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## Figure 4A - Recurrent platinum-sensitive ovarian cancer

Highly similar code is used to conduct all analyses in Figures 4A-G, Figure 5D, and Supplementary Figure 5B; excepting that plot ranges and labels are adjusted to their data sets.

For each of Figures 4A-G, and 5D, the same range of response correlation is employed, based on the distribution of response correlations in PDX data:  $\rho = 0.28 \pm 0.2$ .

In order to obtain the same level of response correlation for each data set, a parameter “amountofrankrandomization” has been adjusted by trial and error to produce the suitable degree of correlation in response; this differs simply because different data sets are obtained from published images of different sizes, which therefore contain different numbers of pixels per image.

### Importing survival data as tabulated in 'Table of survival distributions.xlsx' :

```
Figure4ARawData = Import[NotebookDirectory[] <> "Table of survival distributions.xlsx", "XLSX"][[
  3(* the third tab of this spreadsheet contains the PFS data for platinum-
    sensitive recurrent ovarian cancer treated with chemotherapy plus olaparib*)]];

ChemotherapySurvivalDistribution =
  Select[Figure4ARawData[[8 ;;, 2(* column 2 of this spreadsheet contains PFS data for chemotherapy*)]], NumberQ];
OlaparibSurvivalDistribution = Select[Figure4ARawData[[8 ;;, 3(* column 3 of this spreadsheet contains PFS data for olaparib*)]], NumberQ];
ComboSurvivalDistribution = Select[Figure4ARawData[[8 ;;, 4
  (* column 4 of this spreadsheet contains PFS data for the combination of chemotherapy plus olaparib*)]], NumberQ];
```

### Randomly sampling monotherapy response distributions with partial correlation

This is achieved by starting with the two monotherapies response distributions in a perfectly correlated joint distribution, and then adding a random number (up to a user-specified size) to the rank (that is, row number) of each entry. As the degree of rank-randomization increases, the rank correlation decreases from 1 and approaches 0. Identifying the appropriate value of the rank randomization parameter to produce a desired Spearman Rank Correlation is matter of manual adjustment.

First, our goal is  $\rho = 0.28$

```
(* these two distributions are not of exactly the same length
  (this depends on image size and resolution of the Kaplan-Meier plots from which data was extracted). Therefore,
  we shall need to randomly subsample the longer distribution to produce distributions with exactly matching lengths. To
  minimize the introduction of error from the possibility that one part of the distribution is sampled less than other parts,
  we introduce a parameter 'resampling factor' such that this process is repeated many times over (here, we take 10 times). In practice this
  produces highly reproducible results on repeat executions of the program (demonstrated below in a histogram of response correlation) *)
Length[OlaparibSurvivalDistribution]
Length[ChemotherapySurvivalDistribution]

1647
1470

(* how many repeats of the complete data set to merge together
  (for purpose of minimizing variance between individual repeats of the 'rank randomization' process) *)
resamplingfactor = 10;
(* within each 'resample', need to sub-sample the olaparib distribution (more vertical pixels than the chemotherapy distribution). The
  number of pixels is vastly in excess of the number of patients so no individual patient's information is lost. *)
ReSampledOLAPSurvivalDistribution =
  Reverse[Sort[Flatten[Table[RandomSample[OlaparibSurvivalDistribution, Length[ChemotherapySurvivalDistribution]], {resamplingfactor}]]]];
ReSampledChemotherapySurvivalDistribution = Reverse[Sort[Flatten[Table[ChemotherapySurvivalDistribution, {resamplingfactor}]]]];

(* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.28 *)
amountofrankrandomization = 13000;

SlightlyRandomizedCHEMODistribution =
  Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledChemotherapySurvivalDistribution[[i]],
    {i, 1, Length[ReSampledChemotherapySurvivalDistribution]}], #1[[1]] < #2[[1]] &];
SlightlyRandomizedOLAPDistribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
  ReSampledOLAPSurvivalDistribution[[i]], {i, 1, Length[ReSampledOLAPSurvivalDistribution]}], #1[[1]] < #2[[1]] &];
BestOfMidCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedCHEMODistribution[[i, 2]], SlightlyRandomizedOLAPDistribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedCHEMODistribution]}];

SpearmanRho[SlightlyRandomizedCHEMODistribution[[All, 2]], SlightlyRandomizedOLAPDistribution[[All, 2]]]

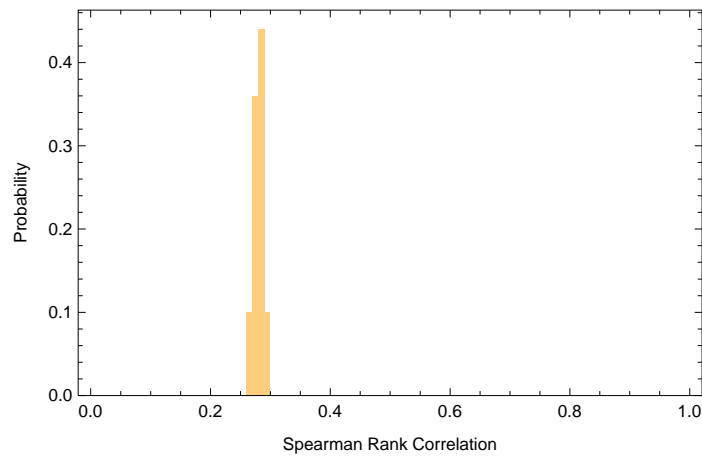
0.29131
```

```
(* Repeating the randomization procedure 100 times to show that
response correlation is tightly distributed around the targeted value of 0.28 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 13000;
  SlightlyRandomizedCHEMODistribution =
    Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledChemotherapySurvivalDistribution[[i]],
    {i, 1, Length[ReSampledChemotherapySurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedOLAPDistribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
    ReSampledOLAPSurvivalDistribution[[i]], {i, 1, Length[ReSampledOLAPSurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedCHEMODistribution[[All, 2]], SlightlyRandomizedOLAPDistribution[[All, 2]]
, {100}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

Mean response correlation = 0.281



(\* after generating the distribution of survival times predicted by independent drug action,  
we can remove the 'resampling' to plot the results. With a resampling factor of 10,  
this is achieved by sorting the distribution and keeping every 10th entry \*)

```
SubSampledBestOfMidCorrelatedMonoPairs = Take[Reverse[Sort[BestOfMidCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

## Randomly sampling monotherapy response distributions with partial correlation

Second, our goal is  $\rho = 0.08$

(\* how many repeats of the complete data set to merge together

(for purpose of minimizing variance between individual repeats of the 'rank randomization' process) \*)

```
resamplingfactor = 10;
```

(\* within each 'resample', need to sub-sample the olaparib distribution (more vertical pixels than the chemotherapy distribution). The  
number of pixels is vastly in excess of the number of patients so no individual patient's information is lost. \*)

```
ReSampledOLAPSurvivalDistribution =
```

```
Reverse[Sort[Flatten[Table[RandomSample[OlaparibSurvivalDistribution, Length[ChemotherapySurvivalDistribution]], {resamplingfactor}]]]]];
```

```
ReSampledChemotherapySurvivalDistribution = Reverse[Sort[Flatten[Table[ChemotherapySurvivalDistribution, {resamplingfactor}]]]]];
```

(\* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.28 \*)

```
amountofrankrandomization = 44400;
```

```
SlightlyRandomizedCHEMODistribution =
```

```
Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledChemotherapySurvivalDistribution[[i]],
  {i, 1, Length[ReSampledChemotherapySurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedOLAPDistribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
  ReSampledOLAPSurvivalDistribution[[i]], {i, 1, Length[ReSampledOLAPSurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
BestOfLowCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedCHEMODistribution[[i, 2]], SlightlyRandomizedOLAPDistribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedCHEMODistribution]}];
```

```
SpearmanRho[SlightlyRandomizedCHEMODistribution[[All, 2]], SlightlyRandomizedOLAPDistribution[[All, 2]]
```

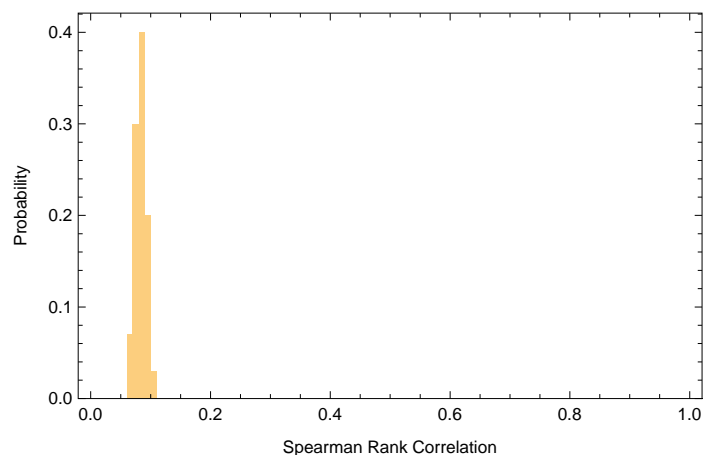
```
0.0828941
```

```
(* Repeating the randomization procedure 100 times to show that
response correlation is tightly distributed around the targeted value of 0.08 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 44400;
  SlightlyRandomizedCHEMODistribution =
    Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledChemotherapySurvivalDistribution[[i]],
    {i, 1, Length[ReSampledChemotherapySurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedOLAPDistribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
    ReSampledOLAPSurvivalDistribution[[i]], {i, 1, Length[ReSampledOLAPSurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedCHEMODistribution[[All, 2]], SlightlyRandomizedOLAPDistribution[[All, 2]]
, {100}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

Mean response correlation = 0.083



(\* after generating the distribution of survival times predicted by independent drug action, we can remove the 'resampling' to plot the results. With a resampling factor of 10, this is achieved by sorting the distribution and keeping every 10th entry \*)

```
SubSampledBestOfLowCorrelatedMonoPairs = Take[Reverse[Sort[BestOfLowCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

## Randomly sampling monotherapy response distributions with partial correlation

Thirdly, our goal is  $\rho = 0.48$

(\* how many repeats of the complete data set to merge together

(for purpose of minimizing variance between individual repeats of the 'rank randomization' process) \*)

```
resamplingfactor = 10;
```

(\* within each 'resample', need to sub-sample the olaparib distribution (more vertical pixels than the chemotherapy distribution). The number of pixels is vastly in excess of the number of patients so no individual patient's information is lost. \*)

```
ReSampledOLAPSurvivalDistribution =
```

```
Reverse[Sort[Flatten[Table[RandomSample[OlaparibSurvivalDistribution, Length[ChemotherapySurvivalDistribution]], {resamplingfactor}]]]]];
```

```
ReSampledChemotherapySurvivalDistribution = Reverse[Sort[Flatten[Table[ChemotherapySurvivalDistribution, {resamplingfactor}]]]]];
```

(\* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.48 \*)

```
amountofrankrandomization = 7600;
```

```
SlightlyRandomizedCHEMODistribution =
```

```
Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledChemotherapySurvivalDistribution[[i]],
  {i, 1, Length[ReSampledChemotherapySurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedOLAPDistribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
  ReSampledOLAPSurvivalDistribution[[i]], {i, 1, Length[ReSampledOLAPSurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
BestOfHighCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedCHEMODistribution[[i, 2]], SlightlyRandomizedOLAPDistribution[[i, 2]]}],
  {i, 1, Length[SlightlyRandomizedCHEMODistribution]}];
```

```
SpearmanRho[SlightlyRandomizedCHEMODistribution[[All, 2]], SlightlyRandomizedOLAPDistribution[[All, 2]]
```

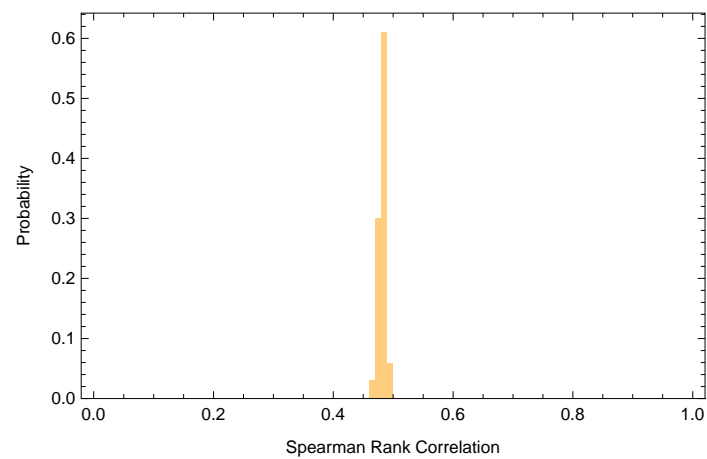
```
0.477962
```

```
(* Repeating the randomization procedure 100 times to show that
response correlation is tightly distributed around the targeted value of 0.48 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 7600;
  SlightlyRandomizedCHEMODistribution =
    Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledChemotherapySurvivalDistribution[[i]],
    {i, 1, Length[ReSampledChemotherapySurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedOLAPDistribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
    ReSampledOLAPSurvivalDistribution[[i]], {i, 1, Length[ReSampledOLAPSurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedCHEMODistribution[[All, 2]], SlightlyRandomizedOLAPDistribution[[All, 2]]
, {100}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

```
Mean response correlation = 0.482
```



```
(* after generating the distribution of survival times predicted by independent drug action,
we can remove the 'resampling' to plot the results. With a resampling factor of 10,
this is achieved by sorting the distribution and keeping every 10th entry *)
```

```
SubSampledBestOfHighCorrelatedMonoPairs = Take[Reverse[Sort[BestOfHighCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

Computing median PFS for each condition: the observed individual therapies (chemotherapy or olaparib), the observed combination, and the simulated effects with high, medium, or low response correlation (respectively,  $\rho = 0.48, 0.28, 0.08$ )

```
Mono1Median = Round[Median[ChemotherapySurvivalDistribution], 0.01]
Mono2Median = Round[Median[OlaparibSurvivalDistribution], 0.01]
ComboMedian = Round[Median[ComboSurvivalDistribution], 0.01]
Sim1Median = Round[Median[SubSampledBestOfHighCorrelatedMonoPairs], 0.01]
Sim2Median = Round[Median[SubSampledBestOfMidCorrelatedMonoPairs], 0.01]
Sim3Median = Round[Median[SubSampledBestOfLowCorrelatedMonoPairs], 0.01]
```

```
9.5
```

```
8.89
```

```
12.15
```

```
11.11
```

```
12.22
```

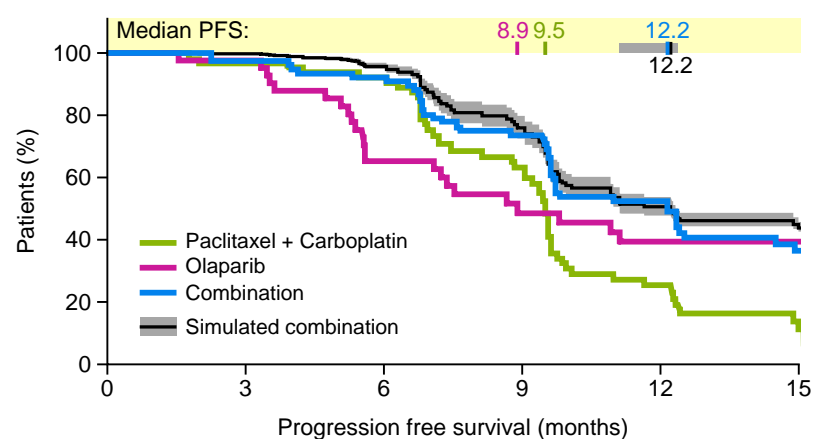
```
12.38
```

## Plotting the observed and simulated survival functions

```
(* these parameters are used to adjust the position of the legend inset *)
(*legend vertical offset*)
lo = 0.05;
(* vertical offset of the 'simulated' legend entry*)slo = -0.03;
(* legend horizontal offset *)
lho = -0.1;

Plot[{
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfHighCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfMidCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfLowCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[ChemotherapySurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[OlaparibSurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[ComboSurvivalDistribution]][x]
}, {x, 0, 16}, PlotRange -> {{0, 15.0}, {0, 1.11}}, Exclusions -> None,
PlotStyle -> {Directive[Black, Opacity[0]], Directive[Black, AbsoluteThickness[1.7]], Directive[Black, Opacity[0]], Directive[ColorData[3, 4],
  AbsoluteThickness[3]], Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[3]], Directive[ColorData[3, 6], AbsoluteThickness[3]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 12}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.015}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.015}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)", Style["Patients (%)"]]},
Prolog -> {Gray, Thickness[Medium], Lighter[Yellow, 0.75], EdgeForm[None], Rectangle[{0, 1}, {18, 1.11}],
  Black, AbsoluteThickness[1.7], GrayLevel[0.65], Rectangle[{Sim1Median, 1}, {Sim3Median, 1.03}],
  Black, Opacity[1], Line[{{Sim2Median, 1}, {Sim2Median, 1.03}}], Text["Median PFS:", {0.2, 1.03}, {-1, -1}],
  Darker[ColorData[3, 4], 0.1], Text[ToString[NumberForm[Mono1Median, {3, 1}]], {Mono1Median, 1.03}, {-0.25, -1}],
  RGBColor[0.8, 0.1, 0.6], Text[ToString[NumberForm[Mono2Median, {3, 1}]], {Mono2Median, 1.03}, {0.25, -1}],
  ColorData[3, 6], Text[ToString[NumberForm[ComboMedian, {3, 1}]], {ComboMedian, 1.03}, {0, -1}], Black,
  Black, Text[ToString[NumberForm[Sim2Median, {3, 1}]], {Sim2Median, 1.0}, {0, 1}], AbsoluteThickness[2],
  Darker[ColorData[3, 4], 0.1], Line[{{Mono1Median, 1}, {Mono1Median, 1.03}}], RGBColor[0.8, 0.1, 0.6],
  Line[{{Mono2Median, 1}, {Mono2Median, 1.03}}], ColorData[3, 6], Line[{{ComboMedian, 1}, {ComboMedian, 1.03}}]},
AspectRatio -> 1 / 2, Filling -> {1 -> {3}}, FillingStyle -> Directive[GrayLevel[0.65], Opacity[1]],
ImageSize -> {{1000}, {250}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 500,
Epilog -> {EdgeForm[Directive[Black, Thickness[Medium]]], White, Opacity[1], EdgeForm[None], CapForm["Butt"], AbsoluteThickness[3],
  AbsolutePointSize[8], ColorData[3, 4], Line[{{lho + 0.8, 0.34 + lo}, {lho + 1.6, 0.34 + lo}}], RGBColor[0.8, 0.1, 0.6],
  Line[{{lho + 0.8, 0.26 + lo}, {lho + 1.6, 0.26 + lo}}], ColorData[3, 6], Line[{{lho + 0.8, 0.18 + lo}, {lho + 1.6, 0.18 + lo}}],
  Opacity[1], GrayLevel[0.65], Rectangle[{lho + 0.8, 0.1 - 0.03 + lo + slo}, {lho + 1.6, 0.1 + 0.03 + lo + slo}], Black,
  Opacity[1], AbsoluteThickness[1.7], Line[{{lho + 0.8, 0.1 + lo + slo}, {lho + 1.6, 0.1 + lo + slo}}], FontFamily -> "Arial",
  FontSize -> 11, Text[Style["Paclitaxel + Carboplatin", FontSize -> 11], {lho + 1.8, 0.34 + lo}, {-1, 0}],
  Text[Style["Olaparib", FontSize -> 11], {lho + 1.8, 0.26 + lo}, {-1, 0}], Text[Style["Combination", FontSize -> 11],
  {lho + 1.8, 0.18 + lo}, {-1, 0}], Text[Style["Simulated combination", FontSize -> 11], {lho + 1.8, 0.1 + lo + slo}, {-1, 0}]]]

Export[NotebookDirectory[] <> "Figure 4A.pdf", %, "PDF"]
```





Calculating the improvement in hazard ratio attributable to drug synergy.  
This is the hazard ratio between the observed combination trial results, and the combination trial results calculated on the assumption of 'no additivity or synergy'.

```
CensoringTime = 12 (* months *);

PatientsPerArmOfSimulatedTrial = 1000;
IndependentActionSimulatedTrial[] := RandomChoice[SubSampledBestOfMidCorrelatedMonoPairs, PatientsPerArmOfSimulatedTrial]
CombinationSimulatedTrial[] := RandomChoice[ComboSurvivalDistribution, PatientsPerArmOfSimulatedTrial]

GenerateCensoredEventData[PatientResponses_, CensoringTime_] :=
Module[{ResponsesShorterThanCensoringTime, ResponsesLongerThanCensoringTime},
  ResponsesShorterThanCensoringTime = Select[PatientResponses, # <= CensoringTime &];
  ResponsesLongerThanCensoringTime = Select[PatientResponses, # > CensoringTime &];
  EventData[Join[ResponsesShorterThanCensoringTime, ResponsesLongerThanCensoringTime],
    Join[Table[0, {Length[ResponsesShorterThanCensoringTime]}], Table[1, {Length[ResponsesLongerThanCensoringTime]}]]]
]

IndependentActionSimulatedEventData[] := GenerateCensoredEventData[IndependentActionSimulatedTrial[], CensoringTime]
CombinationSimulatedEventData[] := GenerateCensoredEventData[CombinationSimulatedTrial[], CensoringTime]

(* custom function to join two sets of event data - this is necessary to implement the Cox Proportional Hazards model *)
JoinEventData[EventData1_, EventData2_] := EventData[Join[EventData1[[2, 1]], EventData2[[2, 1]], Join[EventData1[[2, 2]], EventData2[[2, 2]]]]

MergedEventData[] := JoinEventData[IndependentActionSimulatedEventData[], CombinationSimulatedEventData[]];
Descriptors[] := Join[Table["Independence", {PatientsPerArmOfSimulatedTrial}], Table["Observed", {PatientsPerArmOfSimulatedTrial}]];
```

Note that the error range in the hazard ratio depends on the population size in a simulated trial of the combination, and the duration on trial, that is, the rate of censoring events.  
Here we compute error ranges expected from 200 patients per trial arm, with any that are progression-free after a defined time being ‘censored’. This limits imprecision arising from the source PFS data having few patients ‘on-trial’ at late times, which is cause of increasing error range in PFS probability at longer times.

The range in hazard ratio is robustly identified by taking the mean range over 100 simulations of such trials.

```
NumberOfReplicateTrials = 100;

(* this function returns the relative risk, and confidence interval, in the format:
  (95% lower confidence interval, median estimate, 95% upper confidence interval )
*)
RelativeRiskCalculation[descriptors_, eventdata_, PrintTable_
  (* set to 1 to print to screen the statistical table of Cox Model output; set to 0 to not show output *)] := Module[{},
  MyModelFit = CoxModelFit[{descriptors, eventdata}, {treatment}, {treatment}, NominalVariables -> treatment];

  If[PrintTable == 1, Print[MyModelFit["ParameterTable"]]];

  RelativeRisk = MyModelFit["RelativeRisk"][[1]];
  RelativeRiskLowerConfidenceInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1, 1]];
  RelativeRiskUpperConfidenceInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1, 2]];

  {RelativeRiskLowerConfidenceInterval, RelativeRisk, RelativeRiskUpperConfidenceInterval}
]

(* single execution of the simulated trial *)
RelativeRiskCalculation[Descriptors[], MergedEventData[], 1]

```

	Estimate	Standard Error	Relative Risk	Wald- $\chi^2$	DF	P-Value
treatment[Observed]	0.041069	0.0635114	1.04192	0.418142	1	0.517865

```
{0.919973, 1.04192, 1.18004}

(* many replicate trial simulations, to accurately determine the range in hazard ratio *)
OvarianHazardRatioRange = Quiet@Mean[Table[RelativeRiskCalculation[Descriptors[], MergedEventData[], 0], {NumberOfReplicateTrials}]]
{0.874801, 0.992305, 1.12559}
```

## Comparison of Independent Drug Action with Synergy models by Akaike Information Criterion (AIC)

```
(* first, we compute a survival distribution based on the monotherapy distributions assuming no synergy,
and perfect correlation in response between drugs. Therefore at each time point,
PFS is the higher of the single-drug PFS rates at that time. *)
MaximumOfMonotherapyResponses = Map[Max, {Sort[ReSampledOLAPSurvivalDistribution], Sort[ReSampledChemotherapySurvivalDistribution]}^T];
MaximumOfMonotherapyResponses = Take[Reverse[Sort[MaximumOfMonotherapyResponses]], 1 ;; -1 ;; resamplingfactor];

(* Maximum time, in months, over which to compare survival distributions *)
LongestTime = 15;
```

A ‘synergy-fitting’ model is created by defining two adjustable parameters:

a vertical scaling, which affects a fractional decrease in progression probability at each time

a horizontal scaling, which affects a fractional extension in duration of progression-free survival for all patients

SynergyModel[0,0] has no synergistic effect.

SynergyModel[X,0] has, for each patient, +X\*100% longer PFS time. E.g. in SynergyModel[0.5, 0], all patients have +50% longer PFS.

SynergyModel[0,Y] has, at each time point, a 1/Y probability of progression. E.g. in SynergyModel[0, 1], at each time the progression rate is halved.

```
SynergyModel[HorizontalScaling_, VerticalScaling_] :=
  Join[MaximumOfMonotherapyResponses * (1 + HorizontalScaling), Table[LongestTime, {VerticalScaling * Length[MaximumOfMonotherapyResponses]}]]

(* for Kolmogorov-Smirnov test to be comparable across data sets and model types,
the population size that comprises each survival distribution is normalized to a consistent
value. This does not change the distribution shape except for insignificant rounding differences. *)
TrialPopulationSize = 200;

SetMaximumTimeAndNormalizePopulationSize[survivaldistribution_, LongestTime_, PopulationSize_] := Module[{},
  SurvivalDistributionWithMaximumTime = Sort[Map[Min[{LongestTime, #}] &, survivaldistribution]];
  SurvivalDistributionWithDefinedPopulationSize =
    Sort[Flatten[Table[SurvivalDistributionWithMaximumTime, {PopulationSize}]]][1 ;; -1 ;; Length[SurvivalDistributionWithMaximumTime]]
]

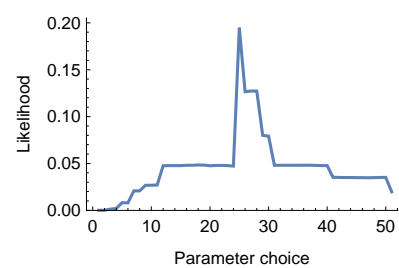
(* the observed data; set to consistent population size and capped with a consistent maximum survival time *)
ObservedDistribution = SetMaximumTimeAndNormalizePopulationSize[ComboSurvivalDistribution, LongestTime, TrialPopulationSize];

(* computing which synergy model, using the horizontal parameter only, has the highest likelihood of consistency with the observed data *)
MaximumHorizontalScaling = 0.2;
Steps = 50;

SynergyModelOnlyHorizontalParameterFits = Table[{HorizontalScaling, KolmogorovSmirnovTest[ObservedDistribution,
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[HorizontalScaling, 0], LongestTime, TrialPopulationSize], "PValue"]},
  {HorizontalScaling, 0, MaximumHorizontalScaling, MaximumHorizontalScaling / Steps}];

BestLikelihoodWithHorizontalParameter = Max[SynergyModelOnlyHorizontalParameterFits[[All, 2]]]
0.194886
```

```
(* confirming that the synergy parameter spanned the optimal range *)
ListPlot[SynergyModelOnlyHorizontalParameterFits[[All, 2]], Joined → True, PlotRange → {0, All},
  ImageSize → 200, Frame → {{True, False}, {True, False}}, FrameLabel → {"Parameter choice", "Likelihood"}]
```

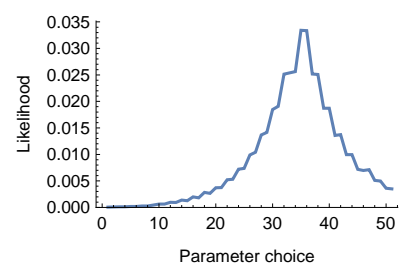


```
(* computing which synergy model, using the vertical parameter only, has the highest likelihood of consistency with the observed data *)
MaximumVerticalScaling = 0.3;
Steps = 50;
```

```
SynergyModelOnlyVerticalParameterFits = Table[{VerticalScaling, KolmogorovSmirnovTest[ObservedDistribution,
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[0, VerticalScaling], LongestTime, TrialPopulationSize], "PValue"]},
  {VerticalScaling, 0, MaximumVerticalScaling, MaximumVerticalScaling / Steps}];
```

```
BestLikelihoodWithVerticalParameter = Max[SynergyModelOnlyVerticalParameterFits[[All, 2]]]
0.0334129
```

```
(* confirming that the synergy parameter spanned the optimal range *)
ListPlot[SynergyModelOnlyVerticalParameterFits[[All, 2]], Joined → True, PlotRange → {0, All},
  ImageSize → 200, Frame → {{True, False}, {True, False}}, FrameLabel → {"Parameter choice", "Likelihood"}]
```



```

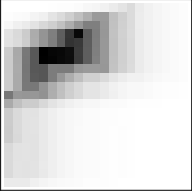
(* computing which synergy model, using two parameters, has the highest likelihood of consistency with the observed data *)
MaximumHorizontalScaling = 0.2;
MaximumVerticalScaling = 0.3;
StepsPerParameter = 20;

SynergyModelTwoParameterFits =
  Table[{HorizontalScaling, VerticalScaling, KolmogorovSmirnovTest[ObservedDistribution, SetMaximumTimeAndNormalizePopulationSize[
    SynergyModel[HorizontalScaling, VerticalScaling], LongestTime, TrialPopulationSize], "PValue"]},
    {HorizontalScaling, 0, MaximumHorizontalScaling, MaximumHorizontalScaling / StepsPerParameter},
    {VerticalScaling, 0, MaximumVerticalScaling, MaximumVerticalScaling / StepsPerParameter}];

BestLikelihoodWithTwoParameterFit = Max[Flatten[SynergyModelTwoParameterFits[[All, All, 3]]]
0.236928

(* confirming that the synergy parameters spanned the optimal range *)
ArrayPlot[SynergyModelTwoParameterFits[[All, All, 3]], ImageSize -> 100]

```



```

(* computing the likelihood that the Independent Drug Action model (with zero fitted parameters) is consistent with the observed data *)
(* To minimize noise from the sampling procedure of the independent action model, we take the average of many simulations *)
IndependentActionSimulation[] := Module[{},
  (* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.28 *)
  amountofrankrandomization = 13000;
  SlightlyRandomizedCHEMODistribution =
    Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledChemotherapySurvivalDistribution[[i]],
      {i, 1, Length[ReSampledChemotherapySurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedOLAPDistribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
    ReSampledOLAPSurvivalDistribution[[i]], {i, 1, Length[ReSampledOLAPSurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  BestOfMidCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedCHEMODistribution[[i, 2]], SlightlyRandomizedOLAPDistribution[[i, 2]]}],
    {i, 1, Length[SlightlyRandomizedCHEMODistribution]}];
  SubSampledBestOfMidCorrelatedMonoPairs = Take[Reverse[Sort[BestOfMidCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor]
]

NumberOfIndependentActionSimulations = 20;
ReplicateIndependentActionSimulations = Sort[Flatten[Table[IndependentActionSimulation[], {NumberOfIndependentActionSimulations}]]];
(* final model is the population-normalized average of many replicate simulations *)
IndependentActionModel = SetMaximumTimeAndNormalizePopulationSize[ReplicateIndependentActionSimulations, LongestTime, TrialPopulationSize];
(* computing the likelihood that the Independent Drug Action model (with zero fitted parameters) is consistent with the observed data *)
IndependentActionModelLikelihood = KolmogorovSmirnovTest[ObservedDistribution, IndependentActionModel, "PValue"]
0.282906

(* Tabulating the likelihood that the observed combination drug response
would be observed if the true distribution were one of the various models, in the order:
{ independent drug action, synergy with horizontal parameter, synergy with vertical parameter, synergy with two parameters } *)
OvarianModelLikelihoods = {IndependentActionModelLikelihood,
  BestLikelihoodWithHorizontalParameter, BestLikelihoodWithVerticalParameter, BestLikelihoodWithTwoParameterFit}
{0.282906, 0.194886, 0.0334129, 0.236928}

