FrameLabel → {"Progression free survival (months)", "PDX patients (%)"},
 PlotStyle → {Directive[GrayLevel[0.6], AbsoluteThickness[2]],
   Directive[ColorData[3, 4], AbsoluteThickness[2]],
   Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[2]],
   Directive[Black, AbsoluteThickness[2]]}, BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 12 * 61 / 2, 61 / 2}],
   Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}]}, PlotRangePadding → None,
 PlotRange → {{0, 4 * 61 / 2}, {0, 1.06}}, ImagePadding → {{120, 10}, {50, 10}},
 ImageSize -> {{1000}, {300 + 14 (* for the median bar*)}},
 AspectRatio → 1 * (1.06 (*median bar*)), PlotLabel → Style[ModelNames[[tumortype]], Black],
 PlotLegends →
  LineLegend[
   ({"Untreated", StringSplit[MonotherapiesByGroup[[tumortype, i]], "-50mpk"][[1]],
      StringSplit[MonotherapiesByGroup[[tumortype, j]], "-50mpk"][[1]],
      "Independent\ndrug action"} /. NameSubstitutions), Spacings → {0.25, 0.4},
   LegendMarkerSize → {20, 12}, LabelStyle → {FontSize → 12}],
 Prolog → {Thickness[Medium], Lighter[Yellow, 0.75], EdgeForm[None],
   Rectangle[{0, 1}, {4 * 30.5, 1.06}]},
 Epilog → {Black, Text[Style["Median:", FontSize → 12], {2, 1.0}, {-1, -1}],
   AbsoluteThickness[2], ColorData[3, 4], Line[{{MedianA, 1.0}, {MedianA, 1.06}}],
   RGBColor[0.8, 0.1, 0.6], Line[{{MedianB, 1.0}, {MedianB, 1.06}}], Black,
   Line[{{MedianIndependent, 1.0}, {MedianIndependent, 1.06}}]}
]

Export[NotebookDirectory[] <> "Figure 5B," <> ModelNames[[tumortype]] <>
   " best prediction survival plot.pdf", %, "PDF"];
```



```
(* Rank correlation *)
SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]
```

```
0.0769231
```

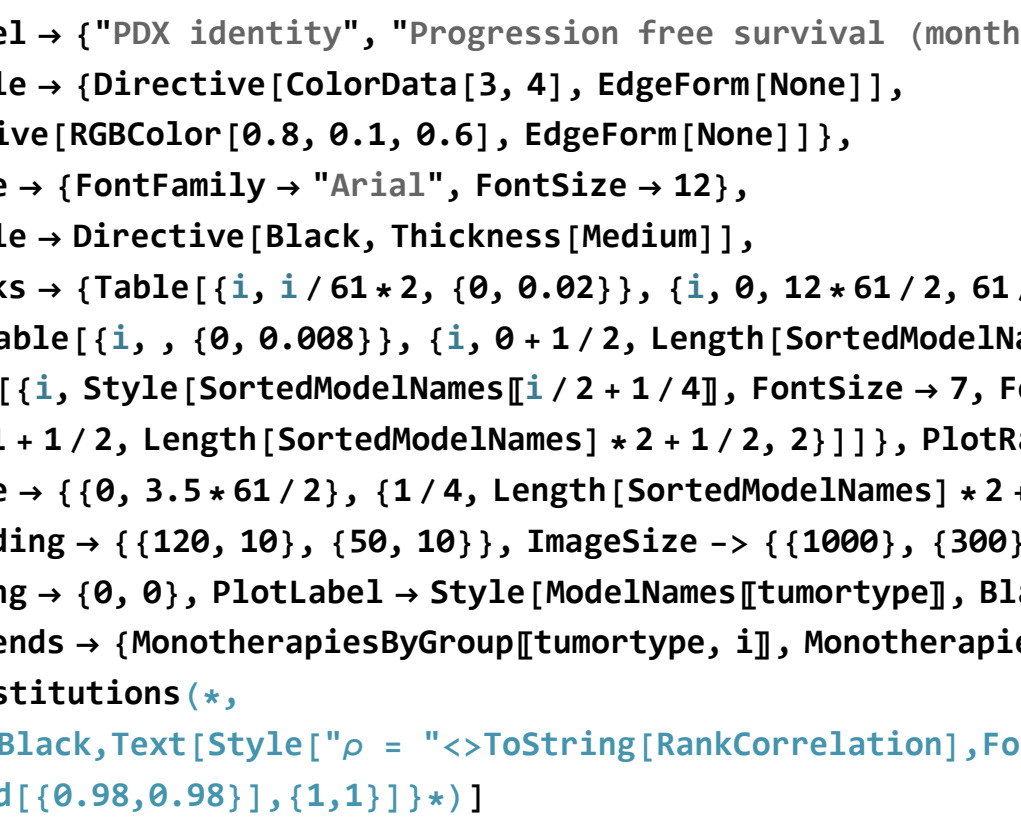
Colorectal

```
tumortype = 4;
ModelNames[[tumortype]]
i = 8;
j = 2;
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, i]],
   MonotherapiesByGroup[[tumortype, j]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]][[3]];

SortedResponses = Sort[{DrugAresponsesInIntersection[[All]], DrugBresponsesInIntersection[[All]]}^T,
   #1[[1, 9]] > #2[[1, 9]] &];
SortedModelNames = SortedResponses[[All, 1, 1]];

BarChart[{SortedResponses[[All, 1, 9]], SortedResponses[[All, 2, 9]]}^T, BarOrigin → Left,
 Axes → {False, False}, Frame → {{True, False}, {True, False}},
 FrameLabel → {"PDX identity", "Progression free survival (months)"},
 ChartStyle → {Directive[ColorData[3, 4], EdgeForm[None]],
   Directive[RGBColor[0.8, 0.1, 0.6], EdgeForm[None]]},
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 12 * 61 / 2, 61 / 2}],
   Join[Table[{i, , {0, 0.008}}, {i, 0 + 1 / 2, Length[SortedModelNames] * 2 + 1 / 2, 2}],
    Table[{i, Style[SortedModelNames[[i / 2 + 1 / 4]], FontSize → 7, FontFamily → "Consolas"], {0, 0}},
     {i, 1 + 1 / 2, Length[SortedModelNames] * 2 + 1 / 2, 2}]]}, PlotRangePadding → None,
 PlotRange → {{0, 3.5 * 61 / 2}, {1 / 4, Length[SortedModelNames] * 2 + 1 / 2}},
 ImagePadding → {{120, 10}, {50, 10}}, ImageSize -> {{1000}, {300}}, AspectRatio → 1,
 BarSpacing → {0, 0}, PlotLabel → Style[ModelNames[[tumortype]], Black],
 ChartLegends → {MonotherapiesByGroup[[tumortype, i]], MonotherapiesByGroup[[tumortype, j]]} /.
  NameSubstitutions(*,
 Epilog→{Black,Text[Style["ρ = "<>ToString[RankCorrelation],FontSize→12],
    Scaled[{0.98,0.98}],{1,1}]}*)]

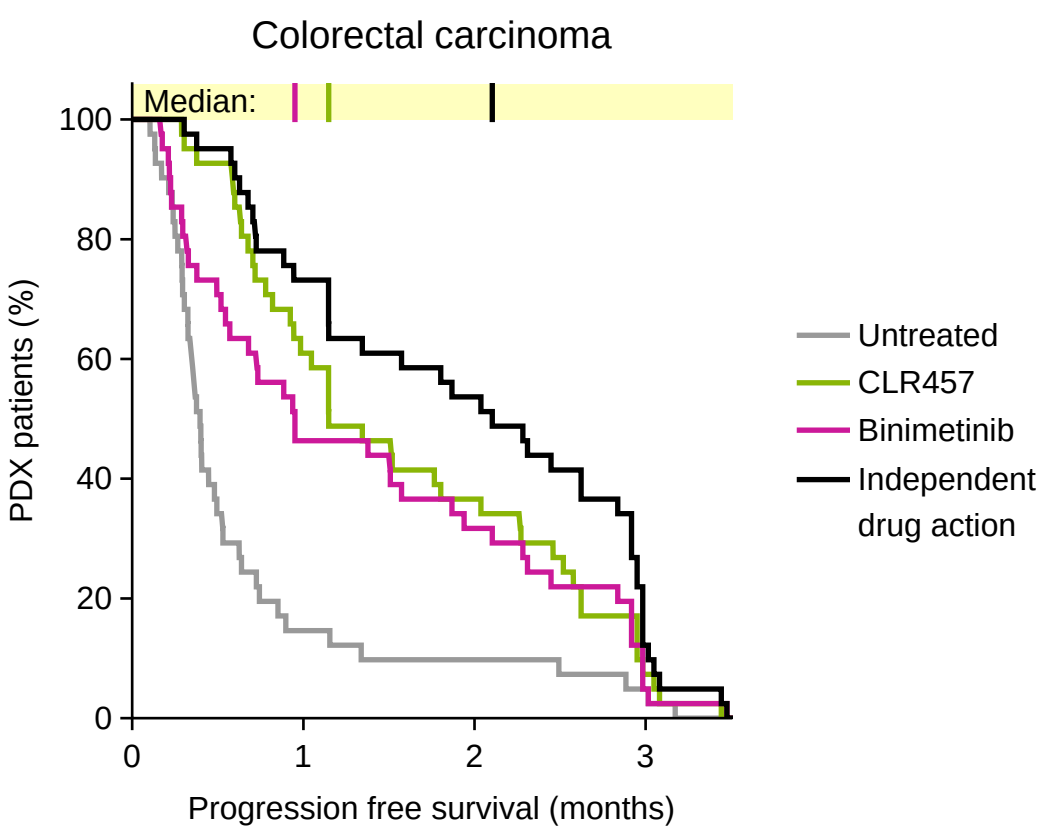
Export[NotebookDirectory[] <> "Figure 5B," <> ModelNames[[tumortype]] <>
   " best prediction barchart.pdf", %, "PDF"];
```



```
MedianA = Median[SortedResponses[[All, 1, 9]]];
MedianB = Median[SortedResponses[[All, 2, 9]]];
MedianIndependent = Median[BestOfMonotherapyResponses[[All, 9]]];

Plot[{SurvivalFunction[EmpiricalDistribution[UntreatedResponsesInIntersection[[All, 9]]]][x],
  SurvivalFunction[EmpiricalDistribution[SortedResponses[[All, 1, 9]]]][x],
  SurvivalFunction[EmpiricalDistribution[SortedResponses[[All, 2, 9]]]][x],
  SurvivalFunction[EmpiricalDistribution[BestOfMonotherapyResponses[[All, 9]]]][x]},
 {x, 0, 4 * 30.5}, Exclusions → None, PlotPoints → 500, Axes → {False, False},
 Frame → {{True, False}, {True, False}},
 FrameLabel → {"Progression free survival (months)", "PDX patients (%)"},
 PlotStyle → {Directive[GrayLevel[0.6], AbsoluteThickness[2]],
   Directive[ColorData[3, 4], AbsoluteThickness[2]],
   Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[2]],
   Directive[Black, AbsoluteThickness[2]]}, BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 12 * 61 / 2, 61 / 2}],
   Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}]}, PlotRangePadding → None,
 PlotRange → {{0, 3.5 * 61 / 2}, {0, 1.06}}, ImagePadding → {{120, 10}, {50, 10}},
 ImageSize -> {{1000}, {300 + 14(* for the median bar*)}},
 AspectRatio → 1 * (1.06(*median bar*)), PlotLabel → Style[ModelNames[[tumortype]], Black],
 PlotLegends →
  LineLegend[
   ({"Untreated", StringSplit[MonotherapiesByGroup[[tumortype, i]], "-50mpk"][[1]],
      StringSplit[MonotherapiesByGroup[[tumortype, j]], "-50mpk"][[1]],
      "Independent\ndrug action"} /. NameSubstitutions), Spacings → {0.25, 0.4},
   LegendMarkerSize → {20, 12}, LabelStyle → {FontSize → 12}],
 Prolog → {Thickness[Medium], Lighter[Yellow, 0.75], EdgeForm[None],
   Rectangle[{0, 1}, {4 * 30.5, 1.06}]},
 Epilog → {Black, Text[Style["Median:", FontSize → 12], {2, 1.0}, {-1, -1}],
   AbsoluteThickness[2], ColorData[3, 4], Line[{{MedianA, 1.0}, {MedianA, 1.06}}],
   RGBColor[0.8, 0.1, 0.6], Line[{{MedianB, 1.0}, {MedianB, 1.06}}], Black,
   Line[{{MedianIndependent, 1.0}, {MedianIndependent, 1.06}}]}
]

Export[NotebookDirectory[] <> "Figure 5B," <> ModelNames[[tumortype]] <>
   " best prediction survival plot.pdf", %, "PDF"];
```



```
(* Rank correlation *)
SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]
```

```
0.372156
```

Breast cancer

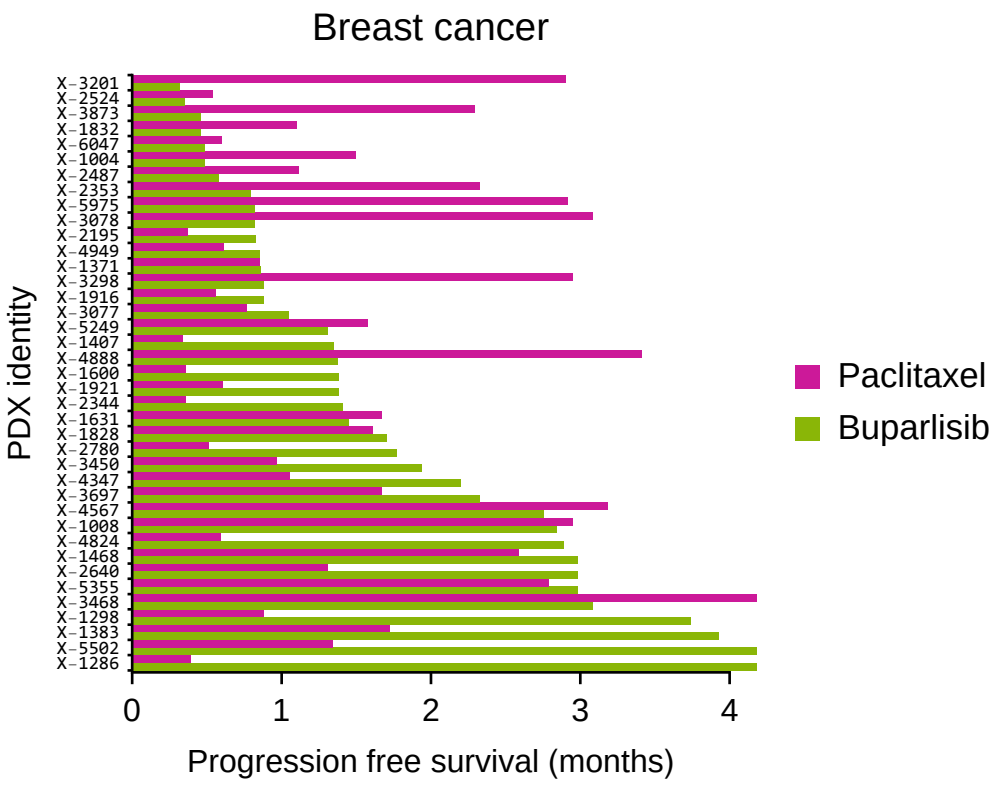
```
tumortype = 5;
ModelNames[[tumortype]]
i = 3;
j = 14;
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, i]],
   MonotherapiesByGroup[[tumortype, j]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]][[3]];

SortedResponses = Sort[{DrugAresponsesInIntersection[[All]], DrugBresponsesInIntersection[[All]]}^T,
   #1[[1, 9]] > #2[[1, 9]] &];
SortedModelNames = SortedResponses[[All, 1, 1]];

BarChart[{SortedResponses[[All, 1, 9]], SortedResponses[[All, 2, 9]]}^T, BarOrigin → Left,
 Axes → {False, False}, Frame → {{True, False}, {True, False}},
 FrameLabel → {"PDX identity", "Progression free survival (months)"},
 ChartStyle → {Directive[ColorData[3, 4], EdgeForm[None]],
   Directive[RGBColor[0.8, 0.1, 0.6], EdgeForm[None]]},
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 12 * 61 / 2, 61 / 2}],
   Join[Table[{i, , {0, 0.008}}, {i, 0 + 1 / 2, Length[SortedModelNames] * 2 + 1 / 2, 2}],
    Table[{i, Style[SortedModelNames[[i / 2 + 1 / 4]], FontSize → 7, FontFamily → "Consolas"], {0, 0}},
     {i, 1 + 1 / 2, Length[SortedModelNames] * 2 + 1 / 2, 2}]]}, PlotRangePadding → None,
 PlotRange → {{0, 4 * 61 / 2}, {1 / 4, Length[SortedModelNames] * 2 + 1 / 2}},
 ImagePadding → {{120, 10}, {50, 10}}, ImageSize -> {{1000}, {300}}, AspectRatio → 1,
 BarSpacing → {0, 0}, PlotLabel → Style[ModelNames[[tumortype]], Black],
 ChartLegends → {MonotherapiesByGroup[[tumortype, i]], MonotherapiesByGroup[[tumortype, j]]} /.
  NameSubstitutions(*,
 Epilog→{Black,Text[Style["ρ = "<>ToString[RankCorrelation],FontSize→12],
    Scaled[{0.98,0.98}],{1,1}]}*)]

Export[NotebookDirectory[] <> "Figure 5B," <> ModelNames[[tumortype]] <>
   " best prediction barchart.pdf", %, "PDF"];
```

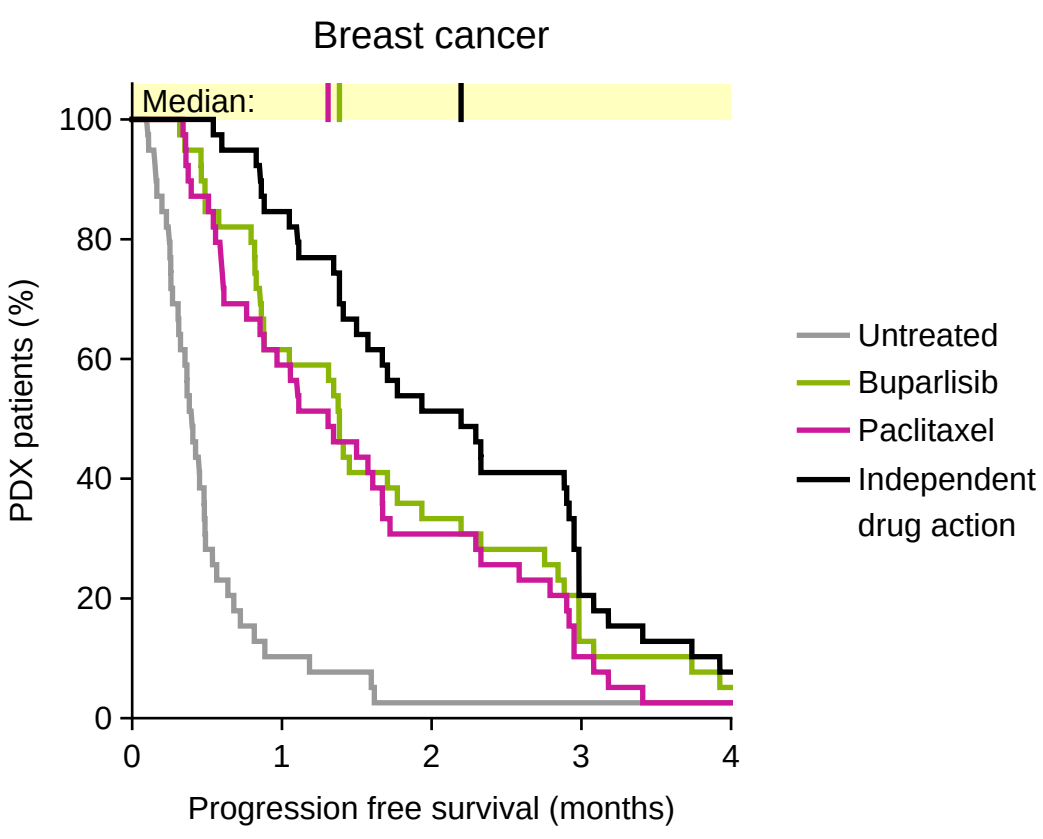
```
Breast cancer
```



```
MedianA = Median[SortedResponses[[All, 1, 9]]];
MedianB = Median[SortedResponses[[All, 2, 9]]];
MedianIndependent = Median[BestOfMonotherapyResponses[[All, 9]]];

Plot[{SurvivalFunction[EmpiricalDistribution[UntreatedResponsesInIntersection[[All, 9]]]][x],
  SurvivalFunction[EmpiricalDistribution[SortedResponses[[All, 1, 9]]]][x],
  SurvivalFunction[EmpiricalDistribution[SortedResponses[[All, 2, 9]]]][x],
  SurvivalFunction[EmpiricalDistribution[BestOfMonotherapyResponses[[All, 9]]]][x]},
 {x, 0, 4 * 30.5}, Exclusions → None, PlotPoints → 500, Axes → {False, False},
 Frame → {{True, False}, {True, False}},
 FrameLabel → {"Progression free survival (months)", "PDX patients (%)"},
 PlotStyle → {Directive[GrayLevel[0.6], AbsoluteThickness[2]],
   Directive[ColorData[3, 4], AbsoluteThickness[2]],
   Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[2]],
   Directive[Black, AbsoluteThickness[2]]}, BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 12 * 61 / 2, 61 / 2}],
   Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}]}, PlotRangePadding → None,
 PlotRange → {{0, 4 * 61 / 2}, {0, 1.06}}, ImagePadding → {{120, 10}, {50, 10}},
 ImageSize -> {{1000}, {300 + 14 (* for the median bar*)}},
 AspectRatio → 1 * (1.06 (*median bar*)), PlotLabel → Style[ModelNames[[tumortype]], Black],
 PlotLegends →
  LineLegend[
   ({"Untreated", StringSplit[MonotherapiesByGroup[[tumortype, i]], "-50mpk"][[1]],
      StringSplit[MonotherapiesByGroup[[tumortype, j]], "-50mpk"][[1]],
      "Independent\ndrug action"} /. NameSubstitutions), Spacings → {0.25, 0.4},
   LegendMarkerSize → {20, 12}, LabelStyle → {FontSize → 12}],
 Prolog → {Thickness[Medium], Lighter[Yellow, 0.75], EdgeForm[None],
   Rectangle[{0, 1}, {4 * 30.5, 1.06}]},
 Epilog → {Black, Text[Style["Median:", FontSize → 12], {2, 1.0}, {-1, -1}],
   AbsoluteThickness[2], ColorData[3, 4], Line[{{MedianA, 1.0}, {MedianA, 1.06}}],
   RGBColor[0.8, 0.1, 0.6], Line[{{MedianB, 1.0}, {MedianB, 1.06}}], Black,
   Line[{{MedianIndependent, 1.0}, {MedianIndependent, 1.06}}]}
]

Export[NotebookDirectory[] <> "Figure 5B," <> ModelNames[[tumortype]] <>
   " best prediction survival plot.pdf", %, "PDF"];
```



```
(* Rank correlation *)
SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]
```