```

## plotting model fits

```

MaximumOfMonotherapyResponsesModel =
  SetMaximumTimeAndNormalizePopulationSize[MaximumOfMonotherapyResponses, LongestTime, TrialPopulationSize];

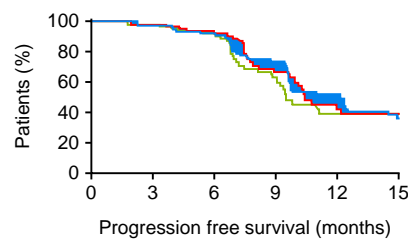
```



```
BestHorizontalSynergyParameter = Sort[SynergyModelOnlyHorizontalParameterFits, #1[[2]] > #2[[2]] &] [[1, 1]];
BestHorizontalSynergyModel =
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[BestHorizontalSynergyParameter, 0], LongestTime, TrialPopulationSize];
```

```
Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]] [x],
  SurvivalFunction[EmpiricalDistribution[BestHorizontalSynergyModel]] [x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]] [x]}
, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None, PlotStyle ->
  {Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Red, AbsoluteThickness[1]], Directive[ColorData[3, 6], AbsoluteThickness[1]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 10}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]}, AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[ColorData[3, 6], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]
```

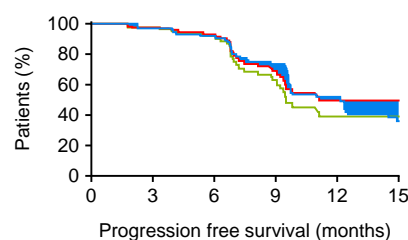
```
Export[NotebookDirectory[] <> "OvarianCancerOlaparibChemotherapyBestHorizontalSynergy.pdf", %, "PDF"]
```



```
BestVerticalSynergyParameter = Sort[SynergyModelOnlyVerticalParameterFits, #1[[2]] > #2[[2]] &] [[1, 1]];
BestVerticalSynergyModel =
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[0, BestVerticalSynergyParameter], LongestTime, TrialPopulationSize];
```

```
Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]] [x],
  SurvivalFunction[EmpiricalDistribution[BestVerticalSynergyModel]] [x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]] [x]}
, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None, PlotStyle ->
  {Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Red, AbsoluteThickness[1]], Directive[ColorData[3, 6], AbsoluteThickness[1]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 10}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]}, AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[ColorData[3, 6], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]
```

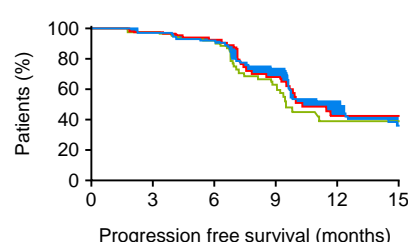
```
Export[NotebookDirectory[] <> "OvarianCancerOlaparibChemotherapyBestVerticalSynergy.pdf", %, "PDF"]
```



```
BestTwoParameterSynergyParameters = Sort[Flatten[SynergyModelTwoParameterFits, 1], #1[[3]] > #2[[3]] &] [[1, {1, 2}]];
BestTwoParameterSynergyModel = SetMaximumTimeAndNormalizePopulationSize[
  SynergyModel[BestTwoParameterSynergyParameters[[1]], BestTwoParameterSynergyParameters[[2]], LongestTime, TrialPopulationSize];
```

```
Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]] [x],
  SurvivalFunction[EmpiricalDistribution[BestTwoParameterSynergyModel]] [x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]] [x]}
, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None, PlotStyle ->
  {Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Red, AbsoluteThickness[1]], Directive[ColorData[3, 6], AbsoluteThickness[1]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 10}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]}, AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[ColorData[3, 6], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]
```

```
Export[NotebookDirectory[] <> "OvarianCancerOlaparibChemotherapyBestTwoParameterSynergy.pdf", %, "PDF"]
```

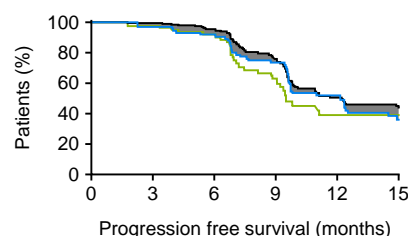


```

Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]][x],
  SurvivalFunction[EmpiricalDistribution[IndependentActionModel]][x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]][x]}
, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None,
PlotStyle -> {Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Black, AbsoluteThickness[1]],
  Directive[ColorData[3, 6], AbsoluteThickness[1]]}, BaseStyle -> {FontFamily -> "Arial", FontSize -> 10},
FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)", Style["Patients (%)"]], AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[GrayLevel[0.5], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]

Export[NotebookDirectory[] <> "OvarianCancerOlaparibChemotherapyIndependentModel.pdf", %, "PDF"]

```



## Supplementary figure - how PFS depends on response correlation

```

(* this function takes as its input an amount of rank randomization,
and returns a response correlation and predicted median PFS at this level of correlation in drug response *)
PFSvsCorrelation[amountofrankrandomization_] := Module[{},

  SubSampledOLAPSurvivalDistribution = Sort[RandomSample[OlaparibSurvivalDistribution, Length[ChemotherapySurvivalDistribution]]];
  SlightlyRandomizedCHEMODistribution =
    Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ChemotherapySurvivalDistribution[[i]],
      {i, 1, Length[ChemotherapySurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedOLAPDistribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
    SubSampledOLAPSurvivalDistribution[[i]], {i, 1, Length[SubSampledOLAPSurvivalDistribution]}], #1[[1]] < #2[[1]] &];

  ResponseCorrelation = SpearmanRho[SlightlyRandomizedCHEMODistribution[[All, 2]], SlightlyRandomizedOLAPDistribution[[All, 2]]];
  BestOfPartiallyCorrelatedSamplesofMonotherapyResponses =
    Table[Max[{SlightlyRandomizedCHEMODistribution[[i, 2]], SlightlyRandomizedOLAPDistribution[[i, 2]]}],
      {i, 1, Length[SlightlyRandomizedCHEMODistribution]}];

  MedianPFS = Quantile[BestOfPartiallyCorrelatedSamplesofMonotherapyResponses, 0.5];

  {ResponseCorrelation, MedianPFS}
]

(* executing the above function over a wide range of rank randomization values (log-distributed to achieve the necessary range) *)
PFSvsCorrelationTable = Table[PFSvsCorrelation[10^i], {i, 1.5, 5, 0.02}];

(* fitting a linear-plus-sigmoidal curve to the relationship between response correlation and
PFS. We attach no importance to the specific function - this is simply a versatile line to show the trend *)
nh = 2;

model = b - h *  $\frac{(x)^{nh}}{(x)^{nh} + k^{nh}}$  - m * x;

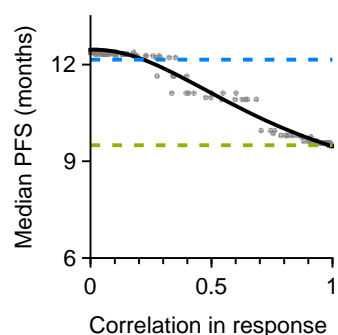
sigmoidfit50 = NonlinearModelFit[PFSvsCorrelationTable, model, {{b, 8}, {h, 10}, {k, 3}, {m, 1}}, x]

FittedModel[ $12.462 + 0.197069 x - \frac{5.35023 x^2}{0.674309 + x^2}$ ]

```

```
(* supplementary figure: relationship between median PFS and correlation, showing each simulation point *)
Show[
ListPlot[PFSvsCorrelationTable, PlotRange -> {{0, 1}, {6, 13.5}}, PlotStyle -> Directive[GrayLevel[0.5], Opacity[0.7], AbsolutePointSize[3]],
Frame -> {{True, False}, {True, False}}, FrameStyle -> Directive[Black, Thickness[Medium]], Axes -> False,
BaseStyle -> {FontFamily -> "Arial", FontSize -> 12}, AspectRatio -> 1, ImageSize -> {{1000}, {170}}, FrameTicks ->
{Join[Table[{N[i], i, {0, 0.04}}, {i, -1, 1, 1/2}], Table[{N[i], , {0, 0.025}}, {i, -1, 1, 1/10}]] /. {1/2 -> "0.5", -1/2 -> "-0.5"},
Table[{i, i, {0, 0.035}}, {i, 0, 20, 3}]}, FrameLabel -> {"Correlation in response ", "Median PFS (months)"}]
,
Plot[{sigmoidfit50[x], ComboMedian, Mono1Median}, {x, 0, 1},
PlotStyle -> {Directive[Black, AbsoluteThickness[2]], Directive[Dashing[{0.04, 0.05}], ColorData[3, 6], AbsoluteThickness[2]],
Directive[Dashing[{0.04, 0.05}], ColorData[3, 4], AbsoluteThickness[2]],
Directive[Dashing[{0.05, 0.03}], RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[2]]}, Filling -> None,
FillingStyle -> Directive[ColorData[3, 6], Opacity[0.3]], PlotRange -> {{0, 1}, {6, 13.5}}, Frame -> {{True, False}, {True, False}},
FrameStyle -> Directive[Black, Thickness[Medium]], Axes -> False, BaseStyle -> {FontFamily -> "Arial", FontSize -> 12},
AspectRatio -> 1, ImageSize -> {{1000}, {170}}, ImagePadding -> {{45, 10}, {45, 10}}, FrameTicks ->
{Join[Table[{N[i], i, {0, 0.04}}, {i, -1, 1, 1/2}], Table[{N[i], , {0, 0.025}}, {i, -1, 1, 1/10}]] /. {1/2 -> "0.5", -1/2 -> "-0.5"},
Table[{i, i, {0, 0.035}}, {i, 0, 20, 3}]}, FrameLabel -> {"Correlation in response ", "Median PFS (months)"}]
]

Export[NotebookDirectory[] <> "Supplementary Figure S5A, olaparib and chemotherapy.pdf", %, "PDF"]
```



## Figure 4B - HER2-positive breast cancer

Near-identical code as for Figure 4A is here employed to generate Figure 4B. Comments will be more brief.

```
Figure4BRawData = Import[NotebookDirectory[] <> "Table of survival distributions.xlsx", "XLSX"][[4(* the fourth tab of this spreadsheet*)]];

Therapy1SurvivalDistribution =
Select[Figure4BRawData[[8 ;;, 2(* column 2 of this spreadsheet contains PFS data for chemotherapy*)]], NumberQ];
Therapy2SurvivalDistribution = Select[Figure4BRawData[[8 ;;, 3
(* column 3 of this spreadsheet contains PFS data for trastuzumab*)]], NumberQ];
ComboSurvivalDistribution = Select[Figure4BRawData[[8 ;;, 4(* column 4 of this spreadsheet contains PFS data for the combination*)]],
NumberQ];

ρ = 0.28

Length[Therapy1SurvivalDistribution]
Length[Therapy2SurvivalDistribution]

1974

3028

(* how many repeats of the complete data set to merge together
(for purpose of minimizing variance between individual repeats of the 'rank randomization' process) *)
resamplingfactor = 10;
(* within each 'resample', need to sub-sample the trastuzumab distribution (more vertical pixels than the chemotherapy distribution). The
number of pixels is vastly in excess of the number of patients so no individual patient's information is lost. *)
ReSampledTherapy1SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy1SurvivalDistribution, {resamplingfactor}]]]];
ReSampledTherapy2SurvivalDistribution =
Reverse[Sort[Flatten[Table[RandomSample[Therapy2SurvivalDistribution, Length[Therapy1SurvivalDistribution]], {resamplingfactor}]]]];

(* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.28 *)
amountofrankrandomization = 17400;

SlightlyRandomizedTherapy1Distribution =
Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
{i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
BestOfMidCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
{i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];

SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]]

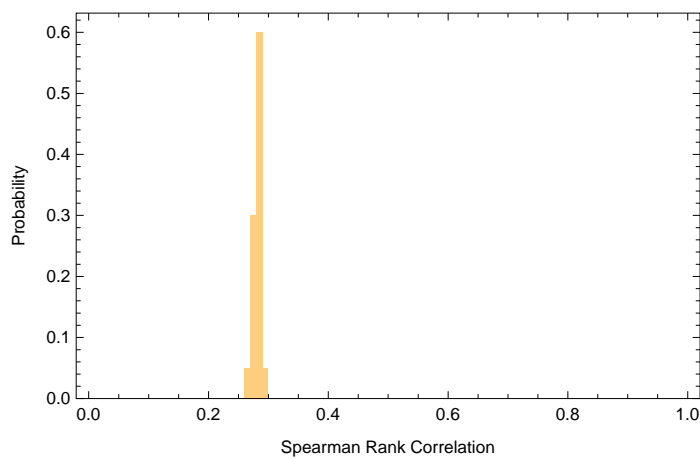
0.283396
```

```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.28 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 17400;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
    {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
  , {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

Mean response correlation = 0.28



(\* after generating the distribution of survival times predicted by independent drug action, we can remove the 'resampling' to plot the results. With a resampling factor of 10, this is achieved by sorting the distribution and keeping every 10th entry \*)

```
SubSampledBestOfMidCorrelatedMonoPairs = Take[Reverse[Sort[BestOfMidCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

$\rho = 0.08$

```
resamplingfactor = 10;
```

```
ReSampledTherapy1SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy1SurvivalDistribution, {resamplingfactor}]]]]];
```

```
ReSampledTherapy2SurvivalDistribution =
```

```
  Reverse[Sort[Flatten[Table[RandomSample[Therapy2SurvivalDistribution, Length[Therapy1SurvivalDistribution]], {resamplingfactor}]]]]];
```

(\* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.08 \*)

```
amountofrankrandomization = 63000;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
  Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
  {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
BestOfLowCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
```

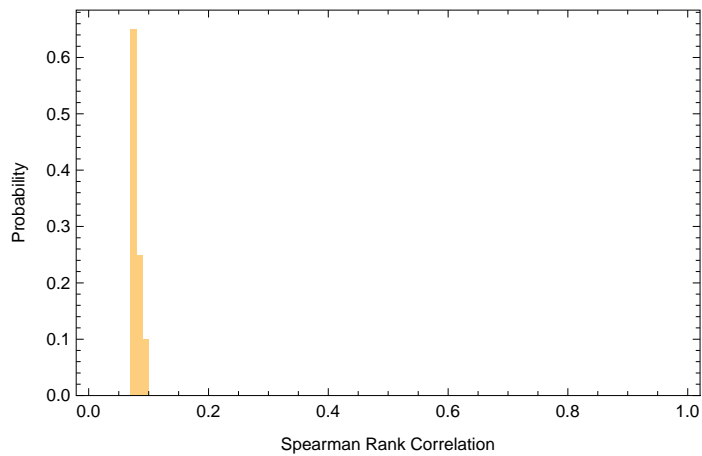
```
0.0715766
```

```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.08 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 63000;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
    , {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

Mean response correlation = 0.079



(\* after generating the distribution of survival times predicted by independent drug action, we can remove the 'resampling' to plot the results. With a resampling factor of 10, this is achieved by sorting the distribution and keeping every 10th entry \*)

```
SubSampledBestOfLowCorrelatedMonoPairs = Take[Reverse[Sort[BestOfLowCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

$\rho = 0.48$

```
resamplingfactor = 10;
```

```
ReSampledTherapy1SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy1SurvivalDistribution, {resamplingfactor}]]]]];
```

```
ReSampledTherapy2SurvivalDistribution =
```

```
  Reverse[Sort[Flatten[Table[RandomSample[Therapy2SurvivalDistribution, Length[Therapy1SurvivalDistribution]], {resamplingfactor}]]]]];
```

(\* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.48 \*)

```
amountofrankrandomization = 10200;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
  Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
    {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

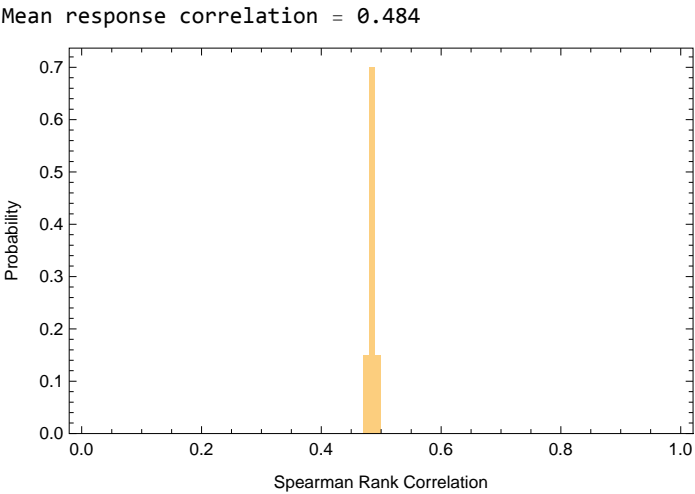
```
BestOfHighCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
```

```
0.476538
```

```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.48 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 10200;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
    , {20}];

Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame -> True, FrameLabel -> {"Spearman Rank Correlation", "Probability"}]
```



```
(* after generating the distribution of survival times predicted by independent drug action,
we can remove the 'resampling' to plot the results. With a resampling factor of 10,
this is acheived by sorting the distribution and keeping every 10th entry *)
SubSampledBestOfHighCorrelatedMonoPairs = Take[Reverse[Sort[BestOfHighCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

Computing median PFS for each condition: the observed individual therapies, the observed combination, and the simulated effects with high, medium, or low response correlation (respectively,  $\rho = 0.48, 0.28, 0.08$ )

```
Mono1Median = Round[Median[Therapy1SurvivalDistribution], 0.01]
Mono2Median = Round[Median[Therapy2SurvivalDistribution], 0.01]
ComboMedian = Round[Median[ComboSurvivalDistribution], 0.01]
Sim1Median = Round[Median[SubSampledBestOfHighCorrelatedMonoPairs], 0.01]
Sim2Median = Round[Median[SubSampledBestOfMidCorrelatedMonoPairs], 0.01]
Sim3Median = Round[Median[SubSampledBestOfLowCorrelatedMonoPairs], 0.01]

4.58

4.8

7.38

6.86

7.26

7.89
```

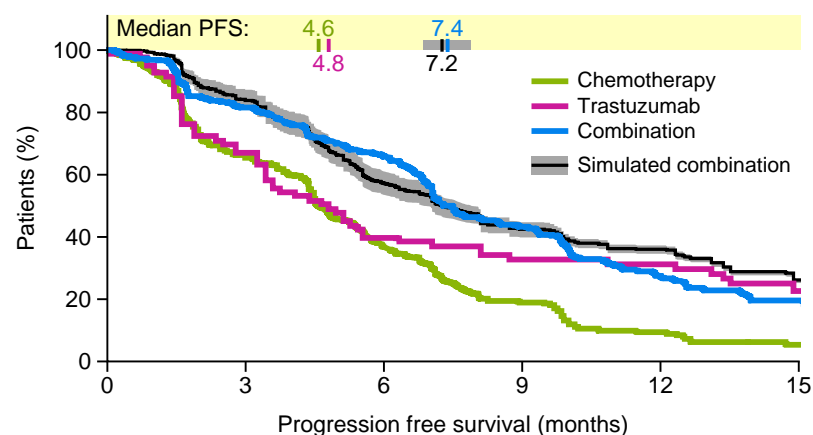


## Plotting the observed and simulated survival functions

```
(*legend offset*)
lo = 0.56;
(*simulated*)slo = -0.03;
(* legend horizontal offset *)
lho = 8.4;

Plot[{
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfHighCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfMidCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfLowCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[Therapy1SurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[Therapy2SurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[ComboSurvivalDistribution]][x]
}, {x, 0, 19}, PlotRange -> {{0, 15}, {0, 1.11}}, Exclusions -> None,
PlotStyle -> {Directive[Black, Opacity[0]], Directive[Black, AbsoluteThickness[1.7]], Directive[Black, Opacity[0]], Directive[ColorData[3, 4],
  AbsoluteThickness[3]], Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[3]], Directive[ColorData[3, 6], AbsoluteThickness[3]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 12}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.015}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.015}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)", Style["Patients (%)"]},
Prolog -> {Gray, Thickness[Medium], Lighter[Yellow, 0.75], EdgeForm[None], Rectangle[{0, 1}, {18, 1.11}],
  Black, AbsoluteThickness[1.7], GrayLevel[0.65], Rectangle[{Sim1Median, 1}, {Sim3Median, 1.03}], Black, Opacity[1],
  Line[{Sim2Median, 1}, {Sim2Median, 1.03}], Text["Median PFS:", {0.2, 1.03}, {-1, -1}], Darker[ColorData[3, 4], 0.1],
  Text["4.6", {Mono1Median, 1.03}, {0, -1}], RGBColor[0.8, 0.1, 0.6], Text["4.8", {Mono2Median, 1.00}, {0, 1}],
  ColorData[3, 6], Text["7.4", {ComboMedian, 1.03}, {0, -1}], Black, Black, Text["7.2", {Sim2Median, 1.0}, {0, 1}],
  AbsoluteThickness[2], Darker[ColorData[3, 4], 0.1], Line[{Mono1Median, 1}, {Mono1Median, 1.03}], RGBColor[0.8, 0.1, 0.6],
  Line[{Mono2Median, 1}, {Mono2Median, 1.03}], ColorData[3, 6], Line[{ComboMedian, 1}, {ComboMedian, 1.03}]},
AspectRatio -> 1 / 2, Filling -> {1 -> {3}}, FillingStyle -> Directive[GrayLevel[0.65], Opacity[1]],
ImageSize -> {{1000}, {250}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 500,
Epilog -> {EdgeForm[Directive[Black, Thickness[Medium]]], White, Opacity[1], EdgeForm[None], CapForm["Butt"], AbsoluteThickness[3],
  AbsolutePointSize[8], ColorData[3, 4], Line[{lho + 0.8, 0.34 + lo}, {lho + 1.6, 0.34 + lo}], RGBColor[0.8, 0.1, 0.6],
  Line[{lho + 0.8, 0.26 + lo}, {lho + 1.6, 0.26 + lo}], ColorData[3, 6], Line[{lho + 0.8, 0.18 + lo}, {lho + 1.6, 0.18 + lo}],
  Opacity[1], GrayLevel[0.65], Rectangle[{lho + 0.8, 0.1 - 0.03 + lo + slo}, {lho + 1.6, 0.1 + 0.03 + lo + slo}],
  Black, Opacity[1], AbsoluteThickness[1.7], Line[{lho + 0.8, 0.1 + lo + slo}, {lho + 1.6, 0.1 + lo + slo}],
  FontFamily -> "Arial", FontSize -> 11, Text[Style["Chemotherapy", FontSize -> 11], {lho + 1.8, 0.34 + lo}, {-1, 0}],
  Text[Style["Trastuzumab", FontSize -> 11], {lho + 1.8, 0.26 + lo}, {-1, 0}], Text[Style["Combination", FontSize -> 11],
  {lho + 1.8, 0.18 + lo}, {-1, 0}], Text[Style["Simulated combination", FontSize -> 11], {lho + 1.8, 0.1 + lo + slo}, {-1, 0}]}]

Export[NotebookDirectory[] <> "Figure 4B.pdf", %, "PDF"]
```



Calculating the improvement in hazard ratio attributable to drug synergy.  
This is the hazard ratio between the observed combination trial results, and the combination trial results calculated on the assumption of 'no additivity or synergy'.

```
CensoringTime = 12 (* months *);

PatientsPerArmOfSimulatedTrial = 1000;
IndependentActionSimulatedTrial[] := RandomChoice[SubSampledBestOfMidCorrelatedMonoPairs, PatientsPerArmOfSimulatedTrial]
CombinationSimulatedTrial[] := RandomChoice[ComboSurvivalDistribution, PatientsPerArmOfSimulatedTrial]

GenerateCensoredEventData[PatientResponses_, CensoringTime_] :=
Module[{ResponsesShorterThanCensoringTime, ResponsesLongerThanCensoringTime},
  ResponsesShorterThanCensoringTime = Select[PatientResponses, # <= CensoringTime &];
  ResponsesLongerThanCensoringTime = Select[PatientResponses, # > CensoringTime &];
  EventData[Join[ResponsesShorterThanCensoringTime, ResponsesLongerThanCensoringTime],
    Join[Table[0, {Length[ResponsesShorterThanCensoringTime]}], Table[1, {Length[ResponsesLongerThanCensoringTime]}]]]
]

IndependentActionSimulatedEventData[] := GenerateCensoredEventData[IndependentActionSimulatedTrial[], CensoringTime]
CombinationSimulatedEventData[] := GenerateCensoredEventData[CombinationSimulatedTrial[], CensoringTime]

(* custom function to join two sets of event data - this is necessary to implement the Cox Proportional Hazards model *)
JoinEventData[EventData1_, EventData2_] := EventData[Join[EventData1[[2, 1]], EventData2[[2, 1]], Join[EventData1[[2, 2]], EventData2[[2, 2]]]]

MergedEventData[] := JoinEventData[IndependentActionSimulatedEventData[], CombinationSimulatedEventData[]];
Descriptors[] := Join[Table["Independence", {PatientsPerArmOfSimulatedTrial}], Table["Observed", {PatientsPerArmOfSimulatedTrial}]];
```

Note that the error range in the hazard ratio depends on the population size in a simulated trial of the combination, and the duration on trial, that is, the rate of censoring events.  
Here we compute error ranges expected from 200 patients per trial arm, with any that are progression-free after a defined time being ‘censored’. This limits imprecision arising from the source PFS data having few patients ‘on-trial’ at late times, which is cause of increasing error range in PFS probability at longer times.

The range in hazard ratio is robustly identified by taking the mean range over 100 simulations of such trials.

```
NumberOfReplicateTrials = 100;

(* this function returns the relative risk, and confidence interval, in the format:
  (95% lower confidence interval, median estimate, 95% upper confidence interval )
*)
RelativeRiskCalculation[descriptors_, eventdata_, PrintTable_
  (* set to 1 to print to screen the statistical table of Cox Model output; set to 0 to not show output *) := Module[{},
    MyModelFit = CoxModelFit[{descriptors, eventdata}, {treatment}, {treatment}, NominalVariables -> treatment];

    If[PrintTable == 1, Print[MyModelFit["ParameterTable"]]];

    RelativeRisk = MyModelFit["RelativeRisk"][[1]];
    RelativeRiskLowerConfidenceInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1, 1]];
    RelativeRiskUpperConfidenceInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1, 2]];

    {RelativeRiskLowerConfidenceInterval, RelativeRisk, RelativeRiskUpperConfidenceInterval}
  ]

(* single execution of the simulated trial *)
RelativeRiskCalculation[Descriptors[], MergedEventData[], 1]

```

	Estimate	Standard Error	Relative Risk	Wald- $\chi^2$	DF	P-Value
treatment[Observed]	0.175128	0.0544855	1.1914	10.3311	1	0.00130806

```
{1.07073, 1.1914, 1.32567}

(* many replicate trial simulations, to accurately determine the range in hazard ratio *)
BreastCancerHazardRatioRange = Quiet@Mean[Table[RelativeRiskCalculation[Descriptors[], MergedEventData[], 0], {NumberOfReplicateTrials}]]
{1.02487, 1.13981, 1.26764}
```

## Comparison of Independent Drug Action with Synergy models by Akaike Information Criterion (AIC)

```
(* first, we compute a survival distribution based on the monotherapy distributions assuming no synergy,
and perfect correlation in response between drugs. Therefore at each time point,
PFS is the higher of the single-drug PFS rates at that time. *)
MaximumOfMonotherapyResponses = Map[Max, {Sort[ReSampledTherapy1SurvivalDistribution], Sort[ReSampledTherapy2SurvivalDistribution]}^T];
MaximumOfMonotherapyResponses = Take[Reverse[Sort[MaximumOfMonotherapyResponses]], 1 ;; -1 ;; resamplingfactor];

(* Maximum time, in months, over which to compare survival distributions *)
LongestTime = 15;
```

A ‘synergy-fitting’ model is created by defining two adjustable parameters:

a vertical scaling, which affects a fractional decrease in progression probability at each time

a horizontal scaling, which affects a fractional extension in duration of progression-free survival for all patients

SynergyModel[0,0] has no synergistic effect.

SynergyModel[X,0] has, for each patient, +X\*100% longer PFS time. E.g. in SynergyModel[0.5, 0], all patients have +50% longer PFS.