```
0.0639838
```

Gastric

```
tumortype = 6;
ModelNames[[tumortype]]
i = 4;
j = 13;
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, i]],
   MonotherapiesByGroup[[tumortype, j]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]][[3]];

SortedResponses = Sort[{DrugAresponsesInIntersection[[All]], DrugBresponsesInIntersection[[All]]}^T,
   #1[[1, 9]] > #2[[1, 9]] &];
SortedModelNames = SortedResponses[[All, 1, 1]];

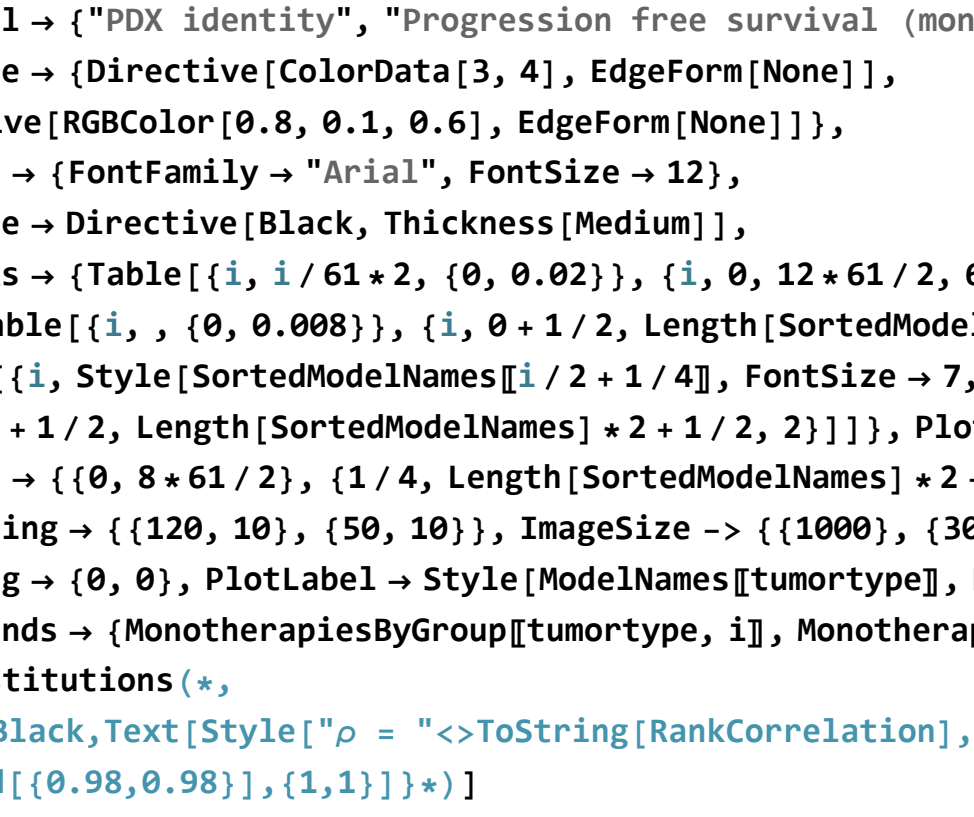
(* Rank correlation *)
RankCorrelation =
 Round[SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]],
  0.01]
```

```
BarChart[{SortedResponses[[All, 1, 9]], SortedResponses[[All, 2, 9]]}^T, BarOrigin → Left,
 Axes → {False, False}, Frame → {{True, False}, {True, False}},
 FrameLabel → {"PDX identity", "Progression free survival (months)"},
 ChartStyle → {Directive[ColorData[3, 4], EdgeForm[None]],
   Directive[RGBColor[0.8, 0.1, 0.6], EdgeForm[None]]},
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 12 * 61 / 2, 61 / 2}],
   Join[Table[{i, , {0, 0.008}}, {i, 0 + 1 / 2, Length[SortedModelNames] * 2 + 1 / 2, 2}],
    Table[{i, Style[SortedModelNames[[i / 2 + 1 / 4]], FontSize → 7, FontFamily → "Consolas"], {0, 0}},
     {i, 1 + 1 / 2, Length[SortedModelNames] * 2 + 1 / 2, 2}]]}, PlotRangePadding → None,
 PlotRange → {{0, 8 * 61 / 2}, {1 / 4, Length[SortedModelNames] * 2 + 1 / 2}},
 ImagePadding → {{120, 10}, {50, 10}}, ImageSize -> {{1000}, {300}}, AspectRatio → 1,
 BarSpacing → {0, 0}, PlotLabel → Style[ModelNames[[tumortype]], Black],
 ChartLegends → {MonotherapiesByGroup[[tumortype, i]], MonotherapiesByGroup[[tumortype, j]]} /.
  NameSubstitutions(*,
 Epilog→{Black,Text[Style["ρ = "<>ToString[RankCorrelation],FontSize→12],
    Scaled[{0.98,0.98}],{1,1}]}*)]

Export[NotebookDirectory[] <> ModelNames[[tumortype]] <> " best prediction barchart.pdf", %, "PDF"];
```

```
Gastric cancer
```

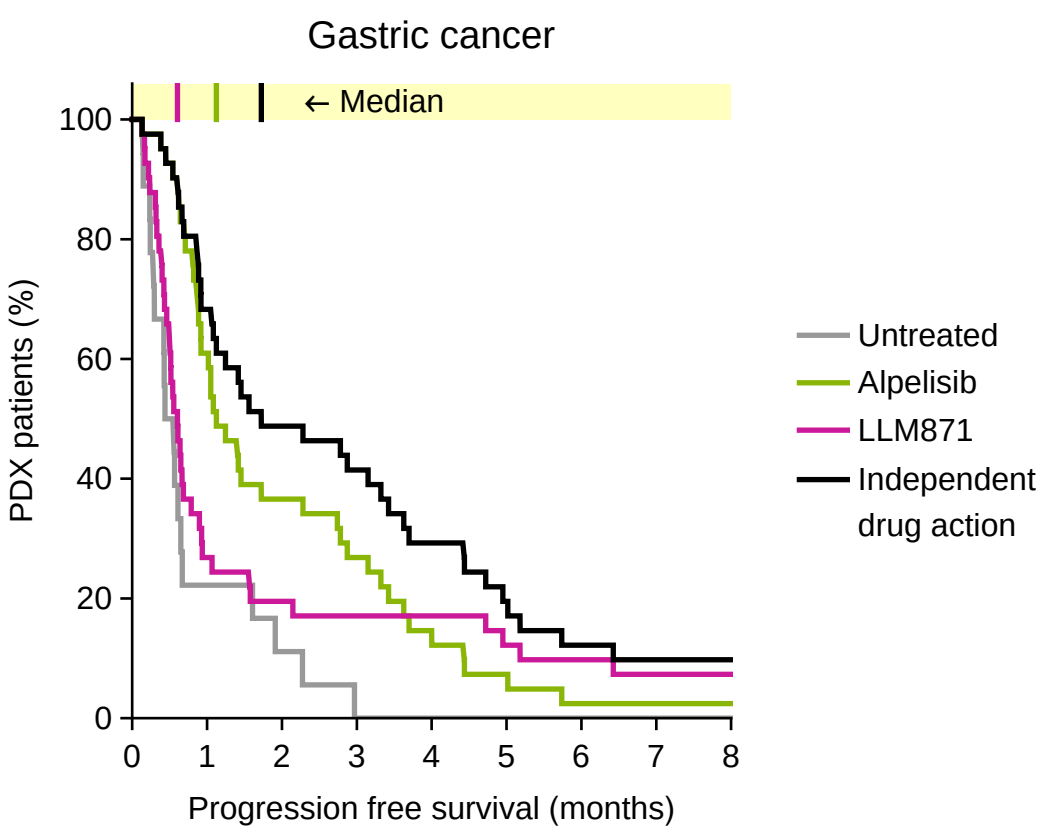
```
0.28
```



```
MedianA = Median[SortedResponses[[All, 1, 9]]];
MedianB = Median[SortedResponses[[All, 2, 9]]];
MedianIndependent = Median[BestOfMonotherapyResponses[[All, 9]]];

Plot[{SurvivalFunction[EmpiricalDistribution[UntreatedResponsesInIntersection[[All, 9]]]][x],
  SurvivalFunction[EmpiricalDistribution[SortedResponses[[All, 1, 9]]]][x],
  SurvivalFunction[EmpiricalDistribution[SortedResponses[[All, 2, 9]]]][x],
  SurvivalFunction[EmpiricalDistribution[BestOfMonotherapyResponses[[All, 9]]]][x]},
 {x, 0, 9 * 30.5}, Exclusions → None, PlotPoints → 500, Axes → {False, False},
 Frame → {{True, False}, {True, False}},
 FrameLabel → {"Progression free survival (months)", "PDX patients (%)"},
 PlotStyle → {Directive[GrayLevel[0.6], AbsoluteThickness[2]],
   Directive[ColorData[3, 4], AbsoluteThickness[2]],
   Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[2]],
   Directive[Black, AbsoluteThickness[2]]}, BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {Table[{i, i / 61 * 2, {0, 0.02}}, {i, 0, 12 * 61 / 2, 61 / 2}],
   Table[{i, i * 100, {0, 0.02}}, {i, 0, 1, 1 / 5}]}, PlotRangePadding → None,
 PlotRange → {{0, 8 * 61 / 2}, {0, 1.06}}, ImagePadding → {{120, 10}, {50, 10}},
 ImageSize -> {{1000}, {300 + 14 (* for the median bar*)}},
 AspectRatio → 1 * (1.06 (*median bar*)), PlotLabel → Style[ModelNames[[tumortype]], Black],
 PlotLegends →
  LineLegend[
   ({"Untreated", StringSplit[MonotherapiesByGroup[[tumortype, i]], "-50mpk"][[1]],
      StringSplit[MonotherapiesByGroup[[tumortype, j]], "-50mpk"][[1]],
      "Independent\ndrug action"} /. NameSubstitutions), Spacings → {0.25, 0.4},
   LegendMarkerSize → {20, 12}, LabelStyle → {FontSize → 12}],
 Prolog → {Thickness[Medium], Lighter[Yellow, 0.75], EdgeForm[None],
   Rectangle[{0, 1}, {8 * 30.5, 1.06}]},
 Epilog → {Black, Text[Style["← Median", FontSize → 12], {70, 1.0}, {-1, -1}],
   AbsoluteThickness[2], ColorData[3, 4], Line[{{MedianA, 1.0}, {MedianA, 1.06}}],
   RGBColor[0.8, 0.1, 0.6], Line[{{MedianB, 1.0}, {MedianB, 1.06}}], Black,
   Line[{{MedianIndependent, 1.0}, {MedianIndependent, 1.06}}]}
]

Export[NotebookDirectory[] <> ModelNames[[tumortype]] <> " best prediction survival plot.pdf",
  %, "PDF"];
```



```
(* Rank correlation *)
SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]
```

```
0.281197
```

Examining drug pairs of similar mechanisms and computing their response correlations

```
(* we begin with an empty list and gradually fill it with response correlations
 between drugs with similar mechanism of action *)
SimilarDrugCorrelations = {};

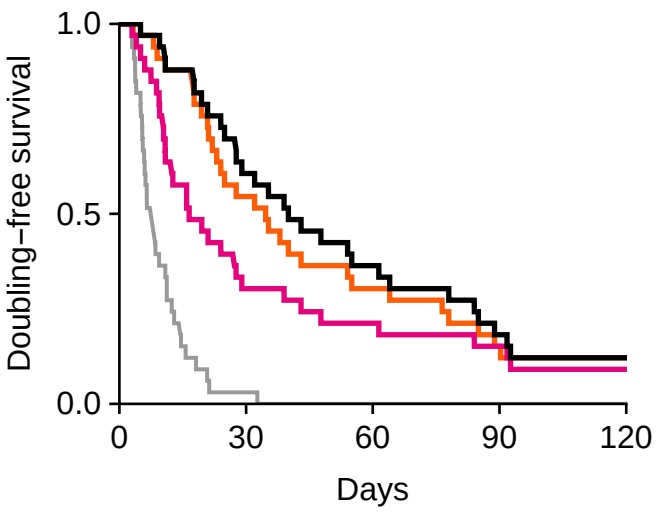
(* RAF and MEK inhibitors in melanoma *)
tumortype = 1;
MonotherapiesByGroup[[tumortype, 1]]
MonotherapiesByGroup[[tumortype, 6]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 1]],
 MonotherapiesByGroup[[tumortype, 6]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

```
binimetinib
```

```
encorafenib
```

```
{6.65785, 1.11166,
```




```
, 0.474933, {0.866532, 0.56132}}
```

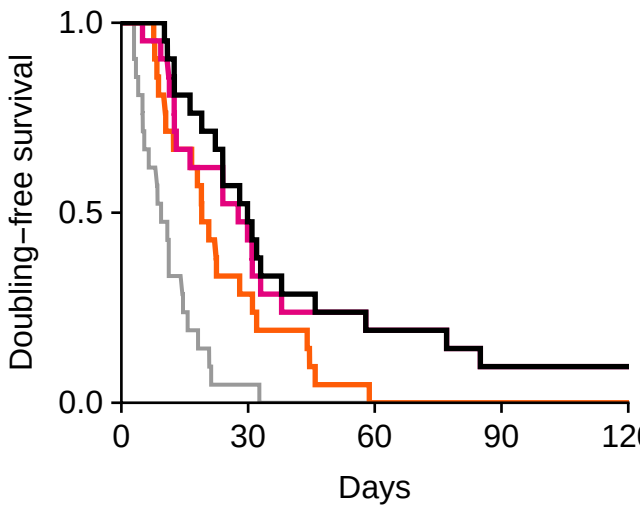
```
(* two PI3K inhibitors in melanoma *)
tumortype = 1;
MonotherapiesByGroup[[tumortype, 2]]
MonotherapiesByGroup[[tumortype, 4]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 2]],
 MonotherapiesByGroup[[tumortype, 4]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

BKM120

CLR457

{3.96514, 1.06976,



, 0.482624, {1.24817, 0.480336}}

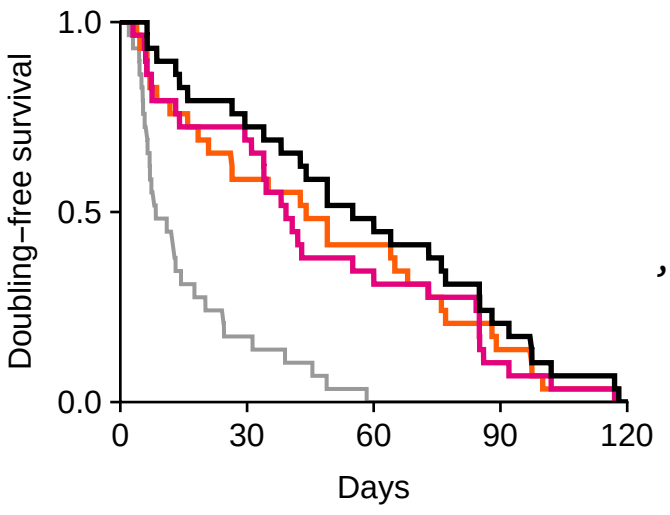
```
(* MAPK and MEK inhibitors in NSCLC *)
tumortype = 2;
MonotherapiesByGroup[[tumortype, 2]]
MonotherapiesByGroup[[tumortype, 7]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 2]],
 MonotherapiesByGroup[[tumortype, 7]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

binimetinib

CKX620

{3.63446, 1.1981,



, 0.712737, {0.973023, 0.920083}}

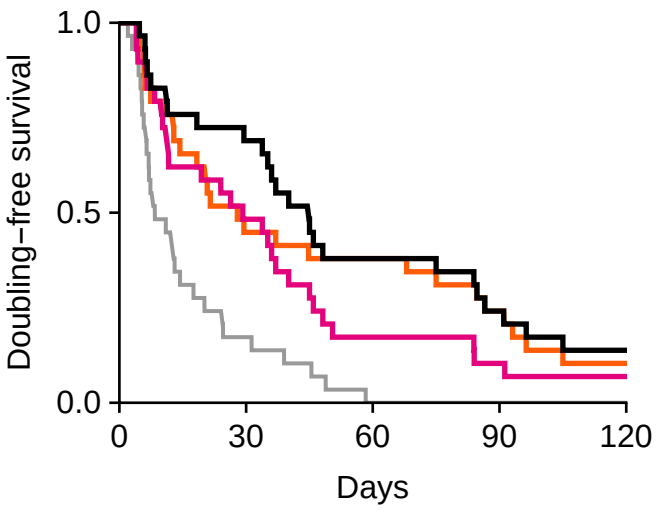
```
(* two PI3K inhibitors in NSCLC *)
tumortype = 2;
MonotherapiesByGroup[[tumortype, 3]]
MonotherapiesByGroup[[tumortype, 4]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 3]],
 MonotherapiesByGroup[[tumortype, 4]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

```
BKM120

BYL719
```

```
{3.55397, 1.16896,
```




```
, 0.591626, {0.79287, 0.384359}}
```

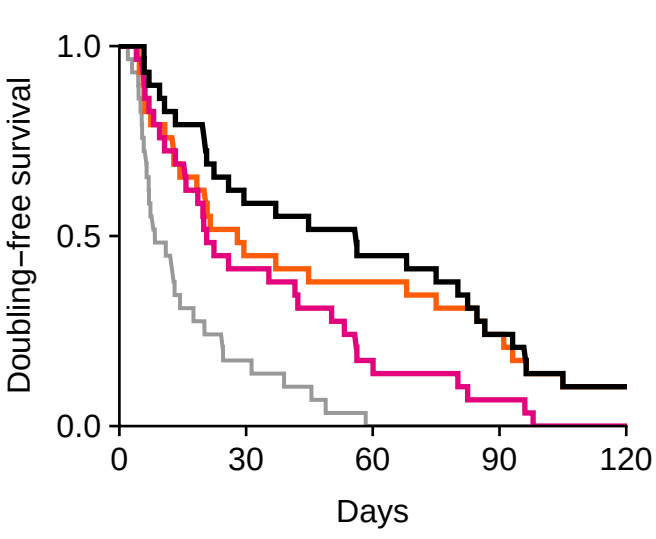
```
(* another two PI3K inhibitors in NSCLC *)
tumortype = 2;
MonotherapiesByGroup[[tumortype, 3]]
MonotherapiesByGroup[[tumortype, 8]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 3]],
 MonotherapiesByGroup[[tumortype, 8]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

```
BKM120

CLR457
```

```
{3.58071, 1.17775,
```




```
, 0.453202, {0.881644, 0.631879}}
```

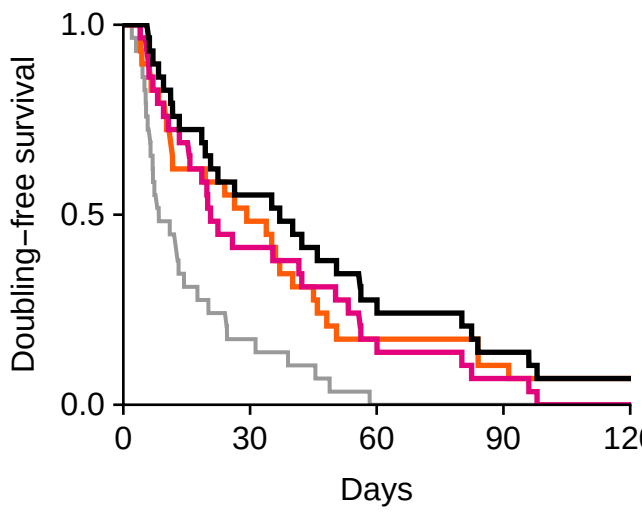
```
(* another two PI3K inhibitors in NSCLC *)
tumortype = 2;
MonotherapiesByGroup[[tumortype, 4]]
MonotherapiesByGroup[[tumortype, 8]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 4]],
 MonotherapiesByGroup[[tumortype, 8]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

BYL719

CLR457

{2.89448, 1.2061,



, 0.756158, {1.00462, 0.986262}}

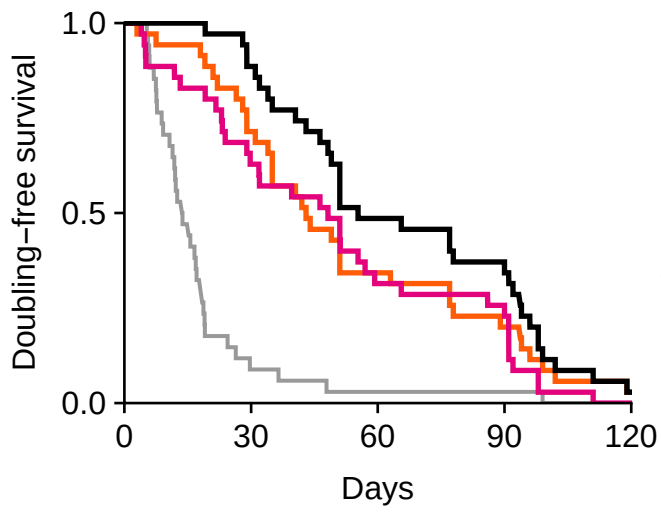
```
(* two MEK inhibitors in PDAC *)
tumortype = 3;
MonotherapiesByGroup[[tumortype, 2]]
MonotherapiesByGroup[[tumortype, 13]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 2]],
 MonotherapiesByGroup[[tumortype, 13]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

binimetinib

trametinib

{3.72833, 1.25483,



, 0.157094, {0.773778, 0.306188}}

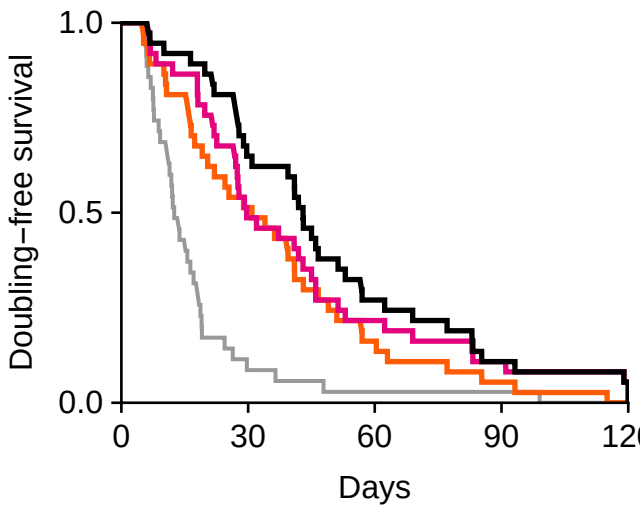
```
(* two PI3K inhibitors in PDAC *)
tumortype = 3;
MonotherapiesByGroup[[tumortype, 4]]
MonotherapiesByGroup[[tumortype, 5]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 4]],
 MonotherapiesByGroup[[tumortype, 5]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

BKM120

BYL719

{2.83684, 1.16612,



, 0.503172, {1.13676, 0.607701}}

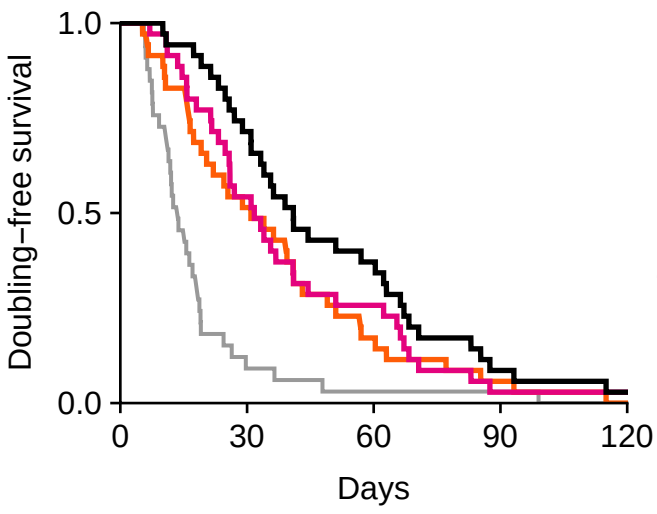
```
(* another two PI3K inhibitors in PDAC *)
tumortype = 3;
MonotherapiesByGroup[[tumortype, 4]]
MonotherapiesByGroup[[tumortype, 6]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 4]],
 MonotherapiesByGroup[[tumortype, 6]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