SynergyModel[0,Y] has, at each time point, a 1/Y probability of progression. E.g. in SynergyModel[0, 1], at each time the progression rate is halved.

```
SynergyModel[HorizontalScaling_, VerticalScaling_] :=
  Join[MaximumOfMonotherapyResponses * (1 + HorizontalScaling), Table[LongestTime, {VerticalScaling * Length[MaximumOfMonotherapyResponses]}]]

(* for Kolmogorov-Smirnov test to be comparable across data sets and model types,
the population size that comprises each survival distribution is normalized to a consistent
value. This does not change the distribution shape except for insignificant rounding differences. *)
TrialPopulationSize = 200;

SetMaximumTimeAndNormalizePopulationSize[survivaldistribution_, LongestTime_, PopulationSize_] := Module[{},
  SurvivalDistributionWithMaximumTime = Sort[Map[Min[{LongestTime, #}] &, survivaldistribution]];
  SurvivalDistributionWithDefinedPopulationSize =
    Sort[Flatten[Table[SurvivalDistributionWithMaximumTime, {PopulationSize}]]][1 ;; -1 ;; Length[SurvivalDistributionWithMaximumTime]]
]

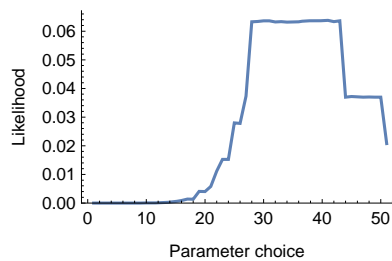
(* the observed data; set to consistent population size and capped with a consistent maximum survival time *)
ObservedDistribution = SetMaximumTimeAndNormalizePopulationSize[ComboSurvivalDistribution, LongestTime, TrialPopulationSize];

(* computing which synergy model, using the horizontal parameter only, has the highest likelihood of consistency with the observed data *)
MaximumHorizontalScaling = 0.7;
Steps = 50;

SynergyModelOnlyHorizontalParameterFits = Table[{HorizontalScaling, KolmogorovSmirnovTest[ObservedDistribution,
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[HorizontalScaling, 0], LongestTime, TrialPopulationSize], "PValue"]},
  {HorizontalScaling, 0, MaximumHorizontalScaling, MaximumHorizontalScaling / Steps}];

BestLikelihoodWithHorizontalParameter = Max[SynergyModelOnlyHorizontalParameterFits[[All, 2]]]
0.0637858

(* confirming that the synergy parameter spanned the optimal range *)
ListPlot[SynergyModelOnlyHorizontalParameterFits[[All, 2]], Joined → True, PlotRange → {0, All},
  ImageSize → 200, Frame → {{True, False}, {True, False}}, FrameLabel → {"Parameter choice", "Likelihood"}]
```

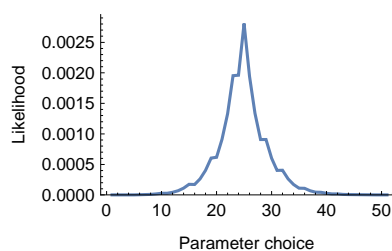


```
(* computing which synergy model, using the vertical parameter only, has the highest likelihood of consistency with the observed data *)
MaximumVerticalScaling = 0.4;
Steps = 50;
```

```
SynergyModelOnlyVerticalParameterFits = Table[{VerticalScaling, KolmogorovSmirnovTest[ObservedDistribution,
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[0, VerticalScaling], LongestTime, TrialPopulationSize], "PValue"]},
  {VerticalScaling, 0, MaximumVerticalScaling, MaximumVerticalScaling / Steps}];
```

```
BestLikelihoodWithVerticalParameter = Max[SynergyModelOnlyVerticalParameterFits[[All, 2]]]
0.00280818
```

```
(* confirming that the synergy parameter spanned the optimal range *)
ListPlot[SynergyModelOnlyVerticalParameterFits[[All, 2]], Joined → True, PlotRange → {0, All},
  ImageSize → 200, Frame → {{True, False}, {True, False}}, FrameLabel → {"Parameter choice", "Likelihood"}]
```



```

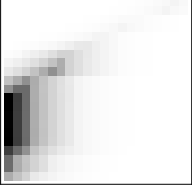
(* computing which synergy model, using two parameters, has the highest likelihood of consistency with the observed data *)
MaximumHorizontalScaling = 0.7;
MaximumVerticalScaling = 0.2;
StepsPerParameter = 20;

SynergyModelTwoParameterFits =
  Table[{HorizontalScaling, VerticalScaling, KolmogorovSmirnovTest[ObservedDistribution, SetMaximumTimeAndNormalizePopulationSize[
    SynergyModel[HorizontalScaling, VerticalScaling], LongestTime, TrialPopulationSize], "PValue"]},
    {HorizontalScaling, 0, MaximumHorizontalScaling, MaximumHorizontalScaling / StepsPerParameter},
    {VerticalScaling, 0, MaximumVerticalScaling, MaximumVerticalScaling / StepsPerParameter}];

BestLikelihoodWithTwoParameterFit = Max[Flatten[SynergyModelTwoParameterFits[[All, All, 3]]]
0.0637858

(* confirming that the synergy parameters spanned the optimal range *)
ArrayPlot[SynergyModelTwoParameterFits[[All, All, 3]], ImageSize -> 100]

```



```

(* computing the likelihood that the Independent Drug Action model (with zero fitted parameters) is consistent with the observed data *)
(* To minimize noise from the sampling procedure of the independent action model, we take the average of many simulations *)
IndependentActionSimulation[] := Module[{},
  (* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.28 *)
  amountofrankrandomization = 17400;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  BestOfMidCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]}],
    {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
  SubSampledBestOfMidCorrelatedMonoPairs = Take[Reverse[Sort[BestOfMidCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor]
]

NumberOfIndependentActionSimulations = 20;
ReplicateIndependentActionSimulations = Sort[Flatten[Table[IndependentActionSimulation[], {NumberOfIndependentActionSimulations}]]];
(* final model is the population-normalized average of many replicate simulations *)
IndependentActionModel = SetMaximumTimeAndNormalizePopulationSize[ReplicateIndependentActionSimulations, LongestTime, TrialPopulationSize];
(* computing the likelihood that the Independent Drug Action model (with zero fitted parameters) is consistent with the observed data *)
IndependentActionModelLikelihood = KolmogorovSmirnovTest[ObservedDistribution, IndependentActionModel, "PValue"]
0.256073

(* Tabulating the likelihood that the observed combination drug response
would be observed if the true distribution were one of the various models, in the order:
{ independent drug action, synergy with horizontal parameter, synergy with vertical parameter, synergy with two parameters } *)
BreastCancerModelLikelihoods = {IndependentActionModelLikelihood,
  BestLikelihoodWithHorizontalParameter, BestLikelihoodWithVerticalParameter, BestLikelihoodWithTwoParameterFit}
{0.256073, 0.0637858, 0.00280818, 0.0637858}

```

## plotting model fits

```

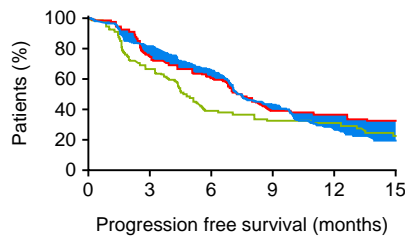
MaximumOfMonotherapyResponsesModel =
  SetMaximumTimeAndNormalizePopulationSize[MaximumOfMonotherapyResponses, LongestTime, TrialPopulationSize];

```

```
BestHorizontalSynergyParameter = Sort[SynergyModelOnlyHorizontalParameterFits, #1[[2]] > #2[[2]] &] [[1, 1]];
BestHorizontalSynergyModel =
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[BestHorizontalSynergyParameter, 0], LongestTime, TrialPopulationSize];
```

```
Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]] [x],
  SurvivalFunction[EmpiricalDistribution[BestHorizontalSynergyModel]] [x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]] [x]}
, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None, PlotStyle ->
  {Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Red, AbsoluteThickness[1]], Directive[ColorData[3, 6], AbsoluteThickness[1]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 10}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]}, AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[ColorData[3, 6], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]
```

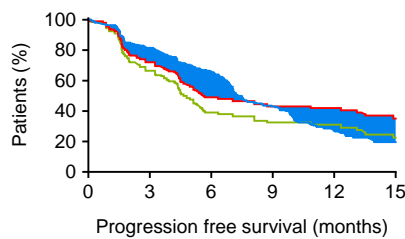
```
Export[NotebookDirectory[] <> "BreastCancerTrastuzumabChemotherapyBestHorizontalSynergy.pdf", %, "PDF"];
```



```
BestVerticalSynergyParameter = Sort[SynergyModelOnlyVerticalParameterFits, #1[[2]] > #2[[2]] &] [[1, 1]];
BestVerticalSynergyModel =
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[0, BestVerticalSynergyParameter], LongestTime, TrialPopulationSize];
```

```
Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]] [x],
  SurvivalFunction[EmpiricalDistribution[BestVerticalSynergyModel]] [x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]] [x]}
, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None, PlotStyle ->
  {Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Red, AbsoluteThickness[1]], Directive[ColorData[3, 6], AbsoluteThickness[1]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 10}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]}, AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[ColorData[3, 6], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]
```

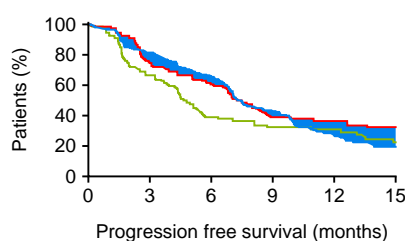
```
Export[NotebookDirectory[] <> "BreastCancerTrastuzumabChemotherapyBestVerticalSynergy.pdf", %, "PDF"];
```



```
BestTwoParameterSynergyParameters = Sort[Flatten[SynergyModelTwoParameterFits, 1], #1[[3]] > #2[[3]] &] [[1, {1, 2}]];
BestTwoParameterSynergyModel = SetMaximumTimeAndNormalizePopulationSize[
  SynergyModel[BestTwoParameterSynergyParameters[[1]], BestTwoParameterSynergyParameters[[2]], LongestTime, TrialPopulationSize];
```

```
Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]] [x],
  SurvivalFunction[EmpiricalDistribution[BestTwoParameterSynergyModel]] [x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]] [x]}
, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None, PlotStyle ->
  {Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Red, AbsoluteThickness[1]], Directive[ColorData[3, 6], AbsoluteThickness[1]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 10}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]}, AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[ColorData[3, 6], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]
```

```
Export[NotebookDirectory[] <> "BreastCancerTrastuzumabChemotherapyBestTwoParameterSynergy.pdf", %, "PDF"];
```



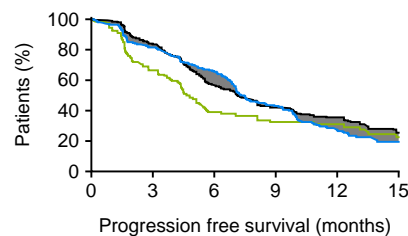


```

Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]][x],
  SurvivalFunction[EmpiricalDistribution[IndependentActionModel]][x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]][x]}
, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None,
PlotStyle -> {Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Black, AbsoluteThickness[1]],
  Directive[ColorData[3, 6], AbsoluteThickness[1]]}, BaseStyle -> {FontFamily -> "Arial", FontSize -> 10},
FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)", Style["Patients (%)"]], AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[GrayLevel[0.5], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]

Export[NotebookDirectory[] <> "BreastCancerTrastuzumabChemotherapyIndependentModel.pdf", %, "PDF"];

```



## Figure 4C - Advanced pancreatic cancer

Near-identical code as for Figure 4A is here employed to generate Figure 4C. Comments will be more brief.

```

Figure4CRawData = Import[NotebookDirectory[] <> "Table of survival distributions.xlsx", "XLSX"][[5(* the fifth tab of this spreadsheet*)]];

Therapy1SurvivalDistribution =
  Select[Figure4CRawData[[8 ;;, 2(* column 2 of this spreadsheet contains PFS data for gemcitabine*)]], NumberQ];
Therapy2SurvivalDistribution = Select[Figure4CRawData[[8 ;;, 3(* column 3 of this spreadsheet contains PFS data for erlotinib*)]], NumberQ];
ComboSurvivalDistribution =
  Select[Figure4CRawData[[8 ;;, 4(* column 4 of this spreadsheet contains PFS data for the combination*)]], NumberQ];

ρ = 0.28

Length[Therapy1SurvivalDistribution]
Length[Therapy2SurvivalDistribution]

3136

3600

(* how many repeats of the complete data set to merge together
  (for purpose of minimizing variance between individual repeats of the 'rank randomization' process) *)
resamplingfactor = 10;
(* within each 'resample', need to sub-sample the erlotinib distribution (more vertical pixels than the gemcitabine distribution). The
  number of pixels is vastly in excess of the number of patients so no individual patient's information is lost. *)
ReSampledTherapy1SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy1SurvivalDistribution, {resamplingfactor}]]]];
ReSampledTherapy2SurvivalDistribution =
  Reverse[Sort[Flatten[Table[RandomSample[Therapy2SurvivalDistribution, Length[Therapy1SurvivalDistribution]], {resamplingfactor}]]]];

(* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.28 *)
amountofrankrandomization = 28000;

SlightlyRandomizedTherapy1Distribution =
  Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
    {i, 1, Length[ReSampledTherapy1SurvivalDistribution]]}, #1[[1]] < #2[[1]] &];
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]]}, #1[[1]] < #2[[1]] &];
BestOfMidCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];

SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]]

0.279778

```

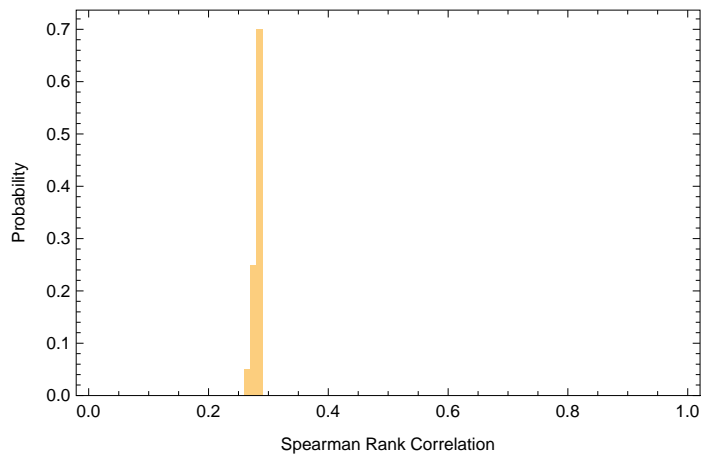


```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.28 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 28000;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
    , {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

```
Mean response correlation = 0.281
```



```
(* after generating the distribution of survival times predicted by independent drug action,
we can remove the 'resampling' to plot the results. With a resampling factor of 10,
this is achieved by sorting the distribution and keeping every 10th entry *)
```

```
SubSampledBestOfMidCorrelatedMonoPairs = Take[Reverse[Sort[BestOfMidCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

$\rho = 0.08$

```
resamplingfactor = 10;
```

```
ReSampledTherapy1SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy1SurvivalDistribution, {resamplingfactor}]]]]];
```

```
ReSampledTherapy2SurvivalDistribution =
```

```
  Reverse[Sort[Flatten[Table[RandomSample[Therapy2SurvivalDistribution, Length[Therapy1SurvivalDistribution]], {resamplingfactor}]]]]];
```

```
(* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.08 *)
```

```
amountofrankrandomization = 100000;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
  Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
    {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
BestOfLowCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
```

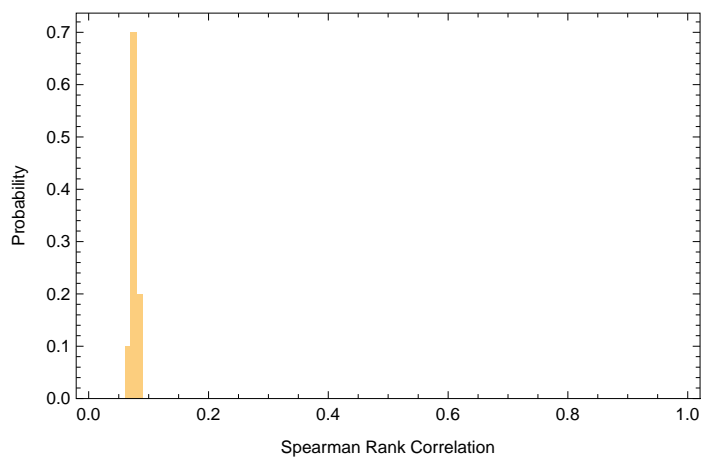
```
0.0703271
```

```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.08 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 100 000;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
    , {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

Mean response correlation = 0.077



(\* after generating the distribution of survival times predicted by independent drug action, we can remove the 'resampling' to plot the results. With a resampling factor of 10, this is achieved by sorting the distribution and keeping every 10th entry \*)

```
SubSampledBestOfLowCorrelatedMonoPairs = Take[Reverse[Sort[BestOfLowCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

$\rho = 0.48$

```
resamplingfactor = 10;
```

```
ReSampledTherapy1SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy1SurvivalDistribution, {resamplingfactor}]]]]];
```

```
ReSampledTherapy2SurvivalDistribution =
```

```
  Reverse[Sort[Flatten[Table[RandomSample[Therapy2SurvivalDistribution, Length[Therapy1SurvivalDistribution]], {resamplingfactor}]]]]];
```

(\* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.48 \*)

```
amountofrankrandomization = 16 300;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
  Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
    {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
BestOfHighCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
```

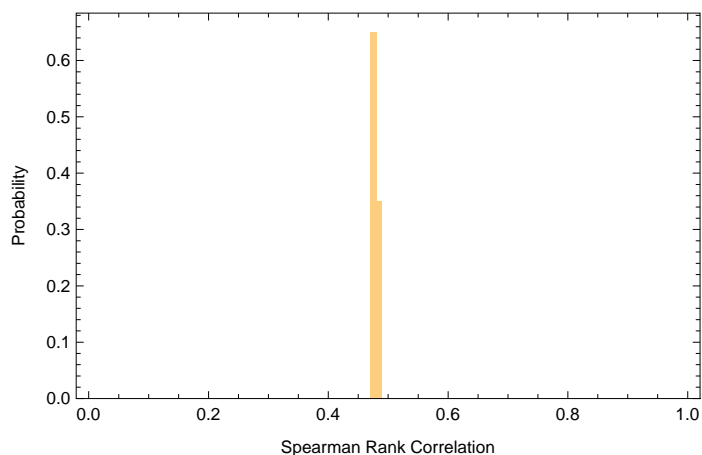
```
0.476546
```

```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.48 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 16300;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
    , {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

```
Mean response correlation = 0.479
```



(\* after generating the distribution of survival times predicted by independent drug action, we can remove the 'resampling' to plot the results. With a resampling factor of 10, this is achieved by sorting the distribution and keeping every 10th entry \*)

```
SubSampledBestOfHighCorrelatedMonoPairs = Take[Reverse[Sort[BestOfHighCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

Computing median PFS for each condition: the observed individual therapies, the observed combination, and the simulated effects with high, medium, or low response correlation (respectively,  $\rho = 0.48, 0.28, 0.08$ )

```
Mono1Median = Round[Median[Therapy1SurvivalDistribution], 0.01]
Mono2Median = Round[Median[Therapy2SurvivalDistribution], 0.01]
ComboMedian = Round[Median[ComboSurvivalDistribution], 0.01]
Sim1Median = Round[Median[SubSampledBestOfHighCorrelatedMonoPairs], 0.01]
Sim2Median = Round[Median[SubSampledBestOfMidCorrelatedMonoPairs], 0.01]
Sim3Median = Round[Median[SubSampledBestOfLowCorrelatedMonoPairs], 0.01]
```

```
3.48
```

```
1.58
```

```
3.68
```

```
3.65
```

```
3.8
```

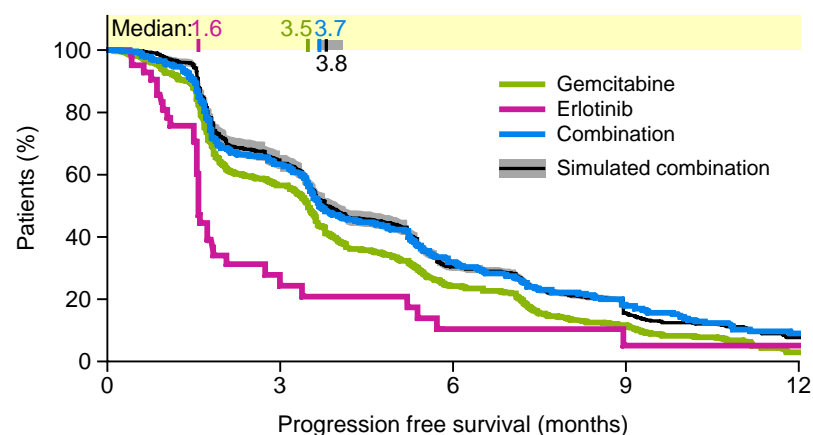
```
4.09
```

## Plotting the observed and simulated survival functions

```
(*legend vertical offset*)
lo = 0.55;
(*simulated*)slo = -0.03;
(* legend horizontal offset *)
lho = 6;

Plot[{
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfHighCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfMidCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfLowCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[Therapy1SurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[Therapy2SurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[ComboSurvivalDistribution]][x]
}, {x, 0, 13}, PlotRange -> {{0, 12.0}, {0, 1.11}}, Exclusions -> None,
PlotStyle -> {Directive[Black, Opacity[0]], Directive[Black, AbsoluteThickness[1.7]], Directive[Black, Opacity[0]], Directive[ColorData[3, 4],
  AbsoluteThickness[3]], Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[3]], Directive[ColorData[3, 6], AbsoluteThickness[3]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 12}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.015}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.015}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]},
Prolog -> {Gray, Thickness[Medium], Lighter[Yellow, 0.75], EdgeForm[None], Rectangle[{0, 1}, {18, 1.11}],
  Black, AbsoluteThickness[1.7], GrayLevel[0.65], Rectangle[{Sim1Median, 1}, {Sim3Median, 1.03}], Black, Opacity[1],
  Line[{Sim2Median, 1}, {Sim2Median, 1.03}], Text["Median:", {0.07, 1.03}, {-1, -1}], Darker[ColorData[3, 4], 0.1],
  Text["3.5", {Mono1Median, 1.03}, {0.7, -1}], RGBColor[0.8, 0.1, 0.6], Text["1.6", {Mono2Median, 1.03}, {-0.5, -1}],
  ColorData[3, 6], Text["3.7", {ComboMedian, 1.03}, {-0.7, -1}], Black, Text["3.8", {Sim2Median, 1.0}, {-0.35, 1}],
  AbsoluteThickness[2], Darker[ColorData[3, 4], 0.1], Line[{Mono1Median, 1}, {Mono1Median, 1.03}], RGBColor[0.8, 0.1, 0.6],
  Line[{Mono2Median, 1}, {Mono2Median, 1.03}], ColorData[3, 6], Line[{ComboMedian, 1}, {ComboMedian, 1.03}]},
AspectRatio -> 1 / 2, Filling -> {1 -> {3}}, FillingStyle -> Directive[GrayLevel[0.65], Opacity[1]],
ImageSize -> {{1000}, {250}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 500,
Epilog -> {EdgeForm[Directive[Black, Thickness[Medium]]], White, Opacity[1], EdgeForm[None], CapForm["Butt"], AbsoluteThickness[3],
  AbsolutePointSize[8], ColorData[3, 4], Line[{lho + 0.8, 0.34 + lo}, {lho + 1.6, 0.34 + lo}], RGBColor[0.8, 0.1, 0.6],
  Line[{lho + 0.8, 0.26 + lo}, {lho + 1.6, 0.26 + lo}], ColorData[3, 6], Line[{lho + 0.8, 0.18 + lo}, {lho + 1.6, 0.18 + lo}],
  Opacity[1], GrayLevel[0.65], Rectangle[{lho + 0.8, 0.1 - 0.03 + lo + slo}, {lho + 1.6, 0.1 + 0.03 + lo + slo}],
  Black, Opacity[1], AbsoluteThickness[1.7], Line[{lho + 0.8, 0.1 + lo + slo}, {lho + 1.6, 0.1 + lo + slo}],
  FontFamily -> "Arial", FontSize -> 11, Text[Style["Gemcitabine", FontSize -> 11], {lho + 1.8, 0.34 + lo}, {-1, 0}],
  Text[Style["Erlotinib", FontSize -> 11], {lho + 1.8, 0.26 + lo}, {-1, 0}], Text[Style["Combination", FontSize -> 11],
  {lho + 1.8, 0.18 + lo}, {-1, 0}], Text[Style["Simulated combination", FontSize -> 11], {lho + 1.8, 0.1 + lo + slo}, {-1, 0}]]]

Export[NotebookDirectory[] <> "Figure 4C.pdf", %, "PDF"];
```



## Calculating the improvement in hazard ratio attributable to drug synergy.

This is the hazard ratio between the observed combination trial results, and the combination trial results calculated on the assumption of 'no additivity or synergy'.

```
CensoringTime = 12(* months *);

PatientsPerArmOfSimulatedTrial = 1000;
IndependentActionSimulatedTrial[] := RandomChoice[SubSampledBestOfMidCorrelatedMonoPairs, PatientsPerArmOfSimulatedTrial]
CombinationSimulatedTrial[] := RandomChoice[ComboSurvivalDistribution, PatientsPerArmOfSimulatedTrial]

GenerateCensoredEventData[PatientResponses_, CensoringTime_] :=
Module[{ResponsesShorterThanCensoringTime, ResponsesLongerThanCensoringTime},
  ResponsesShorterThanCensoringTime = Select[PatientResponses, # ≤ CensoringTime &];
  ResponsesLongerThanCensoringTime = Select[PatientResponses, # > CensoringTime &];
  EventData[Join[ResponsesShorterThanCensoringTime, ResponsesLongerThanCensoringTime],
    Join[Table[0, {Length[ResponsesShorterThanCensoringTime]}], Table[1, {Length[ResponsesLongerThanCensoringTime]}]]]
]

IndependentActionSimulatedEventData[] := GenerateCensoredEventData[IndependentActionSimulatedTrial[], CensoringTime]
CombinationSimulatedEventData[] := GenerateCensoredEventData[CombinationSimulatedTrial[], CensoringTime]

(* custom function to join two sets of event data - this is necessary to implement the Cox Proportional Hazards model *)
JoinEventData[EventData1_, EventData2_] := EventData[Join[EventData1[[2, 1]], EventData2[[2, 1]], Join[EventData1[[2, 2]], EventData2[[2, 2]]]]

MergedEventData[] := JoinEventData[IndependentActionSimulatedEventData[], CombinationSimulatedEventData[]];
Descriptors[] := Join[Table["Independence", {PatientsPerArmOfSimulatedTrial}], Table["Observed", {PatientsPerArmOfSimulatedTrial}]];
```

Note that the error range in the hazard ratio depends on the population size in a simulated trial of the combination, and the duration on trial, that is, the rate of censoring events.

Here we compute error ranges expected from 200 patients per trial arm, with any that are progression-free after a defined time being 'censored'. This limits imprecision arising from the source PFS data having few patients 'on-trial' at late times, which is cause of increasing error range in PFS probability at longer times.

The range in hazard ratio is robustly identified by taking the mean range over 100 simulations of such trials.

```
NumberOfReplicateTrials = 100;

(* this function returns the relative risk, and confidence interval, in the format:
  (95% lower confidence interval, median estimate, 95% upper confidence interval )
*)
RelativeRiskCalculation[descriptors_, eventdata_, PrintTable_
  (* set to 1 to print to screen the statistical table of Cox Model output; set to 0 to not show output *) := Module[{},
    MyModelFit = CoxModelFit[{descriptors, eventdata}, {treatment}, {treatment}, NominalVariables → treatment];

    If[PrintTable == 1, Print[MyModelFit["ParameterTable"]]];

    RelativeRisk = MyModelFit["RelativeRisk"][[1]];
    RelativeRiskLowerConfidenceInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1, 1]];
    RelativeRiskUpperConfidenceInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1, 2]];

    {RelativeRiskLowerConfidenceInterval, RelativeRisk, RelativeRiskUpperConfidenceInterval}
  ]

(* single execution of the simulated trial *)
RelativeRiskCalculation[Descriptors[], MergedEventData[], 1]

```

	Estimate	Standard Error	Relative Risk	Wald- $\chi^2$	DF	P-Value
treatment[Observed]	0.017748	0.0463678	1.01791	0.146509	1	0.701894

```
{0.929479, 1.01791, 1.11475}

(* many replicate trial simulations, to accurately determine the range in hazard ratio *)
PancreaticCancerHazardRatioRange =
  Quiet@Mean[Table[RelativeRiskCalculation[Descriptors[], MergedEventData[], 0], {NumberOfReplicateTrials}]]
{0.908937, 0.996176, 1.09179}
```

## Comparison of Independent Drug Action with Synergy models by Akaike Information Criterion (AIC)

```
(* first, we compute a survival distribution based on the monotherapy distributions assuming no synergy,
and perfect correlation in response between drugs. Therefore at each time point,
PFS is the higher of the single-drug PFS rates at that time. *)
MaximumOfMonotherapyResponses = Map[Max, {Sort[ReSampledTherapy1SurvivalDistribution], Sort[ReSampledTherapy2SurvivalDistribution]}];
MaximumOfMonotherapyResponses = Take[Reverse[Sort[MaximumOfMonotherapyResponses]], 1 ;; -1 ;; resamplingfactor];
```

```
(* Maximum time, in months, over which to compare survival distributions *)
LongestTime = 12;
```

A 'synergy-fitting' model is created by defining two adjustable parameters:

a vertical scaling, which affects a fractional decrease in progression probability at each time

a horizontal scaling, which affects a fractional extension in duration of progression-free survival for all patients

SynergyModel[0,0] has no synergistic effect.

SynergyModel[X,0] has, for each patient, +X\*100% longer PFS time. E.g. in SynergyModel[0.5, 0], all patients have +50% longer PFS.

SynergyModel[0,Y] has, at each time point, a 1/Y probability of progression. E.g. in SynergyModel[0, 1], at each time the progression rate is halved.

```
SynergyModel[HorizontalScaling_, VerticalScaling_] :=
  Join[MaximumOfMonotherapyResponses * (1 + HorizontalScaling), Table[LongestTime, {VerticalScaling * Length[MaximumOfMonotherapyResponses]}]]
```

```
(* for Kolmogorov-Smirnov test to be comparable across data sets and model types,
the population size that comprises each survival distribution is normalized to a consistent
value. This does not change the distribution shape except for insignificant rounding differences. *)
TrialPopulationSize = 200;
```

```
SetMaximumTimeAndNormalizePopulationSize[survivaldistribution_, LongestTime_, PopulationSize_] := Module[{},
  SurvivalDistributionWithMaximumTime = Sort[Map[Min[{LongestTime, #}] &, survivaldistribution]];
  SurvivalDistributionWithDefinedPopulationSize =
    Sort[Flatten[Table[SurvivalDistributionWithMaximumTime, {PopulationSize}]]][1 ;; -1 ;; Length[SurvivalDistributionWithMaximumTime]]
]
```

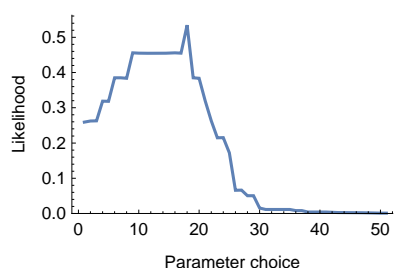
```
(* the observed data; set to consistent population size and capped with a consistent maximum survival time *)
ObservedDistribution = SetMaximumTimeAndNormalizePopulationSize[ComboSurvivalDistribution, LongestTime, TrialPopulationSize];
```

```
(* computing which synergy model, using the horizontal parameter only, has the highest likelihood of consistency with the observed data *)
MaximumHorizontalScaling = 0.3;
Steps = 50;
```

```
SynergyModelOnlyHorizontalParameterFits = Table[{HorizontalScaling, KolmogorovSmirnovTest[ObservedDistribution,
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[HorizontalScaling, 0], LongestTime, TrialPopulationSize], "PValue"]},
  {HorizontalScaling, 0, MaximumHorizontalScaling, MaximumHorizontalScaling / Steps}];
```

```
BestLikelihoodWithHorizontalParameter = Max[SynergyModelOnlyHorizontalParameterFits[[All, 2]]]
0.534329
```

```
(* confirming that the synergy parameter spanned the optimal range *)
ListPlot[SynergyModelOnlyHorizontalParameterFits[[All, 2]], Joined → True, PlotRange → {0, All},
  ImageSize → 200, Frame → {{True, False}, {True, False}}, FrameLabel → {"Parameter choice", "Likelihood"}]
```

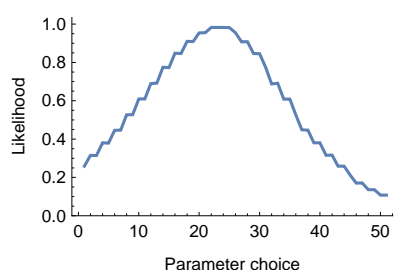


```
(* computing which synergy model, using the vertical parameter only, has the highest likelihood of consistency with the observed data *)
MaximumVerticalScaling = 0.2;
Steps = 50;
```

```
SynergyModelOnlyVerticalParameterFits = Table[{VerticalScaling, KolmogorovSmirnovTest[ObservedDistribution,
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[0, VerticalScaling], LongestTime, TrialPopulationSize], "PValue"]},
  {VerticalScaling, 0, MaximumVerticalScaling, MaximumVerticalScaling / Steps}];
```

```
BestLikelihoodWithVerticalParameter = Max[SynergyModelOnlyVerticalParameterFits[[All, 2]]]
0.982653
```

```
(* confirming that the synergy parameter spanned the optimal range *)
ListPlot[SynergyModelOnlyVerticalParameterFits[[All, 2]], Joined → True, PlotRange → {0, All},
  ImageSize → 200, Frame → {{True, False}, {True, False}}, FrameLabel → {"Parameter choice", "Likelihood"}]
```

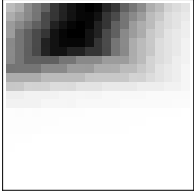




```
(* computing which synergy model, using two parameters, has the highest likelihood of consistency with the observed data *)
MaximumHorizontalScaling = 0.3;
MaximumVerticalScaling = 0.2;
StepsPerParameter = 20;

SynergyModelTwoParameterFits =
  Table[{HorizontalScaling, VerticalScaling, KolmogorovSmirnovTest[ObservedDistribution, SetMaximumTimeAndNormalizePopulationSize[
    SynergyModel[HorizontalScaling, VerticalScaling], LongestTime, TrialPopulationSize], "PValue"]},
    {HorizontalScaling, 0, MaximumHorizontalScaling, MaximumHorizontalScaling / StepsPerParameter},
    {VerticalScaling, 0, MaximumVerticalScaling, MaximumVerticalScaling / StepsPerParameter}];

BestLikelihoodWithTwoParameterFit = Max[Flatten[SynergyModelTwoParameterFits[[All, All, 3]]]
0.98425

(* confirming that the synergy parameters spanned the optimal range *)
ArrayPlot[SynergyModelTwoParameterFits[[All, All, 3]], ImageSize -> 100]


(* computing the likelihood that the Independent Drug Action model (with zero fitted parameters) is consistent with the observed data *)
(* To minimize noise from the sampling procedure of the independent action model, we take the average of many simulations *)
IndependentActionSimulation[] := Module[{},
  (* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.28 *)
  amountofrankrandomization = 28000;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  BestOfMidCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
    {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
  SubSampledBestOfMidCorrelatedMonoPairs = Take[Reverse[Sort[BestOfMidCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor]
];

NumberOfIndependentActionSimulations = 20;
ReplicateIndependentActionSimulations = Sort[Flatten[Table[IndependentActionSimulation[], {NumberOfIndependentActionSimulations}]]];
(* final model is the population-normalized average of many replicate simulations *)
IndependentActionModel = SetMaximumTimeAndNormalizePopulationSize[ReplicateIndependentActionSimulations, LongestTime, TrialPopulationSize];
(* computing the likelihood that the Independent Drug Action model (with zero fitted parameters) is consistent with the observed data *)
IndependentActionModelLikelihood = KolmogorovSmirnovTest[ObservedDistribution, IndependentActionModel, "PValue"]
0.84823

(* Tabulating the likelihood that the observed combination drug response
would be observed if the true distribution were one of the various models, in the order:
{ independent drug action, synergy with horizontal parameter, synergy with vertical parameter, synergy with two parameters } *)
PancreaticCancerModelLikelihoods = {IndependentActionModelLikelihood,
  BestLikelihoodWithHorizontalParameter, BestLikelihoodWithVerticalParameter, BestLikelihoodWithTwoParameterFit}
{0.84823, 0.534329, 0.982653, 0.98425}
```

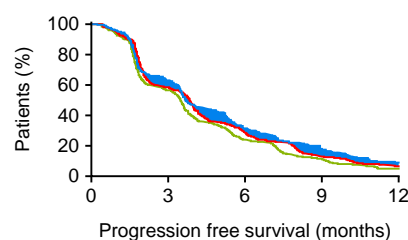
## plotting model fits

```
MaximumOfMonotherapyResponsesModel =
  SetMaximumTimeAndNormalizePopulationSize[MaximumOfMonotherapyResponses, LongestTime, TrialPopulationSize];
```

```
BestHorizontalSynergyParameter = Sort[SynergyModelOnlyHorizontalParameterFits, #1[[2]] > #2[[2]] &] [[1, 1]];
BestHorizontalSynergyModel =
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[BestHorizontalSynergyParameter, 0], LongestTime, TrialPopulationSize];
```

```
Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]] [x],
  SurvivalFunction[EmpiricalDistribution[BestHorizontalSynergyModel]] [x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]] [x]}
, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None, PlotStyle ->
  {Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Red, AbsoluteThickness[1]], Directive[ColorData[3, 6], AbsoluteThickness[1]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 10}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]}, AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[ColorData[3, 6], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]
```

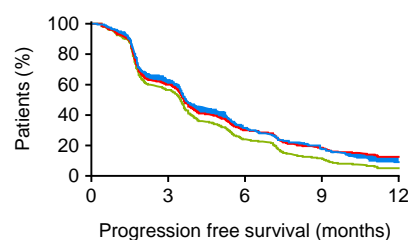
```
Export[NotebookDirectory[] <> "PancreaticCancerErlotinibGemcitabineBestHorizontalSynergy.pdf", %, "PDF"];
```



```
BestVerticalSynergyParameter = Sort[SynergyModelOnlyVerticalParameterFits, #1[[2]] > #2[[2]] &] [[1, 1]];
BestVerticalSynergyModel =
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[0, BestVerticalSynergyParameter], LongestTime, TrialPopulationSize];
```

```
Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]] [x],
  SurvivalFunction[EmpiricalDistribution[BestVerticalSynergyModel]] [x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]] [x]}
, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None, PlotStyle ->
  {Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Red, AbsoluteThickness[1]], Directive[ColorData[3, 6], AbsoluteThickness[1]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 10}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]}, AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[ColorData[3, 6], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]
```

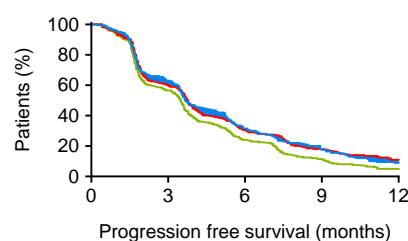
```
Export[NotebookDirectory[] <> "PancreaticCancerErlotinibGemcitabineBestVerticalSynergy.pdf", %, "PDF"];
```



```
BestTwoParameterSynergyParameters = Sort[Flatten[SynergyModelTwoParameterFits, 1], #1[[3]] > #2[[3]] &] [[1, {1, 2}]];
BestTwoParameterSynergyModel = SetMaximumTimeAndNormalizePopulationSize[
  SynergyModel[BestTwoParameterSynergyParameters[[1]], BestTwoParameterSynergyParameters[[2]], LongestTime, TrialPopulationSize];
```

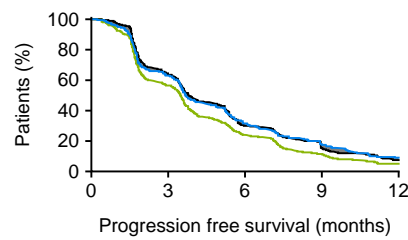
```
Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]] [x],
  SurvivalFunction[EmpiricalDistribution[BestTwoParameterSynergyModel]] [x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]] [x]}
, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None, PlotStyle ->
  {Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Red, AbsoluteThickness[1]], Directive[ColorData[3, 6], AbsoluteThickness[1]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 10}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]}, AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[ColorData[3, 6], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]
```

```
Export[NotebookDirectory[] <> "PancreaticCancerErlotinibGemcitabineBestTwoParameterSynergy.pdf", %, "PDF"];
```



```
Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]][x],
  SurvivalFunction[EmpiricalDistribution[IndependentActionModel]][x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]][x]}
, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None,
PlotStyle -> {Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Black, AbsoluteThickness[1]],
  Directive[ColorData[3, 6], AbsoluteThickness[1]]}, BaseStyle -> {FontFamily -> "Arial", FontSize -> 10},
FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)", Style["Patients (%)"]], AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[GrayLevel[0.5], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]

Export[NotebookDirectory[] <> "PancreaticCancerErlotinibGemcitabineIndependentModel.pdf", %, "PDF"];
```



## Figure 4D - BRAF-mutant metastatic melanoma

Near-identical code as for Figure 4A is here employed to generate Figure 4D. Comments will be more brief.

```
Figure4DrawData = Import[NotebookDirectory[] <> "Table of survival distributions.xlsx", "XLSX"][[6(* the sixth tab of this spreadsheet*)]];
Therapy1SurvivalDistribution = Select[Figure4DrawData[[8 ;;, 2(* column 2 of this spreadsheet contains PFS data for dabrafenib*)]], NumberQ];
Therapy2SurvivalDistribution = Select[Figure4DrawData[[8 ;;, 3(* column 3 of this spreadsheet contains PFS data for trametinib*)]], NumberQ];
ComboSurvivalDistribution =
  Select[Figure4DrawData[[8 ;;, 4(* column 4 of this spreadsheet contains PFS data for the combination*)]], NumberQ];
```

$\rho = 0.28$

```
Length[Therapy1SurvivalDistribution]
Length[Therapy2SurvivalDistribution]

2384
1998

(* how many repeats of the complete data set to merge together
  (for purpose of minimizing variance between individual repeats of the 'rank randomization' process) *)
resamplingfactor = 10;
(* within each 'resample', need to sub-sample the dabrafenib distribution (more vertical pixels than the trastuzumab distribution). The
  number of pixels is vastly in excess of the number of patients so no individual patient's information is lost. *)
ReSampledTherapy1SurvivalDistribution =
  Reverse[Sort[Flatten[Table[RandomSample[Therapy1SurvivalDistribution, Length[Therapy2SurvivalDistribution]], {resamplingfactor}]]]];
ReSampledTherapy2SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy2SurvivalDistribution, {resamplingfactor}]]]];

(* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.28 *)
amountofrankrandomization = 17500;

SlightlyRandomizedTherapy1Distribution =
  Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
    {i, 1, Length[ReSampledTherapy1SurvivalDistribution]]}, #1[[1]] < #2[[1]] &];
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]]}, #1[[1]] < #2[[1]] &];
BestOfMidCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];

SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]]

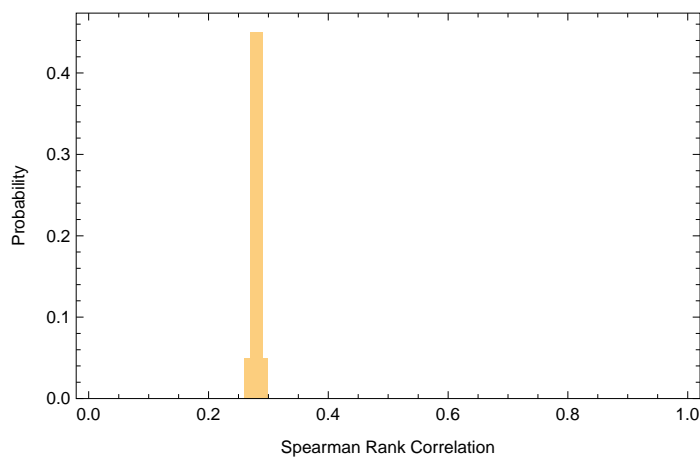
0.281583
```

```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.28 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 17500;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
    , {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

Mean response correlation = 0.28



(\* after generating the distribution of survival times predicted by independent drug action,  
we can remove the 'resampling' to plot the results. With a resampling factor of 10,  
this is achieved by sorting the distribution and keeping every 10th entry \*)

```
SubSampledBestOfMidCorrelatedMonoPairs = Take[Reverse[Sort[BestOfMidCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

$\rho = 0.08$

```
resamplingfactor = 10;
```

```
ReSampledTherapy1SurvivalDistribution =
```

```
Reverse[Sort[Flatten[Table[RandomSample[Therapy1SurvivalDistribution, Length[Therapy2SurvivalDistribution]], {resamplingfactor}]]];
```

```
ReSampledTherapy2SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy2SurvivalDistribution, {resamplingfactor}]]];
```

(\* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.08 \*)

```
amountofrankrandomization = 63000;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
  {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
BestOfLowCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
```

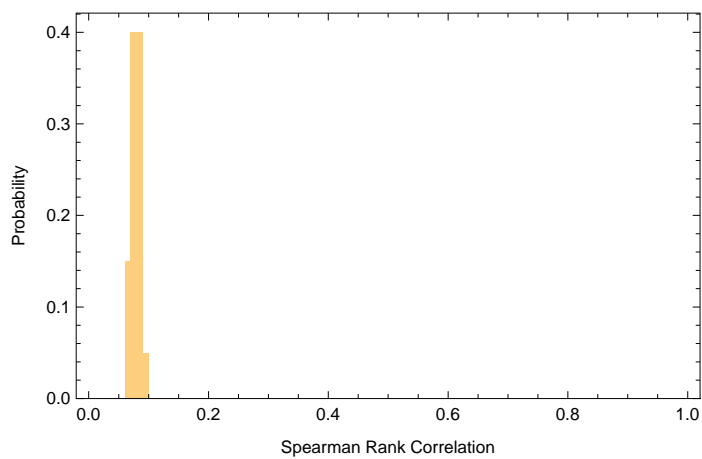
```
0.0698649
```

```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.08 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 63000;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
    , {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

Mean response correlation = 0.078



(\* after generating the distribution of survival times predicted by independent drug action, we can remove the 'resampling' to plot the results. With a resampling factor of 10, this is achieved by sorting the distribution and keeping every 10th entry \*)

```
SubSampledBestOfLowCorrelatedMonoPairs = Take[Reverse[Sort[BestOfLowCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

$\rho = 0.48$

```
resamplingfactor = 10;
```

```
ReSampledTherapy1SurvivalDistribution =
```

```
Reverse[Sort[Flatten[Table[RandomSample[Therapy1SurvivalDistribution, Length[Therapy2SurvivalDistribution]], {resamplingfactor}]]];
```

```
ReSampledTherapy2SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy2SurvivalDistribution, {resamplingfactor}]]];
```

(\* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.48 \*)

```
amountofrankrandomization = 10300;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
  {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

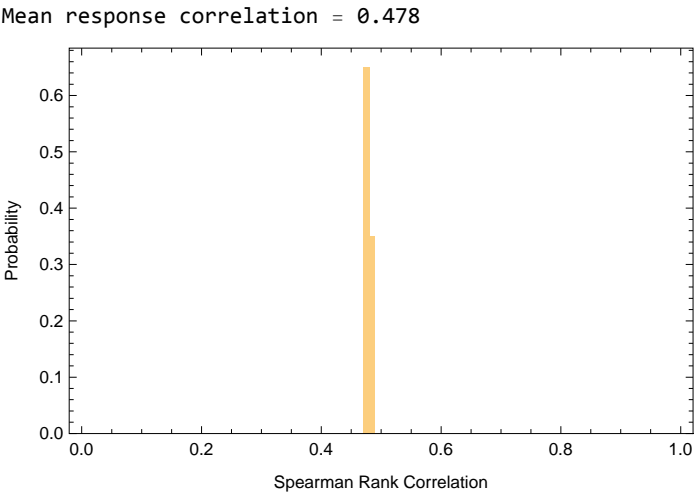
```
BestOfHighCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
```

```
0.483912
```

```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.48 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 10300;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
    , {20}];

Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame -> True, FrameLabel -> {"Spearman Rank Correlation", "Probability"}]
```



```
(* after generating the distribution of survival times predicted by independent drug action,
we can remove the 'resampling' to plot the results. With a resampling factor of 10,
this is acheived by sorting the distribution and keeping every 10th entry *)
SubSampledBestOfHighCorrelatedMonoPairs = Take[Reverse[Sort[BestOfHighCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

Computing median PFS for each condition: the observed individual therapies, the observed combination, and the simulated effects with high, medium, or low response correlation (respectively,  $\rho = 0.48, 0.28, 0.08$ )

```
Mono1Median = Round[Median[Therapy1SurvivalDistribution], 0.01]
Mono2Median = Round[Median[Therapy2SurvivalDistribution], 0.01]
ComboMedian = Round[Median[ComboSurvivalDistribution], 0.01]
Sim1Median = Round[Median[SubSampledBestOfHighCorrelatedMonoPairs], 0.01]
Sim2Median = Round[Median[SubSampledBestOfMidCorrelatedMonoPairs], 0.01]
Sim3Median = Round[Median[SubSampledBestOfLowCorrelatedMonoPairs], 0.01]

8.75

3.83

9.28

9.11

9.26

10.76
```

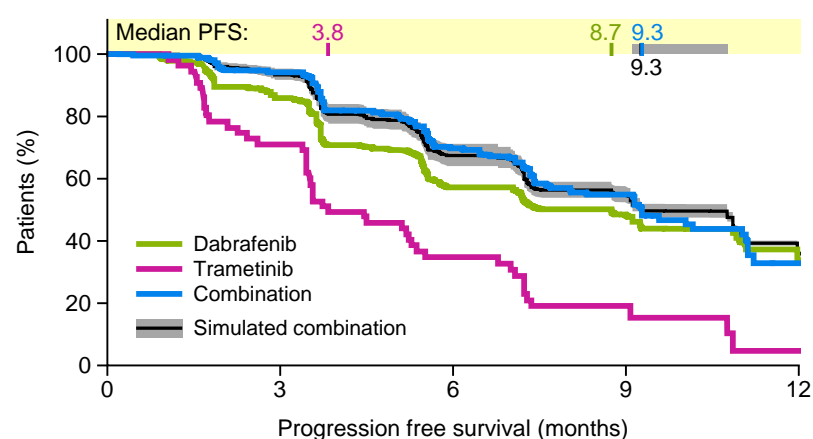


## Plotting the observed and simulated survival functions

```
(*legend vertical offset*)
lo = 0.05;
(*simulated*)slo = -0.03;
(* legend horizontal offset *)
lho = -0.3;

Plot[{
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfHighCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfMidCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfLowCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[Therapy1SurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[Therapy2SurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[ComboSurvivalDistribution]][x]
}, {x, 0, 13}, PlotRange -> {{0, 12.0}, {0, 1.11}}, Exclusions -> None,
PlotStyle -> {Directive[Black, Opacity[0]], Directive[Black, AbsoluteThickness[1.7]], Directive[Black, Opacity[0]], Directive[ColorData[3, 4],
  AbsoluteThickness[3]], Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[3]], Directive[ColorData[3, 6], AbsoluteThickness[3]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 12}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.015}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.015}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]},
Prolog -> {Gray, Thickness[Medium], Lighter[Yellow, 0.75], EdgeForm[None], Rectangle[{0, 1}, {18, 1.11}],
  Black, AbsoluteThickness[1.7], GrayLevel[0.65], Rectangle[{Sim1Median, 1}, {Sim3Median, 1.03}], Black, Opacity[1],
  Line[{Sim2Median, 1}, {Sim2Median, 1.03}], Text["Median PFS:", {0.15, 1.03}, {-1, -1}], Darker[ColorData[3, 4], 0.1],
  Text["8.7", {Mono1Median, 1.03}, {0.35, -1}], RGBColor[0.8, 0.1, 0.6], Text["3.8", {Mono2Median, 1.03}, {0, -1}],
  ColorData[3, 6], Text["9.3", {ComboMedian, 1.03}, {-0.35, -1}], Black, Text["9.3", {Sim2Median, 1.0}, {-0.35, 1}],
  AbsoluteThickness[2], Darker[ColorData[3, 4], 0.1], Line[{Mono1Median, 1}, {Mono1Median, 1.03}], RGBColor[0.8, 0.1, 0.6],
  Line[{Mono2Median, 1}, {Mono2Median, 1.03}], ColorData[3, 6], Line[{ComboMedian, 1}, {ComboMedian, 1.03}]],
AspectRatio -> 1 / 2, Filling -> {1 -> {3}}, FillingStyle -> Directive[GrayLevel[0.65], Opacity[1]],
ImageSize -> {{1000}, {250}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 500,
Epilog -> {EdgeForm[Directive[Black, Thickness[Medium]]], White, Opacity[1], EdgeForm[None], CapForm["Butt"], AbsoluteThickness[3],
  AbsolutePointSize[8], ColorData[3, 4], Line[{lho + 0.8, 0.34 + lo}, {lho + 1.6, 0.34 + lo}], RGBColor[0.8, 0.1, 0.6],
  Line[{lho + 0.8, 0.26 + lo}, {lho + 1.6, 0.26 + lo}], ColorData[3, 6], Line[{lho + 0.8, 0.18 + lo}, {lho + 1.6, 0.18 + lo}],
  Opacity[1], GrayLevel[0.65], Rectangle[{lho + 0.8, 0.1 - 0.03 + lo + slo}, {lho + 1.6, 0.1 + 0.03 + lo + slo}],
  Black, Opacity[1], AbsoluteThickness[1.7], Line[{lho + 0.8, 0.1 + lo + slo}, {lho + 1.6, 0.1 + lo + slo}],
  FontFamily -> "Arial", FontSize -> 11, Text[Style["Dabrafenib", FontSize -> 11], {lho + 1.8, 0.34 + lo}, {-1, 0}],
  Text[Style["Trametinib", FontSize -> 11], {lho + 1.8, 0.26 + lo}, {-1, 0}], Text[Style["Combination", FontSize -> 11],
  {lho + 1.8, 0.18 + lo}, {-1, 0}], Text[Style["Simulated combination", FontSize -> 11], {lho + 1.8, 0.1 + lo + slo}, {-1, 0}]]}

Export[NotebookDirectory[] <> "Figure 4D.pdf", %, "PDF"];
```



Calculating the improvement in hazard ratio attributable to drug synergy.  
This is the hazard ratio between the observed combination trial results, and the combination trial results calculated on the assumption of 'no additivity or synergy'.

```
CensoringTime = 12 (* months *);

PatientsPerArmOfSimulatedTrial = 1000;
IndependentActionSimulatedTrial[] := RandomChoice[SubSampledBestOfMidCorrelatedMonoPairs, PatientsPerArmOfSimulatedTrial]
CombinationSimulatedTrial[] := RandomChoice[ComboSurvivalDistribution, PatientsPerArmOfSimulatedTrial]

GenerateCensoredEventData[PatientResponses_, CensoringTime_] :=
Module[{ResponsesShorterThanCensoringTime, ResponsesLongerThanCensoringTime},
  ResponsesShorterThanCensoringTime = Select[PatientResponses, # <= CensoringTime &];
  ResponsesLongerThanCensoringTime = Select[PatientResponses, # > CensoringTime &];
  EventData[Join[ResponsesShorterThanCensoringTime, ResponsesLongerThanCensoringTime],
    Join[Table[0, {Length[ResponsesShorterThanCensoringTime]}], Table[1, {Length[ResponsesLongerThanCensoringTime]}]]]
]

IndependentActionSimulatedEventData[] := GenerateCensoredEventData[IndependentActionSimulatedTrial[], CensoringTime]
CombinationSimulatedEventData[] := GenerateCensoredEventData[CombinationSimulatedTrial[], CensoringTime]

(* custom function to join two sets of event data - this is necessary to implement the Cox Proportional Hazards model *)
JoinEventData[EventData1_, EventData2_] := EventData[Join[EventData1[[2, 1]], EventData2[[2, 1]], Join[EventData1[[2, 2]], EventData2[[2, 2]]]]

MergedEventData[] := JoinEventData[IndependentActionSimulatedEventData[], CombinationSimulatedEventData[]];
Descriptors[] := Join[Table["Independence", {PatientsPerArmOfSimulatedTrial}], Table["Observed", {PatientsPerArmOfSimulatedTrial}]];
```

Note that the error range in the hazard ratio depends on the population size in a simulated trial of the combination, and the duration on trial, that is, the rate of censoring events.  
Here we compute error ranges expected from 200 patients per trial arm, with any that are progression-free after a defined time being ‘censored’. This limits imprecision arising from the source PFS data having few patients ‘on-trial’ at late times, which is cause of increasing error range in PFS probability at longer times.

The range in hazard ratio is robustly identified by taking the mean range over 100 simulations of such trials.

```
NumberOfReplicateTrials = 100;

(* this function returns the relative risk, and confidence interval, in the format:
  (95% lower confidence interval, median estimate, 95% upper confidence interval )
*)
RelativeRiskCalculation[descriptors_, eventdata_, PrintTable_
  (* set to 1 to print to screen the statistical table of Cox Model output; set to 0 to not show output *) := Module[{},
    MyModelFit = CoxModelFit[{descriptors, eventdata}, {treatment}, {treatment}, NominalVariables -> treatment];

    If[PrintTable == 1, Print[MyModelFit["ParameterTable"]]];

    RelativeRisk = MyModelFit["RelativeRisk"][[1]];
    RelativeRiskLowerConfidenceInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1, 1]];
    RelativeRiskUpperConfidenceInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1, 2]];

    {RelativeRiskLowerConfidenceInterval, RelativeRisk, RelativeRiskUpperConfidenceInterval}
  ]

(* single execution of the simulated trial *)
RelativeRiskCalculation[Descriptors[], MergedEventData[], 1]

```

	Estimate	Standard Error	Relative Risk	Wald- $\chi^2$	DF	P-Value
treatment[Observed]	0.0127832	0.0551564	1.01287	0.0537135	1	0.816723

```
{0.909081, 1.01287, 1.1285}

(* many replicate trial simulations, to accurately determine the range in hazard ratio *)
MelanomaKinaseHazardRatioRange = Quiet@Mean[Table[RelativeRiskCalculation[Descriptors[], MergedEventData[], 0], {NumberOfReplicateTrials}]]
{0.91982, 1.02509, 1.14241}
```

# Comparison of Independent Drug Action with Synergy models by Akaike Information Criterion (AIC)

```
(* first, we compute a survival distribution based on the monotherapy distributions assuming no synergy,
and perfect correlation in response between drugs. Therefore at each time point,
PFS is the higher of the single-drug PFS rates at that time. *)
MaximumOfMonotherapyResponses = Map[Max, {Sort[ReSampledTherapy1SurvivalDistribution], Sort[ReSampledTherapy2SurvivalDistribution]}^T];
MaximumOfMonotherapyResponses = Take[Reverse[Sort[MaximumOfMonotherapyResponses]], 1 ;; -1 ;; resamplingfactor];

(* Maximum time, in months, over which to compare survival distributions *)
LongestTime = 12;
```

A ‘synergy-fitting’ model is created by defining two adjustable parameters:

a vertical scaling, which affects a fractional decrease in progression probability at each time

a horizontal scaling, which affects a fractional extension in duration of progression-free survival for all patients

SynergyModel[0,0] has no synergistic effect.

SynergyModel[X,0] has, for each patient, +X\*100% longer PFS time. E.g. in SynergyModel[0.5, 0], all patients have +50% longer PFS.

SynergyModel[0,Y] has, at each time point, a 1/Y probability of progression. E.g. in SynergyModel[0, 1], at each time the progression rate is halved.

```
SynergyModel[HorizontalScaling_, VerticalScaling_] :=
  Join[MaximumOfMonotherapyResponses * (1 + HorizontalScaling), Table[LongestTime, {VerticalScaling * Length[MaximumOfMonotherapyResponses]}]]

(* for Kolmogorov-Smirnov test to be comparable across data sets and model types,
the population size that comprises each survival distribution is normalized to a consistent
value. This does not change the distribution shape except for insignificant rounding differences. *)
TrialPopulationSize = 200;

SetMaximumTimeAndNormalizePopulationSize[survivaldistribution_, LongestTime_, PopulationSize_] := Module[{},
  SurvivalDistributionWithMaximumTime = Sort[Map[Min[{LongestTime, #}] &, survivaldistribution]];
  SurvivalDistributionWithDefinedPopulationSize =
    Sort[Flatten[Table[SurvivalDistributionWithMaximumTime, {PopulationSize}]]][1 ;; -1 ;; Length[SurvivalDistributionWithMaximumTime]]
];

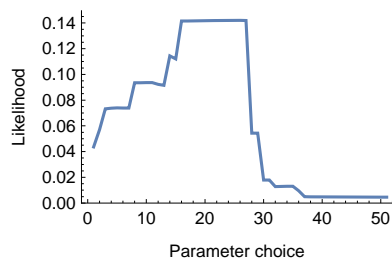
(* the observed data; set to consistent population size and capped with a consistent maximum survival time *)
ObservedDistribution = SetMaximumTimeAndNormalizePopulationSize[ComboSurvivalDistribution, LongestTime, TrialPopulationSize];

(* computing which synergy model, using the horizontal parameter only, has the highest likelihood of consistency with the observed data *)
MaximumHorizontalScaling = 0.4;
Steps = 50;

SynergyModelOnlyHorizontalParameterFits = Table[{HorizontalScaling, KolmogorovSmirnovTest[ObservedDistribution,
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[HorizontalScaling, 0], LongestTime, TrialPopulationSize], "PValue"]},
  {HorizontalScaling, 0, MaximumHorizontalScaling, MaximumHorizontalScaling / Steps}];

BestLikelihoodWithHorizontalParameter = Max[SynergyModelOnlyHorizontalParameterFits[[All, 2]]]
0.142044

(* confirming that the synergy parameter spanned the optimal range *)
ListPlot[SynergyModelOnlyHorizontalParameterFits[[All, 2]], Joined → True, PlotRange → {0, All},
  ImageSize → 200, Frame → {{True, False}, {True, False}}, FrameLabel → {"Parameter choice", "Likelihood"}]
```



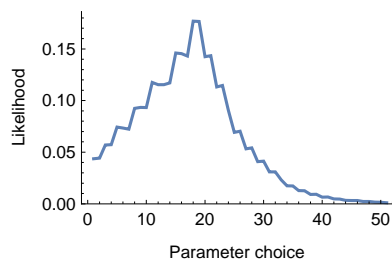
```
(* computing which synergy model, using the vertical parameter only, has the highest likelihood of consistency with the observed data *)
MaximumVerticalScaling = 0.3;
Steps = 50;
```

```
SynergyModelOnlyVerticalParameterFits = Table[{VerticalScaling, KolmogorovSmirnovTest[ObservedDistribution,
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[0, VerticalScaling], LongestTime, TrialPopulationSize], "PValue"]},
  {VerticalScaling, 0, MaximumVerticalScaling, MaximumVerticalScaling / Steps}];
```

```
BestLikelihoodWithVerticalParameter = Max[SynergyModelOnlyVerticalParameterFits[[All, 2]]]
```

```
0.176931
```

```
(* confirming that the synergy parameter spanned the optimal range *)
ListPlot[SynergyModelOnlyVerticalParameterFits[[All, 2]], Joined → True, PlotRange → {0, All},
  ImageSize → 200, Frame → {{True, False}, {True, False}}, FrameLabel → {"Parameter choice", "Likelihood"}]
```



```

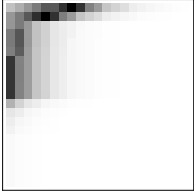
(* computing which synergy model, using two parameters, has the highest likelihood of consistency with the observed data *)
MaximumHorizontalScaling = 0.4;
MaximumVerticalScaling = 0.3;
StepsPerParameter = 20;

SynergyModelTwoParameterFits =
  Table[{HorizontalScaling, VerticalScaling, KolmogorovSmirnovTest[ObservedDistribution, SetMaximumTimeAndNormalizePopulationSize[
    SynergyModel[HorizontalScaling, VerticalScaling], LongestTime, TrialPopulationSize], "PValue"]},
    {HorizontalScaling, 0, MaximumHorizontalScaling, MaximumHorizontalScaling / StepsPerParameter},
    {VerticalScaling, 0, MaximumVerticalScaling, MaximumVerticalScaling / StepsPerParameter}];

BestLikelihoodWithTwoParameterFit = Max[Flatten[SynergyModelTwoParameterFits[[All, All, 3]]]
0.178926

(* confirming that the synergy parameters spanned the optimal range *)
ArrayPlot[SynergyModelTwoParameterFits[[All, All, 3]], ImageSize -> 100]