BKM120

CLR457

{2.77196, 1.2538,



, 0.356022, {1.24105, 0.404016}}

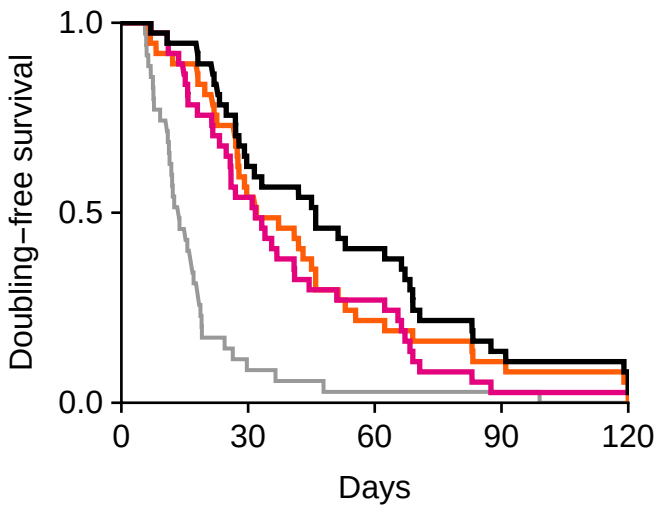
```
(* another two PI3K inhibitors in PDAC *)
tumortype = 3;
MonotherapiesByGroup[[tumortype, 5]]
MonotherapiesByGroup[[tumortype, 6]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 5]],
 MonotherapiesByGroup[[tumortype, 6]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

BYL719

CLR457

{3.00422, 1.21416,



, 0.603912, {1.09091, 0.729637}}

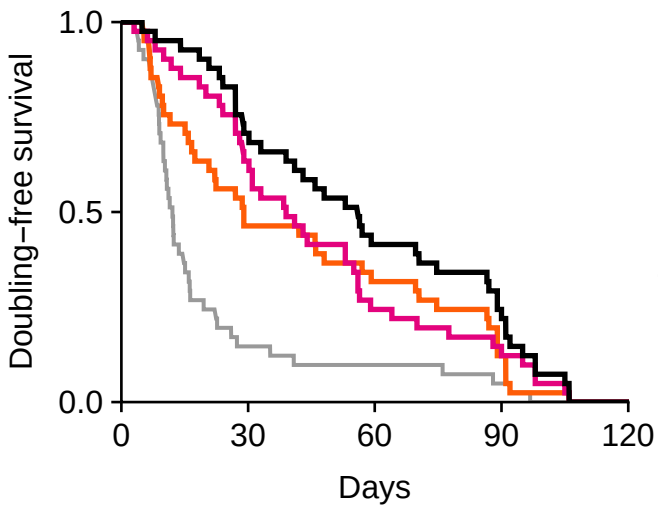
```
(* MEK and MAPK inhibitors in CRC *)
tumortype = 4;
MonotherapiesByGroup[[tumortype, 2]]
MonotherapiesByGroup[[tumortype, 7]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 2]],
 MonotherapiesByGroup[[tumortype, 7]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

binimetinib

CKX620

{2.76542, 1.24508,



, 0.531465, {0.746183, 0.187551}}

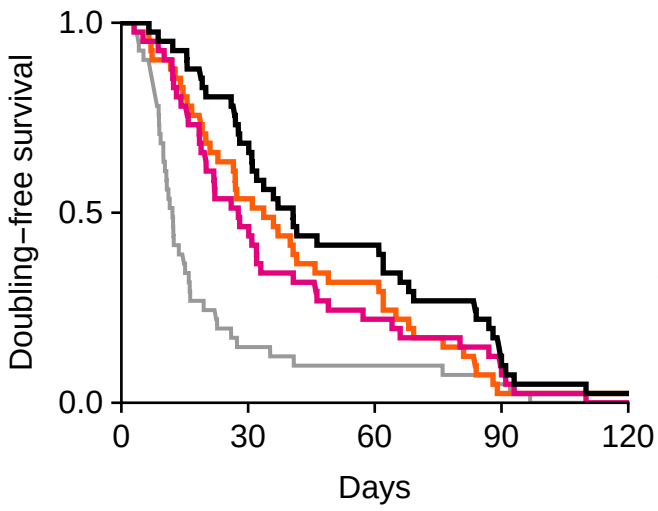
```
(* two PI3K inhibitors in CRC *)
tumortype = 4;
MonotherapiesByGroup[[tumortype, 3]]
MonotherapiesByGroup[[tumortype, 4]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 3]],
 MonotherapiesByGroup[[tumortype, 4]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

BKM120

BYL719

{2.46726, 1.22051,



, 0.460909, {0.942082, 0.791467}}

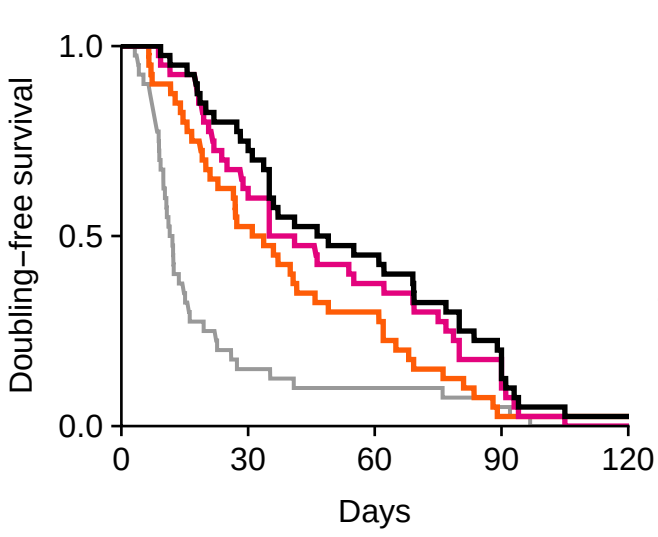
```
(* another two PI3K inhibitors in CRC *)
tumortype = 4;
MonotherapiesByGroup[[tumortype, 3]]
MonotherapiesByGroup[[tumortype, 8]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 3]],
 MonotherapiesByGroup[[tumortype, 8]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

BKM120

CLR457

{2.63591, 1.12884,



, 0.626654, {0.839859, 0.438914}}

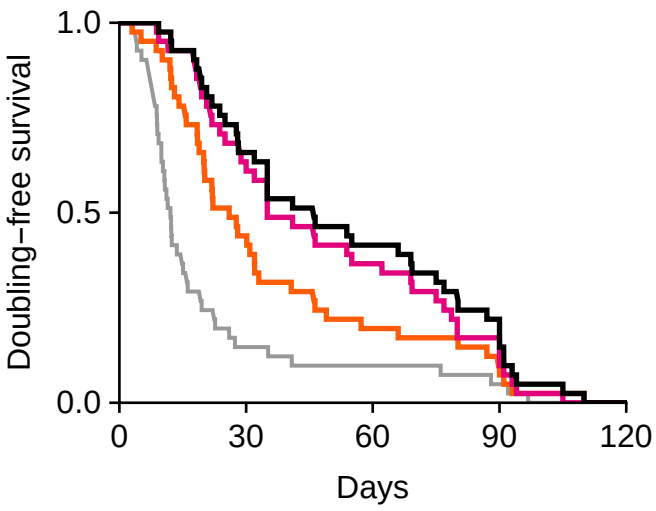
```
(* another two PI3K inhibitors in CRC *)
tumortype = 4;
MonotherapiesByGroup[[tumortype, 4]]
MonotherapiesByGroup[[tumortype, 8]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 4]],
 MonotherapiesByGroup[[tumortype, 8]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

BYL719

CLR457

{2.52551, 1.08842,



, 0.625158, {0.858792, 0.49992}}

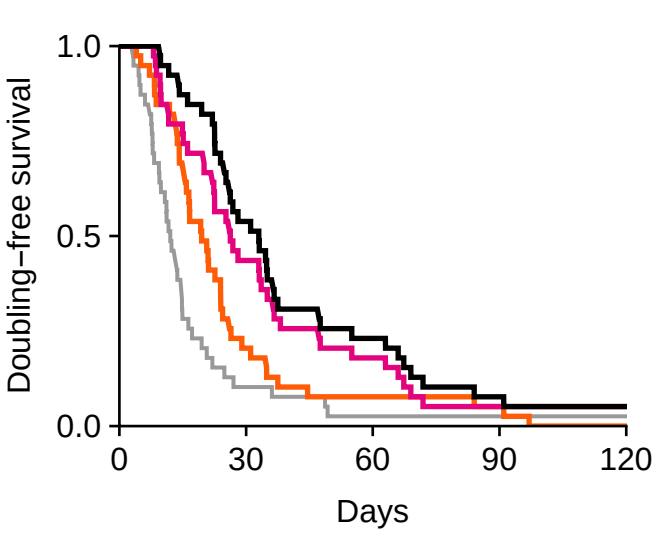
```
(* FGFR mAb and FGFR kinase inhibitors in Breast *)
tumortype = 5;
MonotherapiesByGroup[[tumortype, 1]]
MonotherapiesByGroup[[tumortype, 13]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 1]],
 MonotherapiesByGroup[[tumortype, 13]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

BGJ398

LLM871

{2.35002, 1.15819,



, 0.159109, {1.46271, 0.102496}}

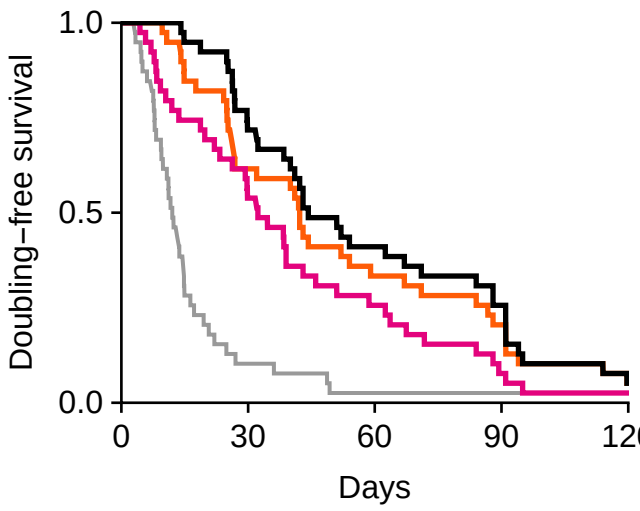
```
(* two PI3K kinase inhibitors in Breast *)
tumortype = 5;
MonotherapiesByGroup[[tumortype, 3]]
MonotherapiesByGroup[[tumortype, 4]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 3]],
 MonotherapiesByGroup[[tumortype, 4]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

```
BKM120

BYL719
```

```
{3.37191, 1.12003,
```




```
, 0.526348, {0.861524, 0.517195}}
```

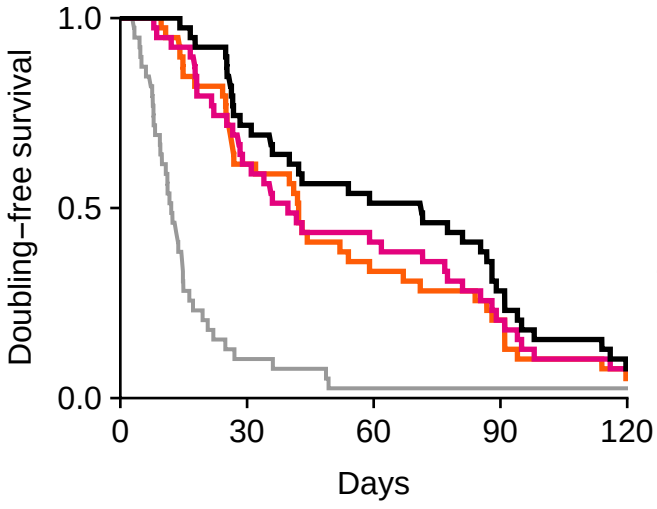
```
(* another two PI3K kinase inhibitors in Breast *)
tumortype = 5;
MonotherapiesByGroup[[tumortype, 3]]
MonotherapiesByGroup[[tumortype, 6]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 3]],
 MonotherapiesByGroup[[tumortype, 6]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

```
BKM120

CLR457
```

```
{3.7479, 1.20669,
```




```
, 0.594857, {0.767943, 0.248179}}
```

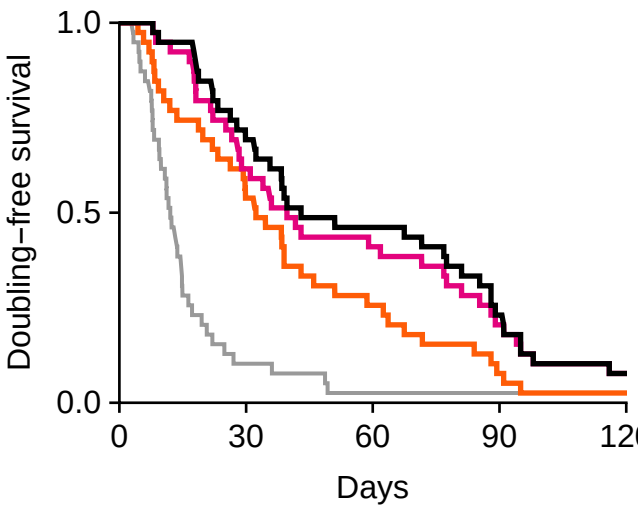
```
(* another two PI3K kinase inhibitors in Breast *)
tumortype = 5;
MonotherapiesByGroup[[tumortype, 4]]
MonotherapiesByGroup[[tumortype, 6]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 4]],
 MonotherapiesByGroup[[tumortype, 6]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

BYL719

CLR457

{3.36781, 1.08431,



, 0.637988, {0.880618, 0.577602}}

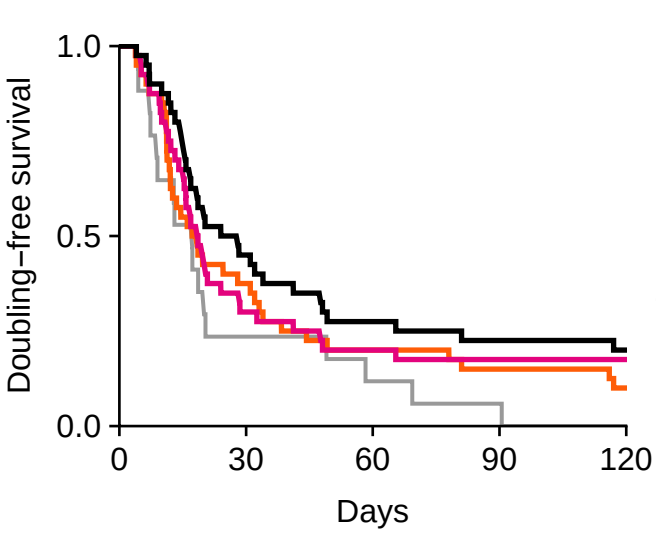
```
(* FGFR mAb and FGFR kinase inhibitors in Gastric *)
tumortype = 6;
MonotherapiesByGroup[[tumortype, 1]]
MonotherapiesByGroup[[tumortype, 13]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 1]],
 MonotherapiesByGroup[[tumortype, 13]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

BGJ398

LLM871

{2.58465, 1.16223,



, 0.630206, {0.987064, 0.955614}}

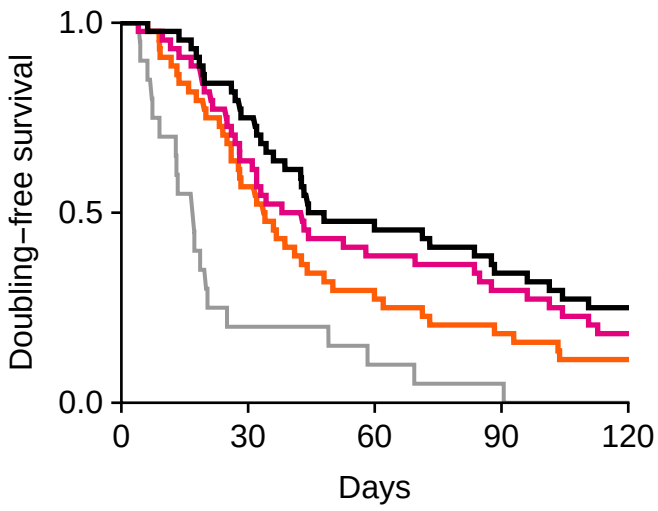
```
(* two PI3K kinase inhibitors in Gastric *)
tumortype = 6;
MonotherapiesByGroup[[tumortype, 3]]
MonotherapiesByGroup[[tumortype, 4]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 3]],
 MonotherapiesByGroup[[tumortype, 4]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

BKM120

BYL719

{3.49594, 1.24967,



, 0.441892, {0.76488, 0.214691}}

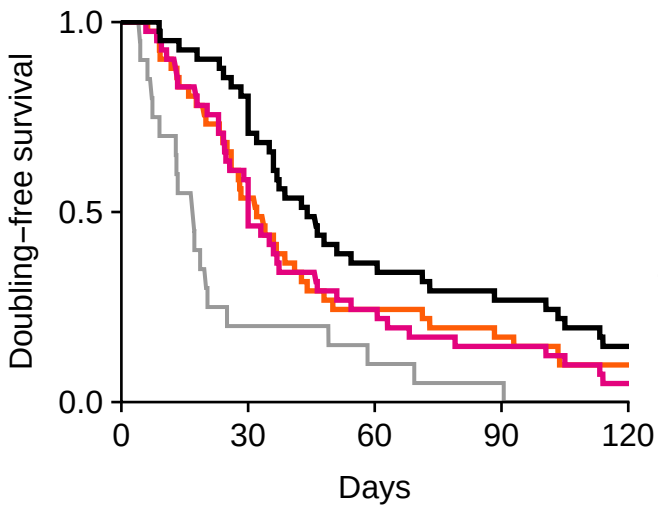
```
(* another two PI3K kinase inhibitors in Gastric *)
tumortype = 6;
MonotherapiesByGroup[[tumortype, 3]]
MonotherapiesByGroup[[tumortype, 5]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 3]],
 MonotherapiesByGroup[[tumortype, 5]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

BKM120

CLR457

{2.93201, 1.28012,



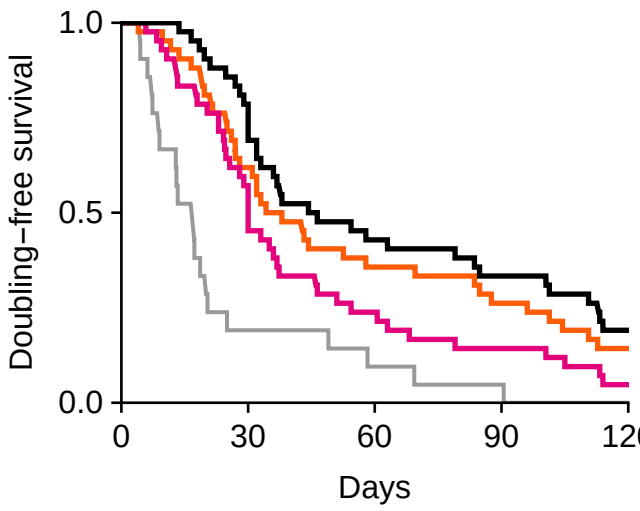
, 0.244267, {0.860817, 0.501491}}

```
(* another two PI3K kinase inhibitors in Gastric *)
tumortype = 6;
MonotherapiesByGroup[[tumortype, 4]]
MonotherapiesByGroup[[tumortype, 5]]
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, 4]],
 MonotherapiesByGroup[[tumortype, 5]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]]

SimilarDrugCorrelations = Append[SimilarDrugCorrelations,
   SpearmanRho[DrugAresponsesInIntersection[[All, 9]], DrugBresponsesInIntersection[[All, 9]]]];
```

BYL719

CLR457

{3.13573, 1.16098, 

, 0.389943, {0.833774, 0.405538}}

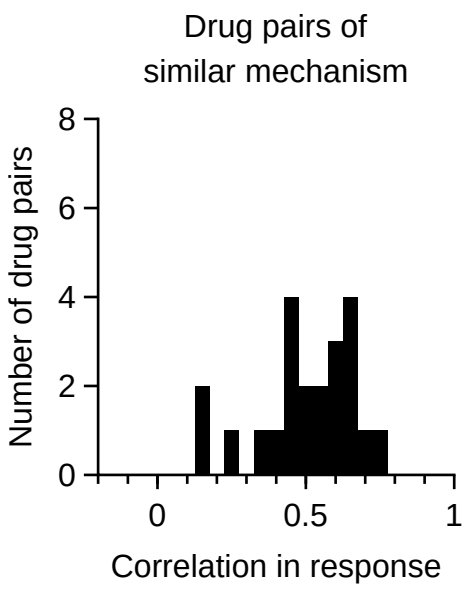
analyzing results

```
Mean[SimilarDrugCorrelations]
Median[SimilarDrugCorrelations]
```

0.498194

0.51476

```
Histogram[SimilarDrugCorrelations, {-0.225, 1.125, 0.05}, "Count", ChartLayout → "Stacked",
 Frame → {{True, False}, {True, False}}, FrameStyle → Directive[Black, Thickness[Medium]],
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 ChartStyle → {Directive[EdgeForm[None], Opacity[1], Black]},
 FrameLabel → {"Correlation in response", "Number of drug pairs"},
 FrameTicks → {{Table[{i, i, {0, 0.04}}, {i, 0, 10, 2}], None},
   {Join[{{0, 0, {0, 0.04}}, {0.5, "0.5", {0, 0.04}}, {1, 1, {0, 0.04}}},
    Table[{i, , {0, 0.025}}, {i, -0.2, 1, 0.1}]], None}}, PlotRange → {{-0.2, 1.}, {0, 8}},
PlotRangePadding → None, AspectRatio → 1, ImageSize → {{500}, {220}},
ImagePadding → {{45, 10}, {45, 10}},
PlotLabel → Style["Drug pairs of\nsimilar mechanism", FontSize → 12, Black]]
```



Plotting response correlations

```
AllActiveAgentsCorrelations = Join[
   MelanomaResponseCorrelationsActiveAgentsOnly,
   NSCLCResponseCorrelationsActiveAgentsOnly,
   PDACResponseCorrelationsActiveAgentsOnly,
   CRCResponseCorrelationsActiveAgentsOnly,
   BCResponseCorrelationsActiveAgentsOnly,
   GCResponseCorrelationsActiveAgentsOnly
  ];

Mean[AllActiveAgentsCorrelations]
Median[AllActiveAgentsCorrelations]
```

```
0.369107
```

```
0.372123
```

```
(* from the list of all response correlations between active agents,
remove those entries corresponding to drugs with similar mechanisms,
because these are plotted separately in a "stacked" histogram *)
AllActiveAgentsExcludingSimilarMechanismPairs =
  Complement[AllActiveAgentsCorrelations, SimilarDrugCorrelations];
```