```



```

(* computing the likelihood that the Independent Drug Action model (with zero fitted parameters) is consistent with the observed data *)
(* To minimize noise from the sampling procedure of the independent action model, we take the average of many simulations *)
IndependentActionSimulation[] := Module[{},
  (* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.28 *)
  amountofrankrandomization = 17500;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  BestOfMidCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]}],
    {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
  SubSampledBestOfMidCorrelatedMonoPairs = Take[Reverse[Sort[BestOfMidCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor]
]

NumberOfIndependentActionSimulations = 20;
ReplicateIndependentActionSimulations = Sort[Flatten[Table[IndependentActionSimulation[], {NumberOfIndependentActionSimulations}]]];
(* final model is the population-normalized average of many replicate simulations *)
IndependentActionModel = SetMaximumTimeAndNormalizePopulationSize[ReplicateIndependentActionSimulations, LongestTime, TrialPopulationSize];
(* computing the likelihood that the Independent Drug Action model (with zero fitted parameters) is consistent with the observed data *)
IndependentActionModelLikelihood = KolmogorovSmirnovTest[ObservedDistribution, IndependentActionModel, "PValue"]
0.686

(* Tabulating the likelihood that the observed combination drug response
would be observed if the true distribution were one of the various models, in the order:
{ independent drug action, synergy with horizontal parameter, synergy with vertical parameter, synergy with two parameters } *)
MelanomaKinaseModelLikelihoods = {IndependentActionModelLikelihood,
  BestLikelihoodWithHorizontalParameter, BestLikelihoodWithVerticalParameter, BestLikelihoodWithTwoParameterFit}
{0.686, 0.142044, 0.176931, 0.178926}

```

## plotting model fits

```

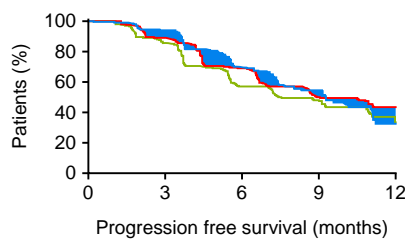
MaximumOfMonotherapyResponsesModel =
  SetMaximumTimeAndNormalizePopulationSize[MaximumOfMonotherapyResponses, LongestTime, TrialPopulationSize];

```

```
BestHorizontalSynergyParameter = Sort[SynergyModelOnlyHorizontalParameterFits, #1[[2]] > #2[[2]] &] [[1, 1]];
BestHorizontalSynergyModel =
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[BestHorizontalSynergyParameter, 0], LongestTime, TrialPopulationSize];
```

```
Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]] [x],
  SurvivalFunction[EmpiricalDistribution[BestHorizontalSynergyModel]] [x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]] [x]}
, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None, PlotStyle ->
  {Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Red, AbsoluteThickness[1]], Directive[ColorData[3, 6], AbsoluteThickness[1]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 10}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]}, AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[ColorData[3, 6], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]
```

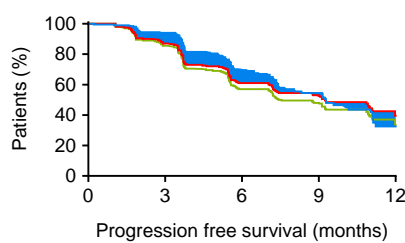
```
Export[NotebookDirectory[] <> "MelanomaDabrafenibTrametinibBestHorizontalSynergy.pdf", %, "PDF"];
```



```
BestVerticalSynergyParameter = Sort[SynergyModelOnlyVerticalParameterFits, #1[[2]] > #2[[2]] &] [[1, 1]];
BestVerticalSynergyModel =
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[0, BestVerticalSynergyParameter], LongestTime, TrialPopulationSize];
```

```
Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]] [x],
  SurvivalFunction[EmpiricalDistribution[BestVerticalSynergyModel]] [x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]] [x]}
, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None, PlotStyle ->
  {Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Red, AbsoluteThickness[1]], Directive[ColorData[3, 6], AbsoluteThickness[1]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 10}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]}, AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[ColorData[3, 6], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]
```

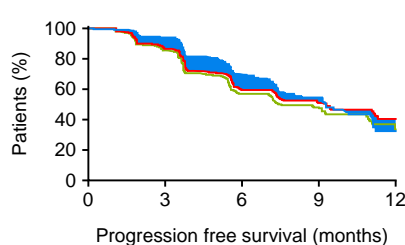
```
Export[NotebookDirectory[] <> "MelanomaDabrafenibTrametinibBestVerticalSynergy.pdf", %, "PDF"];
```



```
BestTwoParameterSynergyParameters = Sort[Flatten[SynergyModelTwoParameterFits, 1], #1[[3]] > #2[[3]] &] [[1, {1, 2}]];
BestTwoParameterSynergyModel = SetMaximumTimeAndNormalizePopulationSize[
  SynergyModel[BestTwoParameterSynergyParameters[[1]], BestTwoParameterSynergyParameters[[2]], LongestTime, TrialPopulationSize];
```

```
Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]] [x],
  SurvivalFunction[EmpiricalDistribution[BestTwoParameterSynergyModel]] [x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]] [x]}
, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None, PlotStyle ->
  {Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Red, AbsoluteThickness[1]], Directive[ColorData[3, 6], AbsoluteThickness[1]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 10}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]}, AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[ColorData[3, 6], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]
```

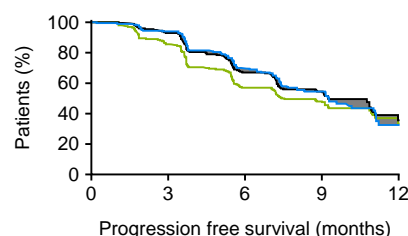
```
Export[NotebookDirectory[] <> "MelanomaDabrafenibTrametinibBestTwoParameterSynergy.pdf", %, "PDF"];
```





```
Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]][x],
  SurvivalFunction[EmpiricalDistribution[IndependentActionModel]][x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]][x]}
, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None,
PlotStyle -> {Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Black, AbsoluteThickness[1]],
  Directive[ColorData[3, 6], AbsoluteThickness[1]]}, BaseStyle -> {FontFamily -> "Arial", FontSize -> 10},
FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)", Style["Patients (%)"]], AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[GrayLevel[0.5], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]

Export[NotebookDirectory[] <> "MelanomaDabrafenibTrametinibIndependentModel.pdf", %, "PDF"];
```



## Metastatic melanoma, combination Immunotherapy

Code here is not used for main figures of Ipilimumab plus Nivolumab, but is used to compute hazard ratio attributable to synergy, and to apply Akaike Information Criterion to model selection.

Near-identical code as for Figure 4A is here employed to generate Figure 4D. Comments will be more brief.

```
Figure1BRawData = Import[NotebookDirectory[] <> "Table of survival distributions.xlsx", "XLSX"][[2(* the second tab of this spreadsheet*)]];
Therapy1SurvivalDistribution = Select[Figure1BRawData[[8 ;;, 2(* column 2 of this spreadsheet contains PFS data for Ipilimumab*)]], NumberQ];
Therapy2SurvivalDistribution = Select[Figure1BRawData[[8 ;;, 3(* column 3 of this spreadsheet contains PFS data for Nivolumab*)]], NumberQ];
ComboSurvivalDistribution =
  Select[Figure1BRawData[[8 ;;, 4(* column 4 of this spreadsheet contains PFS data for the combination*)]], NumberQ];
```

$\rho = 0.28$

```
Length[Therapy1SurvivalDistribution]
Length[Therapy2SurvivalDistribution]
```

```
1938
```

```
1938
```

```
(* how many repeats of the complete data set to merge together
(for purpose of minimizing variance between individual repeats of the 'rank randomization' process) *)
resamplingfactor = 10;
```

```
ReSampledTherapy1SurvivalDistribution =
  Reverse[Sort[Flatten[Table[RandomSample[Therapy1SurvivalDistribution, Length[Therapy2SurvivalDistribution]], {resamplingfactor}]]]];
ReSampledTherapy2SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy2SurvivalDistribution, {resamplingfactor}]]]];
(* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.28 *)
amountofrankrandomization = 16500;
```

```
SlightlyRandomizedTherapy1Distribution =
  Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
    {i, 1, Length[ReSampledTherapy1SurvivalDistribution]]}, #1[[1]] < #2[[1]] &];
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]]}, #1[[1]] < #2[[1]] &];
BestOfMidCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
0.278794
```

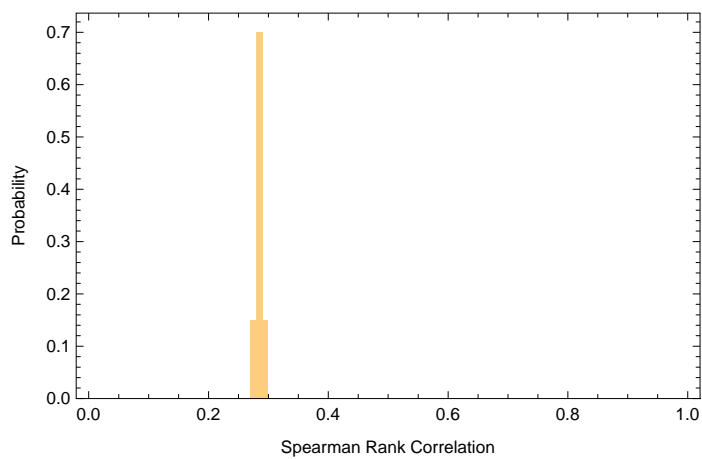


```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.28 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 16500;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
    , {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

Mean response correlation = 0.285



(\* after generating the distribution of survival times predicted by independent drug action, we can remove the 'resampling' to plot the results. With a resampling factor of 10, this is achieved by sorting the distribution and keeping every 10th entry \*)

```
SubSampledBestOfMidCorrelatedMonoPairs = Take[Reverse[Sort[BestOfMidCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

$\rho = 0.08$

```
resamplingfactor = 10;
```

```
ReSampledTherapy1SurvivalDistribution =
```

```
Reverse[Sort[Flatten[Table[RandomSample[Therapy1SurvivalDistribution, Length[Therapy2SurvivalDistribution]], {resamplingfactor}]]];
```

```
ReSampledTherapy2SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy2SurvivalDistribution, {resamplingfactor}]]];
```

(\* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.08 \*)

```
amountofrankrandomization = 63000;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
  {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
BestOfLowCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
```

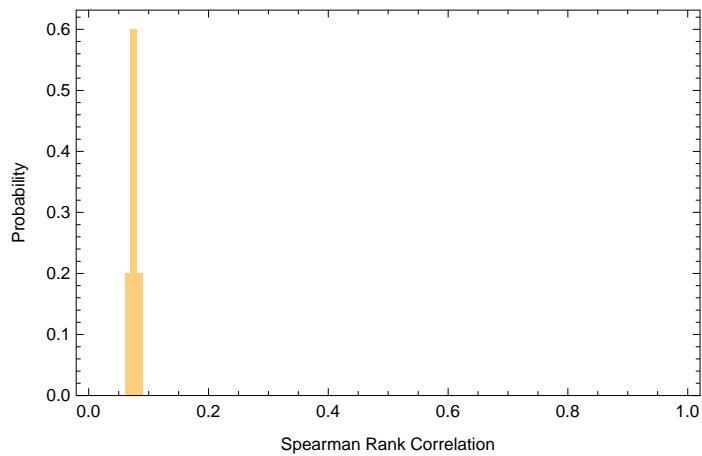
```
0.0716178
```

```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.08 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 63000;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
    , {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

Mean response correlation = 0.075



(\* after generating the distribution of survival times predicted by independent drug action, we can remove the 'resampling' to plot the results. With a resampling factor of 10, this is achieved by sorting the distribution and keeping every 10th entry \*)

```
SubSampledBestOfLowCorrelatedMonoPairs = Take[Reverse[Sort[BestOfLowCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

$\rho = 0.48$

```
resamplingfactor = 10;
```

```
ReSampledTherapy1SurvivalDistribution =
```

```
Reverse[Sort[Flatten[Table[RandomSample[Therapy1SurvivalDistribution, Length[Therapy2SurvivalDistribution]], {resamplingfactor}]]];
```

```
ReSampledTherapy2SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy2SurvivalDistribution, {resamplingfactor}]]];
```

(\* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.48 \*)

```
amountofrankrandomization = 9800;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
  {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
BestOfHighCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
```

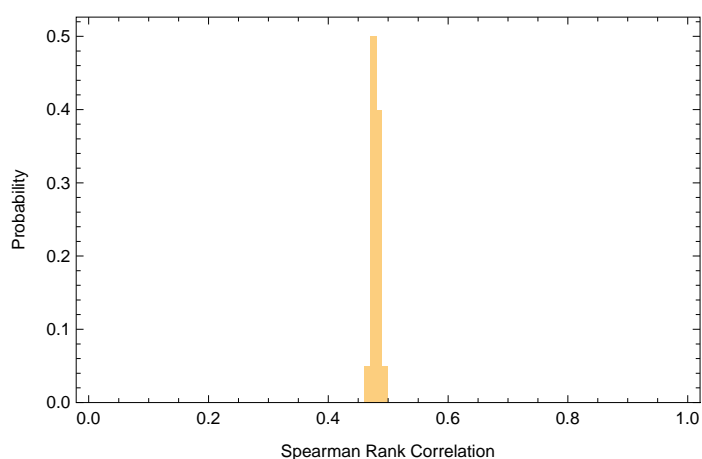
```
0.481184
```

```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.48 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 9800;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
    , {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

Mean response correlation = 0.479



(\* after generating the distribution of survival times predicted by independent drug action, we can remove the 'resampling' to plot the results. With a resampling factor of 10, this is achieved by sorting the distribution and keeping every 10th entry \*)

```
SubSampledBestOfHighCorrelatedMonoPairs = Take[Reverse[Sort[BestOfHighCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

Computing median PFS for each condition: the observed individual therapies, the observed combination, and the simulated effects with high, medium, or low response correlation (respectively,  $\rho = 0.48, 0.28, 0.08$ )

```
Mono1Median = Round[Median[Therapy1SurvivalDistribution], 0.1]
Mono2Median = Round[Median[Therapy2SurvivalDistribution], 0.1]
ComboMedian = Round[Median[ComboSurvivalDistribution], 0.01]
Sim1Median = Round[Median[SubSampledBestOfHighCorrelatedMonoPairs], 0.1]
Sim2Median = Round[Median[SubSampledBestOfMidCorrelatedMonoPairs], 0.1]
Sim3Median = Round[Median[SubSampledBestOfLowCorrelatedMonoPairs], 0.1]
```

3.

7.1

12.9

11.3

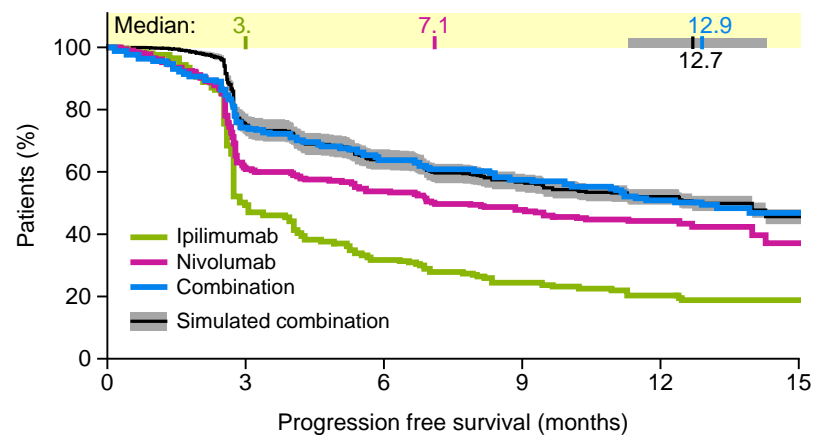
12.7

14.3

## Plotting the observed and simulated survival functions

```
(*legend vertical offset*)
lo = 0.05;
(*simulated*)slo = -0.03;
(* legend horizontal offset *)
lho = -0.3;

Plot[{
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfHighCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfMidCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfLowCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[Therapy1SurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[Therapy2SurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[ComboSurvivalDistribution]][x]
}, {x, 0, 16}, PlotRange -> {{0, 15.0}, {0, 1.11}}, Exclusions -> None,
PlotStyle -> {Directive[Black, Opacity[0]], Directive[Black, AbsoluteThickness[1.7]], Directive[Black, Opacity[0]], Directive[ColorData[3, 4],
  AbsoluteThickness[3]], Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[3]], Directive[ColorData[3, 6], AbsoluteThickness[3]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 12}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.015}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.015}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]},
Prolog -> {Gray, Thickness[Medium], Lighter[Yellow, 0.75], EdgeForm[None], Rectangle[{0, 1}, {18, 1.11}],
  Black, AbsoluteThickness[1.7], GrayLevel[0.65], Rectangle[{Sim1Median, 1}, {Sim3Median, 1.03}],
  Black, Opacity[1], Line[{Sim2Median, 1}, {Sim2Median, 1.03}], Text["Median:", {0.15, 1.03}, {-1, -1}],
  Darker[ColorData[3, 4], 0.1], Text[ToString[Mono1Median], {Mono1Median, 1.03}, {0.35, -1}],
  RGBColor[0.8, 0.1, 0.6], Text[ToString[Mono2Median], {Mono2Median, 1.03}, {0, -1}], ColorData[3, 6],
  Text[ToString[ComboMedian], {ComboMedian, 1.03}, {-0.35, -1}], Black, Text[ToString[Sim2Median], {Sim2Median, 1.0}, {-0.35, 1}],
  AbsoluteThickness[2], Darker[ColorData[3, 4], 0.1], Line[{Mono1Median, 1}, {Mono1Median, 1.03}], RGBColor[0.8, 0.1, 0.6],
  Line[{Mono2Median, 1}, {Mono2Median, 1.03}], ColorData[3, 6], Line[{ComboMedian, 1}, {ComboMedian, 1.03}]},
AspectRatio -> 1 / 2, Filling -> {1 -> {3}}, FillingStyle -> Directive[GrayLevel[0.65], Opacity[1]],
ImageSize -> {{1000}, {250}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 500,
Epilog -> {EdgeForm[Directive[Black, Thickness[Medium]]], White, Opacity[1], EdgeForm[None], CapForm["Butt"], AbsoluteThickness[3],
  AbsolutePointSize[8], ColorData[3, 4], Line[{lho + 0.8, 0.34 + lo}, {lho + 1.6, 0.34 + lo}], RGBColor[0.8, 0.1, 0.6],
  Line[{lho + 0.8, 0.26 + lo}, {lho + 1.6, 0.26 + lo}], ColorData[3, 6], Line[{lho + 0.8, 0.18 + lo}, {lho + 1.6, 0.18 + lo}],
  Opacity[1], GrayLevel[0.65], Rectangle[{lho + 0.8, 0.1 - 0.03 + lo + slo}, {lho + 1.6, 0.1 + 0.03 + lo + slo}],
  Black, Opacity[1], AbsoluteThickness[1.7], Line[{lho + 0.8, 0.1 + lo + slo}, {lho + 1.6, 0.1 + lo + slo}],
  FontFamily -> "Arial", FontSize -> 11, Text[Style["Ipilimumab", FontSize -> 11], {lho + 1.8, 0.34 + lo}, {-1, 0}],
  Text[Style["Nivolumab", FontSize -> 11], {lho + 1.8, 0.26 + lo}, {-1, 0}], Text[Style["Combination", FontSize -> 11],
  {lho + 1.8, 0.18 + lo}, {-1, 0}], Text[Style["Simulated combination", FontSize -> 11], {lho + 1.8, 0.1 + lo + slo}, {-1, 0}]}]
(*
Export[NotebookDirectory[] <> "Figure 1B, using PDX level of correlation.pdf", %, "PDF"];
*)
```



## Calculating the improvement in hazard ratio attributable to drug synergy.

This is the hazard ratio between the observed combination trial results, and the combination trial results calculated on the assumption of 'no additivity or synergy'.

```
CensoringTime = 15 (* months *);

PatientsPerArmOfSimulatedTrial = 1000;
IndependentActionSimulatedTrial[] := RandomChoice[SubSampledBestOfMidCorrelatedMonoPairs, PatientsPerArmOfSimulatedTrial]
CombinationSimulatedTrial[] := RandomChoice[ComboSurvivalDistribution, PatientsPerArmOfSimulatedTrial]

GenerateCensoredEventData[PatientResponses_, CensoringTime_] :=
Module[{ResponsesShorterThanCensoringTime, ResponsesLongerThanCensoringTime},
  ResponsesShorterThanCensoringTime = Select[PatientResponses, # ≤ CensoringTime &];
  ResponsesLongerThanCensoringTime = Select[PatientResponses, # > CensoringTime &];
  EventData[Join[ResponsesShorterThanCensoringTime, ResponsesLongerThanCensoringTime],
    Join[Table[0, {Length[ResponsesShorterThanCensoringTime]}], Table[1, {Length[ResponsesLongerThanCensoringTime]}]]]
]

IndependentActionSimulatedEventData[] := GenerateCensoredEventData[IndependentActionSimulatedTrial[], CensoringTime]
CombinationSimulatedEventData[] := GenerateCensoredEventData[CombinationSimulatedTrial[], CensoringTime]

(* custom function to join two sets of event data - this is necessary to implement the Cox Proportional Hazards model *)
JoinEventData[EventData1_, EventData2_] := EventData[Join[EventData1[[2, 1]], EventData2[[2, 1]], Join[EventData1[[2, 2]], EventData2[[2, 2]]]]

MergedEventData[] := JoinEventData[IndependentActionSimulatedEventData[], CombinationSimulatedEventData[]];
Descriptors[] := Join[Table["Independence", {PatientsPerArmOfSimulatedTrial}], Table["Observed", {PatientsPerArmOfSimulatedTrial}]];
```

Note that the error range in the hazard ratio depends on the population size in a simulated trial of the combination, and the duration on trial, that is, the rate of censoring events.

Here we compute error ranges expected from 200 patients per trial arm, with any that are progression-free after a defined time being 'censored'. This limits imprecision arising from the source PFS data having few patients 'on-trial' at late times, which is cause of increasing error range in PFS probability at longer times.

The range in hazard ratio is robustly identified by taking the mean range over 100 simulations of such trials.

```
NumberOfReplicateTrials = 100;

(* this function returns the relative risk, and confidence interval, in the format:
  (95% lower confidence interval, median estimate, 95% upper confidence interval )
*)
RelativeRiskCalculation[descriptors_, eventdata_, PrintTable_
  (* set to 1 to print to screen the statistical table of Cox Model output; set to 0 to not show output *)] := Module[{},
  MyModelFit = CoxModelFit[{descriptors, eventdata}, {treatment}, {treatment}, NominalVariables → treatment];

  If[PrintTable == 1, Print[MyModelFit["ParameterTable"]]];

  RelativeRisk = MyModelFit["RelativeRisk"][[1]];
  RelativeRiskLowerConfidenceInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1, 1]];
  RelativeRiskUpperConfidenceInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1, 2]];

  {RelativeRiskLowerConfidenceInterval, RelativeRisk, RelativeRiskUpperConfidenceInterval}
]

(* single execution of the simulated trial *)
RelativeRiskCalculation[Descriptors[], MergedEventData[], 1]

```

	Estimate	Standard Error	Relative Risk	Wald- $\chi^2$	DF	P-Value
treatment[Observed]	-0.0234031	0.061786	0.976869	0.143472	1	0.704854

```
{0.865454, 0.976869, 1.10263}

(* many replicate trial simulations, to accurately determine the range in hazard ratio *)
MelanomaImmunotherapyHazardRatioRange =
  Quiet@Mean[Table[RelativeRiskCalculation[Descriptors[], MergedEventData[], 0], {NumberOfReplicateTrials}]]
{0.889764, 1.00278, 1.13015}
```

## Comparison of Independent Drug Action with Synergy models by Akaike Information Criterion (AIC)

```
(* first, we compute a survival distribution based on the monotherapy distributions assuming no synergy,
and perfect correlation in response between drugs. Therefore at each time point,
PFS is the higher of the single-drug PFS rates at that time. *)
MaximumOfMonotherapyResponses = Map[Max, {Sort[ReSampledTherapy1SurvivalDistribution], Sort[ReSampledTherapy2SurvivalDistribution]}];
MaximumOfMonotherapyResponses = Take[Reverse[Sort[MaximumOfMonotherapyResponses]], 1 ;; -1 ;; resamplingfactor];
```

```
(* Maximum time, in months, over which to compare survival distributions *)
LongestTime = 15;
```

A 'synergy-fitting' model is created by defining two adjustable parameters:

a vertical scaling, which affects a fractional decrease in progression probability at each time

a horizontal scaling, which affects a fractional extension in duration of progression-free survival for all patients

SynergyModel[0,0] has no synergistic effect.

SynergyModel[X,0] has, for each patient, +X\*100% longer PFS time. E.g. in SynergyModel[0.5, 0], all patients have +50% longer PFS.

SynergyModel[0,Y] has, at each time point, a 1/Y probability of progression. E.g. in SynergyModel[0, 1], at each time the progression rate is halved.

```
SynergyModel[HorizontalScaling_, VerticalScaling_] :=
  Join[MaximumOfMonotherapyResponses * (1 + HorizontalScaling), Table[LongestTime, {VerticalScaling * Length[MaximumOfMonotherapyResponses]}]]
```

```
(* for Kolmogorov-Smirnov test to be comparable across data sets and model types,
the population size that comprises each survival distribution is normalized to a consistent
value. This does not change the distribution shape except for insignificant rounding differences. *)
TrialPopulationSize = 200;
```

```
SetMaximumTimeAndNormalizePopulationSize[survivaldistribution_, LongestTime_, PopulationSize_] := Module[{},
  SurvivalDistributionWithMaximumTime = Sort[Map[Min[{LongestTime, #}] &, survivaldistribution]];
  SurvivalDistributionWithDefinedPopulationSize =
    Sort[Flatten[Table[SurvivalDistributionWithMaximumTime, {PopulationSize}]]][1 ;; -1 ;; Length[SurvivalDistributionWithMaximumTime]]
]
```

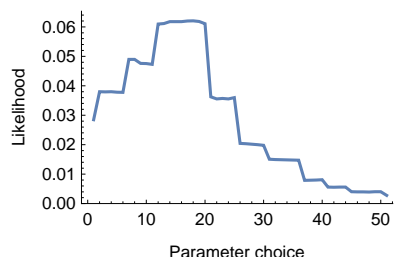
```
(* the observed data; set to consistent population size and capped with a consistent maximum survival time *)
ObservedDistribution = SetMaximumTimeAndNormalizePopulationSize[ComboSurvivalDistribution, LongestTime, TrialPopulationSize];
```

```
(* computing which synergy model, using the horizontal parameter only, has the highest likelihood of consistency with the observed data *)
MaximumHorizontalScaling = 0.5;
Steps = 50;
```

```
SynergyModelOnlyHorizontalParameterFits = Table[{HorizontalScaling, KolmogorovSmirnovTest[ObservedDistribution,
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[HorizontalScaling, 0], LongestTime, TrialPopulationSize], "PValue"]},
  {HorizontalScaling, 0, MaximumHorizontalScaling, MaximumHorizontalScaling / Steps}];
```

```
BestLikelihoodWithHorizontalParameter = Max[SynergyModelOnlyHorizontalParameterFits[[All, 2]]
0.0620466
```

```
(* confirming that the synergy parameter spanned the optimal range *)
ListPlot[SynergyModelOnlyHorizontalParameterFits[[All, 2]], Joined → True, PlotRange → {0, All},
  ImageSize → 200, Frame → {{True, False}, {True, False}}, FrameLabel → {"Parameter choice", "Likelihood"}]
```

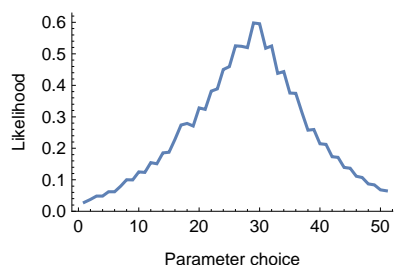


```
(* computing which synergy model, using the vertical parameter only, has the highest likelihood of consistency with the observed data *)
MaximumVerticalScaling = 0.4;
Steps = 50;
```

```
SynergyModelOnlyVerticalParameterFits = Table[{VerticalScaling, KolmogorovSmirnovTest[ObservedDistribution,
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[0, VerticalScaling], LongestTime, TrialPopulationSize], "PValue"]},
  {VerticalScaling, 0, MaximumVerticalScaling, MaximumVerticalScaling / Steps}];
```

```
BestLikelihoodWithVerticalParameter = Max[SynergyModelOnlyVerticalParameterFits[[All, 2]]
0.597943
```

```
(* confirming that the synergy parameter spanned the optimal range *)
ListPlot[SynergyModelOnlyVerticalParameterFits[[All, 2]], Joined → True, PlotRange → {0, All},
  ImageSize → 200, Frame → {{True, False}, {True, False}}, FrameLabel → {"Parameter choice", "Likelihood"}]
```





```

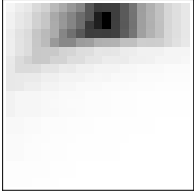
(* computing which synergy model, using two parameters, has the highest likelihood of consistency with the observed data *)
MaximumHorizontalScaling = 0.4;
MaximumVerticalScaling = 0.4;
StepsPerParameter = 20;

SynergyModelTwoParameterFits =
  Table[{HorizontalScaling, VerticalScaling, KolmogorovSmirnovTest[ObservedDistribution, SetMaximumTimeAndNormalizePopulationSize[
    SynergyModel[HorizontalScaling, VerticalScaling], LongestTime, TrialPopulationSize], "PValue"]},
    {HorizontalScaling, 0, MaximumHorizontalScaling, MaximumHorizontalScaling / StepsPerParameter},
    {VerticalScaling, 0, MaximumVerticalScaling, MaximumVerticalScaling / StepsPerParameter}];

BestLikelihoodWithTwoParameterFit = Max[Flatten[SynergyModelTwoParameterFits[[All, All, 3]]]
0.685605

(* confirming that the synergy parameters spanned the optimal range *)
ArrayPlot[SynergyModelTwoParameterFits[[All, All, 3]], ImageSize -> 100]

```



```

(* computing the likelihood that the Independent Drug Action model (with zero fitted parameters) is consistent with the observed data *)
(* To minimize noise from the sampling procedure of the independent action model, we take the average of many simulations *)
IndependentActionSimulation[] := Module[{},
  (* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.28 *)
  amountofrankrandomization = 16500;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  BestOfMidCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]}],
    {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
  SubSampledBestOfMidCorrelatedMonoPairs = Take[Reverse[Sort[BestOfMidCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor]
]

NumberOfIndependentActionSimulations = 20;
ReplicateIndependentActionSimulations = Sort[Flatten[Table[IndependentActionSimulation[], {NumberOfIndependentActionSimulations}]]];
(* final model is the population-normalized average of many replicate simulations *)
IndependentActionModel = SetMaximumTimeAndNormalizePopulationSize[ReplicateIndependentActionSimulations, LongestTime, TrialPopulationSize];
(* computing the likelihood that the Independent Drug Action model (with zero fitted parameters) is consistent with the observed data *)
IndependentActionModelLikelihood = KolmogorovSmirnovTest[ObservedDistribution, IndependentActionModel, "PValue"]
0.18755

(* Tabulating the likelihood that the observed combination drug response
would be observed if the true distribution were one of the various models, in the order:
{ independent drug action, synergy with horizontal parameter, synergy with vertical parameter, synergy with two parameters } *)
MelanomaImmunotherapyModelLikelihoods = {IndependentActionModelLikelihood,
  BestLikelihoodWithHorizontalParameter, BestLikelihoodWithVerticalParameter, BestLikelihoodWithTwoParameterFit}
{0.18755, 0.0620466, 0.597943, 0.685605}

```

## plotting model fits

```

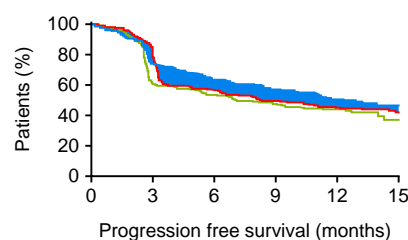
MaximumOfMonotherapyResponsesModel =
  SetMaximumTimeAndNormalizePopulationSize[MaximumOfMonotherapyResponses, LongestTime, TrialPopulationSize];

```

```
BestHorizontalSynergyParameter = Sort[SynergyModelOnlyHorizontalParameterFits, #1[[2]] > #2[[2]] &] [[1, 1]];
BestHorizontalSynergyModel =
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[BestHorizontalSynergyParameter, 0], LongestTime, TrialPopulationSize];
```

```
Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]][x],
  SurvivalFunction[EmpiricalDistribution[BestHorizontalSynergyModel]][x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]][x]
}, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None, PlotStyle ->
{Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Red, AbsoluteThickness[1]], Directive[ColorData[3, 6], AbsoluteThickness[1]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 10}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]}, AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[ColorData[3, 6], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]
```

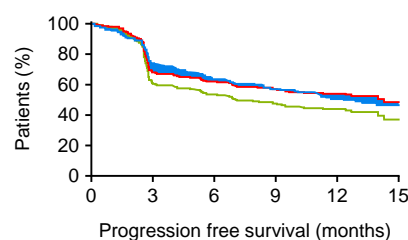
```
Export[NotebookDirectory[] <> "MelanomaIpilimumabNivolumabBestHorizontalSynergy.pdf", %, "PDF"];
```



```
BestVerticalSynergyParameter = Sort[SynergyModelOnlyVerticalParameterFits, #1[[2]] > #2[[2]] &] [[1, 1]];
BestVerticalSynergyModel =
  SetMaximumTimeAndNormalizePopulationSize[SynergyModel[0, BestVerticalSynergyParameter], LongestTime, TrialPopulationSize];
```

```
Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]][x],
  SurvivalFunction[EmpiricalDistribution[BestVerticalSynergyModel]][x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]][x]
}, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None, PlotStyle ->
{Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Red, AbsoluteThickness[1]], Directive[ColorData[3, 6], AbsoluteThickness[1]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 10}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]}, AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[ColorData[3, 6], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]
```

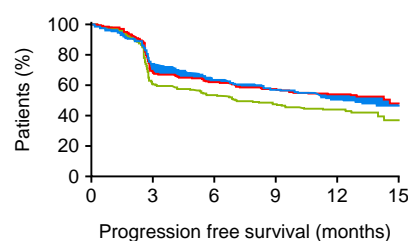
```
Export[NotebookDirectory[] <> "MelanomaIpilimumabNivolumabBestVerticalSynergy.pdf", %, "PDF"];
```



```
BestTwoParameterSynergyParameters = Sort[Flatten[SynergyModelTwoParameterFits, 1], #1[[3]] > #2[[3]] &] [[1, {1, 2}]];
BestTwoParameterSynergyModel = SetMaximumTimeAndNormalizePopulationSize[
  SynergyModel[BestTwoParameterSynergyParameters[[1]], BestTwoParameterSynergyParameters[[2]], LongestTime, TrialPopulationSize];
```

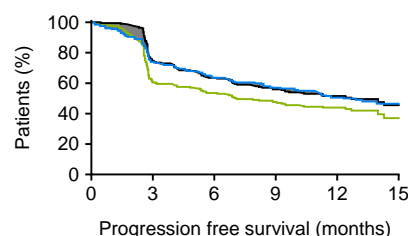
```
Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]][x],
  SurvivalFunction[EmpiricalDistribution[BestTwoParameterSynergyModel]][x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]][x]
}, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None, PlotStyle ->
{Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Red, AbsoluteThickness[1]], Directive[ColorData[3, 6], AbsoluteThickness[1]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 10}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]}, AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[ColorData[3, 6], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]
```

```
Export[NotebookDirectory[] <> "MelanomaIpilimumabNivolumabBestTwoParameterSynergy.pdf", %, "PDF"];
```



```
Plot[{
  SurvivalFunction[EmpiricalDistribution[MaximumOfMonotherapyResponsesModel]][x],
  SurvivalFunction[EmpiricalDistribution[IndependentActionModel]][x],
  SurvivalFunction[EmpiricalDistribution[ObservedDistribution]][x]}
, {x, 0, LongestTime}, PlotRange -> {{0, LongestTime}, {0, 1.01}}, Exclusions -> None,
PlotStyle -> {Directive[ColorData[3, 4], AbsoluteThickness[1]], Directive[Black, AbsoluteThickness[1]],
  Directive[ColorData[3, 6], AbsoluteThickness[1]]}, BaseStyle -> {FontFamily -> "Arial", FontSize -> 10},
FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)", Style["Patients (%)"]], AspectRatio -> 1 / 2, Filling -> {2 -> {3}},
FillingStyle -> Directive[GrayLevel[0.5], Opacity[1]], ImageSize -> {{1000}, {150}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 100]

Export[NotebookDirectory[] <> "MelanomaIpilimumabNivolumabIndependentModel.pdf", %, "PDF"];
```



## Comparison of Akaike Information Criterion across 5 trials of combination therapies that are proposed to be consistent with independent drug action

From prior code analyzing each trial we have a list of likelihoods, according to the Kolmogorov Smirnov test, that the clinically observed distribution of progression free survival times was sampled from a given model distribution.

For each trial these likelihoods are listed in the following order of models:

- Independent Drug Action
- Synergy modeled by horizontal scaling of PFS
- Synergy modeled by vertical scaling of PFS
- Synergy modeled by both horizontal and vertical scaling of PFS

**OvarianModelLikelihoods**

```
{0.282906, 0.194886, 0.0334129, 0.236928}
```

**BreastCancerModelLikelihoods**

```
{0.256073, 0.0637858, 0.00280818, 0.0637858}
```

**PancreaticCancerModelLikelihoods**

```
{0.84823, 0.534329, 0.982653, 0.98425}
```

**MelanomaImmunotherapyModelLikelihoods**

```
{0.18755, 0.0620466, 0.597943, 0.685605}
```

**MelanomaKinaseModelLikelihoods**

```
{0.686, 0.142044, 0.176931, 0.178926}
```

For each model, the likelihood that the observed PFS distributions from each of the above trials were sampled from that model is the product of the likelihoods across the above trials.

**ProductOfLikelihoods = OvarianModelLikelihoods \* BreastCancerModelLikelihoods \***

**PancreaticCancerModelLikelihoods \* MelanomaImmunotherapyModelLikelihoods \* MelanomaKinaseModelLikelihoods**

```
{0.0079061, 0.0000585401, 9.75445 × 10-6, 0.0018247}
```

Akaike Information Criterion is calculated as

$$AIC = \text{Log}(\text{likelihood}) - 2 \times k$$

where  $k$  is the number of fitted parameters.

**Log[ProductOfLikelihoods]**

```
{-4.84012, -9.7458, -11.5378, -6.30634}
```

```
(* The Independent action model, as implemented here, applied one parameter - response correlation -
for all five trials. Though in this case it is not 'fitted' but determined from experimental data (see Figure 2A) *)
IndependentActionParameterCount = 1;
(* the 'horizontal parameter' and 'vertical parameter' synergy models involve one scaling parameter per trial,
for a total of 5 fitted parameters *)
SynergyHorizontalParameterCount = 5;
SynergyVerticalParameterCount = 5;
(* the 'horizontal and vertical' scaling synergy model involves two parameters per trial, for a total of 10 fitted parameters *)
SynergyHorizontalandVerticalParameterCount = 10;

(* calculating AIC scores *)
IndependentActionAIC = 2 * IndependentActionParameterCount - 2 * Log[ProductOfLikelihoods[[1]]]
SynergyHorizontalAIC = 2 * SynergyHorizontalParameterCount - 2 * Log[ProductOfLikelihoods[[2]]]
SynergyVerticalAIC = 2 * SynergyVerticalParameterCount - 2 * Log[ProductOfLikelihoods[[3]]]
SynergyTwoParameterAIC = 2 * SynergyHorizontalandVerticalParameterCount - 2 * Log[ProductOfLikelihoods[[4]]]
11.6802

29.4916

33.0756

32.6127

(* the smallest AIC value is used to calculate the relative likelihoods that different models minimize information loss *)
AICmin = Min[{IndependentActionAIC, SynergyHorizontalAIC, SynergyVerticalAIC, SynergyTwoParameterAIC}]
11.6802
```

The relative likelihood that a given model minimizes information\loss, according to Akaike, is  $\text{Exp}(\frac{\text{AIC}_{\text{minimum}} - \text{AIC}}{2})$

```
RelativeLikelihoodOfIndependentAction = Exp[(AICmin - IndependentActionAIC) / 2]
RelativeLikelihoodOfSynergyHorizontal = Exp[(AICmin - SynergyHorizontalAIC) / 2]
RelativeLikelihoodOfSynergyVertical = Exp[(AICmin - SynergyVerticalAIC) / 2]
RelativeLikelihoodOfSynergyTwoParameter = Exp[(AICmin - SynergyTwoParameterAIC) / 2]
1.

0.000135617

0.0000225976

0.0000284826

(* calculating the inverse of the relative likelihood to express
likelihood as a ratio (see table in Supplementary Note on Akaike Information Criterion) *)
RelativeLikelihoodOfIndependentAction / RelativeLikelihoodOfSynergyHorizontal
RelativeLikelihoodOfIndependentAction / RelativeLikelihoodOfSynergyVertical
RelativeLikelihoodOfIndependentAction / RelativeLikelihoodOfSynergyTwoParameter
7373.72

44252.4

35109.1
```

Akaike information criterion is not applied to the trials analyzed in Figures 4E, F, G because the clinically observed responses clearly surpass the model of independent action and must involve additive or synergistic benefit within individual patients.

## Figure 4E - Recurrent platinum-sensitive ovarian cancer (bevacizumab + gemcitabine/carboplatin)

Near-identical code as for Figure 4A is here employed to generate Figure 4E. Comments will be more brief.

```
Figure4ERawData = Import[NotebookDirectory[] <> "Table of survival distributions.xlsx", "XLSX"][[7(* the seventh tab of this spreadsheet*)]];
Therapy1SurvivalDistribution =
  Select[Figure4ERawData[[8 ;;, 2(* column 2 of this spreadsheet contains PFS data for gemcitabine+carboplatin*)]], NumberQ];
Therapy2SurvivalDistribution = Select[Figure4ERawData[[8 ;;, 3
  (* column 3 of this spreadsheet contains PFS data for bevacizumab*)]], NumberQ];
ComboSurvivalDistribution = Select[Figure4ERawData[[8 ;;, 4(* column 4 of this spreadsheet contains PFS data for the combination*)]],
  NumberQ];

ρ = 0.28

Length[Therapy1SurvivalDistribution]
Length[Therapy2SurvivalDistribution]
2185

1719
```

```
(* how many repeats of the complete data set to merge together
(for purpose of minimizing variance between individual repeats of the 'rank randomization' process) *)
resamplingfactor = 10;
(* within each 'resample',
need to sub-sample the gemcitabine+carboplatin distribution (more vertical pixels than the bevacizumab distribution). The
number of pixels is vastly in excess of the number of patients so no individual patient's information is lost. *)
ReSampledTherapy1SurvivalDistribution =
  Reverse[Sort[Flatten[Table[RandomSample[Therapy1SurvivalDistribution, Length[Therapy2SurvivalDistribution]], {resamplingfactor}]]]];
ReSampledTherapy2SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy2SurvivalDistribution, {resamplingfactor}]]]];

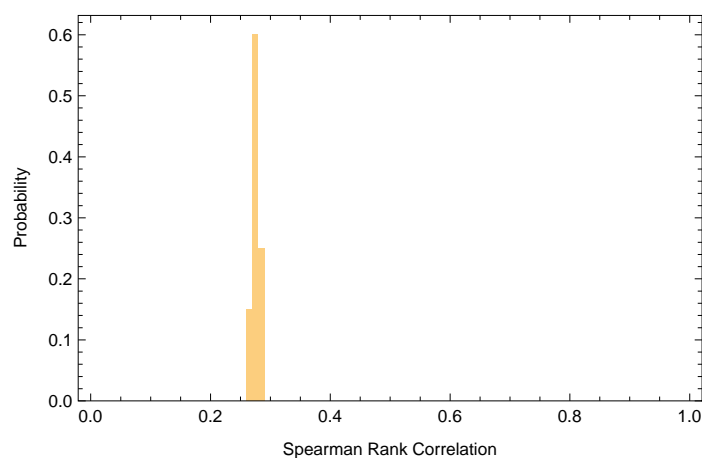
(* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.28 *)
amountofrankrandomization = 15500;

SlightlyRandomizedTherapy1Distribution =
  Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
    {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
BestOfMidCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];

SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]]
0.281865

(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.28 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 15500;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]]
  , {20}];

Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame -> True, FrameLabel -> {"Spearman Rank Correlation", "Probability"}]
Mean response correlation = 0.276
```



```
(* after generating the distribution of survival times predicted by independent drug action,
we can remove the 'resampling' to plot the results. With a resampling factor of 10,
this is achieved by sorting the distribution and keeping every 10th entry *)
SubSampledBestOfMidCorrelatedMonoPairs = Take[Reverse[Sort[BestOfMidCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

$\rho = 0.08$

```
resamplingfactor = 10;
ReSampledTherapy1SurvivalDistribution =
  Reverse[Sort[Flatten[Table[RandomSample[Therapy1SurvivalDistribution, Length[Therapy2SurvivalDistribution]], {resamplingfactor}]]]];
ReSampledTherapy2SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy2SurvivalDistribution, {resamplingfactor}]]]];

(* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.08 *)
amountofrankrandomization = 53000;

SlightlyRandomizedTherapy1Distribution =
  Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
    {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
BestOfLowCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];

SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]]
0.0789296
```

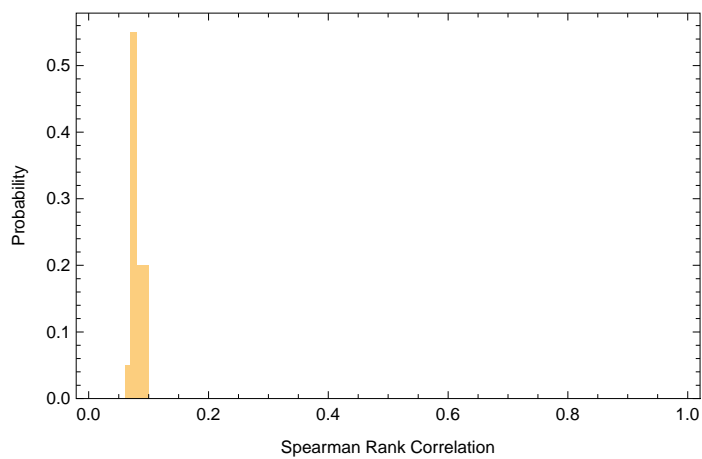


```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.08 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 53000;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
    , {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

Mean response correlation = 0.08



(\* after generating the distribution of survival times predicted by independent drug action,  
we can remove the 'resampling' to plot the results. With a resampling factor of 10,  
this is achieved by sorting the distribution and keeping every 10th entry \*)

```
SubSampledBestOfLowCorrelatedMonoPairs = Take[Reverse[Sort[BestOfLowCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

$\rho = 0.48$

```
resamplingfactor = 10;
```

```
ReSampledTherapy1SurvivalDistribution =
```

```
Reverse[Sort[Flatten[Table[RandomSample[Therapy1SurvivalDistribution, Length[Therapy2SurvivalDistribution]], {resamplingfactor}]]]]];
```

```
ReSampledTherapy2SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy2SurvivalDistribution, {resamplingfactor}]]]]];
```

(\* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.48 \*)

```
amountofrankrandomization = 8900;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
  {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
BestOfHighCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
```

```
0.487883
```

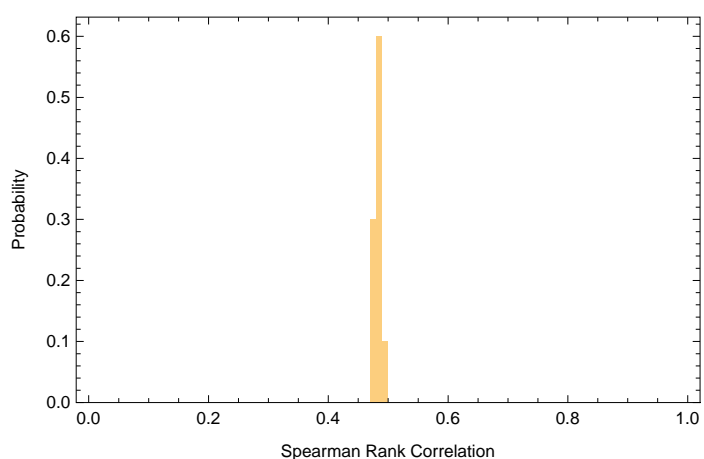


```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.48 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 8900;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
    , {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

```
Mean response correlation = 0.483
```



```
(* after generating the distribution of survival times predicted by independent drug action,
we can remove the 'resampling' to plot the results. With a resampling factor of 10,
this is achieved by sorting the distribution and keeping every 10th entry *)
```

```
SubSampledBestOfHighCorrelatedMonoPairs = Take[Reverse[Sort[BestOfHighCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

Computing median PFS for each condition: the observed individual therapies, the observed combination, and the simulated effects with high, medium, or low response correlation (respectively,  $\rho = 0.48, 0.28, 0.08$ )

```
Mono1Median = Round[Median[Therapy1SurvivalDistribution], 0.01]
Mono2Median = Round[Median[Therapy2SurvivalDistribution], 0.01]
ComboMedian = Round[Median[ComboSurvivalDistribution], 0.01]
Sim1Median = Round[Median[SubSampledBestOfHighCorrelatedMonoPairs], 0.01]
Sim2Median = Round[Median[SubSampledBestOfMidCorrelatedMonoPairs], 0.01]
Sim3Median = Round[Median[SubSampledBestOfLowCorrelatedMonoPairs], 0.01]
```

```
8.31
```

```
4.63
```

```
12.24
```

```
10.2
```

```
10.32
```

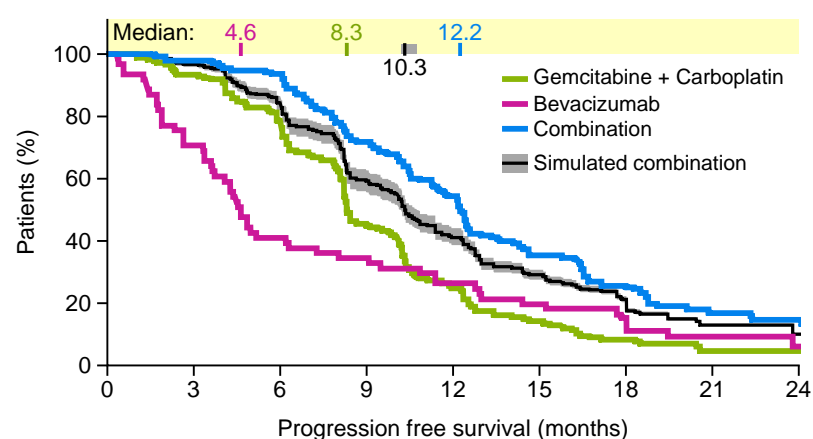
```
10.74
```

## Plotting the observed and simulated survival functions

```
(*legend vertical offset*)
lo = 0.58;
(*simulated*)slo = -0.03;
(* legend horizontal offset *)
lho = 13;

Plot[{
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfHighCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfMidCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfLowCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[Therapy1SurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[Therapy2SurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[ComboSurvivalDistribution]][x]
}, {x, 0, 26}, PlotRange -> {{0, 24.0}, {0, 1.11}}, Exclusions -> None,
PlotStyle -> {Directive[Black, Opacity[0]], Directive[Black, AbsoluteThickness[1.7]], Directive[Black, Opacity[0]], Directive[ColorData[3, 4],
  AbsoluteThickness[3]], Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[3]], Directive[ColorData[3, 6], AbsoluteThickness[3]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 12}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.015}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.015}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]},
Prolog -> {Gray, Thickness[Medium], Lighter[Yellow, 0.75], EdgeForm[None], Rectangle[{0, 1}, {24, 1.11}],
  Black, AbsoluteThickness[1.7], GrayLevel[0.65], Rectangle[{Sim1Median, 1}, {Sim3Median, 1.03}], Black, Opacity[1],
  Line[{Sim2Median, 1}, {Sim2Median, 1.03}], Text["Median:", {0.2, 1.03}, {-1, -1}], Darker[ColorData[3, 4], 0.1],
  Text["8.3", {Mono1Median, 1.03}, {0, -1}], RGBColor[0.8, 0.1, 0.6], Text["4.6", {Mono2Median, 1.03}, {0, -1}],
  ColorData[3, 6], Text["12.2", {ComboMedian, 1.03}, {0, -1}], Black, Text["10.3", {Sim2Median, 1.0}, {0, 1}],
  AbsoluteThickness[2], Darker[ColorData[3, 4], 0.1], Line[{Mono1Median, 1}, {Mono1Median, 1.03}], RGBColor[0.8, 0.1, 0.6],
  Line[{Mono2Median, 1}, {Mono2Median, 1.03}], ColorData[3, 6], Line[{ComboMedian, 1}, {ComboMedian, 1.03}]},
AspectRatio -> 1 / 2, Filling -> {1 -> {3}}, FillingStyle -> Directive[GrayLevel[0.65], Opacity[1]],
ImageSize -> {{1000}, {250}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 500,
Epilog -> {EdgeForm[Directive[Black, Thickness[Medium]]], White, Opacity[1], EdgeForm[None], CapForm["Butt"], AbsoluteThickness[3],
  AbsolutePointSize[8], ColorData[3, 4], Line[{lho + 0.7, 0.34 + lo}, {lho + 1.6, 0.34 + lo}], RGBColor[0.8, 0.1, 0.6],
  Line[{lho + 0.7, 0.26 + lo}, {lho + 1.6, 0.26 + lo}], ColorData[3, 6], Line[{lho + 0.7, 0.18 + lo}, {lho + 1.6, 0.18 + lo}],
  Opacity[1], GrayLevel[0.65], Rectangle[{lho + 0.7, 0.1 - 0.03 + lo + slo}, {lho + 1.6, 0.1 + 0.03 + lo + slo}], Black,
  Opacity[1], AbsoluteThickness[1.7], Line[{lho + 0.7, 0.1 + lo + slo}, {lho + 1.6, 0.1 + lo + slo}], FontFamily -> "Arial",
  FontSize -> 11, Text[Style["Gemcitabine + Carboplatin", FontSize -> 11], {lho + 1.8, 0.34 + lo}, {-1, 0}],
  Text[Style["Bevacizumab", FontSize -> 11], {lho + 1.8, 0.26 + lo}, {-1, 0}], Text[Style["Combination", FontSize -> 11],
  {lho + 1.8, 0.18 + lo}, {-1, 0}], Text[Style["Simulated combination", FontSize -> 11], {lho + 1.8, 0.1 + lo + slo}, {-1, 0}]}]

Export[NotebookDirectory[] <> "Figure 4E.pdf", %, "PDF"];
```



## Calculating the improvement in hazard ratio attributable to drug synergy.

This is the hazard ratio between the observed combination trial results, and the combination trial results calculated on the assumption of 'no additivity or synergy'.

```
CensoringTime = 12 (* months *);

PatientsPerArmOfSimulatedTrial = 1000;
IndependentActionSimulatedTrial[] := RandomChoice[SubSampledBestOfMidCorrelatedMonoPairs, PatientsPerArmOfSimulatedTrial]
CombinationSimulatedTrial[] := RandomChoice[ComboSurvivalDistribution, PatientsPerArmOfSimulatedTrial]

GenerateCensoredEventData[PatientResponses_, CensoringTime_] :=
Module[{ResponsesShorterThanCensoringTime, ResponsesLongerThanCensoringTime},
  ResponsesShorterThanCensoringTime = Select[PatientResponses, # ≤ CensoringTime &];
  ResponsesLongerThanCensoringTime = Select[PatientResponses, # > CensoringTime &];
  EventData[Join[ResponsesShorterThanCensoringTime, ResponsesLongerThanCensoringTime],
    Join[Table[0, {Length[ResponsesShorterThanCensoringTime]}], Table[1, {Length[ResponsesLongerThanCensoringTime]}]]]
]

IndependentActionSimulatedEventData[] := GenerateCensoredEventData[IndependentActionSimulatedTrial[], CensoringTime]
CombinationSimulatedEventData[] := GenerateCensoredEventData[CombinationSimulatedTrial[], CensoringTime]

(* custom function to join two sets of event data - this is necessary to implement the Cox Proportional Hazards model *)
JoinEventData[EventData1_, EventData2_] := EventData[Join[EventData1[[2, 1]], EventData2[[2, 1]], Join[EventData1[[2, 2]], EventData2[[2, 2]]]]

MergedEventData[] := JoinEventData[IndependentActionSimulatedEventData[], CombinationSimulatedEventData[]];
Descriptors[] := Join[Table["Independence", {PatientsPerArmOfSimulatedTrial}], Table["Observed", {PatientsPerArmOfSimulatedTrial}]];
```

Note that the error range in the hazard ratio depends on the population size in a simulated trial of the combination, and the duration on trial, that is, the rate of censoring events.

Here we compute error ranges expected from 200 patients per trial arm, with any that are progression-free after a defined time being 'censored'. This limits imprecision arising from the source PFS data having few patients 'on-trial' at late times, which is cause of increasing error range in PFS probability at longer times.

The range in hazard ratio is robustly identified by taking the mean over 100 simulations of such trials.

```
NumberOfReplicateTrials = 100;

(* this function returns the relative risk, and confidence interval, in the format:
  (95% lower confidence interval, median estimate, 95% upper confidence interval )
*)
RelativeRiskCalculation[descriptors_, eventdata_, PrintTable_
  (* set to 1 to print to screen the statistical table of Cox Model output; set to 0 to not show output *) := Module[{},
    MyModelFit = CoxModelFit[{descriptors, eventdata}, {treatment}, {treatment}, NominalVariables → treatment];

    If[PrintTable == 1, Print[MyModelFit["ParameterTable"]]];

    RelativeRisk = MyModelFit["RelativeRisk"][[1]];
    RelativeRiskLowerConfidenceInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1, 1]];
    RelativeRiskUpperConfidenceInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1, 2]];

    {RelativeRiskLowerConfidenceInterval, RelativeRisk, RelativeRiskUpperConfidenceInterval}
  ]

(* single execution of the simulated trial *)
RelativeRiskCalculation[Descriptors[], MergedEventData[], 1]

```

	Estimate	Standard Error	Relative Risk	Wald- $\chi^2$	DF	P-Value
treatment[Observed]	-0.339906	0.0620858	0.711837	29.9733	1	$4.3804 \times 10^{-8}$

```
{0.630279, 0.711837, 0.803948}

(* many replicate trial simulations, to accurately determine the range in hazard ratio *)
OvarianBevacizumabHazardRatioRange =
  Quiet@Mean[Table[RelativeRiskCalculation[Descriptors[], MergedEventData[], 0], {NumberOfReplicateTrials}]]
{0.592173, 0.669245, 0.75635}
```

## Figure 4F - Previously treated metastatic colorectal carcinoma

Near-identical code as for Figure 4A is here employed to generate Figure 4F. Comments will be more brief.