Identifying correlations between chemotherapy and targeted therapy

```
(* melanoma: mono #5 is the only classic cytotoxic chemotherapy *)
MonotherapiesByGroup[[1]]
MonotherapiesByGroup[[1, {1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12}]]
```

```
{binimetinib, BKM120, CGM097, CLR457, dacarbazine,
 encorafenib, LDE225, LDK378, LEE011, LGW813, TAS266, WNT974}
```

```
{binimetinib, BKM120, CGM097, CLR457, encorafenib, LDE225, LDK378, LEE011, LGW813, TAS266, WNT974}
```

```
MelanomaChemoTargetedCorrelations = AllMelanomaPairs[[5, {1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12}, 4]]
```

```
{0.0922428, 0.397579, 0.372123, 0.503899, 0.291399,
 0.546405, 0.358518, 0.479685, 0.170548, 0.245186, 0.34657}
```

```
(* NSCLC: mono #16 is the only classic cytotoxic chemotherapy *)
MonotherapiesByGroup[[2]]
MonotherapiesByGroup[[2, {1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15}]]
```

```
{BGJ398, binimetinib, BKM120, BYL719, cetuximab, CGM097, CKX620,
 CLR457, erlotinib, HDM201, HSP990, INC280, LEE011, LGH447, LLM871, paclitaxel}
```

```
{BGJ398, binimetinib, BKM120, BYL719, cetuximab, CGM097,
 CKX620, CLR457, erlotinib, HDM201, HSP990, INC280, LEE011, LGH447, LLM871}
```

```
NSCLCChemoTargetedCorrelations = AllNSCLCPairs[[16, {2, 3, 4, 7, 8, 9, 11, 13, 15}, 4]]
```

```
{0.215684, 0.53202, 0.555008, 0.193787, 0.594417, 0.690297, 0.452417, 0.128697, 0.591761}
```

```
(* PDAC: mono #1 and #8 is the only classic cytotoxic chemotherapy; but #1, abraxane,
had no effect in mice. *)
MonotherapiesByGroup[[3]]
MonotherapiesByGroup[[3, {2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14}]]
```

```
{abraxane, binimetinib, binimetinib-3.5mpk, BKM120, BYL719, CLR457,
 figitumumab", gemcitabine-50mpk, HDM201, INC424, LEE011, LKA136, trametinib, WNT974}
```

```
{binimetinib, binimetinib-3.5mpk, BKM120, BYL719, CLR457,
 figitumumab", HDM201, INC424, LEE011, LKA136, trametinib, WNT974}
```

```
PDACChemoTargetedCorrelations = AllPDACPairs[[8, {2, 4, 5, 6, 9, 10, 11, 13}, 4]]
```

```
{0.0769231, -0.111807, 0.0553263, -0.0509735, 0.305365, -0.144428, 0.00751535, 0.0960268}
```

```
(* CRC: mono #1 is the only classic cytotoxic chemotherapy *)
MonotherapiesByGroup[[4]]
MonotherapiesByGroup[[4, {2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13}]]
```

```
{5FU, binimetinib, BKM120, BYL719, cetuximab, CGM097,
 CKX620, CLR457, encorafenib, HDM201, LEE011, LJC049, LKA136}
```

```
{binimetinib, BKM120, BYL719, cetuximab, CGM097,
 CKX620, CLR457, encorafenib, HDM201, LEE011, LJC049, LKA136}
```

```
CRCChemoTargetedCorrelations = AllCRCPairs[[1, {2, 3, 4, 5, 7, 8, 11}, 4]]
```

```
{0.338859, 0.309056, 0.103809, 0.352644, 0.0833878, 0.122445, 0.15187}
```

```
(* Breast: mono #14 is the only classic cytotoxic chemotherapy *)
MonotherapiesByGroup[[5]]
MonotherapiesByGroup[[5, {1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16}]]
```

```
{BGJ398, binimetinib, BKM120, BYL719, CGM097, CLR457, HDM201, INC424,
 LEE011, LFA102, LJM716, LKA136, LLM871, paclitaxel, tamoxifen, trastuzumab}
```

```
{BGJ398, binimetinib, BKM120, BYL719, CGM097, CLR457, HDM201,
 INC424, LEE011, LFA102, LJM716, LKA136, LLM871, tamoxifen, trastuzumab}
```

```
BCChemoTargetedCorrelations = AllBCPairs[[14, {1, 2, 3, 4, 6, 7, 8, 9, 11, 13}, 4]]
```

```
{0.223696, 0.289604, 0.0639838, 0.429294, 0.250316, 0.448504, 0.379493, 0.360038, 0.33858, 0.352751}
```

```
(* Gastric: no classic cytotoxic chemotherapy *)
MonotherapiesByGroup[[6]]
MonotherapiesByGroup[[6, {1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14}]]
```

```
{BGJ398, binimetinib, BKM120, BYL719, CLR457, everolimus,
 figitumumab", HDM201, HSP990, INC280, LEE011, LJM716, LLM871, trastuzumab}
```

```
{BGJ398, binimetinib, BKM120, BYL719, CLR457, everolimus,
 figitumumab", HDM201, HSP990, INC280, LEE011, LJM716, LLM871, trastuzumab}
```

```
AllChemoTargetedCorrelations = Join[
    MelanomaChemoTargetedCorrelations,
    NSCLCChemoTargetedCorrelations,
    PDACChemoTargetedCorrelations,
    CRCChemoTargetedCorrelations,
    BCChemoTargetedCorrelations
   ];
```

```
Mean[AllActiveAgentsCorrelations]
Mean[AllChemoTargetedCorrelations]
Mean[SimilarDrugCorrelations]
```

```
0.369107
```

```
0.279789
```

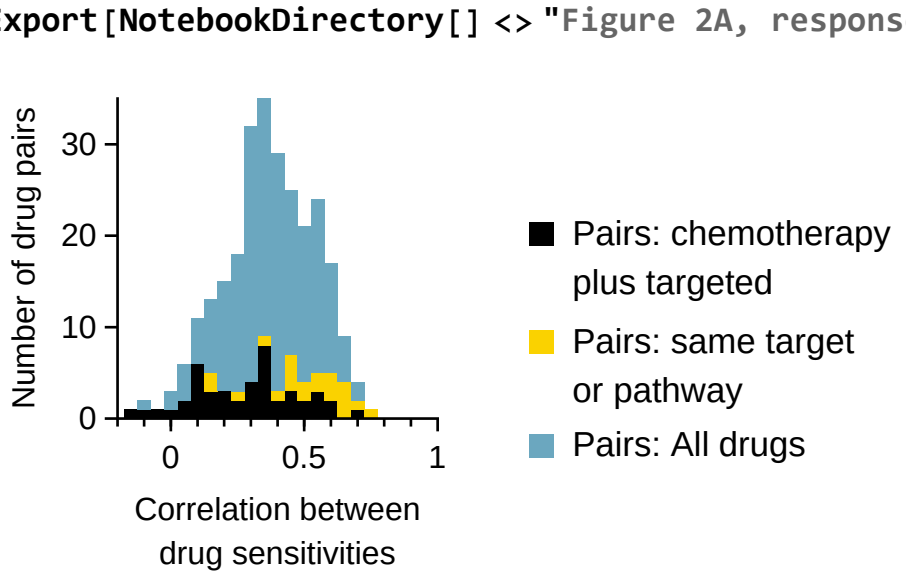
```
0.498194
```

```
(* from the list of all response correlations between active agents,
remove those entries corresponding to drugs with similar mechanisms,
and entries corresponding to chemotherapies combined with targeted therapies,
because these are plotted separately in a "stacked" histogram *)
AllActiveAgentsExcludingSimilarMechanismAndChemoTargetedPairs =
  Complement[AllActiveAgentsCorrelations, SimilarDrugCorrelations,
   AllChemoTargetedCorrelations];

(* this option allows legends to be included in exported images without interfering
 with image size *)
SetOptions[$FrontEndSession, PrintingStyleEnvironment → "Working"]

Histogram[{AllChemoTargetedCorrelations, SimilarDrugCorrelations,
  AllActiveAgentsExcludingSimilarMechanismAndChemoTargetedPairs}, {-0.225, 1.125, 0.05},
 "Count", ChartLayout → "Stacked", Frame → {{True, False}, {True, False}},
 FrameStyle → Directive[Black, Thickness[Medium]],
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 ChartStyle → {Directive[EdgeForm[None], Black, Opacity[1]],
   Directive[EdgeForm[None], RGBColor[250 / 255, 210 / 255, 0.], Opacity[1]],
   Directive[EdgeForm[None], Opacity[1],
    Blend[{RGBColor[0 / 255, 150 / 255, 210 / 255], GrayLevel[0.7]}, 0.6]]},
 FrameLabel → {"Correlation between\ndrug sensitivities", "Number of drug pairs"},
 FrameTicks → {{Table[{i, i, {0, 0.04}}, {i, 0, 50, 10}], None},
   {Join[{{0, 0, {0, 0.04}}, {0.5, "0.5", {0, 0.04}}, {1, 1, {0, 0.04}}},
     Table[{i, , {0, 0.025}}, {i, -0.2, 1, 0.1}]], None}}, PlotRange → {{-0.2, 1.}, {0, All}},
 PlotRangePadding → None, AspectRatio → 1, ImageSize → {{500}, {200}},
 ImagePadding → {{50, 20}, {70, 10}},
 ChartLegends → {"Pairs: chemotherapy\nplus targeted", "Pairs: same target\nor pathway",
   "Pairs: All drugs"}]

Export[NotebookDirectory[] <> "Figure 2A, response correlations in PDX trials.pdf", %, "PDF"];
```



```
(* range of correlation in chemotherapy plus targeted therapy drug pairs *)
Mean[AllChemoTargetedCorrelations]
Mean[AllChemoTargetedCorrelations] + StandardDeviation[AllChemoTargetedCorrelations]
Mean[AllChemoTargetedCorrelations] - StandardDeviation[AllChemoTargetedCorrelations]
```

```
0.279789
```

```
0.476402
```

```
0.083177
```

```
(* range of correlation in drugs acting on common target or pathway *)
Mean[SimilarDrugCorrelations]
Mean[SimilarDrugCorrelations] + StandardDeviation[SimilarDrugCorrelations]
Mean[SimilarDrugCorrelations] - StandardDeviation[SimilarDrugCorrelations]
```

```
0.498194
```

```
0.6598
```

```
0.336589
```

Response correlations have similar distributions in each tumor type:

```
Histogram[Intersection[MelanomaResponseCorrelationsActiveAgentsOnly], {-1.05, 1.05, 0.1},
 Frame → {{True, False}, {True, False}}, FrameStyle → Directive[Black, Thickness[Medium]],
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 ChartStyle → Directive[EdgeForm[Directive[Thickness[Medium], Opacity[1], GrayLevel[0.4]]],
   GrayLevel[0.5]],
 FrameLabel → {"Rank correlation between\ndrug sensitivities", "Number of drug pairs"},
 FrameTicks → {{Table[{i, i, {0, 0.02}}, {i, 0, 200, 5}], None},
   {Join[Table[{i, i, {0, 0.02}}, {i, -1, 1, 1}], Table[{i, , {0, 0.02}}, {i, -0.5, 0.5, 1}]],
    None}}, PlotRange → {{-1., 1.}, {0, 17}}, PlotRangePadding → None, AspectRatio → 1,
 ImageSize → {{1000}, {250}}, ImagePadding → {{50, 50}, {80, 10}},
 PlotLabel → Style["Melanoma", FontSize → 12, Black]]

Histogram[Intersection[NSCLCResponseCorrelationsActiveAgentsOnly], {-1.05, 1.05, 0.1},
 Frame → {{True, False}, {True, False}}, FrameStyle → Directive[Black, Thickness[Medium]],
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 ChartStyle → Directive[EdgeForm[Directive[Thickness[Medium], Opacity[1], GrayLevel[0.4]]],
   GrayLevel[0.5]],
 FrameLabel → {"Rank correlation between\ndrug sensitivities", "Number of drug pairs"},
 FrameTicks → {{Table[{i, i, {0, 0.02}}, {i, 0, 200, 5}], None},
   {Join[Table[{i, i, {0, 0.02}}, {i, -1, 1, 1}], Table[{i, , {0, 0.02}}, {i, -0.5, 0.5, 1}]],
    None}}, PlotRange → {{-1., 1.}, {0, 12}}, PlotRangePadding → None, AspectRatio → 1,
 ImageSize → {{1000}, {250}}, ImagePadding → {{50, 50}, {80, 10}},
 PlotLabel → Style["Non-small cell lung cancer", FontSize → 12, Black]]

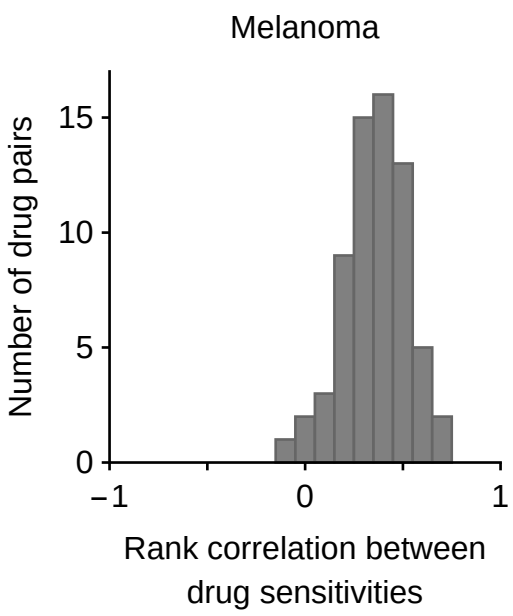
Histogram[Intersection[PDACResponseCorrelationsActiveAgentsOnly], {-1.05, 1.05, 0.1},
 Frame → {{True, False}, {True, False}}, FrameStyle → Directive[Black, Thickness[Medium]],
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 ChartStyle → Directive[EdgeForm[Directive[Thickness[Medium], Opacity[1], GrayLevel[0.4]]],
   GrayLevel[0.5]],
 FrameLabel → {"Rank correlation between\ndrug sensitivities", "Number of drug pairs"},
 FrameTicks → {{Table[{i, i, {0, 0.02}}, {i, 0, 200, 5}], None},
   {Join[Table[{i, i, {0, 0.02}}, {i, -1, 1, 1}], Table[{i, , {0, 0.02}}, {i, -0.5, 0.5, 1}]],
    None}}, PlotRange → {{-1., 1.}, {0, 13}}, PlotRangePadding → None, AspectRatio → 1,
 ImageSize → {{1000}, {250}}, ImagePadding → {{50, 50}, {80, 10}},
 PlotLabel → Style["Pancreatic ductal adenocarcinoma", FontSize → 12, Black]]

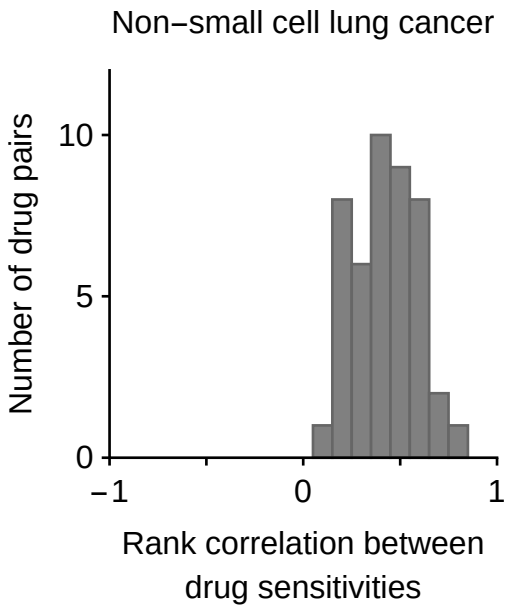
Histogram[Intersection[CRCResponseCorrelationsActiveAgentsOnly], {-1.05, 1.05, 0.1},
```

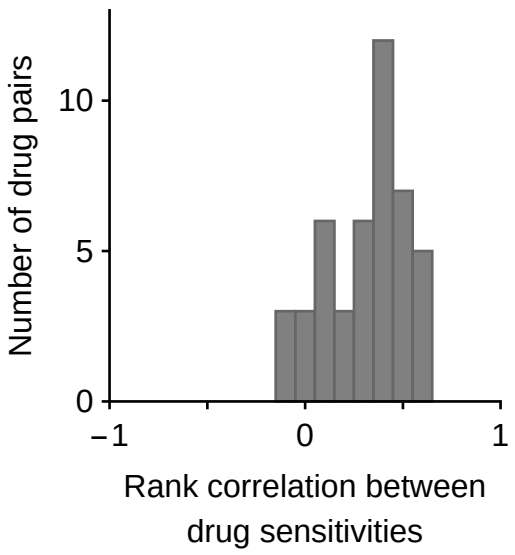
```
 Frame → {{True, False}, {True, False}}, FrameStyle → Directive[Black, Thickness[Medium]],
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 ChartStyle → Directive[EdgeForm[Directive[Thickness[Medium], Opacity[1], GrayLevel[0.4]]],
   GrayLevel[0.5]],
 FrameLabel → {"Rank correlation between\ndrug sensitivities", "Number of drug pairs"},
 FrameTicks → {{Table[{i, i, {0, 0.02}}, {i, 0, 200, 5}], None},
   {Join[Table[{i, i, {0, 0.02}}, {i, -1, 1, 1}], Table[{i, , {0, 0.02}}, {i, -0.5, 0.5, 1}]],
    None}}, PlotRange → {{-1., 1.}, {0, 10}}, PlotRangePadding → None, AspectRatio → 1,
 ImageSize → {{1000}, {250}}, ImagePadding → {{50, 50}, {80, 10}},
 PlotLabel → Style["Colorectal carcinoma", FontSize → 12, Black]]

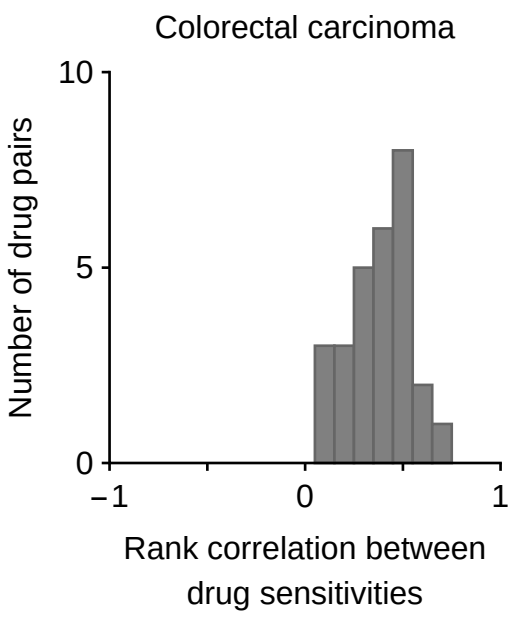
Histogram[Intersection[BCResponseCorrelationsActiveAgentsOnly], {-1.05, 1.05, 0.1},
 Frame → {{True, False}, {True, False}}, FrameStyle → Directive[Black, Thickness[Medium]],
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 ChartStyle → Directive[EdgeForm[Directive[Thickness[Medium], Opacity[1], GrayLevel[0.4]]],
   GrayLevel[0.5]],
 FrameLabel → {"Rank correlation between\ndrug sensitivities", "Number of drug pairs"},
 FrameTicks → {{Table[{i, i, {0, 0.02}}, {i, 0, 200, 5}], None},
   {Join[Table[{i, i, {0, 0.02}}, {i, -1, 1, 1}], Table[{i, , {0, 0.02}}, {i, -0.5, 0.5, 1}]],
    None}}, PlotRange → {{-1., 1.}, {0, 20}}, PlotRangePadding → None, AspectRatio → 1,
 ImageSize → {{1000}, {250}}, ImagePadding → {{50, 50}, {80, 10}},
 PlotLabel → Style["Breast cancer", FontSize → 12, Black]]

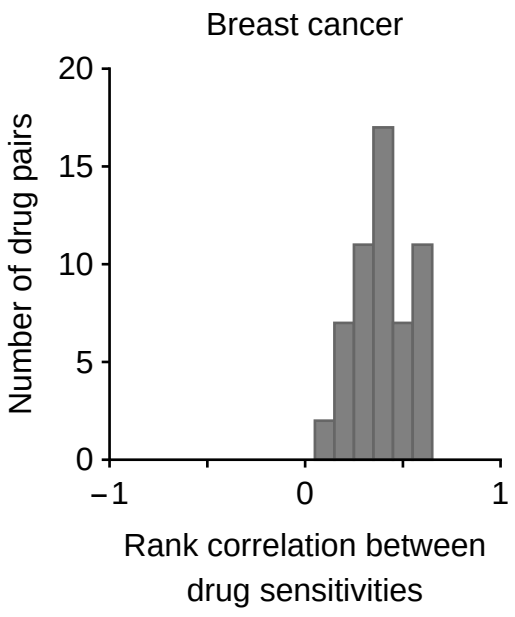
Histogram[Intersection[GCResponseCorrelationsActiveAgentsOnly], {-1.05, 1.05, 0.1},
 Frame → {{True, False}, {True, False}}, FrameStyle → Directive[Black, Thickness[Medium]],
 BaseStyle → {FontFamily → "Arial", FontSize → 12},
 ChartStyle → Directive[EdgeForm[Directive[Thickness[Medium], Opacity[1], GrayLevel[0.4]]],
   GrayLevel[0.5]],
 FrameLabel → {"Rank correlation between\ndrug sensitivities", "Number of drug pairs"},
 FrameTicks → {{Table[{i, i, {0, 0.02}}, {i, 0, 200, 2}], None},
   {Join[Table[{i, i, {0, 0.02}}, {i, -1, 1, 1}], Table[{i, , {0, 0.02}}, {i, -0.5, 0.5, 1}]],
    None}}, PlotRange → {{-1., 1.}, {0, 8}}, PlotRangePadding → None, AspectRatio → 1,
 ImageSize → {{1000}, {250}}, ImagePadding → {{50, 50}, {80, 10}},
 PlotLabel → Style["Gastric cancer", FontSize → 12, Black]]
```

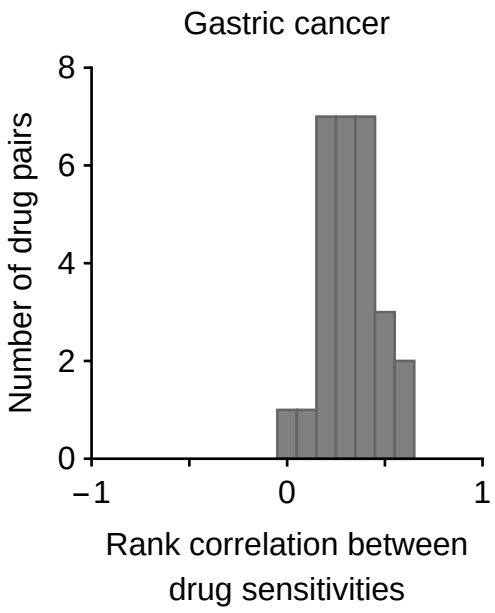



Non−small cell lung cancer
Number of drug pairs
10
5
0
−1
0
1
Rank correlation between
drug sensitivities


Pancreatic ductal adenocarcinoma
Number of drug pairs
10
5
0
−1
0
1
Rank correlation between
drug sensitivities


Colorectal carcinoma
Number of drug pairs
10
5
0
−1
0
1
Rank correlation between
drug sensitivities


Breast cancer
Number of drug pairs
20
15
10
5
0
−1
0
1
Rank correlation between
drug sensitivities



Pairs of Chemotherapy plus targeted, and pairs of drugs with similar mechanism, are each significantly different from the distribution of response correlations of all active agents:

```
TTest[{AllActiveAgentsCorrelations, AllChemoTargetedCorrelations}]
```

0.00150949

```
TTest[{AllActiveAgentsCorrelations, SimilarDrugCorrelations}]
```

0.000631931

Pooled comparison of best predicted combinations and best observed combinations

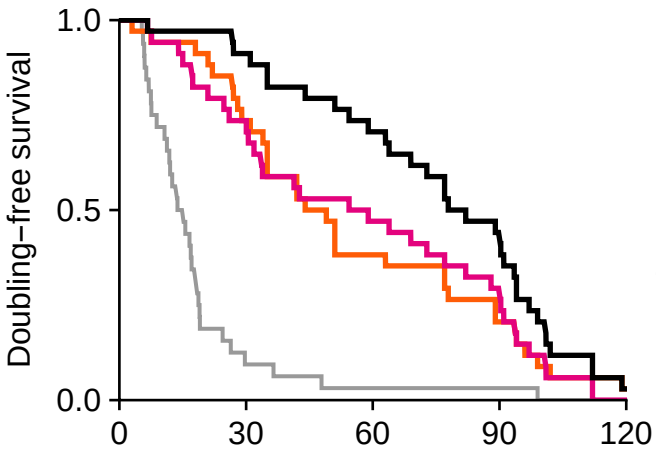
PDAC

```
tumortype = 3;
(* what is the best survival over untreated predicted for any combination? *)
PDACBestPrediction = Max[AllPDACPairs[[All, All, 1]]];
(* where does that best prediction lie in the matrix over all combination
 predictions? The drug names are in the corresponding positions of
 MonotherapiesByGroup[[tumortype]] . *)
PDACBestPredictionPosition = Position[AllPDACPairs[[All, All, 1]], PDACBestPrediction][[1]];
drug1index = PDACBestPredictionPosition[[1]];
drug2index = PDACBestPredictionPosition[[2]];
drug1name = MonotherapiesByGroup[[tumortype, drug1index]]
drug2name = MonotherapiesByGroup[[tumortype, drug2index]]
```

```
(* running the combination prediction for this best pair,
to load into memory the best monotherapy responses (BestOfMonotherapyResponses),
and also the set of PDX models involved in this prediction (ModelsInBothMonotherapies). No
 larger set of models is possible;
the prediction does not exist when the model has not been treated with both monotherapies. *)
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, drug1index]],
 MonotherapiesByGroup[[tumortype, drug2index]], AllModelGroups[[tumortype]],
 ModelNames[[tumortype]]]
```

```
binimetinib

gemcitabine-50mpk
```




```
{4.12802, 1.31849,                                    , 0.0769231, {0.654136, 0.0823313}}
```

```
(* taking these terms from the IndependentActionPrediction function and giving them disease-
 class-specific names (e.g. PDAC...) *)
PDACModelsInBothMonotherapies = ModelsInBothMonotherapies;
PDACBestPredictedResponses = BestOfMonotherapyResponses;
```

```
(* looking along the diagonal of the all pair predictions -
 here drug1 and drug2 are identical - to determine the monotherapy with the best single-
 agent improvement over untreated (quantified by average PFS) *)
BestPDACMonotherapyResponseOverUntreated =
  Max[Table[AllPDACPairs[[i, i, 1]], {i, 1, Length[AllPDACPairs]}]];
PositionOfBestPDACMonotherapyResponseOverUntreated =
  Position[Table[AllPDACPairs[[i, i, 1]], {i, 1, Length[AllPDACPairs]}],
    BestPDACMonotherapyResponseOverUntreated][[1, 1]];
(* what is this therapy's name? *)
BestPDACMonotherapyResponseOverUntreatedCompound =
 MonotherapiesByGroup[[tumortype, PositionOfBestPDACMonotherapyResponseOverUntreated]]
(* what PDX models were in this best monotherapy? *)
PDACModelsInBestMonotherapy =
  Select[PDXclinicaltrialresponses,
    And[MemberQ[AllModelGroups[[tumortype]], #[[1]]],
      #[[2]] == BestPDACMonotherapyResponseOverUntreatedCompound] &][[All, 1]];

gemcitabine-50mpk
(* gather all empirically tested combination therapy responses for this disease class *)
PDACCombinationTherapyResponses =
  Table[Select[PDXclinicaltrialresponses,
    And[MemberQ[AllModelGroups[[tumortype]], #[[1]]],
      #[[2]] == CombinationTherapiesByGroup[[tumortype, i]]] &],
   {i, 1, Length[CombinationTherapiesByGroup[[tumortype]]]}];
(* ... and their survival functions *)
PDACCombinationSurvivalFunctions =
  Table[SurvivalFunction[EmpiricalDistribution[PDACCombinationTherapyResponses[[i, All, 9]]]][x],
   {i, 1, Length[PDACCombinationTherapyResponses]}];
```

```
(* cap the survival time to 360 days,
and then take the average across all models to measure the "area under the PFS curve",
from t=0 to ~t=1 year *)
AUCfromSurvivalDistribution[survivaldistribution_] := Module[{},
  IntegrationTime = 360;
  Mean[Map[Min[{#, IntegrationTime}] &, survivaldistribution]]
  (* equivalent to
   NIntegrate[SurvivalFunction[EmpiricalDistribution[PDACCombinationTherapyResponses[[1]]]][x],
    {x,0,IntegrationTime}]
  *)
 ]

(* which combination had the best AUC (integrated over 1 year)? *)
PDACBestCombinationAUC = Map[AUCfromSurvivalDistribution,
   PDACCombinationTherapyResponses[[All, All, 9]]](* [[All,All,9]] = All combinations,
 All rows describing the individual PDXs tested for a given combination,
 9th column is time to double. *);
PDACPositionOfBestCombination =
  Position[PDACBestCombinationAUC, Max[PDACBestCombinationAUC]][[1, 1]];
(* what are the names of the therapies in this combination? *)
PDACBestCombinationName = CombinationTherapiesByGroup[[tumortype, PDACPositionOfBestCombination]]
(* which PDX models of this disease group were tested with this combination? *)
PDACModelsInBestCombination =
 Select[PDXclinicaltrialresponses,
   And[MemberQ[AllModelGroups[[tumortype]], #[[1]]],
     #[[2]] == CombinationTherapiesByGroup[[tumortype, PDACPositionOfBestCombination]]] &][[All, 1]]
```

```
BKM120 + binimetinib
```

```
{X-0991, X-1199, X-1362, X-1948, X-2026, X-2043, X-2081, X-2339, X-2428, X-2564, X-2633, X-2684,
 X-2997, X-3028, X-3038, X-3052, X-3209, X-3268, X-3782, X-3800, X-3816, X-3846, X-3898, X-3947,
 X-3990, X-4015, X-4018, X-4145, X-4226, X-4377, X-4378, X-4439, X-4649, X-4676, X-4927, X-5205}
```

```
(* which models were tested in all of the following:
  the best empirical monotherapy,
the best empirical combination therapy,
both monotherapies that comprise the best predicted combination therapy *)
PDACModelsInAllTherapiesForComparison =
  Intersection[PDACModelsInBothMonotherapies, PDACModelsInBestMonotherapy,
   PDACModelsInBestCombination];
```

```
(* Within this set of PDX models...*)
(* what is the observed survival distribution for the best monotherapy? *)
PDACSurvivalDistributionBestMonotherapy =
  Select[PDXclinicaltrialresponses,
    And[MemberQ[PDACModelsInAllTherapiesForComparison, #[[1]]],
      #[[2]] == BestPDACMonotherapyResponseOverUntreatedCompound] &][[All, 9]];
(* what is the observed survival distribution for the best monotherapy? *)
PDACSurvivalDistributionBestCombination =
  Select[PDXclinicaltrialresponses,
    And[MemberQ[PDACModelsInAllTherapiesForComparison, #[[1]]],
      #[[2]] == PDACBestCombinationName] &][[All, 9]];
(* what is the predicted survival distribution for the best heterogeneity-
 addressing pair of monotherapies? *)
PDACSurvivalDistributionBestPredictedPairOfMonotherapies =
  Select[PDACBestPredictedResponses, MemberQ[PDACModelsInAllTherapiesForComparison, #[[1]]] &][[
   All, 9]];
(* what is the observed survival distribution for untreated? *)
PDACSurvivalDistributionUntreated =
  Select[PDXclinicaltrialresponses,
    And[MemberQ[PDACModelsInAllTherapiesForComparison, #[[1]]], #[[2]] == "untreated"] &][[All, 9]];
```

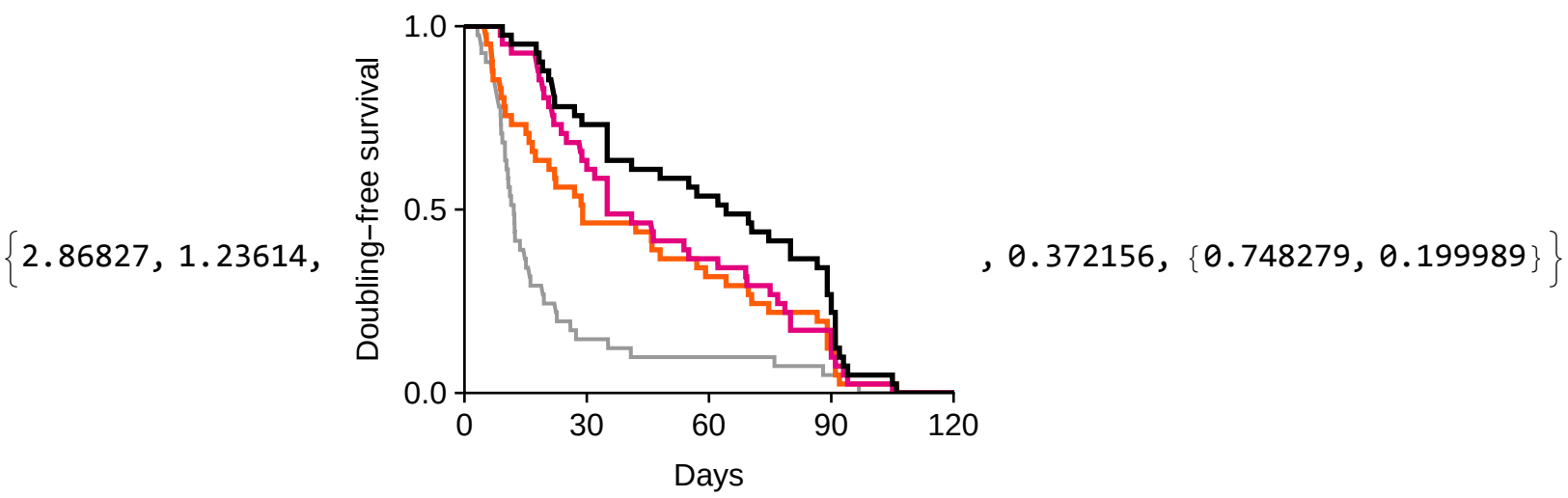
CRC

```
tumortype = 4;
(* what is the best survival over untreated predicted for any combination? *)
CRCBestPrediction = Max[AllCRCPairs[[All, All, 1]]];
(* where does that best prediction lie in the matrix over all combination
 predictions? The drug names are in the corresponding positions of
 MonotherapiesByGroup[[tumortype]] . *)
CRCBestPredictionPosition = Position[AllCRCPairs[[All, All, 1]], CRCBestPrediction][[1]];
drug1index = CRCBestPredictionPosition[[1]];
drug2index = CRCBestPredictionPosition[[2]];
drug1name = MonotherapiesByGroup[[tumortype, drug1index]]
drug2name = MonotherapiesByGroup[[tumortype, drug2index]]

(* running the combination prediction for this best pair,
to load into memory the best monotherapy responses (BestOfMonotherapyResponses),
and also the set of PDX models involved in this prediction (ModelsInBothMonotherapies). No
 larger set of models is possible;
the prediction does not exist when the model has not been treated with both monotherapies. *)
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, drug1index]],
 MonotherapiesByGroup[[tumortype, drug2index]], AllModelGroups[[tumortype]],
 ModelNames[[tumortype]]]
```

```
binimetinib

CLR457
```



```
(* taking these terms from the IndependentActionPrediction function and giving them disease-
 class-specific names (e.g. CRC...) *)
CRCModelsInBothMonotherapies = ModelsInBothMonotherapies;
CRCBestPredictedResponses = BestOfMonotherapyResponses;

(* looking along the diagonal of the all pair predictions -
 here drug1 and drug2 are identical - to determine the monotherapy with the best single-
 agent improvement over untreated (quantified by average PFS) *)
BestCRCMonotherapyResponseOverUntreated =
  Max[Table[AllCRCPairs[[i, i, 1]], {i, 1, Length[AllCRCPairs]}]];
PositionOfBestCRCMonotherapyResponseOverUntreated =
  Position[Table[AllCRCPairs[[i, i, 1]], {i, 1, Length[AllCRCPairs]}],
    BestCRCMonotherapyResponseOverUntreated][[1, 1]];
(* what is this therapy's name? *)
BestCRCMonotherapyResponseOverUntreatedCompound =
 MonotherapiesByGroup[[tumortype, PositionOfBestCRCMonotherapyResponseOverUntreated]]
(* what PDX models were in this best monotherapy? *)
CRCModelsInBestMonotherapy =
  Select[PDXclinicaltrialresponses,
    And[MemberQ[AllModelGroups[[tumortype]], #[[1]]],
      #[[2]] == BestCRCMonotherapyResponseOverUntreatedCompound] &][[All, 1]];
```

CLR457

```
(* gather all empirically tested combination therapy responses for this disease class *)
CRCCombinationTherapyResponses =
  Table[Select[PDXclinicaltrialresponses,
    And[MemberQ[AllModelGroups[[tumortype]], #[[1]]],
      #[[2]] == CombinationTherapiesByGroup[[tumortype, i]]] &],
   {i, 1, Length[CombinationTherapiesByGroup[[tumortype]]]}];
(* ... and their survival functions *)
CRCCombinationSurvivalFunctions =
  Table[SurvivalFunction[EmpiricalDistribution[CRCCombinationTherapyResponses[[i, All, 9]]][x],
   {i, 1, Length[CRCCombinationTherapyResponses]}];
```

```
(* cap the survival time to 360 days,
and then take the average across all models to measure the "area under the PFS curve",
from t=0 to ~t=1 year *)
AUCfromSurvivalDistribution[survivaldistribution_] := Module[{},
  IntegrationTime = 360;
  Mean[Map[Min[{#, IntegrationTime}] &, survivaldistribution]]
  (* equivalent to
   NIntegrate[SurvivalFunction[EmpiricalDistribution[CRCCombinationTherapyResponses[[1]]][x],
    {x,0,IntegrationTime}]
  *)
 ]

(* which combination had the best AUC (integrated over 1 year)? *)
CRCBestCombinationAUC = Map[AUCfromSurvivalDistribution,
   CRCCombinationTherapyResponses[[All, All, 9]](* [[All,All,9]] = All combinations,
 All rows describing the individual PDXs tested for a given combination,
 9th column is time to double. *);
CRCPositionOfBestCombination = Position[CRCBestCombinationAUC, Max[CRCBestCombinationAUC]][[1, 1]];
(* what are the names of the therapies in this combination? *)
CRCBestCombinationName = CombinationTherapiesByGroup[[tumortype, CRCPositionOfBestCombination]]
(* which PDX models of this disease group were tested with this combination? *)
CRCModelsInBestCombination =
 Select[PDXclinicaltrialresponses,
   And[MemberQ[AllModelGroups[[tumortype]], #[[1]]],
     #[[2]] == CombinationTherapiesByGroup[[tumortype, CRCPositionOfBestCombination]] &][[All, 1]]
```

```
BYL719 + binimetinib
```

```
{X-0933, X-1027, X-1055, X-1119, X-1167, X-1173, X-1270, X-1290, X-1303, X-1329,
 X-1441, X-1443, X-1479, X-1500, X-1536, X-1855, X-2145, X-2182, X-2239, X-2374, X-2403,
 X-2483, X-2484, X-2538, X-2573, X-2659, X-2822, X-2846, X-2861, X-3093, X-3205, X-3224,
 X-3267, X-3792, X-4087, X-5254, X-5405, X-5438, X-5446, X-5494, X-5495, X-5578}
```

```
(* which models were tested in all of the following:
  the best empirical monotherapy,
the best empirical combination therapy,
both monotherapies that comprise the best predicted combination therapy *)
CRCModelsInAllTherapiesForComparison =
  Intersection[CRCModelsInBothMonotherapies, CRCModelsInBestMonotherapy,
   CRCModelsInBestCombination];
```

```
(* Within this set of PDX models...*)
(* what is the observed survival distribution for the best monotherapy? *)
CRCSurvivalDistributionBestMonotherapy =
  Select[PDXclinicaltrialresponses,
    And[MemberQ[CRCModelsInAllTherapiesForComparison, #[[1]]],
      #[[2]] == BestCRCMonotherapyResponseOverUntreatedCompound] &][[All, 9]];
(* what is the observed survival distribution for the best monotherapy? *)
CRCSurvivalDistributionBestCombination =
  Select[PDXclinicaltrialresponses,
    And[MemberQ[CRCModelsInAllTherapiesForComparison, #[[1]]], #[[2]] == CRCBestCombinationName] &][[
   All, 9]];
(* what is the predicted survival distribution for the best heterogeneity-
 addressing pair of monotherapies? *)
CRCSurvivalDistributionBestPredictedPairOfMonotherapies =
  Select[CRCBestPredictedResponses, MemberQ[CRCModelsInAllTherapiesForComparison, #[[1]]] &][[
   All, 9]];
(* what is the observed survival distribution for untreated? *)
CRCSurvivalDistributionUntreated =
  Select[PDXclinicaltrialresponses,
    And[MemberQ[CRCModelsInAllTherapiesForComparison, #[[1]]], #[[2]] == "untreated"] &][[All, 9]];
```

Breast Cancer

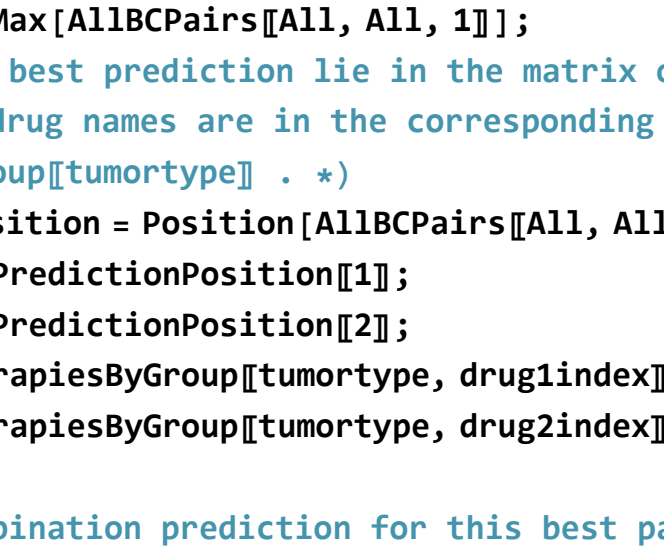
```
tumortype = 5;
(* what is the best survival over untreated predicted for any combination? *)
BCBestPrediction = Max[AllBCPairs[[All, All, 1]]];
(* where does that best prediction lie in the matrix over all combination
 predictions? The drug names are in the corresponding positions of
 MonotherapiesByGroup[[tumortype]] . *)
BCBestPredictionPosition = Position[AllBCPairs[[All, All, 1]], BCBestPrediction][[1]];
drug1index = BCBestPredictionPosition[[1]];
drug2index = BCBestPredictionPosition[[2]];
drug1name = MonotherapiesByGroup[[tumortype, drug1index]]
drug2name = MonotherapiesByGroup[[tumortype, drug2index]]

(* running the combination prediction for this best pair,
to load into memory the best monotherapy responses (BestOfMonotherapyResponses),
and also the set of PDX models involved in this prediction (ModelsInBothMonotherapies). No
 larger set of models is possible;
the prediction does not exist when the model has not been treated with both monotherapies. *)
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, drug1index]],
 MonotherapiesByGroup[[tumortype, drug2index]], AllModelGroups[[tumortype]],
 ModelNames[[tumortype]]]
```

BKM120

paclitaxel

{3.85899, 1.28182,



, 0.0639838, {0.736309, 0.180824}}

```
(* taking these terms from the IndependentActionPrediction function and giving them disease-
 class-specific names (e.g. BC...) *)
BCModelsInBothMonotherapies = ModelsInBothMonotherapies;
BCBestPredictedResponses = BestOfMonotherapyResponses;

(* looking along the diagonal of the all pair predictions -
 here drug1 and drug2 are identical - to determine the monotherapy with the best single-
 agent improvement over untreated (quantified by average PFS) *)
BestBCMonotherapyResponseOverUntreated =
  Max[Table[AllBCPairs[[i, i, 1]], {i, 1, Length[AllBCPairs]}]];
PositionOfBestBCMonotherapyResponseOverUntreated =
  Position[Table[AllBCPairs[[i, i, 1]], {i, 1, Length[AllBCPairs]}],
    BestBCMonotherapyResponseOverUntreated][[1, 1]];
(* what is this therapy's name? *)
BestBCMonotherapyResponseOverUntreatedCompound =
 MonotherapiesByGroup[[tumortype, PositionOfBestBCMonotherapyResponseOverUntreated]]
(* what PDX models were in this best monotherapy? *)
BCModelsInBestMonotherapy =
  Select[PDXclinicaltrialresponses,
    And[MemberQ[AllModelGroups[[tumortype]], #[[1]]],
      #[[2]] == BestBCMonotherapyResponseOverUntreatedCompound] &][[All, 1]];
```