```
Figure4FRawData = Import[NotebookDirectory[] <> "Table of survival distributions.xlsx", "XLSX"][[8 (* the eighth tab of this spreadsheet *)]];
Therapy1SurvivalDistribution = Select[Figure4FRawData[[8 ;;, 2 (* column 2 of this spreadsheet contains PFS data for FOLFOX-4 *)]], NumberQ];
Therapy2SurvivalDistribution =
  Select[Figure4FRawData[[8 ;;, 3 (* column 3 of this spreadsheet contains PFS data for bevacizumab *)]], NumberQ];
ComboSurvivalDistribution = Select[Figure4FRawData[[8 ;;, 4
  (* column 4 of this spreadsheet contains PFS data for the combination *)]], NumberQ];
```

$\rho = 0.28$

```

Length[Therapy1SurvivalDistribution]
Length[Therapy2SurvivalDistribution]

2724

1420

(* how many repeats of the complete data set to merge together
   (for purpose of minimizing variance between individual repeats of the 'rank randomization' process) *)
resamplingfactor = 10;
(* within each 'resample', need to sub-sample the FOLFOX-4 distribution (more vertical pixels than the bevacizumab distribution). The
   number of pixels is vastly in excess of the number of patients so no individual patient's information is lost. *)
ReSampledTherapy1SurvivalDistribution =
  Reverse[Sort[Flatten[Table[RandomSample[Therapy1SurvivalDistribution, Length[Therapy2SurvivalDistribution]], {resamplingfactor}]]]];
ReSampledTherapy2SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy2SurvivalDistribution, {resamplingfactor}]]]];

(* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.28 *)
amountofrankrandomization = 12700;

SlightlyRandomizedTherapy1Distribution =
  Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
    {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
BestOfMidCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];

SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]]

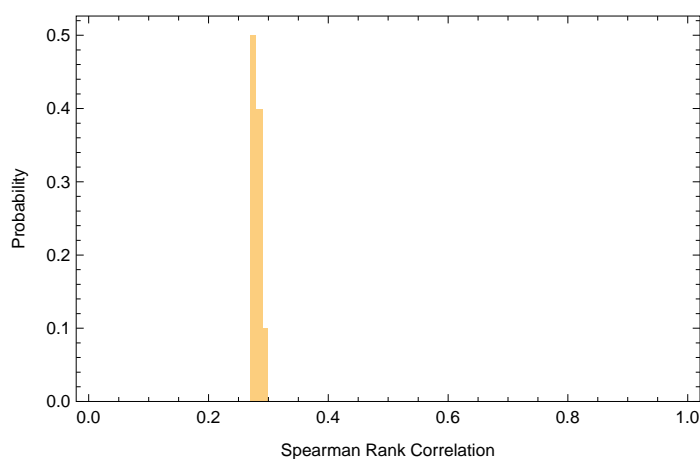
0.27561

(* Repeating the randomization procedure 20 times to show that
   response correlation is tightly distributed around the targeted value of 0.28 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 12700;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]]
  , {20}];

Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame -> True, FrameLabel -> {"Spearman Rank Correlation", "Probability"}]

Mean response correlation = 0.281

```



```

(* after generating the distribution of survival times predicted by independent drug action,
   we can remove the 'resampling' to plot the results. With a resampling factor of 10,
   this is achieved by sorting the distribution and keeping every 10th entry *)
SubSampledBestOfMidCorrelatedMonoPairs = Take[Reverse[Sort[BestOfMidCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];

```

$\rho = 0.08$

```

resamplingfactor = 10;
ReSampledTherapy1SurvivalDistribution =
  Reverse[Sort[Flatten[Table[RandomSample[Therapy1SurvivalDistribution, Length[Therapy2SurvivalDistribution]], {resamplingfactor}]]]];
ReSampledTherapy2SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy2SurvivalDistribution, {resamplingfactor}]]]];

```

```
(* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.08 *)
```

```
amountofrankrandomization = 44500;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],  
{i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],  
ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
BestOfLowCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]}],  
{i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[All, 2], SlightlyRandomizedTherapy2Distribution[All, 2]]
```

```
0.0869299
```

```
(* Repeating the randomization procedure 20 times to show that  
response correlation is tightly distributed around the targeted value of 0.08 *)
```

```
TableOfCorrelationsFromRepeats = Table[
```

```
amountofrankrandomization = 44500;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],  
{i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],  
ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

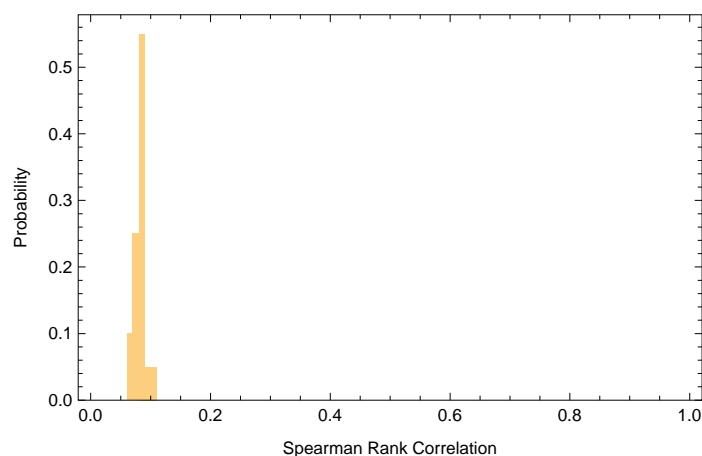
```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[All, 2], SlightlyRandomizedTherapy2Distribution[All, 2]]  
, {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
```

```
"Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

```
Mean response correlation = 0.082
```



```
(* after generating the distribution of survival times predicted by independent drug action,  
we can remove the 'resampling' to plot the results. With a resampling factor of 10,  
this is achieved by sorting the distribution and keeping every 10th entry *)
```

```
SubSampledBestOfLowCorrelatedMonoPairs = Take[Reverse[Sort[BestOfLowCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

$\rho = 0.48$

```
resamplingfactor = 10;
```

```
ReSampledTherapy1SurvivalDistribution =
```

```
Reverse[Sort[Flatten[Table[RandomSample[Therapy1SurvivalDistribution, Length[Therapy2SurvivalDistribution]], {resamplingfactor}]]]]];
```

```
ReSampledTherapy2SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy2SurvivalDistribution, {resamplingfactor}]]]]];
```

```
(* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.48 *)
```

```
amountofrankrandomization = 7400;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],  
{i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],  
ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

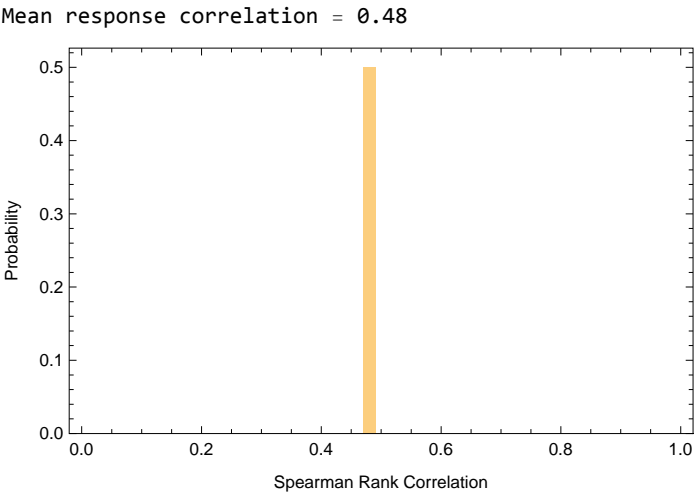
```
BestOfHighCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]}],  
{i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[All, 2], SlightlyRandomizedTherapy2Distribution[All, 2]]
```

```
0.482422
```

```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.48 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 7400;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
    {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
  , {20}];

Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame -> True, FrameLabel -> {"Spearman Rank Correlation", "Probability"}]
```



```
(* after generating the distribution of survival times predicted by independent drug action,
we can remove the 'resampling' to plot the results. With a resampling factor of 10,
this is acheived by sorting the distribution and keeping every 10th entry *)
SubSampledBestOfHighCorrelatedMonoPairs = Take[Reverse[Sort[BestOfHighCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

Computing median PFS for each condition: the observed individual therapies, the observed combination, and the simulated effects with high, medium, or low response correlation (respectively,  $\rho = 0.48, 0.28, 0.08$ )

```
Mono1Median = Round[Median[Therapy1SurvivalDistribution], 0.01]
Mono2Median = Round[Median[Therapy2SurvivalDistribution], 0.01]
ComboMedian = Round[Median[ComboSurvivalDistribution], 0.01]
Sim1Median = Round[Median[SubSampledBestOfHighCorrelatedMonoPairs], 0.01]
Sim2Median = Round[Median[SubSampledBestOfMidCorrelatedMonoPairs], 0.01]
Sim3Median = Round[Median[SubSampledBestOfLowCorrelatedMonoPairs], 0.01]

4.44

2.58

7.35

5.37

5.63

5.84
```

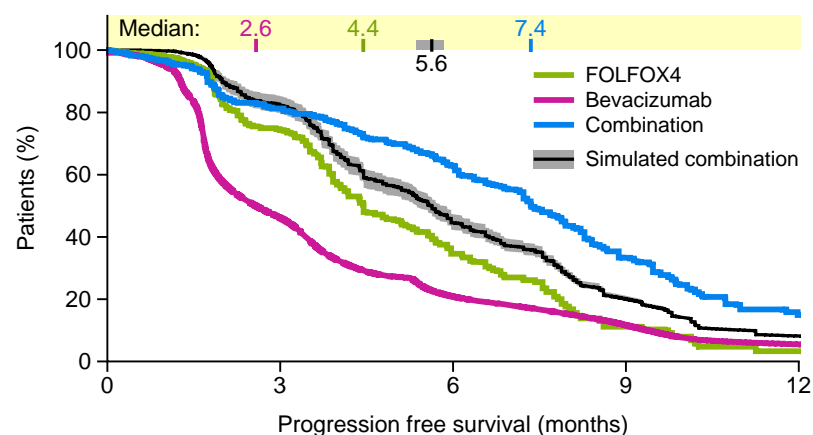


## Plotting the observed and simulated survival functions

```
(*legend vertical offset*)
lo = 0.58;
(*simulated*)slo = -0.03;
(* legend horizontal offset *)
lho = 6.5;

Plot[{
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfHighCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfMidCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfLowCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[Therapy1SurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[Therapy2SurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[ComboSurvivalDistribution]][x]
}, {x, 0, 13}, PlotRange -> {{0, 12.0}, {0, 1.11}}, Exclusions -> None,
PlotStyle -> {Directive[Black, Opacity[0]], Directive[Black, AbsoluteThickness[1.7]], Directive[Black, Opacity[0]], Directive[ColorData[3, 4],
  AbsoluteThickness[3]], Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[3]], Directive[ColorData[3, 6], AbsoluteThickness[3]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 12}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.015}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.015}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)"], Style["Patients (%)"]},
Prolog -> {Gray, Thickness[Medium], Lighter[Yellow, 0.75], EdgeForm[None], Rectangle[{0, 1}, {18, 1.11}],
  Black, AbsoluteThickness[1.7], GrayLevel[0.65], Rectangle[{Sim1Median, 1}, {Sim3Median, 1.03}], Black, Opacity[1],
  Line[{Sim2Median, 1}, {Sim2Median, 1.03}], Text["Median:", {0.2, 1.03}, {-1, -1}], Darker[ColorData[3, 4], 0.1],
  Text["4.4", {Mono1Median, 1.03}, {0, -1}], RGBColor[0.8, 0.1, 0.6], Text["2.6", {Mono2Median, 1.03}, {0, -1}],
  ColorData[3, 6], Text["7.4", {ComboMedian, 1.03}, {0, -1}], Black, Text["5.6", {Sim2Median, 1.0}, {0, 1}],
  AbsoluteThickness[2], Darker[ColorData[3, 4], 0.1], Line[{Mono1Median, 1}, {Mono1Median, 1.03}], RGBColor[0.8, 0.1, 0.6],
  Line[{Mono2Median, 1}, {Mono2Median, 1.03}], ColorData[3, 6], Line[{ComboMedian, 1}, {ComboMedian, 1.03}]},
AspectRatio -> 1 / 2, Filling -> {1 -> {3}}, FillingStyle -> Directive[GrayLevel[0.65], Opacity[1]],
ImageSize -> {{1000}, {250}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 500,
Epilog -> {EdgeForm[Directive[Black, Thickness[Medium]]], White, Opacity[1], EdgeForm[None], CapForm["Butt"], AbsoluteThickness[3],
  AbsolutePointSize[8], ColorData[3, 4], Line[{lho + 0.9, 0.34 + lo}, {lho + 1.6, 0.34 + lo}], RGBColor[0.8, 0.1, 0.6],
  Line[{lho + 0.9, 0.26 + lo}, {lho + 1.6, 0.26 + lo}], ColorData[3, 6], Line[{lho + 0.9, 0.18 + lo}, {lho + 1.6, 0.18 + lo}],
  Opacity[1], GrayLevel[0.65], Rectangle[{lho + 0.9, 0.1 - 0.03 + lo + slo}, {lho + 1.6, 0.1 + 0.03 + lo + slo}],
  Black, Opacity[1], AbsoluteThickness[1.7], Line[{lho + 0.9, 0.1 + lo + slo}, {lho + 1.6, 0.1 + lo + slo}],
  FontFamily -> "Arial", FontSize -> 11, Text[Style["FOLFOX4", FontSize -> 11], {lho + 1.8, 0.34 + lo}, {-1, 0}],
  Text[Style["Bevacizumab", FontSize -> 11], {lho + 1.8, 0.26 + lo}, {-1, 0}], Text[Style["Combination", FontSize -> 11],
  {lho + 1.8, 0.18 + lo}, {-1, 0}], Text[Style["Simulated combination", FontSize -> 11], {lho + 1.8, 0.1 + lo + slo}, {-1, 0}]}]

Export[NotebookDirectory[] <> "Figure 4F.pdf", %, "PDF"];
```



Calculating the improvement in hazard ratio attributable to drug synergy.  
This is the hazard ratio between the observed combination trial results, and the combination trial results calculated on the assumption of 'no additivity or synergy'.

```
CensoringTime = 12(* months *);

PatientsPerArmOfSimulatedTrial = 1000;
IndependentActionSimulatedTrial[] := RandomChoice[SubSampledBestOfMidCorrelatedMonoPairs, PatientsPerArmOfSimulatedTrial]
CombinationSimulatedTrial[] := RandomChoice[ComboSurvivalDistribution, PatientsPerArmOfSimulatedTrial]

GenerateCensoredEventData[PatientResponses_, CensoringTime_] :=
Module[{ResponsesShorterThanCensoringTime, ResponsesLongerThanCensoringTime},
  ResponsesShorterThanCensoringTime = Select[PatientResponses, # <= CensoringTime &];
  ResponsesLongerThanCensoringTime = Select[PatientResponses, # > CensoringTime &];
  EventData[Join[ResponsesShorterThanCensoringTime, ResponsesLongerThanCensoringTime],
    Join[Table[0, {Length[ResponsesShorterThanCensoringTime]}], Table[1, {Length[ResponsesLongerThanCensoringTime]}]]]
]

IndependentActionSimulatedEventData[] := GenerateCensoredEventData[IndependentActionSimulatedTrial[], CensoringTime]
CombinationSimulatedEventData[] := GenerateCensoredEventData[CombinationSimulatedTrial[], CensoringTime]

(* custom function to join two sets of event data - this is necessary to implement the Cox Proportional Hazards model *)
JoinEventData[EventData1_, EventData2_] := EventData[Join[EventData1[[2, 1]], EventData2[[2, 1]], Join[EventData1[[2, 2]], EventData2[[2, 2]]]]

MergedEventData[] := JoinEventData[IndependentActionSimulatedEventData[], CombinationSimulatedEventData[]];
Descriptors[] := Join[Table["Independence", {PatientsPerArmOfSimulatedTrial}], Table["Observed", {PatientsPerArmOfSimulatedTrial}]];
```

Note that the error range in the hazard ratio depends on the population size in a simulated trial of the combination, and the duration on trial, that is, the rate of censoring events.  
Here we compute error ranges expected from 200 patients per trial arm, with any that are progression-free after a defined time being ‘censored’. This limits imprecision arising from the source PFS data having few patients ‘on-trial’ at late times, which is cause of increasing error range in PFS probability at longer times.

The range in hazard ratio is robustly identified by taking the mean range over 100 simulations of such trials.

```
NumberOfReplicateTrials = 100;

(* this function returns the relative risk, and confidence interval, in the format:
  (95% lower confidence interval, median estimate, 95% upper confidence interval )
*)
RelativeRiskCalculation[descriptors_, eventdata_, PrintTable_
  (* set to 1 to print to screen the statistical table of Cox Model output; set to 0 to not show output *) := Module[{},
    MyModelFit = CoxModelFit[{descriptors, eventdata}, {treatment}, {treatment}, NominalVariables -> treatment];

    If[PrintTable == 1, Print[MyModelFit["ParameterTable"]]];

    RelativeRisk = MyModelFit["RelativeRisk"][[1]];
    RelativeRiskLowerConfidenceInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1, 1]];
    RelativeRiskUpperConfidenceInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1, 2]];

    {RelativeRiskLowerConfidenceInterval, RelativeRisk, RelativeRiskUpperConfidenceInterval}
  ]

(* single execution of the simulated trial *)
RelativeRiskCalculation[Descriptors[], MergedEventData[], 1]

```

	Estimate	Standard Error	Relative Risk	Wald- $\chi^2$	DF	P-Value
treatment[Observed]	-0.318613	0.0475723	0.727157	44.8557	1	$2.12097 \times 10^{-11}$

```
{0.662422, 0.727157, 0.798219}

(* many replicate trial simulations, to accurately determine the range in hazard ratio *)
ColorectalBevacizumabHazardRatioRange =
  Quiet@Mean[Table[RelativeRiskCalculation[Descriptors[], MergedEventData[], 0], {NumberOfReplicateTrials}]]
{0.643758, 0.707167, 0.776822}
```

Figure 4G - Advanced pancreatic cancer, 5-fluorouracil plus oxaliplatin  
Near-identical code as for Figure 4A is here employed to generate Figure 4G. Comments will be more brief.

```
Figure4GRawData = Import[NotebookDirectory[] <> "Table of survival distributions.xlsx", "XLSX"][[9(* the ninth tab of this spreadsheet*)]];
```

```

Therapy1SurvivalDistribution =
  Select[Figure4GRawData[[8 ;;, 2(* column 2 of this spreadsheet contains PFS data for 5-fluorouracil*)]], NumberQ];
Therapy2SurvivalDistribution = Select[Figure4GRawData[[8 ;;, 3
  (* column 3 of this spreadsheet contains PFS data for oxaliplatin*)]], NumberQ];
ComboSurvivalDistribution = Select[Figure4GRawData[[8 ;;, 4(* column 4 of this spreadsheet contains PFS data for the combination*)]],
  NumberQ];

ρ = 0.28

Length[Therapy1SurvivalDistribution]
Length[Therapy2SurvivalDistribution]

1413

1415

(* how many repeats of the complete data set to merge together
  (for purpose of minimizing variance between individual repeats of the 'rank randomization' process) *)
resamplingfactor = 10;
ReSampledTherapy1SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy1SurvivalDistribution, {resamplingfactor}]]]];
ReSampledTherapy2SurvivalDistribution =
  Reverse[Sort[Flatten[Table[RandomSample[Therapy2SurvivalDistribution, Length[Therapy1SurvivalDistribution]], {resamplingfactor}]]]];

(* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.28 *)
amountofrankrandomization = 12500;

SlightlyRandomizedTherapy1Distribution =
  Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
    {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
BestOfMidCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]}],
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];

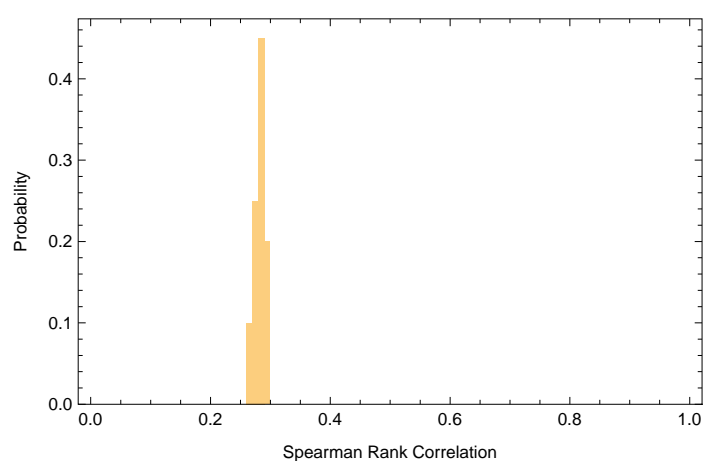
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]]
0.258164

(* Repeating the randomization procedure 20 times to show that
  response correlation is tightly distributed around the targeted value of 0.28 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 12500;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]]
  , {20}];

Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]

```

Mean response correlation = 0.281



```

(* after generating the distribution of survival times predicted by independent drug action,
  we can remove the 'resampling' to plot the results. With a resampling factor of 10,
  this is achieved by sorting the distribution and keeping every 10th entry *)
SubSampledBestOfMidCorrelatedMonoPairs = Take[Reverse[Sort[BestOfMidCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];

```

ρ = 0.08

```

resamplingfactor = 10;
ReSampledTherapy1SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy1SurvivalDistribution, {resamplingfactor}]]]];
ReSampledTherapy2SurvivalDistribution =
  Reverse[Sort[Flatten[Table[RandomSample[Therapy2SurvivalDistribution, Length[Therapy1SurvivalDistribution]], {resamplingfactor}]]]];

```

```
(* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.08 *)
```

```
amountofrankrandomization = 44 000;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],  
{i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],  
ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
BestOfLowCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]}],  
{i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]]
```

```
0.067472
```

```
(* Repeating the randomization procedure 20 times to show that
```

```
response correlation is tightly distributed around the targeted value of 0.08 *)
```

```
TableOfCorrelationsFromRepeats = Table[
```

```
amountofrankrandomization = 44 000;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],  
{i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],  
ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]]
```

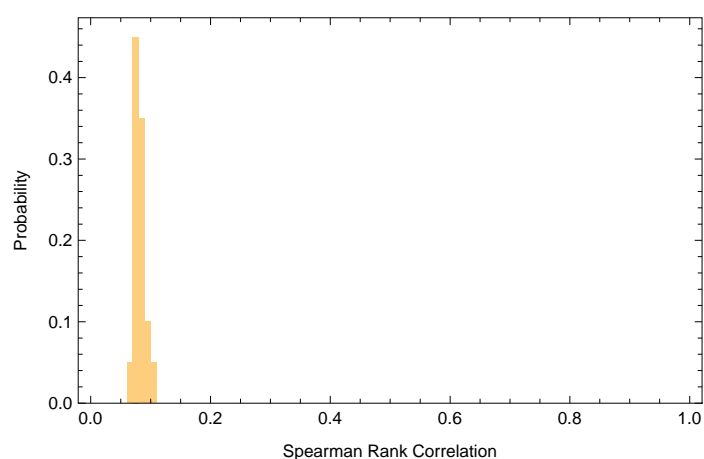
```
, {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
```

```
"Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

```
Mean response correlation = 0.081
```



```
(* after generating the distribution of survival times predicted by independent drug action,
```

```
we can remove the 'resampling' to plot the results. With a resampling factor of 10,
```

```
this is achieved by sorting the distribution and keeping every 10th entry *)
```

```
SubSampledBestOfLowCorrelatedMonoPairs = Take[Reverse[Sort[BestOfLowCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

$\rho = 0.48$

```
resamplingfactor = 10;
```

```
ReSampledTherapy1SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy1SurvivalDistribution, {resamplingfactor}]]]]];
```

```
ReSampledTherapy2SurvivalDistribution =
```

```
Reverse[Sort[Flatten[Table[RandomSample[Therapy2SurvivalDistribution, Length[Therapy1SurvivalDistribution]], {resamplingfactor}]]]]];
```

```
(* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.48 *)
```

```
amountofrankrandomization = 7400;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],  
{i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],  
ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
BestOfHighCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]}],  
{i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]]
```

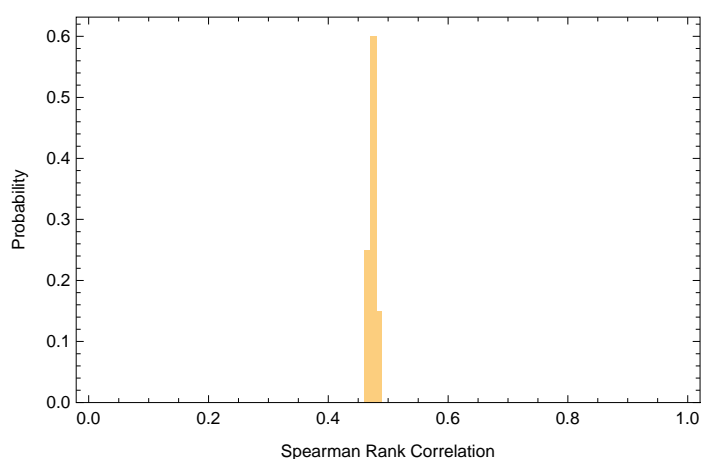
```
0.465801
```

```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.48 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 7400;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
    , {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

```
Mean response correlation = 0.474
```



```
(* after generating the distribution of survival times predicted by independent drug action,
we can remove the 'resampling' to plot the results. With a resampling factor of 10,
this is achieved by sorting the distribution and keeping every 10th entry *)
```

```
SubSampledBestOfHighCorrelatedMonoPairs = Take[Reverse[Sort[BestOfHighCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

Computing median PFS for each condition: the observed individual therapies, the observed combination, and the simulated effects with high, medium, or low response correlation (respectively,  $\rho = 0.48, 0.28, 0.08$ )

```
Mono1Median = Round[Median[Therapy1SurvivalDistribution], 0.01]
Mono2Median = Round[Median[Therapy2SurvivalDistribution], 0.01]
ComboMedian = Round[Median[ComboSurvivalDistribution], 0.01]
Sim1Median = Round[Median[SubSampledBestOfHighCorrelatedMonoPairs], 0.01]
Sim2Median = Round[Median[SubSampledBestOfMidCorrelatedMonoPairs], 0.01]
Sim3Median = Round[Median[SubSampledBestOfLowCorrelatedMonoPairs], 0.01]
```

```
1.49
```

```
1.93
```

```
4.18
```

```
2.01
```

```
2.01
```

```
2.01
```



## Plotting the observed and simulated survival functions

```
(*legend vertical offset*)
lo = 0.58;
(*simulated*)slo = -0.03;
(* legend horizontal offset *)
lho = 4.5;

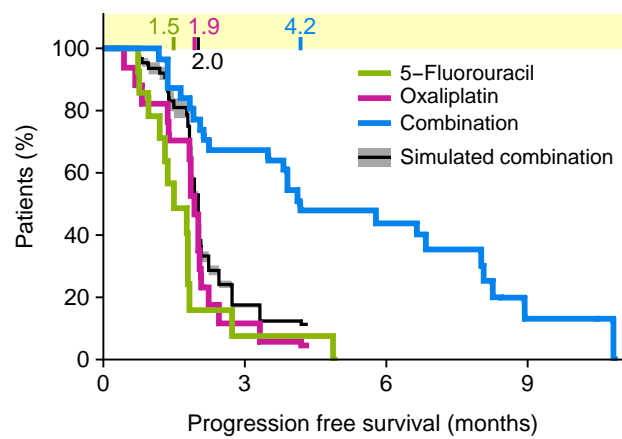
Show[

Plot[{
  SurvivalFunction[EmpiricalDistribution[SubSampledBESTOfHighCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBESTOfMidCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBESTOfLowCorrelatedMonoPairs]][x],

  SurvivalFunction[EmpiricalDistribution[Therapy2SurvivalDistribution]][x]
}, {x, 0, 4.3}, PlotRange -> {{0, 11}, {0, 1.11}}, Exclusions -> None,
PlotStyle -> {Directive[Black, Opacity[0]], Directive[Black, AbsoluteThickness[1.7]], Directive[Black, Opacity[0]],
  (*Directive[ColorData[3,4],AbsoluteThickness[3]](*,Directive[RGBColor[0.8,0.1,0.6],AbsoluteThickness[3]],
  Directive[ColorData[3, 6], AbsoluteThickness[3]]}, BaseStyle -> {FontFamily -> "Arial", FontSize -> 12},
FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.015}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.015}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)", Style["Patients (%)"]], AspectRatio -> 2 / 3, Filling -> {1 -> {3}},
FillingStyle -> Directive[GrayLevel[0.65], Opacity[1]], ImageSize -> {{1000}, {250}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 500]
,
Plot[{
  SurvivalFunction[EmpiricalDistribution[Therapy1SurvivalDistribution]][x]
}, {x, 0, 4.9}, PlotRange -> {{0, 11}, {0, 1.11}}, Exclusions -> None,
PlotStyle -> {(*Directive[Black,Opacity[0]],Directive[Black,AbsoluteThickness[1.7]],Directive[Black,Opacity[0]],*)
  Directive[ColorData[3, 4], AbsoluteThickness[3]](*,Directive[RGBColor[0.8,0.1,0.6],AbsoluteThickness[3]],
  Directive[ColorData[3,6],AbsoluteThickness[3]]*)}, BaseStyle -> {FontFamily -> "Arial", FontSize -> 12},
FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.015}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.015}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)", Style["Patients (%)"]], AspectRatio -> 2 / 3, Filling -> None,
FillingStyle -> Directive[GrayLevel[0.65], Opacity[1]], ImageSize -> {{1000}, {250}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 500]
,
Plot[{
  SurvivalFunction[EmpiricalDistribution[ComboSurvivalDistribution]][x]
}, {x, 0, 10.85}, PlotRange -> {{0, 11}, {0, 1.11}}, Exclusions -> None,
PlotStyle -> {(*Directive[Black,Opacity[0]],Directive[Black,AbsoluteThickness[1.7]],Directive[Black,Opacity[0]],Directive[ColorData[3,4],
  AbsoluteThickness[3]],Directive[RGBColor[0.8,0.1,0.6],AbsoluteThickness[3]],*)Directive[ColorData[3, 6], AbsoluteThickness[3]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 12}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.015}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.015}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)", Style["Patients (%)"]], AspectRatio -> 2 / 3, Filling -> None,
FillingStyle -> Directive[GrayLevel[0.65], Opacity[1]], ImageSize -> {{1000}, {250}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 500]
,
Prolog -> {Gray, Thickness[Medium], Lighter[Yellow, 0.75], EdgeForm[None], Rectangle[{0, 1}, {11, 1.11}],
  Black, AbsoluteThickness[1.7], GrayLevel[0.65], Rectangle[{Sim1Median, 1}, {Sim3Median, 1.03}], Black,
  Opacity[1], Line[{Sim2Median, 1}, {Sim2Median, 1.03}], Text["", {0.12, 1.03}, {-1, -1}], Darker[ColorData[3, 4], 0.1],
  Text["1.5", {Mono1Median, 1.03}, {0, -1}], RGBColor[0.8, 0.1, 0.6], Text["1.9", {Mono2Median, 1.03}, {0, -1}],
  ColorData[3, 6], Text["4.2", {ComboMedian, 1.03}, {0, -1}], Black, Text["2.0", {Sim2Median, 1.0}, {0, 1}],
  AbsoluteThickness[2], Darker[ColorData[3, 4], 0.1], Line[{Mono1Median, 1}, {Mono1Median, 1.03}], RGBColor[0.8, 0.1, 0.6],
  Line[{Mono2Median, 1}, {Mono2Median, 1.03}], ColorData[3, 6], Line[{ComboMedian, 1}, {ComboMedian, 1.03}]]
,
Epilog -> {EdgeForm[Directive[Black, Thickness[Medium]]], White, Opacity[1], EdgeForm[None], CapForm["Butt"], AbsoluteThickness[3],
  AbsolutePointSize[8], ColorData[3, 4], Line[{lho + 0.9, 0.34 + lo}, {lho + 1.6, 0.34 + lo}], RGBColor[0.8, 0.1, 0.6],
  Line[{lho + 0.9, 0.26 + lo}, {lho + 1.6, 0.26 + lo}], ColorData[3, 6], Line[{lho + 0.9, 0.18 + lo}, {lho + 1.6, 0.18 + lo}],
  Opacity[1], GrayLevel[0.65], Rectangle[{lho + 0.9, 0.1 - 0.03 + lo + slo}, {lho + 1.6, 0.1 + 0.03 + lo + slo}],
  Black, Opacity[1], AbsoluteThickness[1.7], Line[{lho + 0.9, 0.1 + lo + slo}, {lho + 1.6, 0.1 + lo + slo}],
  FontFamily -> "Arial", FontSize -> 11, Text[Style["5-Fluorouracil", FontSize -> 11], {lho + 1.8, 0.34 + lo}, {-1, 0}],
  Text[Style["Oxaliplatin", FontSize -> 11], {lho + 1.8, 0.26 + lo}, {-1, 0}], Text[Style["Combination", FontSize -> 11],
  {lho + 1.8, 0.18 + lo}, {-1, 0}], Text[Style["Simulated combination", FontSize -> 11], {lho + 1.8, 0.1 + lo + slo}, {-1, 0}]]
]

Export[NotebookDirectory[] <> "Figure 4G.pdf", %, "PDF"];
```





Calculating the improvement in hazard ratio attributable to drug synergy.

This is the hazard ratio between the observed combination trial results, and the combination trial results calculated on the assumption of 'no additivity or synergy'.

```
CensoringTime = 4.3(* months - the longest reported duration of PFS for Oxaliplatin *);

PatientsPerArmOfSimulatedTrial = 1000;
IndependentActionSimulatedTrial[] := RandomChoice[SubSampledBestOfMidCorrelatedMonoPairs, PatientsPerArmOfSimulatedTrial]
CombinationSimulatedTrial[] := RandomChoice[ComboSurvivalDistribution, PatientsPerArmOfSimulatedTrial]

GenerateCensoredEventData[PatientResponses_, CensoringTime_] :=
Module[{ResponsesShorterThanCensoringTime, ResponsesLongerThanCensoringTime},
  ResponsesShorterThanCensoringTime = Select[PatientResponses, # <= CensoringTime &];
  ResponsesLongerThanCensoringTime = Select[PatientResponses, # > CensoringTime &];
  EventData[Join[ResponsesShorterThanCensoringTime, ResponsesLongerThanCensoringTime],
    Join[Table[0, {Length[ResponsesShorterThanCensoringTime]}], Table[1, {Length[ResponsesLongerThanCensoringTime]}]]]
]

IndependentActionSimulatedEventData[] := GenerateCensoredEventData[IndependentActionSimulatedTrial[], CensoringTime]
CombinationSimulatedEventData[] := GenerateCensoredEventData[CombinationSimulatedTrial[], CensoringTime]

(* custom function to join two sets of event data - this is necessary to implement the Cox Proportional Hazards model *)
JoinEventData[EventData1_, EventData2_] := EventData[Join[EventData1[[2, 1]], EventData2[[2, 1]], Join[EventData1[[2, 2]], EventData2[[2, 2]]]]

MergedEventData[] := JoinEventData[IndependentActionSimulatedEventData[], CombinationSimulatedEventData[]];
Descriptors[] := Join[Table["Independence", {PatientsPerArmOfSimulatedTrial}], Table["Observed", {PatientsPerArmOfSimulatedTrial}]];
```

Note that the error range in the hazard ratio depends on the population size in a simulated trial of the combination, and the duration on trial, that is, the rate of censoring events.