CLR457

```
(* gather all empirically tested combination therapy responses for this disease class *)
BCCombinationTherapyResponses =
  Table[Select[PDXclinicaltrialresponses,
    And[MemberQ[AllModelGroups[[tumortype]], #[[1]]],
      #[[2]] == CombinationTherapiesByGroup[[tumortype, i]]] &],
   {i, 1, Length[CombinationTherapiesByGroup[[tumortype]]]}];
(* ... and their survival functions *)
BCCombinationSurvivalFunctions =
  Table[SurvivalFunction[EmpiricalDistribution[BCCombinationTherapyResponses[[i, All, 9]]]][x],
   {i, 1, Length[BCCombinationTherapyResponses]}];
```

```
(* cap the survival time to 360 days,
and then take the average across all models to measure the "area under the PFS curve",
from t=0 to ~t=1 year *)
AUCfromSurvivalDistribution[survivaldistribution_] := Module[{},
  IntegrationTime = 360;
  Mean[Map[Min[{#, IntegrationTime}] &, survivaldistribution]]
  (* equivalent to
   NIntegrate[SurvivalFunction[EmpiricalDistribution[BCCombinationTherapyResponses[[1]]][x],
    {x,0,IntegrationTime}]
  *)
 ]

(* which combination had the best AUC (integrated over 1 year)? *)
BCBestCombinationAUC = Map[AUCfromSurvivalDistribution,
   BCCombinationTherapyResponses[[All, All, 9]](* [[All,All,9]] = All combinations,
 All rows describing the individual PDXs tested for a given combination,
 9th column is time to double. *);
BCPositionOfBestCombination = Position[BCBestCombinationAUC, Max[BCBestCombinationAUC]][[1, 1]];
(* what are the names of the therapies in this combination? *)
BCBestCombinationName = CombinationTherapiesByGroup[[tumortype, BCPositionOfBestCombination]]
(* which PDX models of this disease group were tested with this combination? *)
BCModelsInBestCombination =
 Select[PDXclinicaltrialresponses,
   And[MemberQ[AllModelGroups[[tumortype]], #[[1]]],
     #[[2]] == CombinationTherapiesByGroup[[tumortype, BCPositionOfBestCombination]] &][[All, 1]]
```

```
LEE011 + everolimus
```

```
{X-1004, X-1008, X-1286, X-1298, X-1383, X-1407, X-1468, X-1600,
 X-1631, X-1828, X-1832, X-1916, X-1921, X-2195, X-2344, X-2353, X-2487, X-2524,
 X-2640, X-2780, X-3077, X-3078, X-3201, X-3298, X-3450, X-3468, X-3697, X-3873,
 X-4347, X-4567, X-4824, X-4888, X-4949, X-5249, X-5355, X-5502, X-5975, X-6047}
```

```
(* which models were tested in all of the following:
  the best empirical monotherapy,
the best empirical combination therapy,
both monotherapies that comprise the best predicted combination therapy *)
BCModelsInAllTherapiesForComparison =
  Intersection[BCModelsInBothMonotherapies, BCModelsInBestMonotherapy,
   BCModelsInBestCombination];
```

```
(* Within this set of PDX models...*)
(* what is the observed survival distribution for the best monotherapy? *)
BCSurvivalDistributionBestMonotherapy =
  Select[PDXclinicaltrialresponses,
    And[MemberQ[BCModelsInAllTherapiesForComparison, #[[1]]],
      #[[2]] == BestBCMonotherapyResponseOverUntreatedCompound] &][[All, 9]];
(* what is the observed survival distribution for the best monotherapy? *)
BCSurvivalDistributionBestCombination =
  Select[PDXclinicaltrialresponses,
    And[MemberQ[BCModelsInAllTherapiesForComparison, #[[1]]], #[[2]] == BCBestCombinationName] &][[
   All, 9]];
(* what is the predicted survival distribution for the best heterogeneity-
 addressing pair of monotherapies? *)
BCSurvivalDistributionBestPredictedPairOfMonotherapies =
  Select[BCBestPredictedResponses, MemberQ[BCModelsInAllTherapiesForComparison, #[[1]]] &][[
   All, 9]];
(* what is the observed survival distribution for untreated? *)
BCSurvivalDistributionUntreated =
  Select[PDXclinicaltrialresponses,
    And[MemberQ[BCModelsInAllTherapiesForComparison, #[[1]]], #[[2]] == "untreated"] &][[All, 9]];
```

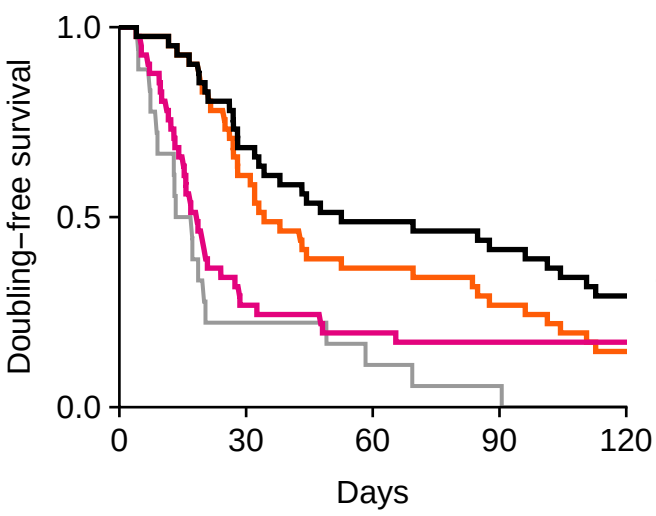
Gastric Cancer

```
tumortype = 6;
(* what is the best survival over untreated predicted for any combination? *)
GCBestPrediction = Max[AllGCPairs[[All, All, 1]]];
(* where does that best prediction lie in the matrix over all combination
 predictions? The drug names are in the corresponding positions of
 MonotherapiesByGroup[[tumortype]] . *)
GCBestPredictionPosition = Position[AllGCPairs[[All, All, 1]], GCBestPrediction][[1]];
drug1index = GCBestPredictionPosition[[1]];
drug2index = GCBestPredictionPosition[[2]];
drug1name = MonotherapiesByGroup[[tumortype, drug1index]]
drug2name = MonotherapiesByGroup[[tumortype, drug2index]]

(* running the combination prediction for this best pair,
to load into memory the best monotherapy responses (BestOfMonotherapyResponses),
and also the set of PDX models involved in this prediction (ModelsInBothMonotherapies). No
 larger set of models is possible;
the prediction does not exist when the model has not been treated with both monotherapies. *)
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, drug1index]],
 MonotherapiesByGroup[[tumortype, drug2index]], AllModelGroups[[tumortype]],
 ModelNames[[tumortype]]]
```

BYL719

LLM871



{3.77806, 1.49375, , 0.281197, {0.64037, 0.0521545}}

```
(* taking these terms from the IndependentActionPrediction function and giving them disease-
 class-specific names (e.g. GC...) *)
GCModelsInBothMonotherapies = ModelsInBothMonotherapies;
GCBestPredictedResponses = BestOfMonotherapyResponses;

(* looking along the diagonal of the all pair predictions -
 here drug1 and drug2 are identical - to determine the monotherapy with the best single-
 agent improvement over untreated (quantified by average PFS) *)
BestGCMonotherapyResponseOverUntreated =
  Max[Table[AllGCPairs[[i, i, 1]], {i, 1, Length[AllGCPairs]}]];
PositionOfBestGCMonotherapyResponseOverUntreated =
  Position[Table[AllGCPairs[[i, i, 1]], {i, 1, Length[AllGCPairs]}],
    BestGCMonotherapyResponseOverUntreated][[1, 1]];
(* what is this therapy's name? *)
BestGCMonotherapyResponseOverUntreatedCompound =
 MonotherapiesByGroup[[tumortype, PositionOfBestGCMonotherapyResponseOverUntreated]]
(* what PDX models were in this best monotherapy? *)
GCModelsInBestMonotherapy =
  Select[PDXclinicaltrialresponses,
    And[MemberQ[AllModelGroups[[tumortype]], #[[1]]],
      #[[2]] == BestGCMonotherapyResponseOverUntreatedCompound] &][[All, 1]];
```

BYL719

```
(* gather all empirically tested combination therapy responses for this disease class *)
GCCombinationTherapyResponses =
  Table[Select[PDXclinicaltrialresponses,
    And[MemberQ[AllModelGroups[[tumortype]], #[[1]]],
      #[[2]] == CombinationTherapiesByGroup[[tumortype, i]]] &],
   {i, 1, Length[CombinationTherapiesByGroup[[tumortype]]]}];
(* ... and their survival functions *)
GCCombinationSurvivalFunctions =
  Table[SurvivalFunction[EmpiricalDistribution[GCCombinationTherapyResponses[[i, All, 9]]]][x],
   {i, 1, Length[GCCombinationTherapyResponses]}];
```

```
(* cap the survival time to 360 days,
and then take the average across all models to measure the "area under the PFS curve",
from t=0 to ~t=1 year *)
AUCfromSurvivalDistribution[survivaldistribution_] := Module[{},
  IntegrationTime = 360;
  Mean[Map[Min[{#, IntegrationTime}] &, survivaldistribution]]
  (* equivalent to
   NIntegrate[SurvivalFunction[EmpiricalDistribution[GCCombinationTherapyResponses[[1]]][x],
    {x,0,IntegrationTime}]
  *)
 ]

(* which combination had the best AUC (integrated over 1 year)? *)
GCBestCombinationAUC = Map[AUCfromSurvivalDistribution,
   GCCombinationTherapyResponses[[All, All, 9]](* [[All,All,9]] = All combinations,
 All rows describing the individual PDXs tested for a given combination,
 9th column is time to double. *);
GCPositionOfBestCombination = Position[GCBestCombinationAUC, Max[GCBestCombinationAUC]][[1, 1]];
(* what are the names of the therapies in this combination? *)
GCBestCombinationName = CombinationTherapiesByGroup[[tumortype, GCPositionOfBestCombination]]
(* which PDX models of this disease group were tested with this combination? *)
GCModelsInBestCombination =
 Select[PDXclinicaltrialresponses,
   And[MemberQ[AllModelGroups[[tumortype]], #[[1]]],
     #[[2]] == CombinationTherapiesByGroup[[tumortype, GCPositionOfBestCombination]] &][[All, 1]]
```

```
LEE011 + everolimus
```

```
{X-007, X-010, X-011, X-015, X-020, X-025, X-028, X-031, X-034, X-035, X-037, X-038, X-056, X-057,
 X-064, X-065, X-067, X-075, X-077, X-084, X-089, X-090, X-091, X-096, X-097, X-098, X-099, X-114,
 X-118, X-119, X-127, X-128, X-129, X-131, X-138, X-154, X-158, X-160, X-161, X-165, X-166, X-171}
```

```
(* which models were tested in all of the following:
  the best empirical monotherapy,
the best empirical combination therapy,
both monotherapies that comprise the best predicted combination therapy *)
GCModelsInAllTherapiesForComparison =
  Intersection[GCModelsInBothMonotherapies, GCModelsInBestMonotherapy,
   GCModelsInBestCombination];
```

```
(* Within this set of PDX models...*)
(* what is the observed survival distribution for the best monotherapy? *)
GCSurvivalDistributionBestMonotherapy =
  Select[PDXclinicaltrialresponses,
    And[MemberQ[GCModelsInAllTherapiesForComparison, #[[1]]],
      #[[2]] == BestGCMonotherapyResponseOverUntreatedCompound] &][[All, 9]];
(* what is the observed survival distribution for the best monotherapy? *)
GCSurvivalDistributionBestCombination =
  Select[PDXclinicaltrialresponses,
    And[MemberQ[GCModelsInAllTherapiesForComparison, #[[1]]], #[[2]] == GCBestCombinationName] &][[
   All, 9]];
(* what is the predicted survival distribution for the best heterogeneity-
 addressing pair of monotherapies? *)
GCSurvivalDistributionBestPredictedPairOfMonotherapies =
  Select[GCBestPredictedResponses, MemberQ[GCModelsInAllTherapiesForComparison, #[[1]]] &][[
   All, 9]];
(* what is the observed survival distribution for untreated? *)
GCSurvivalDistributionUntreated =
  Select[PDXclinicaltrialresponses,
    And[MemberQ[GCModelsInAllTherapiesForComparison, #[[1]]], #[[2]] == "untreated"] &][[All, 9]];
```

Pooling data from different tumor types (PDAC, CRC, Breast cancer, Gastric cancer)

(Melanoma and NSCLC are excluded because their 'best predicted' combinations were experimentally measured and were confirmed as the best or approximately the best combinations; with the combination in melanoma showing efficacy far surpassing independent drug action)

```
AllModelPositionsInBothMonotherapiesOfPrediction = Join[
   Table[Position[WellCoveredModels, PDACModelsInBothMonotherapies[[i]][[1, 1]],
    {i, 1, Length[PDACModelsInBothMonotherapies]}],
   Table[Position[WellCoveredModels, CRCModelsInBothMonotherapies[[i]][[1, 1]],
    {i, 1, Length[CRCModelsInBothMonotherapies]}],
   Table[Position[WellCoveredModels, BCModelsInBothMonotherapies[[i]][[1, 1]],
    {i, 1, Length[BCModelsInBothMonotherapies]}],
   Table[Position[WellCoveredModels, GCModelsInBothMonotherapies[[i]][[1, 1]],
    {i, 1, Length[GCModelsInBothMonotherapies]}]
  ];
% // Length
```

```
155
```

```
AllModelPositionsInBestCombinations = Join[
   Table[Position[WellCoveredModels, PDACModelsInBestCombination[[i]][[1, 1]],
    {i, 1, Length[PDACModelsInBestCombination]}],
   Table[Position[WellCoveredModels, CRCModelsInBestCombination[[i]][[1, 1]],
    {i, 1, Length[CRCModelsInBestCombination]}],
   Table[Position[WellCoveredModels, BCModelsInBestCombination[[i]][[1, 1]],
    {i, 1, Length[BCModelsInBestCombination]}],
   Table[Position[WellCoveredModels, GCModelsInBestCombination[[i]][[1, 1]],
    {i, 1, Length[GCModelsInBestCombination]}]
  ];
% // Length
```

```
158
```

```
(* analysis is limited to 148 PDX models that were tested in both the best observed
 combination, both monotherapy constituents of the best predicted combination,
and the best observed monotherapy *)
AllOverlappingModelsBetweenPredictionsAndBestCombinations =
  Intersection[AllModelPositionsInBothMonotherapiesOfPrediction,
   AllModelPositionsInBestCombinations];
% // Length
```

```
148
```

```
BestPDACMonotherapyResponseOverUntreatedCompound
BestCRCMonotherapyResponseOverUntreatedCompound
BestBCMonotherapyResponseOverUntreatedCompound
BestGCMonotherapyResponseOverUntreatedCompound
```

```
gemcitabine-50mpk
```

```
CLR457
```

```
CLR457
```

```
BYL719
```

```
PDACBestCombinationName
CRCBestCombinationName
BCBestCombinationName
GCBestCombinationName
```

```
BKM120 + binimetinib
```

```
BYL719 + binimetinib
```

```
LEE011 + everolimus
```

```
LEE011 + everolimus
```

```
(* selecting the overall ("one-size-fits-all") best monotherapy per tumor type;
limited to those PDXs profiled in both monotherapies of the prediction,
and the best combination, and the best monotherapy *)
BestMonotherapyPerTypeResponses = Join[
   Select[Table[Select[PDXclinicaltrialresponses,
       And[#[[1]] == WellCoveredModels[[AllOverlappingModelsBetweenPredictionsAndBestCombinations[[
            i]]]], MemberQ[PDACModelsInBothMonotherapies, #[[1]]],
         MemberQ[PDACModelsInBestCombination, #[[1]]],
         #[[2]] == BestPDACMonotherapyResponseOverUntreatedCompound] &],
      {i, 1, Length[AllOverlappingModelsBetweenPredictionsAndBestCombinations]}], # ≠ {} &][[
    All, 1]]
   ,
   Select[Table[Select[PDXclinicaltrialresponses,
       And[#[[1]] == WellCoveredModels[[AllOverlappingModelsBetweenPredictionsAndBestCombinations[[
            i]]]], MemberQ[CRCModelsInBothMonotherapies, #[[1]]],
         MemberQ[CRCModelsInBestCombination, #[[1]]],
         #[[2]] == BestCRCMonotherapyResponseOverUntreatedCompound] &],
      {i, 1, Length[AllOverlappingModelsBetweenPredictionsAndBestCombinations]}], # ≠ {} &][[
    All, 1]]
   ,
   Select[Table[Select[PDXclinicaltrialresponses,
       And[#[[1]] == WellCoveredModels[[AllOverlappingModelsBetweenPredictionsAndBestCombinations[[
            i]]]], MemberQ[BCModelsInBothMonotherapies, #[[1]]],
         MemberQ[BCModelsInBestCombination, #[[1]]],
         #[[2]] == BestBCMonotherapyResponseOverUntreatedCompound] &],
      {i, 1, Length[AllOverlappingModelsBetweenPredictionsAndBestCombinations]}], # ≠ {} &][[
    All, 1]]
   ,
   Select[Table[Select[PDXclinicaltrialresponses,
       And[#[[1]] == WellCoveredModels[[AllOverlappingModelsBetweenPredictionsAndBestCombinations[[
            i]]]], MemberQ[GCModelsInBothMonotherapies, #[[1]]],
         MemberQ[GCModelsInBestCombination, #[[1]]],
         #[[2]] == BestGCMonotherapyResponseOverUntreatedCompound] &],
      {i, 1, Length[AllOverlappingModelsBetweenPredictionsAndBestCombinations]}], # ≠ {} &][[
    All, 1]]
  ];
% // Length
```

148

```
BestCombinationPerTypeResponses = Join[
   Select[Table[Select[PDXclinicaltrialresponses,
       And[#[[1]] == WellCoveredModels[[AllOverlappingModelsBetweenPredictionsAndBestCombinations[[
            i]]]], MemberQ[PDACModelsInBothMonotherapies, #[[1]]],
         MemberQ[PDACModelsInBestCombination, #[[1]]], #[[2]] == PDACBestCombinationName] &],
      {i, 1, Length[AllOverlappingModelsBetweenPredictionsAndBestCombinations]}], # ≠ {} &][[
    All, 1]]
   ,
   Select[Table[Select[PDXclinicaltrialresponses,
       And[#[[1]] == WellCoveredModels[[AllOverlappingModelsBetweenPredictionsAndBestCombinations[[
            i]]]], MemberQ[CRCModelsInBothMonotherapies, #[[1]]],
         MemberQ[CRCModelsInBestCombination, #[[1]]], #[[2]] == CRCBestCombinationName] &],
      {i, 1, Length[AllOverlappingModelsBetweenPredictionsAndBestCombinations]}], # ≠ {} &][[
    All, 1]]
   ,
   Select[Table[Select[PDXclinicaltrialresponses,
       And[#[[1]] == WellCoveredModels[[AllOverlappingModelsBetweenPredictionsAndBestCombinations[[
            i]]]], MemberQ[BCModelsInBothMonotherapies, #[[1]]],
         MemberQ[BCModelsInBestCombination, #[[1]]], #[[2]] == BCBestCombinationName] &],
      {i, 1, Length[AllOverlappingModelsBetweenPredictionsAndBestCombinations]}], # ≠ {} &][[
    All, 1]]
   ,
   Select[Table[Select[PDXclinicaltrialresponses,
       And[#[[1]] == WellCoveredModels[[AllOverlappingModelsBetweenPredictionsAndBestCombinations[[
            i]]]], MemberQ[GCModelsInBothMonotherapies, #[[1]]],
         MemberQ[GCModelsInBestCombination, #[[1]]], #[[2]] == GCBestCombinationName] &],
      {i, 1, Length[AllOverlappingModelsBetweenPredictionsAndBestCombinations]}], # ≠ {} &][[
    All, 1]]
  ];
% // Length
```

```
148
```

```
PredictedResponsesInOverlappingModels =
  Select[Join[PDACBestPredictedResponses, CRCBestPredictedResponses, BCBestPredictedResponses,
    GCBestPredictedResponses],
   MemberQ[WellCoveredModels[[AllOverlappingModelsBetweenPredictionsAndBestCombinations]],
     #[[1]]] &];
% // Length
```

```
148
```

Predicted combinations are expected, by independent action, to be significantly superior to treating each tumor type with its best observed monotherapy (Hazard Ratio = 0.69)

```
(* hazard ratio by Cox Model,
comparing predicted combinations to the observed best overall monotherapy for each
 tumor type *)
myeventdata =
  EventData[Join[BestMonotherapyPerTypeResponses[[All, 9]],
    PredictedResponsesInOverlappingModels[[All, 9]]],
   Table[0,
    {Length[Join[BestMonotherapyPerTypeResponses[[All, 9]],
       PredictedResponsesInOverlappingModels[[All, 9]]]}]];
descriptors =
  Join[Table["observed monotherapies", {Length[BestMonotherapyPerTypeResponses[[All, 9]]}],
   Table["predicted combinations", {Length[PredictedResponsesInOverlappingModels[[All, 9]]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[predicted combinations]	−0.367986	0.11763	0.692127	9.7865	1	0.00175798

```
{{0.549616, 0.87159}}
```

Predicted combinations are expected, by independent action, to be statistically indistinguishable in effect from treating each tumor type with its best observed combination therapy (Hazard Ratio = 0.84)

```
(* hazard ratio by Cox Model,
comparing predicted combinations to the observed best overall combination therapy
 for each tumor type *)
myeventdata =
  EventData[Join[BestCombinationPerTypeResponses[[All, 9]],
    PredictedResponsesInOverlappingModels[[All, 9]]],
   Table[0,
    {Length[Join[BestCombinationPerTypeResponses[[All, 9]],
       PredictedResponsesInOverlappingModels[[All, 9]]]}]];
descriptors =
  Join[Table["observed combinations", {Length[BestCombinationPerTypeResponses[[All, 9]]}],
   Table["predicted combinations", {Length[PredictedResponsesInOverlappingModels[[All, 9]]}]];
MyModelFit = CoxModelFit[{descriptors, myeventdata}, {treatment}, {treatment},
   NominalVariables → treatment];
MyModelFit["ParameterTable"]
MyModelFit["RelativeRiskConfidenceIntervals"]
```

	Estimate	Standard Error	Relative Risk	Wald-χ^2	DF	P-Value
treatment[predicted combinations]	−0.168705	0.118557	0.844758	2.02489	1	0.15474

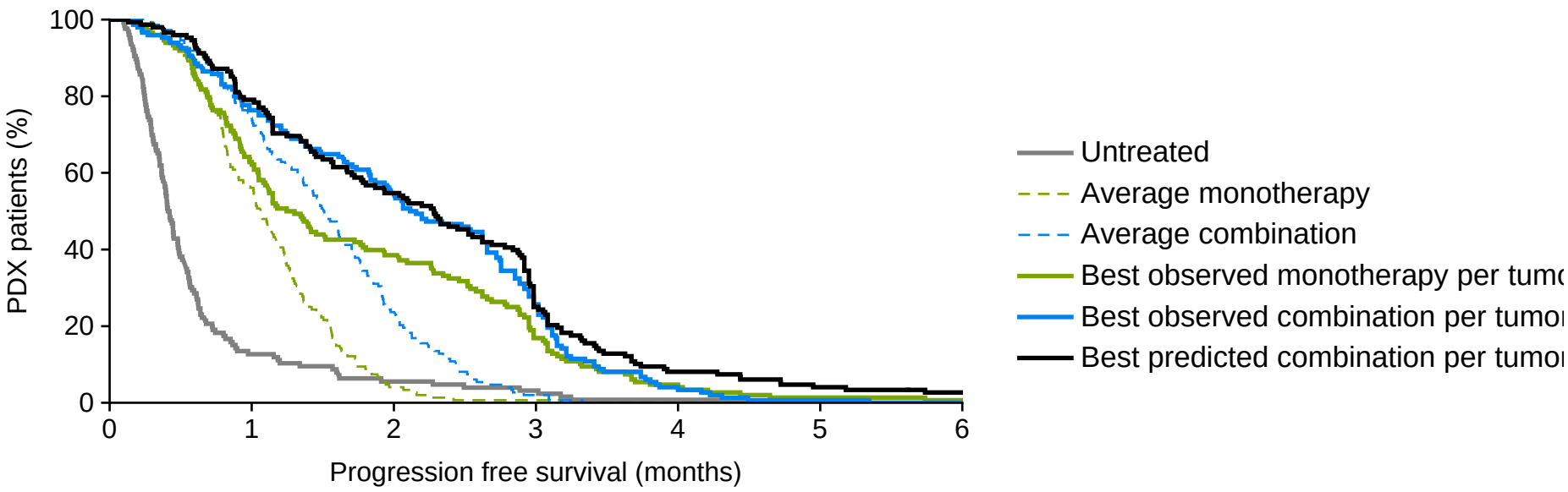
```
{{0.669601, 1.06573}}

UntreatedResponsesWithinOverlappingModels =
  Select[PDXclinicaltrialresponses,
   And[MemberQ[WellCoveredModels[[AllOverlappingModelsBetweenPredictionsAndBestCombinations]],
      #[[1]]], #[[2]] == "untreated"] &];
```

```
(* average effect of all monotherapies, or average of all combination therapies,
in the particular PDX models that have constituted this analysis *)
MeanMonoWithin4IndicationsAndOverlappingModels =
  PerModelMeanMonoResponses[[AllOverlappingModelsBetweenPredictionsAndBestCombinations]];
MeanComboWithin4IndicationsAndOverlappingModels =
  PerModelMeanComboResponses[[AllOverlappingModelsBetweenPredictionsAndBestCombinations]];

Plot[{
  SurvivalFunction[EmpiricalDistribution[UntreatedResponsesWithinOverlappingModels[[All, 9]]]][x],
  SurvivalFunction[EmpiricalDistribution[MeanMonoWithin4IndicationsAndOverlappingModels]][x],
  SurvivalFunction[EmpiricalDistribution[MeanComboWithin4IndicationsAndOverlappingModels]][x],
  SurvivalFunction[EmpiricalDistribution[BestMonotherapyPerTypeResponses[[All, 9]]]][x],
  SurvivalFunction[EmpiricalDistribution[BestCombinationPerTypeResponses[[All, 9]]]][x],
  SurvivalFunction[EmpiricalDistribution[PredictedResponsesInOverlappingModels[[All, 9]]]][x]
 }, {x, 0, 30.5 * 7}, PlotRange → {{0, 30.5 * 6}, {0, 1}}, Exclusions → None, PlotPoints → 1000,
 Frame → {{True, False}, {True, False}}, BaseStyle → {FontFamily → "Arial", FontSize → 12},
 FrameStyle → Directive[Black, Thickness[Medium]],
 FrameTicks → {{Table[{i, i * 100, {0, 0.01}}, {i, 0, 1, 1 / 5}], None},
   {Table[{i, i / 61 * 2, {0, 0.01}}, {i, 0, 300, 61 / 2}], None}},
 PlotStyle → {Directive[Gray, AbsoluteThickness[2]],
   Directive[Darker[ColorData[3, 4], 0.1], Dashing[{0.015, 0.01}], AbsoluteThickness[1]],
   Directive[ColorData[3, 6], Dashing[{0.015, 0.01}], AbsoluteThickness[1]],
   Directive[Darker[ColorData[3, 4], 0.1], AbsoluteThickness[2]],
   Directive[ColorData[3, 6], AbsoluteThickness[2]], Directive[Black, AbsoluteThickness[2]]},
 PlotLegends →
  LineLegend[{"Untreated", "Average monotherapy", "Average combination",
    "Best observed monotherapy per tumor type", "Best observed combination per tumor type",
    "Best predicted combination per tumor type"}, Spacings → {0.25, 0.4},
   LegendMarkerSize → {25, 12}],
 FrameLabel → {"Progression free survival (months)", Rotate["PDX patients (%)", 0]},
 ImageSize → {{1000}, {230}}, ImagePadding → {{50, 10}, {50, 10}}, AspectRatio → 0.45]

Export[NotebookDirectory[] <>
   "Figure 5C, comparison of predicted combinations and observed therapies.pdf", %, "PDF"];
```



Evaluating the expected benefits of predicted combinations in context of animal-to-animal variability.

Can animal-to-animal variability (when the same PDX model is treated with the same therapy in a replicate animal) explain the predicted benefits?

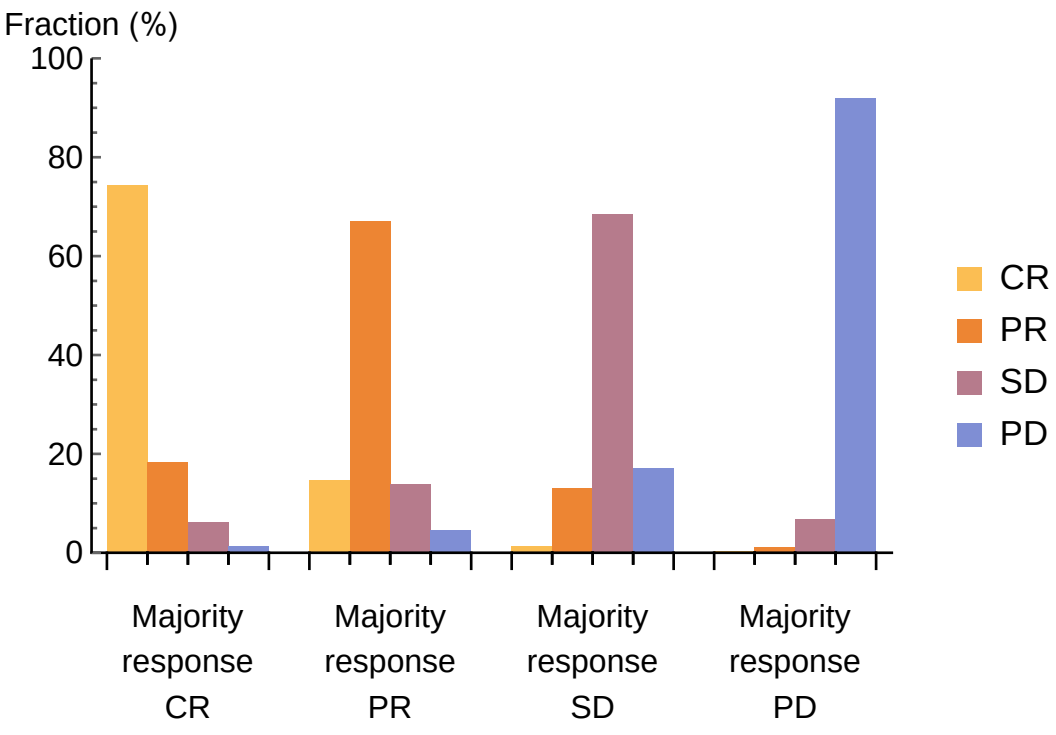
A degree of animal-to-animal variability was reported by Gao et al. Nature Medicine

(Figure 2a of that article) on the basis of 440 treatment models (meaning a specific treatment applied to a specific PDX) that were repeated on average in 5 different mice each, for a total of over 2000 drug-treated animals. Each treatment model was classified according to its ' majority' response criteria (which response was most commonly observed across the repeats). Figure 2a of Gao et al shows the fraction of times that each response criteria was observed within treatment models belonging to each majority response criteria (i.e, how often did an individual animal vary from other replicates of the same treatment model?). For example, treatment models that were most often a complete response (CR) were only CR in 74% of individual animals, being PR in 18% of animals and SD in 6% of animals.
This data was extracted from the published figure by digital image analysis.

Here we use this data as an error model for Gao et al' s PDX drug trials, and compute the expected benefit of repeating each measurement of a drug in a predicted combination twice and choosing the best observed response from two replicates. If this often provides similar benefit to that expected from predicted combinations, then their predicted benefits may be no more than the benefit of random experimental repeats.

```
AnimalToAnimalVariabilityMatrix =
  Import[NotebookDirectory[] <> "Animal to animal consistency probability matrix.csv", "CSV"];

(* Reproducing Figure 2A of Gao et al, Nature Medicine *)
BarChart[100 * AnimalToAnimalVariabilityMatrix[[2 ;;, 2 ;;]], PlotRange → {0, 100},
 PlotRangePadding → None, BarSpacing → {0, 1}, ChartStyle → EdgeForm[None],
 ChartLegends → {"CR", "PR", "SD", "PD"},
 ChartLabels →
  {{"Majority\nresponse\nCR", "Majority\nresponse\nPR", "Majority\nresponse\nSD",
    "Majority\nresponse\nPD"}, {, , ,}}, ImagePadding → {{50, 10}, {70, 30}},
 AxesLabel → {"", "Fraction (%)"}, AxesStyle → Directive[Black, Thickness[Medium]],
 BaseStyle → {FontFamily → "Arial", FontSize → 12}]
```



```
(* this function takes a list of observed response criteria and returns the
 strongest / best response *)
BestResponseOfSet[listofresponsetypes_] := Module[{},
  InitialResponse = Map[StringTake[#, 2] &, listofresponsetypes];
  ReponsesAsNumbers = InitialResponse /. {"CR" → 3, "PR" → 2, "SD" → 1, "PD" → 0};
  BestResponseAsNumber = Max[ReponsesAsNumbers];
  BestResponseType = (BestResponseAsNumber /. {3 → "CR", 2 → "PR", 1 → "SD", 0 → "PD"})
 ]

(* this function takes a response criteria,
and applies the 'error model' - it samples from the animal-to-
 animal variability data so that there is a chance of obtaining a different response,
consistent with observed probabilities of variation *)
SampleResponseInDifferentAnimal[responsecategory_] := Module[{},
  (* which row of probabilities in the ConsistencyMatrix should we look up? *)
  AppropriateRow = Which[
    responsecategory == "CR", 2,
    responsecategory == "PR", 3,
    responsecategory == "SD", 4,
    responsecategory == "PD", 5
   ];
  RandomizedResponseInDifferentAnimal =
   RandomChoice[AnimalToAnimalVariabilityMatrix[[AppropriateRow, 2 ;;]] ->
     {"CR", "PR", "SD", "PD"}]
 ]

(* this function takes a list of response criteria,
and applies the error model to each response in the list *)
SimulatedAnimalToAnimalVariability[listofresponses_] := Module[{},
  (* take just the first two characters (CR, PR, SD, PD) to look at major response categories,
  which is what the animal-to-animal consistency data addresses *)
  ListOfMajorResponses = Map[StringTake[#, 2] &, listofresponses];
  Map[SampleResponseInDifferentAnimal, ListOfMajorResponses]
 ]

(* this function takes a list of response criteria
 (representing different tumors receiving a treatment),
uses the above function to apply the error model,
and then selects for each individual tumor the best of the two responses *)
BestResponsesPerPDXFromRealAnimalAndSimulatedSecondAnimalWithVariability[listofresponses_] :=
 Module[{},
  ListOfMajorResponses = Map[StringTake[#, 2] &, listofresponses];
  SecondAnimalMajorResponses = SimulatedAnimalToAnimalVariability[ListOfMajorResponses];

  Table[BestResponseOfSet[{ListOfMajorResponses[[pdx]], SecondAnimalMajorResponses[[pdx]]}],
   {pdx, 1, Length[ListOfMajorResponses]}]
 ]

(* this function converts a response to a number: 1 for any response (SD, PR, CR),
0 for no response (PD) *)
ResponseAsNumber[responsestring_] := Module[{},
  MajorCategory = StringTake[responsestring, 2];
  MajorCategory /. {"PD" → 0, "SD" → 1, "PR" → 1, "CR" → 1}
 ]
```

This function takes a given tumor type and two monotherapies (according to their number in the list of therapies tested on that tumor type). It performs 100,000

simulations of performing each monotherapy treatment twice, applying the error model to simulate the effect of animal-to-animal variability, and always returning the better response (i.e. calling the result a 'response' if at least one of the two replicates demonstrates a response). These 100,000 simulations provide a distribution from which a P-value is computed for the probability that the predicted benefit of a combination (which stems from inducing responses in different individuals in a population) could be attributed to animal-to-animal variability.

Note that executing this is time-consuming.

```
PvalueForBestResponsesOfDrugPairToBeExplainedByAnimalToAnimalVariability[tumortype_,
  drug1number_, drug2number_] := Module[{},
  (* calling the function for 'independent action prediction' so that drug responses
   in the appropriate set of PDX models are loaded into memory;
  the output itself does not matter,
  only defining the necessary terms (i.e. loading into memory) *)
  LoadingIntoMemory = IndependentActionPrediction[MonotherapiesByGroup[[tumortype, i]],
    MonotherapiesByGroup[[tumortype, j]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]];
 (* binarizing each PDXs response: 1 or 0 for response / no response *)
 DrugAresponsesAsNumbers = Map[ResponseAsNumber, DrugAresponsesInIntersection[[All, -1]]];
 (* binarizing each PDXs response: 1 or 0 for response / no response *)
 DrugBresponsesAsNumbers = Map[ResponseAsNumber, DrugBresponsesInIntersection[[All, -1]]];
 (* assuming independent action: if a PDX responds to one drug,
 it will respond to the second drug *)
 BestOfDrugADrugBresponsesAsNumbers =
  Map[ResponseAsNumber,
   Table[BestResponseOfSet[{DrugAresponsesInIntersection[[pdx, -1]],
      DrugBresponsesInIntersection[[pdx, -1]}],
    {pdx, 1, Length[DrugAresponsesInIntersection]}]];

 (* perform 100,000 repeats of applying the error model to observed monotherapy responses *)
 samplesize = 100000;
 ManyDrugABestsOfSimulatedAnimalPairs =
  Table[
   Mean[Map[ResponseAsNumber,
     BestResponsesPerPDXFromRealAnimalAndSimulatedSecondAnimalWithVariability[
      DrugAresponsesInIntersection[[All, -1]]]], {samplesize}];
 ManyDrugBBestsOfSimulatedAnimalPairs =
  Table[
   Mean[Map[ResponseAsNumber,
     BestResponsesPerPDXFromRealAnimalAndSimulatedSecondAnimalWithVariability[
      DrugBresponsesInIntersection[[All, -1]]]], {samplesize}];

 (* how many of the repeats showed a response rate greater than or equal to the
  predicted effect of the combination? *)
 PvalueFromDrugA =
  Length[Select[ManyDrugABestsOfSimulatedAnimalPairs,
      # ≥ Mean[BestOfDrugADrugBresponsesAsNumbers] &]] / samplesize // N;
 PvalueFromDrugB =
  Length[Select[ManyDrugBBestsOfSimulatedAnimalPairs,
      # ≥ Mean[BestOfDrugADrugBresponsesAsNumbers] &]] / samplesize // N;

 (* from simulations of monotherapy A and monotherapy B,
 report the larger of the two P-values - if either one is large it suggests that animal-
  to-animal variability might explain the predicted effect *)
 Max[{PvalueFromDrugA, PvalueFromDrugB}]
]
```

PDAC

```
tumortype = 3;
ModelNames[[tumortype]]
(* numbers corresponding to the two drugs in the best predicted combination for PDAC *)
i = 2;
j = 8;
MonotherapiesByGroup[[tumortype, i]]
MonotherapiesByGroup[[tumortype, j]]
```

```
Pancreatic ductal adenocarcinoma

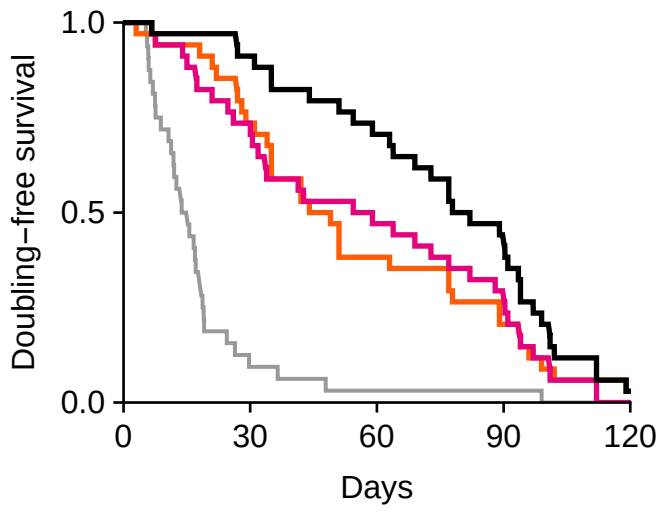
binimetinib

gemcitabine-50mpk
```

```
tumortype = 3;
ModelNames[[tumortype]]
i = 2;
j = 8;
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, i]],
  MonotherapiesByGroup[[tumortype, j]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]][[3]]

PvalueForBestResponsesOfDrugPairToBeExplainedByAnimalToAnimalVariability[tumortype,
 i, j]
```

```
Pancreatic ductal adenocarcinoma
```

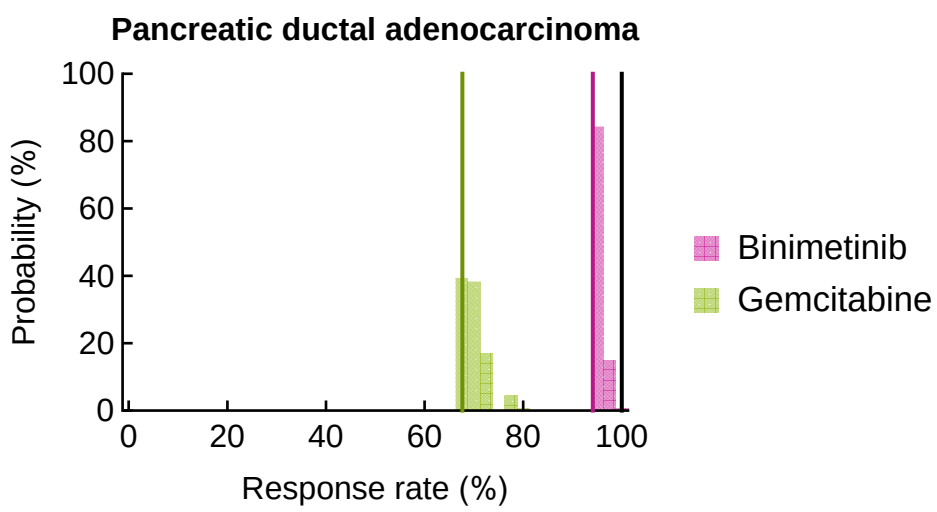



```
0.00674
```

```
binsize = 0.025;
height = 1;

Histogram[{ManyDrugABestsOfSimulatedAnimalPairs, ManyDrugBBestsOfSimulatedAnimalPairs},
 {-binsize / 2, 1 + binsize / 2, binsize}, "Probability",
 PlotRange → {{-binsize / 2, 1 + binsize / 2}, {0, height}}, PlotRangePadding → None,
 FrameStyle → Directive[Black, Thickness[Medium]],
 ChartStyle → {Directive[EdgeForm[None], RGBColor[0.8, 0.1, 0.6], Opacity[0.5]],
   Directive[EdgeForm[None], ColorData[3, 4], Opacity[0.5]]},
 BaseStyle → {FontFamily → "Arial", FontSize → 12}, Frame → {{True, False}, {True, False}},
 Axes → False,
 FrameTicks → {{Table[{i, 100 * i, {0.02, 0}}, {i, 0, 1, 2 / 10}], None},
   {Table[{i, 100 * i, {0.02, 0}}, {i, 0, 1, 1 / 5}], None}},
 Epilog → {AbsoluteThickness[1.5], Opacity[1], Darker[RGBColor[0.8, 0.1, 0.6], 0.1],
   Line[{{Mean[DrugAresponsesAsNumbers], 0}, {Mean[DrugAresponsesAsNumbers], height}}],
   Darker[ColorData[3, 4], 0.2],
   Line[{{Mean[DrugBresponsesAsNumbers], 0}, {Mean[DrugBresponsesAsNumbers], height}}],
   Black, Line[{{Mean[BestOfDrugADrugBresponsesAsNumbers], 0},
     {Mean[BestOfDrugADrugBresponsesAsNumbers], height}}]},
 FrameLabel → {"Response rate (%)", "Probability (%)"}, AspectRatio → 2 / 3,
 ImagePadding → {{80, 10}, {50, 10}}, ImageSize → {{1000}, {200}},
 PlotLabel → Style[ModelNames[[tumortype]], Black, FontSize → 12, Bold],
 ChartLegends → {"Binimetinib", "Gemcitabine"}]

Export[NotebookDirectory[] <> "Supplementary Figure S6, PDAC.pdf", %, "PDF"];
```



```
(* the predicted combination for PDAC reached statistical significance,
but in terms of response rate, being any response better than progressive disease (PD),
the magnitude of effect is small because binimetinib induces at least stable disease
 nearly all PDAC PDX tumors. We therefore repeat the analysis at a more stringent
 level of response, considering only partial response (PR) or complete response (CR) **)
PartialOrCompleteResponseAsNumber[responsestring_] := Module[{},
  MajorCategory = StringTake[responsestring, 2];
  MajorCategory /. {"PD" → 0, "SD" → 0, "PR" → 1, "CR" → 1}
 ]

PartialOrCompletePvalueForBestResponsesOfDrugPairToBeExplainedByAnimalToAnimalVariability[
  tumortype_, drug1number_, drug2number_] := Module[{},
  LoadingIntoMemory = IndependentActionPrediction[MonotherapiesByGroup[[tumortype, i]],
    MonotherapiesByGroup[[tumortype, j]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]];
  DrugAresponsesAsNumbers = Map[PartialOrCompleteResponseAsNumber,
    DrugAresponsesInIntersection[[All, -1]]];
  DrugBresponsesAsNumbers = Map[PartialOrCompleteResponseAsNumber,
    DrugBresponsesInIntersection[[All, -1]]];
BestOfDrugADrugBresponsesAsNumbers =
 Map[PartialOrCompleteResponseAsNumber,
  Table[BestResponseOfSet[{DrugAresponsesInIntersection[[pdx, -1]],
     DrugBresponsesInIntersection[[pdx, -1]]}],
   {pdx, 1, Length[DrugAresponsesInIntersection]}]];

samplesize = 100 000;
ManyDrugABestsOfSimulatedAnimalPairs =
 Table[Mean[Map[PartialOrCompleteResponseAsNumber,
    BestResponsesPerPDXFromRealAnimalAndSimulatedSecondAnimalWithVariability[
     DrugAresponsesInIntersection[[All, -1]]]], {samplesize}];
ManyDrugBBestsOfSimulatedAnimalPairs =
 Table[Mean[Map[PartialOrCompleteResponseAsNumber,
    BestResponsesPerPDXFromRealAnimalAndSimulatedSecondAnimalWithVariability[
     DrugBresponsesInIntersection[[All, -1]]]], {samplesize}];

PvalueFromDrugA =
 Length[Select[ManyDrugABestsOfSimulatedAnimalPairs,
     # > Mean[BestOfDrugADrugBresponsesAsNumbers] &]] / samplesize // N;
PvalueFromDrugB =
 Length[Select[ManyDrugBBestsOfSimulatedAnimalPairs,
     # > Mean[BestOfDrugADrugBresponsesAsNumbers] &]] / samplesize // N;

  Max[{PvalueFromDrugA, PvalueFromDrugB}]
 ]

PartialOrCompletePvalueForBestResponsesOfDrugPairToBeExplainedByAnimalToAnimalVariability[
 tumortype, i, j]
```

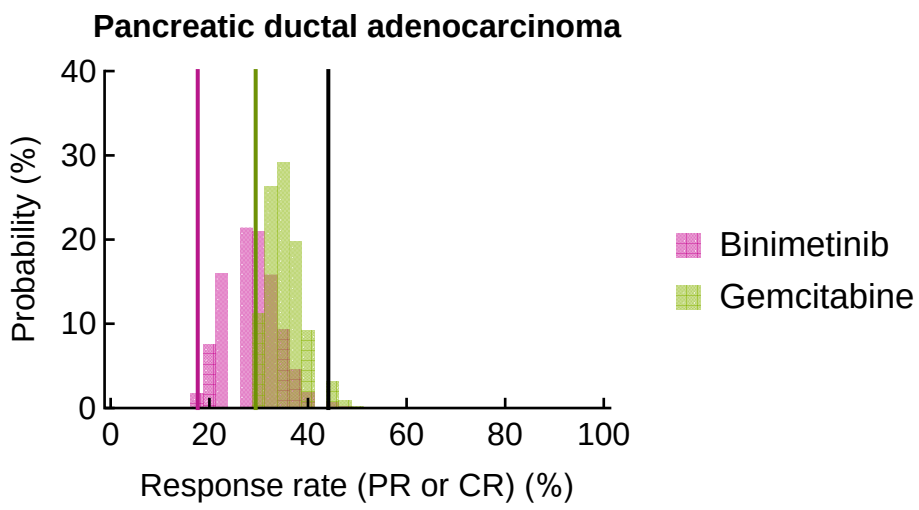
```
0.01091
```

```
height = 0.35;

binsize = 0.025;
height = 0.4;

Histogram[{ManyDrugABestsOfSimulatedAnimalPairs, ManyDrugBBestsOfSimulatedAnimalPairs},
 {-binsize / 2, 1 + binsize / 2, binsize}, "Probability",
 PlotRange → {{-binsize / 2, 1 + binsize / 2}, {0, height}}, PlotRangePadding → None,
 FrameStyle → Directive[Black, Thickness[Medium]],
 ChartStyle → {Directive[EdgeForm[None], RGBColor[0.8, 0.1, 0.6], Opacity[0.5]],
   Directive[EdgeForm[None], ColorData[3, 4], Opacity[0.5]]},
 BaseStyle → {FontFamily → "Arial", FontSize → 12}, Frame → {{True, False}, {True, False}},
 Axes → False,
 FrameTicks → {{Table[{i, 100 * i, {0.02, 0}}, {i, 0, 1, 1 / 10}], None},
   {Table[{i, 100 * i, {0.02, 0}}, {i, 0, 1, 1 / 5}], None}},
 Epilog → {AbsoluteThickness[1.5], Opacity[1], Darker[RGBColor[0.8, 0.1, 0.6], 0.1],
   Line[{{Mean[DrugAresponsesAsNumbers], 0}, {Mean[DrugAresponsesAsNumbers], height}}],
   Darker[ColorData[3, 4], 0.2],
   Line[{{Mean[DrugBresponsesAsNumbers], 0}, {Mean[DrugBresponsesAsNumbers], height}}],
   Black, Line[{{Mean[BestOfDrugADrugBresponsesAsNumbers], 0},
     {Mean[BestOfDrugADrugBresponsesAsNumbers], height}}]},
 FrameLabel → {"Response rate (PR or CR) (%)", "Probability (%)"}, AspectRatio → 2 / 3,
 ImagePadding → {{80, 10}, {50, 10}}, ImageSize → {{1000}, {200}},
 PlotLabel → Style[ModelNames[[tumortype]], Black, FontSize → 12, Bold],
 ChartLegends → {"Binimetinib", "Gemcitabine"}]

Export[NotebookDirectory[] <> "Supplementary Figure S6, PDAC, partial or complete response.pdf",
  %, "PDF"];
```



colorectal cancer

```
tumortype = 4;
ModelNames[[tumortype]]
(* numbers corresponding to the two drugs in the best predicted combination for PDAC *)
i = 2;
j = 8;
MonotherapiesByGroup[[tumortype, i]]
MonotherapiesByGroup[[tumortype, j]]
```

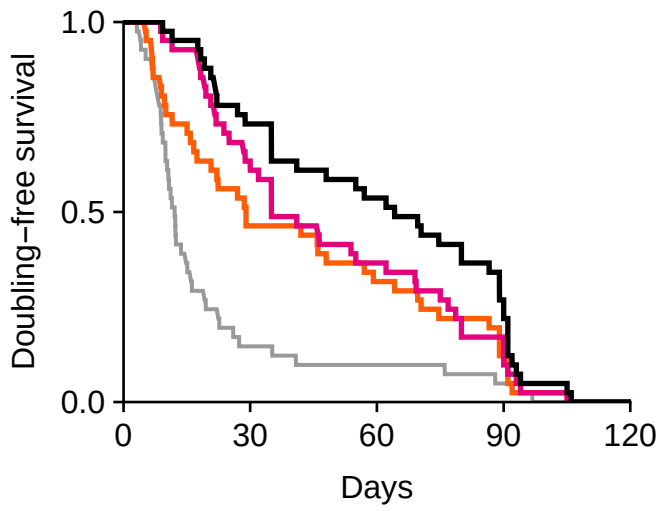
```
Colorectal carcinoma
```

```
binimetinib
```

```
CLR457
```

```
tumortype = 4;
i = 2;
j = 8;
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, i]],
  MonotherapiesByGroup[[tumortype, j]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]][[3]]

PvalueForBestResponsesOfDrugPairToBeExplainedByAnimalToAnimalVariability[tumortype,
 i, j]
```

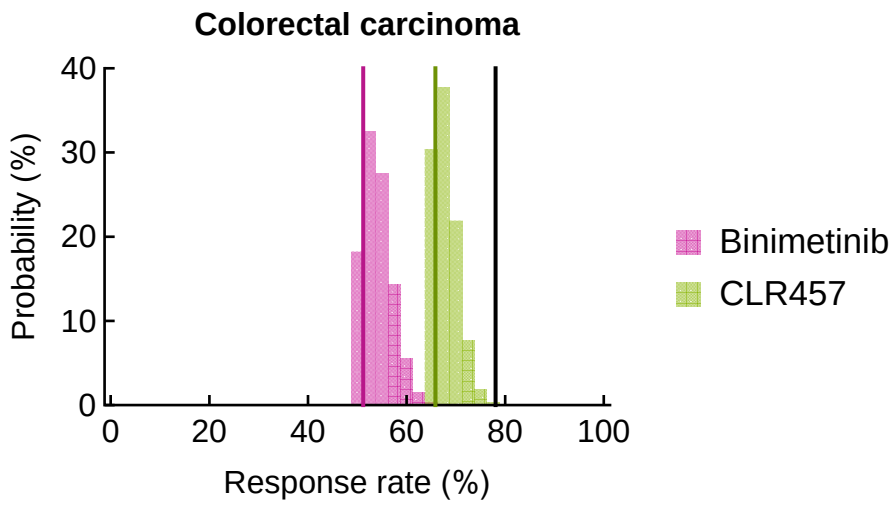



```
0.004

binsize = 0.025;
height = 0.4;

Histogram[{ManyDrugABestsOfSimulatedAnimalPairs, ManyDrugBBestsOfSimulatedAnimalPairs},
 {-binsize / 2, 1 + binsize / 2, binsize}, "Probability",
 PlotRange → {{-binsize / 2, 1 + binsize / 2}, {0, height}}, PlotRangePadding → None,
 FrameStyle → Directive[Black, Thickness[Medium]],
 ChartStyle → {Directive[EdgeForm[None], RGBColor[0.8, 0.1, 0.6], Opacity[0.5]],
   Directive[EdgeForm[None], ColorData[3, 4], Opacity[0.5]]},
 BaseStyle → {FontFamily → "Arial", FontSize → 12}, Frame → {{True, False}, {True, False}},
 Axes → False,
 FrameTicks → {{Table[{i, 100 * i, {0.02, 0}}, {i, 0, 1, 1 / 10}], None},
   {Table[{i, 100 * i, {0.02, 0}}, {i, 0, 1, 1 / 5}], None}},
 Epilog → {AbsoluteThickness[1.5], Opacity[1], Darker[RGBColor[0.8, 0.1, 0.6], 0.1],
   Line[{{Mean[DrugAresponsesAsNumbers], 0}, {Mean[DrugAresponsesAsNumbers], height}}],
   Darker[ColorData[3, 4], 0.2],
   Line[{{Mean[DrugBresponsesAsNumbers], 0}, {Mean[DrugBresponsesAsNumbers], height}}],
   Black, Line[{{Mean[BestOfDrugADrugBresponsesAsNumbers], 0},
     {Mean[BestOfDrugADrugBresponsesAsNumbers], height}}]},
 FrameLabel → {"Response rate (%)", "Probability (%)"}, AspectRatio → 2 / 3,
 ImagePadding → {{80, 10}, {50, 10}}, ImageSize → {{1000}, {200}},
 PlotLabel → Style[ModelNames[[tumortype]], Black, FontSize → 12, Bold],
 ChartLegends → {"Binimetinib", "CLR457"}]

Export[NotebookDirectory[] <> "Supplementary Figure S6, Colorectal carcinoma.pdf", %, "PDF"];
```



breast cancer

```
tumortype = 5;
ModelNames[[tumortype]]
i = 3;
j = 14;
MonotherapiesByGroup[[tumortype, i]]
MonotherapiesByGroup[[tumortype, j]]
```

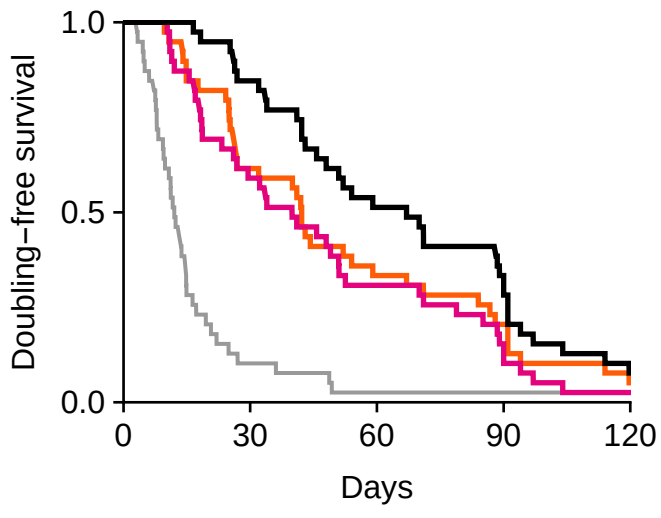
```
Breast cancer
```

```
BKM120
```

```
paclitaxel
```

```
tumortype = 5;
i = 3;
j = 14;
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, i]],
  MonotherapiesByGroup[[tumortype, j]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]][[3]]
```

```
PvalueForBestResponsesOfDrugPairToBeExplainedByAnimalToAnimalVariability[tumortype,
 i, j]
```

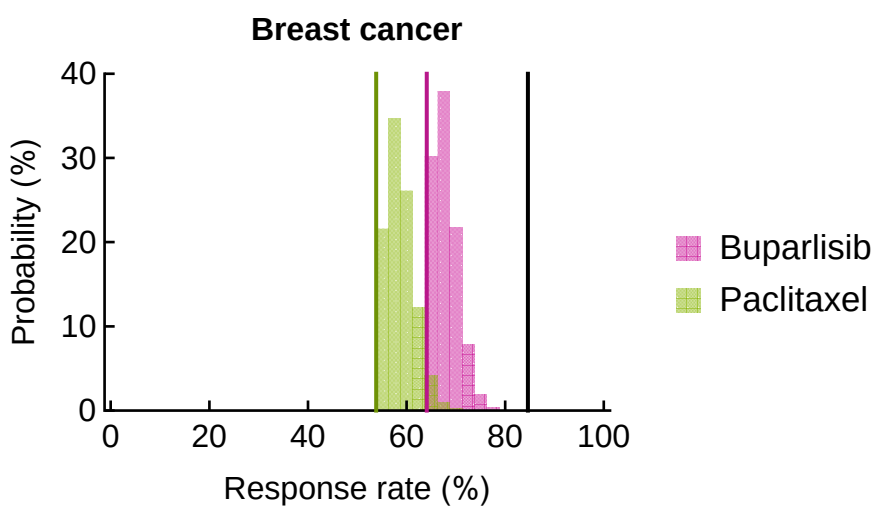



```
0.
```

```
binsize = 0.025;
height = 0.4;

Histogram[{ManyDrugABestsOfSimulatedAnimalPairs, ManyDrugBBestsOfSimulatedAnimalPairs},
 {-binsize / 2, 1 + binsize / 2, binsize}, "Probability",
 PlotRange → {{-binsize / 2, 1 + binsize / 2}, {0, height}}, PlotRangePadding → None,
 FrameStyle → Directive[Black, Thickness[Medium]],
 ChartStyle → {Directive[EdgeForm[None], RGBColor[0.8, 0.1, 0.6], Opacity[0.5]],
   Directive[EdgeForm[None], ColorData[3, 4], Opacity[0.5]]},
 BaseStyle → {FontFamily → "Arial", FontSize → 12}, Frame → {{True, False}, {True, False}},
 Axes → False,
 FrameTicks → {{Table[{i, 100 * i, {0.02, 0}}, {i, 0, 1, 1 / 10}], None},
   {Table[{i, 100 * i, {0.02, 0}}, {i, 0, 1, 1 / 5}], None}},
 Epilog → {AbsoluteThickness[1.5], Opacity[1], Darker[RGBColor[0.8, 0.1, 0.6], 0.1],
   Line[{{Mean[DrugAresponsesAsNumbers], 0}, {Mean[DrugAresponsesAsNumbers], height}}],
   Darker[ColorData[3, 4], 0.2],
   Line[{{Mean[DrugBresponsesAsNumbers], 0}, {Mean[DrugBresponsesAsNumbers], height}}],
   Black, Line[{{Mean[BestOfDrugADrugBresponsesAsNumbers], 0},
     {Mean[BestOfDrugADrugBresponsesAsNumbers], height}}]},
 FrameLabel → {"Response rate (%)", "Probability (%)"}, AspectRatio → 2 / 3,
 ImagePadding → {{80, 10}, {50, 10}}, ImageSize → {{1000}, {200}},
 PlotLabel → Style[ModelNames[[tumortype]], Black, FontSize → 12, Bold],
 ChartLegends → {"Buparlisib", "Paclitaxel"}]

Export[NotebookDirectory[] <> "Supplementary Figure S6, Breast cancer.pdf", %, "PDF"];
```



gastric cancer

```
tumortype = 6;
ModelNames[[tumortype]]
i = 4;
j = 13;
MonotherapiesByGroup[[tumortype, i]]
MonotherapiesByGroup[[tumortype, j]]
```

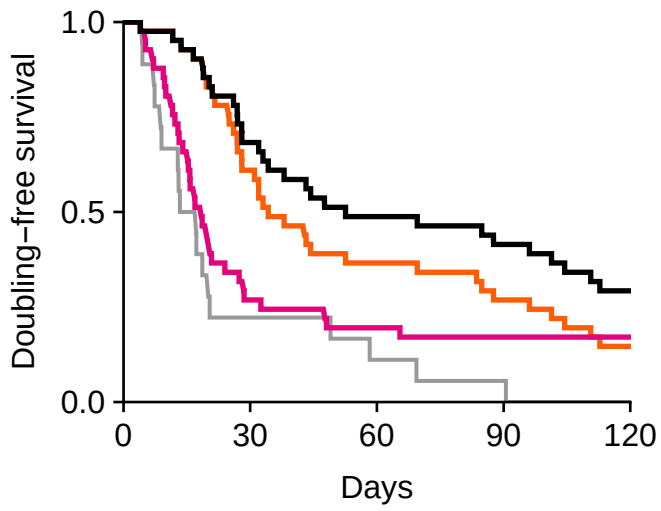
```
Gastric cancer

BYL719

LLM871
```

```
tumortype = 6;
i = 4;
j = 13;
IndependentActionPrediction[MonotherapiesByGroup[[tumortype, i]],
  MonotherapiesByGroup[[tumortype, j]], AllModelGroups[[tumortype]], ModelNames[[tumortype]]][[3]]

PvalueForBestResponsesOfDrugPairToBeExplainedByAnimalToAnimalVariability[tumortype,
 i, j]
```

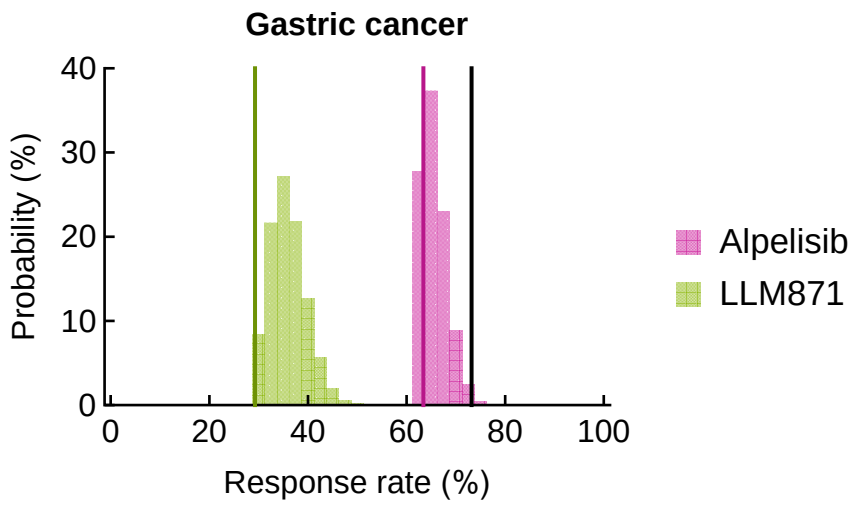



```
0.02994

binsize = 0.025;
height = 0.4;

Histogram[{ManyDrugABestsOfSimulatedAnimalPairs, ManyDrugBBestsOfSimulatedAnimalPairs},
 {-binsize / 2, 1 + binsize / 2, binsize}, "Probability",
 PlotRange → {{-binsize / 2, 1 + binsize / 2}, {0, height}}, PlotRangePadding → None,
 FrameStyle → Directive[Black, Thickness[Medium]],
 ChartStyle → {Directive[EdgeForm[None], RGBColor[0.8, 0.1, 0.6], Opacity[0.5]],
   Directive[EdgeForm[None], ColorData[3, 4], Opacity[0.5]]},
 BaseStyle → {FontFamily → "Arial", FontSize → 12}, Frame → {{True, False}, {True, False}},
 Axes → False,
 FrameTicks → {{Table[{i, 100 * i, {0.02, 0}}, {i, 0, 1, 1 / 10}], None},
   {Table[{i, 100 * i, {0.02, 0}}, {i, 0, 1, 1 / 5}], None}},
 Epilog → {AbsoluteThickness[1.5], Opacity[1], Darker[RGBColor[0.8, 0.1, 0.6], 0.1],
   Line[{{Mean[DrugAresponsesAsNumbers], 0}, {Mean[DrugAresponsesAsNumbers], height}}],
   Darker[ColorData[3, 4], 0.2],
   Line[{{Mean[DrugBresponsesAsNumbers], 0}, {Mean[DrugBresponsesAsNumbers], height}}],
   Black, Line[{{Mean[BestOfDrugADrugBresponsesAsNumbers], 0},
     {Mean[BestOfDrugADrugBresponsesAsNumbers], height}}]},
 FrameLabel → {"Response rate (%)", "Probability (%)"}, AspectRatio → 2 / 3,
 ImagePadding → {{80, 10}, {50, 10}}, ImageSize → {{1000}, {200}},
 PlotLabel → Style[ModelNames[[tumortype]], Black, FontSize → 12, Bold],
 ChartLegends → {"Alpelisib", "LLM871"}]

Export[NotebookDirectory[] <> "Supplementary Figure S6, Gastric cancer.pdf", %, "PDF"];
```



Correlation between MEK and RAF inhibitors in BRAF-mutant melanoma

which melanoma tumors are BRAF mutant, and have been tested under treatment with both RAF inhibition and MEK inhibition?

```
(* Melanoma responses to RAF inhibition by encorafenib *)
RAFresponses = Select[PDXclinicaltrialresponses,
   And[MemberQ[CutaneousMelanomaModels, #[[1]]], #[[2]] == "encorafenib"] &];
(* Melanoma responses to MEK inhibition by binimetinib *)
MEKresponses = Select[PDXclinicaltrialresponses,
   And[MemberQ[CutaneousMelanomaModels, #[[1]]], #[[2]] == "binimetinib"] &];
(* which PDX models were tested with both RAF and MEK inhibition? *)
RAFMEKIntersection = Intersection[MEKresponses[[All, 1]], RAFresponses[[All, 1]]];
(* importing a table of all BRAF mutations in PDX models. This is a subset of the
 mutation data in the Supplementary Materials of Gao et al. Nature Medicine *)
BRAFmutations = Import[NotebookDirectory[] <> "BRAF mutations.csv", "CSV"];

(* identifying PDX models that were tested with both RAF and MEK inhibition,
and which contains BRAF V600 mutations *)
Off[StringTake::strse]
RAKMEKIntersectionWithBRAFV600mutations =
  Select[BRAFmutations[[2 ;;]],
   And[MemberQ[RAFMEKIntersection, #[[1]]], StringTake[#[[5]], 4] == "V600"] &];
% // TableForm
```

X-1906	BRAF	673	MutKnownFunctional	V600E,0.798
X-2602	BRAF	673	MutKnownFunctional	V600E,0.625
X-2613	BRAF	673	MutKnownFunctional	V600E,0.792
X-2723	BRAF	673	MutKnownFunctional	V600E,0.786
X-3211	BRAF	673	MutKnownFunctional	V600K,0.585
X-3483	BRAF	673	MutKnownFunctional	V600E,0.893
X-3676	BRAF	673	MutKnownFunctional	V600E,0.510
X-3746	BRAF	673	MutKnownFunctional	V600E,0.467
X-4530	BRAF	673	MutKnownFunctional	V600E,0.266
X-4538	BRAF	673	MutKnownFunctional	V600E,0.485
X-4644	BRAF	673	MutKnownFunctional	V600E,0.719
X-4668	BRAF	673	MutKnownFunctional	V600E,0.855
X-4849	BRAF	673	MutKnownFunctional	V600E,0.646

```
MEKresponsesinBRAFmutantPDXs =
  Select[MEKresponses, MemberQ[RAKMEKIntersectionWithBRAFV600mutations[[All, 1]], #[[1]]] &];
RAFresponsesinBRAFmutantPDXs =
  Select[RAFresponses, MemberQ[RAKMEKIntersectionWithBRAFV600mutations[[All, 1]], #[[1]]] &];
% // Length
```

```
13
```

```
(* correlation between RAF and MEK responses in BRAF V600 mutant tumors *)
SpearmanRho[MEKresponsesinBRAFmutantPDXs[[All, 9]], RAFresponsesinBRAFmutantPDXs[[All, 9]]]
```

```
0.71978
```