Here we compute error ranges expected from 200 patients per trial arm, with any that are progression-free after a defined time being ‘censored’. This limits imprecision arising from the source PFS data having few patients ‘on-trial’ at late times, which is cause of increasing error range in PFS probability at longer times.

The range in hazard ratio is robustly identified by taking the mean range over 100 simulations of such trials.

```
NumberOfReplicateTrials = 100;

(* this function returns the relative risk, and confidence interval, in the format:
(95% lower confidence interval, median estimate, 95% upper confidence interval )
*)
RelativeRiskCalculation[descriptors_, eventdata_, PrintTable_
  (* set to 1 to print to screen the statistical table of Cox Model output; set to 0 to not show output *) := Module[{},
    MyModelFit = CoxModelFit[{descriptors, eventdata}, {treatment}, {treatment}, NominalVariables -> treatment];

    If[PrintTable == 1, Print[MyModelFit["ParameterTable"]]];

    RelativeRisk = MyModelFit["RelativeRisk"][[1]];
    RelativeRiskLowerConfidenceInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1, 1]];
    RelativeRiskUpperConfidenceInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1, 2]];

    {RelativeRiskLowerConfidenceInterval, RelativeRisk, RelativeRiskUpperConfidenceInterval}
  ]

(* single execution of the simulated trial *)
RelativeRiskCalculation[Descriptors[], MergedEventData[], 1]
```

	Estimate	Standard Error	Relative Risk	Wald- $\chi^2$	DF	P-Value
treatment[Observed]	-1.19591	0.0562834	0.302428	451.48	1	$3.43644 \times 10^{-100}$

{0.27084, 0.302428, 0.337699}

```
(* many replicate trial simulations, to accurately determine the range in hazard ratio *)
PancreaticCancerOXFUHazardRatioRange =
  Quiet@Mean[Table[RelativeRiskCalculation[Descriptors[], MergedEventData[], 0], {NumberOfReplicateTrials}]]
{0.274128, 0.306382, 0.342431}
```

## Figure 4I employs a different analysis due to the available clinical data for cetuximab and chemotherapy in metastatic colorectal cancer

Data was not available for first-line cetuximab monotherapy, but rather, Overall Survival (as compared to Progression Free Survival) for chemotherapy (FOLFIRI or FOLFOX4) with or without cetuximab as first-line treatment, and a comparison of Overall Survival with cetuximab monotherapy or with supportive care (in the absence of any chemotherapy) in the setting of chemotherapy-refractory disease. We take the distribution of overall survival benefit from cetuximab monotherapy in the chemotherapy-refractory setting, and compare it to the overall survival benefit from combining cetuximab with chemotherapy as first-line treatment.

Note that all other models that employ randomly sampling responses make use of Progression Free Survival data, not Overall Survival. We do not conduct any analysis that randomly samples from Overall Survival distributions because of concern that it is highly influenced by health factors that do not depend on a tumor’s drug sensitivity, and therefore overall survival may be highly correlated between drug treatments regardless of differences or similarities in drug mechanism. This analysis of Overall Survival in metastatic colorectal cancer does not randomly sample these distributions, but keeps the distributions sorted from shortest to longest overall survival; this effectively assumes that overall survival is highly correlated: patients with the shortest (or longest) survival when treated with first-line chemotherapy are assumed to correspond to those with shortest (or longest) survival in the distribution of effects of cetuximab in the chemotherapy-refractory setting.

### Importing survival data as tabulated in 'Table of survival distributions.xlsx' :

```
Figure4IRawData = Import[NotebookDirectory[] <> "Table of survival distributions.xlsx", "XLSX"][[10
  (* the tenth tab of this spreadsheet contains overall survival data for chemotherapy and cetuximab in metastatic colorectal cancer *)]];

FirstLineChemotherapySurvivalDistribution =
  Select[Figure4IRawData[[8 ;;, 2(* column 2 of this spreadsheet contains OS data for first-line chemotherapy*)]], NumberQ];
FirstLineCombinationSurvivalDistribution =
  Select[Figure4IRawData[[8 ;;, 3(* column 3 of this spreadsheet contains OS data for first-line chemotherapy plus cetuximab*)]], NumberQ];
RefractorySupportiveCareSurvivalDistribution = Select[Figure4IRawData[[8 ;;, 4
  (* column 4 of this spreadsheet contains OS data for supportive care in chemotherapy-refractory disease*)]], NumberQ];
RefractoryCetuximabSurvivalDistribution = Select[Figure4IRawData[[8 ;;, 5
  (* column 5 of this spreadsheet contains OS data for cetuximab monotherapy in chemotherapy-refractory disease*)]], NumberQ];

(* Median PFS in the chemotherapy refractory setting, with cetuximab or supportive care *)
CetuxMedian = Median[RefractoryCetuximabSurvivalDistribution]
SupportiveMedian = Median[RefractorySupportiveCareSurvivalDistribution]

9.614

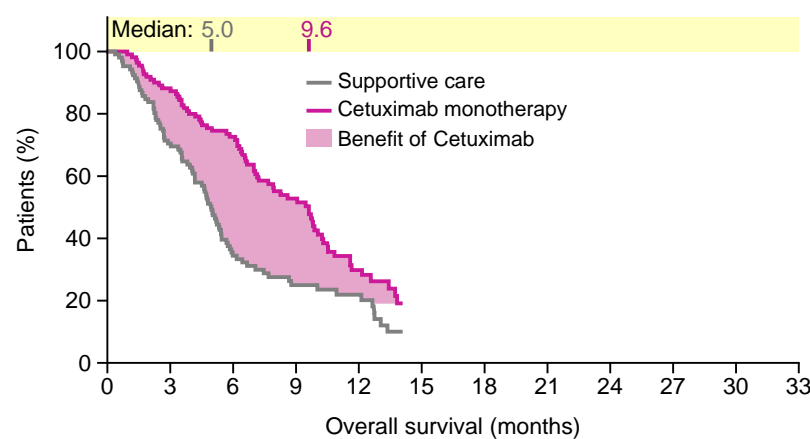
4.961
```

## Plotting the benefit of cetuximab observed in the chemotherapy refractory setting

```
(* vertical offset and horizontal offset parameters to adjust position of the inset plot legend *)
vo = -0.13;
ho = 4;

Plot[{
  SurvivalFunction[EmpiricalDistribution[RefractoryCetuximabSurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[RefractorySupportiveCareSurvivalDistribution]][x],
  (* a truncated version is included in order for the shading to appear only at probability levels reached by both distributions *)
  Max[{0.19, SurvivalFunction[EmpiricalDistribution[RefractorySupportiveCareSurvivalDistribution]][x]]
}, {x, 0, 14}, PlotRange -> {{0, 33}, {0, 1.11}}, Exclusions -> None, PlotStyle -> {Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[2]],
  Directive[GrayLevel[0.5], AbsoluteThickness[2]], Directive[Opacity[0], AbsoluteThickness[0.1]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 12}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.015}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.015}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Overall survival (months)", Style["Patients (%)"]], AspectRatio -> 1 / 2,
Filling -> {1 -> {3}}, FillingStyle -> Directive[RGBColor[0.9, 0.65, 0.8], Opacity[1]], ImageSize -> {{1000}, {250}},
ImagePadding -> {{60, 10}, {60, 10}}, PlotPoints -> 500, Epilog -> {EdgeForm[Directive[Black, Thickness[Medium]]], White,
  Opacity[1], EdgeForm[None], CapForm["Butt"], AbsoluteThickness[2], AbsolutePointSize[8], RGBColor[0.8, 0.1, 0.6],
  Line[{5.5 + ho, 0.94 + vo}, {6.7 + ho, 0.94 + vo}], GrayLevel[0.5], Line[{5.5 + ho, 1.03 + vo}, {6.7 + ho, 1.03 + vo}], Black,
  Opacity[1], FontFamily -> "Arial", FontSize -> 11, Text[Style["Cetuximab monotherapy", FontSize -> 11], {7 + ho, 0.94 + vo}, {-1, 0}],
  Text[Style["Supportive care", FontSize -> 11], {7 + ho, 1.03 + vo}, {-1, 0}], Text[Style["Benefit of Cetuximab", FontSize -> 11],
  {7 + ho, 0.85 + vo}, {-1, 0}], Black, FontSize -> 12, AbsoluteThickness[2], Text["Median:", {0.2, 1.03}, {-1, -1}],
  Darker[GrayLevel[0.5], 0.1], Text[ToString[NumberForm[SupportiveMedian, {3, 1}]], {SupportiveMedian, 1.03}, {-0.4, -1}],
  Line[{SupportiveMedian, 1}, {SupportiveMedian, 1.03 + 0.01}], Darker[RGBColor[0.8, 0.1, 0.6], 0.1],
  Text[ToString[NumberForm[CetuxMedian, {3, 1}]], {CetuxMedian, 1.03}, {-0.5, -1}], Line[{CetuxMedian, 1}, {CetuxMedian, 1.03 + 0.01}]}],
Prolog -> {Opacity[1], RGBColor[0.9, 0.65, 0.8], EdgeForm[None], Rectangle[{5.5 + ho, 0.88 + vo}, {6.7 + ho, 0.825 + vo}],
  Opacity[0.5], AbsoluteThickness[1], Opacity[1], Lighter[Yellow, 0.75], EdgeForm[None], Rectangle[{0, 1}, {33, 1.11}]}]

Export[NotebookDirectory[] <> "Figure 4I, chemotherapy refractory.pdf", %, "PDF"];
```

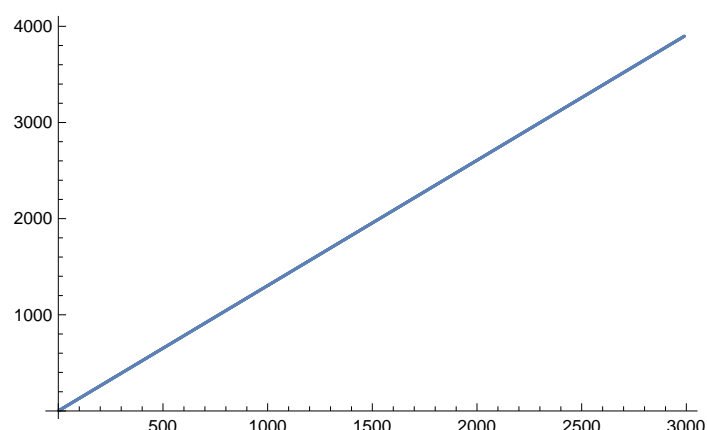


## Calculating the distribution of survival benefits of cetuximab monotherapy compared to supportive care

```
BenefitOfCetuximabDistribution = Sort[RefractoryCetuximabSurvivalDistribution] - Sort[RefractorySupportiveCareSurvivalDistribution];

(* Survival distribution has more elements in the chemotherapy refractory dataset than the first-line dataset *)
Length[BenefitOfCetuximabDistribution]
Length[FirstLineChemotherapySurvivalDistribution]
3898
2991

(* we need to select a subset of the cetuximab benefit distribution that is
  uniformly spaced and contains exactly as many entries as the first-line survival distribution *)
IntegersUniformlyDistributedToLengthOfFirstLineDistribution = Table[Round[i], {i, 1, Length[BenefitOfCetuximabDistribution],
  Length[BenefitOfCetuximabDistribution] / Length[FirstLineChemotherapySurvivalDistribution]}];
(* what we have created is a list of ~3000 integers (the length of the first line chemotherapy survival distribution) which
  are uniformly distributed over the range from 1 to ~3900 (the length of the cetuximab monotherapy survival distribution).*)
ListPlot[IntegersUniformlyDistributedToLengthOfFirstLineDistribution]
```



```
(* The above list of integers is used to select a uniformly distributed, representative sub-
  sampling of the cetuximab monotherapy distribution that is matching in length to the first-line chemotherapy survival distribution *)
BenefitOfCetuximabDistributionLengthMatched = BenefitOfCetuximabDistribution[[IntegersUniformlyDistributedToLengthOfFirstLineDistribution]];
```

## Adding the survival benefits of cetuximab monotherapy (relative to supportive care) to the distribution of survival times observed with first-line chemotherapy

```
(* Now that we have a distribution of the survival benefits of cetuximab monotherapy (compared to supportive care)
that is matching in length to the distribution of survival times with first-line chemotherapy,
these distributions can be added together to produce a 'simulated' survival distribution
expected in the absence of any synergistic drug interaction *)
ChemotherapyPlusCetuximabSimulatedCombination = Sort[FirstLineChemotherapySurvivalDistribution] + BenefitOfCetuximabDistributionLengthMatched;

(* calculating median overall survival observed with first-line chemotherapy or cetuximab plus chemotherapy,
and as simulated in the absence of drug synergy *)
ChemoMedian = Median[FirstLineChemotherapySurvivalDistribution]
ComboMedian = Median[FirstLineCombinationSurvivalDistribution]
SimMedian = Median[ChemotherapyPlusCetuximabSimulatedCombination]

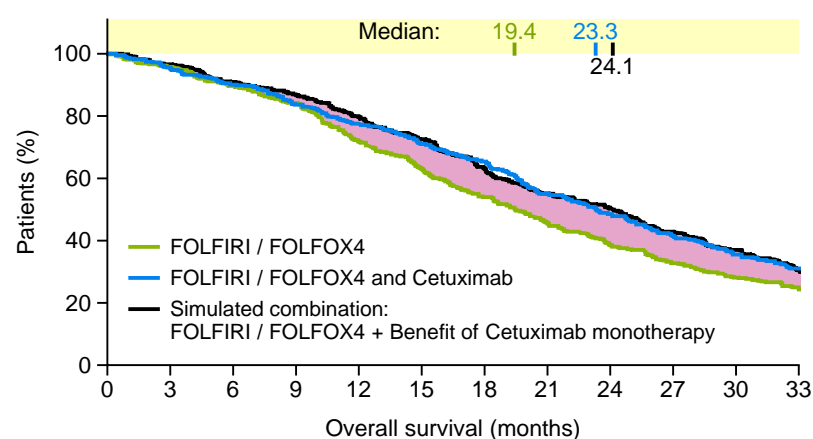
19.433

23.304

24.123

Plot[{
  SurvivalFunction[EmpiricalDistribution[ChemotherapyPlusCetuximabSimulatedCombination]][x],
  SurvivalFunction[EmpiricalDistribution[FirstLineChemotherapySurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[FirstLineCombinationSurvivalDistribution]][x]
}, {x, 0, 35}, PlotRange -> {{0, 33}, {0, 1.11}}, Exclusions -> None, PlotStyle -> {Directive[Black, AbsoluteThickness[2]],
  Directive[ColorData[3, 4], AbsoluteThickness[2]], Directive[ColorData[3, 6], AbsoluteThickness[2]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 12}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.015}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.015}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Overall survival (months)", Style["Patients (%)"]]},
Prolog -> {Gray, Thickness[Medium], Lighter[Yellow, 0.75], EdgeForm[None], Rectangle[{0, 1}, {33, 1.11}],
  Black, Text["Median:", {12, 1.03}, {-1, -1}], Darker[ColorData[3, 4], 0.1], Text[ToString[NumberForm[ChemoMedian, {3, 1}]],
  {ChemoMedian, 1.03}, {0, -1}], ColorData[3, 6], Text[ToString[NumberForm[ComboMedian, {3, 1}]], {ComboMedian, 1.03}, {0, -1}],
  Black, Text[ToString[NumberForm[SimMedian, {3, 1}]], {SimMedian, 1.0}, {0, 1}], AbsoluteThickness[2],
  Darker[ColorData[3, 4], 0.1], Line[{{ChemoMedian, 1}, {ChemoMedian, 1.03}}, ColorData[3, 6],
  Line[{{ComboMedian, 1}, {ComboMedian, 1.03}}, Black, Opacity[1], Line[{{SimMedian, 1}, {SimMedian, 1.03}},
  RGBColor[0.8, 0.1, 0.6], Opacity[0.5], AbsoluteThickness[1]], AspectRatio -> 1 / 2, Filling -> {1 -> {2}},
FillingStyle -> Directive[RGBColor[0.9, 0.65, 0.8], Opacity[1]],
ImageSize -> {{1000}, {250}}, ImagePadding -> {{60, 10}, {60, 10}}, PlotPoints -> 500,
Epilog -> {EdgeForm[Directive[Black, Thickness[Medium]]], White, Opacity[1], EdgeForm[None], CapForm["Butt"], AbsoluteThickness[2],
  ColorData[3, 4], Line[{{1.0, 0.38}, {2.5, 0.38}}, ColorData[3, 6], Line[{{1.0, 0.28}, {2.5, 0.28}}, Black, Opacity[1],
  Line[{{1.0, 0.18}, {2.5, 0.18}}], FontFamily -> "Arial", FontSize -> 11, Text[Style["FOLFIRI / FOLFOX4", FontSize -> 11], {3.0, 0.38}, {-1, 0}],
  Text[Style["FOLFIRI / FOLFOX4 and Cetuximab", FontSize -> 11], {3.0, 0.28}, {-1, 0}], Text[Style["Simulated combination:", FontSize -> 11],
  {3.0, 0.18}, {-1, 0}], Text[Style["FOLFIRI / FOLFOX4 + Benefit of Cetuximab monotherapy", FontSize -> 11], {3.0, 0.1}, {-1, 0}]}}]

Export[NotebookDirectory[] <> "Figure 4I, first line.pdf", %, "PDF"];
```



## Calculating the improvement in hazard ratio attributable to drug synergy.

This is the hazard ratio between the observed combination trial results, and the combination trial results calculated on the assumption of 'no additivity or synergy'.

```
CensoringTime = 33(* months *);

PatientsPerArmOfSimulatedTrial = 1000;
IndependentActionSimulatedTrial[] := RandomChoice[ChemotherapyPlusCetuximabSimulatedCombination, PatientsPerArmOfSimulatedTrial]
CombinationSimulatedTrial[] := RandomChoice[FirstLineCombinationSurvivalDistribution, PatientsPerArmOfSimulatedTrial]

GenerateCensoredEventData[PatientResponses_, CensoringTime_] :=
Module[{ResponsesShorterThanCensoringTime, ResponsesLongerThanCensoringTime},
  ResponsesShorterThanCensoringTime = Select[PatientResponses, # ≤ CensoringTime &];
  ResponsesLongerThanCensoringTime = Select[PatientResponses, # > CensoringTime &];
  EventData[Join[ResponsesShorterThanCensoringTime, ResponsesLongerThanCensoringTime],
    Join[Table[0, {Length[ResponsesShorterThanCensoringTime]}], Table[1, {Length[ResponsesLongerThanCensoringTime]}]]]
]

IndependentActionSimulatedEventData[] := GenerateCensoredEventData[IndependentActionSimulatedTrial[], CensoringTime]
CombinationSimulatedEventData[] := GenerateCensoredEventData[CombinationSimulatedTrial[], CensoringTime]

(* custom function to join two sets of event data - this is necessary to implement the Cox Proportional Hazards model *)
JoinEventData[EventData1_, EventData2_] := EventData[Join[EventData1[[2, 1]], EventData2[[2, 1]], Join[EventData1[[2, 2]], EventData2[[2, 2]]]]

MergedEventData[] := JoinEventData[IndependentActionSimulatedEventData[], CombinationSimulatedEventData[]];
Descriptors[] := Join[Table["Independence", {PatientsPerArmOfSimulatedTrial}], Table["Observed", {PatientsPerArmOfSimulatedTrial}]];
```

Note that the error range in the hazard ratio depends on the population size in a simulated trial of the combination, and the duration on trial, that is, the rate of censoring events.

Here we compute error ranges expected from 200 patients per trial arm, with any that are progression-free after a defined time being 'censored'. This limits imprecision arising from the source PFS data having few patients 'on-trial' at late times, which is cause of increasing error range in PFS probability at longer times.

The range in hazard ratio is robustly identified by taking the mean range over 100 simulations of such trials.

```
NumberOfReplicateTrials = 100;

(* this function returns the relative risk, and confidence interval, in the format:
  (95% lower confidence interval, median estimate, 95% upper confidence interval )
*)
RelativeRiskCalculation[descriptors_, eventdata_, PrintTable_
  (* set to 1 to print to screen the statistical table of Cox Model output; set to 0 to not show output *) := Module[{},
    MyModelFit = CoxModelFit[{descriptors, eventdata}, {treatment}, {treatment}, NominalVariables → treatment];

    If[PrintTable == 1, Print[MyModelFit["ParameterTable"]]];

    RelativeRisk = MyModelFit["RelativeRisk"][[1]];
    RelativeRiskLowerConfidenceInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1, 1]];
    RelativeRiskUpperConfidenceInterval = MyModelFit["RelativeRiskConfidenceIntervals"][[1, 2]];

    {RelativeRiskLowerConfidenceInterval, RelativeRisk, RelativeRiskUpperConfidenceInterval}
  ]

(* single execution of the simulated trial *)
RelativeRiskCalculation[Descriptors[], MergedEventData[], 1]

```

	Estimate	Standard Error	Relative Risk	Wald- $\chi^2$	DF	P-Value
treatment[Observed]	-0.0125822	0.0540988	0.987497	0.0540928	1	0.816089

```
{0.888151, 0.987497, 1.09796}

(* many replicate trial simulations, to accurately determine the range in hazard ratio *)
ColorectalCetuximabHazardRatioRange =
  Quiet@Mean[Table[RelativeRiskCalculation[Descriptors[], MergedEventData[], 0], {NumberOfReplicateTrials}]]
{0.897462, 0.99718, 1.10798}
```



# Hazard Ratio comparison across all trials

This compares the hazard ratio attributable to synergy (that is, the excess benefit over the model of independent action) for all combination trials analyzed.

```
Needs["ErrorBarPlots`"]

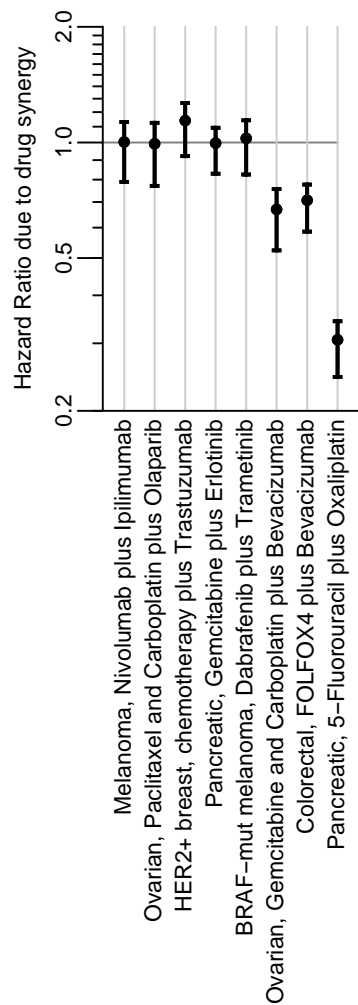
(* custom logarithmic tick marks *)
(*label rotation *)lr = 90 Degree;(* set to "90 Degree" to have hazard ratio labels rotated by 90 degrees *)
HazardRatioLogTicks = Join[{Log[10, 1], Rotate["1.0", lr], {0, 0.1}}, {Log[10, 2.0], Rotate["2.0", lr], {0, 0.1}},
  {Log[10, 0.5], Rotate["0.5", lr], {0, 0.1}}, {Log[10, 0.2], Rotate["0.2", lr], {0, 0.1}}, {Log[10, 0.1], Rotate["0.1", lr], {0, 0.1}}},
  Table[{Log[10, i], , {0, 0.04}}, {i, 1.1, 1.9, 0.1}], Table[{Log[10, i], , {0, 0.04}}, {i, 0.1, 0.9, 0.1}]];

(* custom function for 'ErrorListPlot' to generate data point with error bars on logarithmic scale *)
LogErrorBar[xcoordinate_, LowerMedianUpperDatum_] :=
  {{xcoordinate, Log[10, LowerMedianUpperDatum[[2]]]}, ErrorBar[{Log[10, LowerMedianUpperDatum[[3]]] - Log[10, LowerMedianUpperDatum[[2]]],
    Log[10, LowerMedianUpperDatum[[1]]] - Log[10, LowerMedianUpperDatum[[3]]]}}]

Hazard1LineColor = GrayLevel[0.5];
AlignmentLineColor = GrayLevel[0.8];

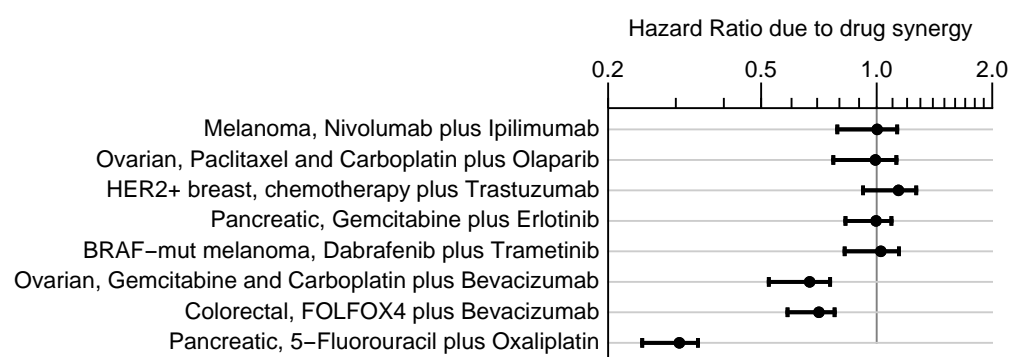
TrialLabels = {
  "Melanoma, Nivolumab plus Ipilimumab",
  "Ovarian, Paclitaxel and Carboplatin plus Olaparib",
  "HER2+ breast, chemotherapy plus Trastuzumab",
  "Pancreatic, Gemcitabine plus Erlotinib",
  "BRAF-mut melanoma, Dabrafenib plus Trametinib",
  "Ovarian, Gemcitabine and Carboplatin plus Bevacizumab",
  "Colorectal, FOLFOX4 plus Bevacizumab",
  "Pancreatic, 5-Fluorouracil plus Oxaliplatin"
};

HazardRatioPlot = ErrorListPlot[{
  {LogErrorBar[1, MelanomaImmunotherapyHazardRatioRange]},
  {LogErrorBar[2, OvarianHazardRatioRange]},
  {LogErrorBar[3, BreastCancerHazardRatioRange]},
  {LogErrorBar[4, PancreaticCancerHazardRatioRange]},
  {LogErrorBar[5, MelanomaKinaseHazardRatioRange]},
  {LogErrorBar[6, OvarianBevacizumabHazardRatioRange]},
  {LogErrorBar[7, ColorectalBevacizumabHazardRatioRange]},
  {LogErrorBar[8, PancreaticCancerOXFUHazardRatioRange]}
], Axes -> False, Frame -> {{True, False}, {True, False}}, FrameStyle -> Directive[Black, Thickness[Medium]],
BaseStyle -> {FontSize -> 12, FontFamily -> "Arial"}, PlotRange -> {{0 + 0.3, 9 - 0.3}, {Log[10, 0.2], Log[10, 2]}},
AspectRatio -> 1.5, Prolog -> Join[{Hazard1LineColor, AbsoluteThickness[1], Line[{{0, 0}, {8, 0}}], AlignmentLineColor},
  Table[Line[{{i, Log[10, 0.2]}, {i, Log[10, 2]}}, {i, 1, 8, 1}]], ImageSize -> {{1000}, {560}}, ImagePadding -> {{80, 30}, {340, 20}},
FrameTicks -> {{HazardRatioLogTicks, None}, {Table[{i, Rotate[TrialLabels[[i]],  $\pi$  / 2], {0, 0}}, {i, 1, 8, 1}], None}},
PlotStyle -> Join[Table[Directive[Black, AbsoluteThickness[2], AbsolutePointSize[6]], {3}], Table[
  Directive[Black, AbsoluteThickness[2], AbsolutePointSize[6]], {3}]], FrameLabel -> {"Hazard Ratio due to drug synergy", "", {"", ""}}]
```





```
Rotate[HazardRatioPlot, - $\pi$  / 2]
```



```
Export[NotebookDirectory[] <> "Hazard ratio plot.pdf", Rotate[HazardRatioPlot, - $\pi$  / 2], "PDF"];
```

## Figure 5D - Predictions of drug combination effect in ALK-rearranged non-small cell lung cancer, based on monotherapy trial data

Similar code as for Figure 4A is here employed to generate Figure 5D.

```
Figure5DRawData =
  Import[NotebookDirectory[] <> "Table of survival distributions.xlsx", "XLSX"][[11(* the eleventh tab of this spreadsheet*)]];

Therapy1SurvivalDistribution = Select[Figure5DRawData[[8 ;;, 2(* column 2 of this spreadsheet contains PFS data for crizotinib*)]], NumberQ];
Therapy2SurvivalDistribution = Select[Figure5DRawData[[8 ;;, 3(* column 3 of this spreadsheet contains PFS data for pemetrexed*)]], NumberQ];
Therapy3SurvivalDistribution = Select[Figure5DRawData[[8 ;;, 4(* column 4 of this spreadsheet contains PFS data for docetaxel*)]], NumberQ];
```

### First simulating the combination of Crizotinib plus Pemetrexed

$\rho = 0.28$

```
Length[Therapy1SurvivalDistribution]
Length[Therapy2SurvivalDistribution]

1703
1703

(* how many repeats of the complete data set to merge together
   (for purpose of minimizing variance between individual repeats of the 'rank randomization' process) *)
resamplingfactor = 10;
ReSampledTherapy1SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy1SurvivalDistribution, {resamplingfactor}]]]];
ReSampledTherapy2SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy2SurvivalDistribution, {resamplingfactor}]]]];

(* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.28 *)
amountofrankrandomization = 15000;

SlightlyRandomizedTherapy1Distribution =
  Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
    {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{-amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
BestOfMidCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];

SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]]

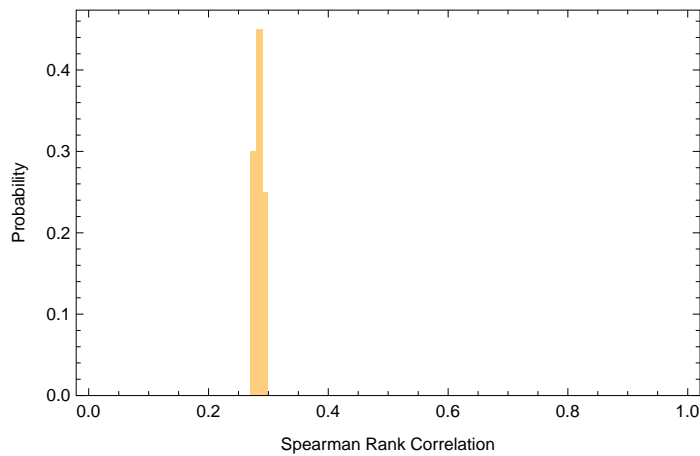
0.282477
```

```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.28 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 15000;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
    {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
  , {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

Mean response correlation = 0.285



(\* after generating the distribution of survival times predicted by independent drug action, we can remove the 'resampling' to plot the results. With a resampling factor of 10, this is achieved by sorting the distribution and keeping every 10th entry \*)

```
SubSampledBestOfMidCorrelatedMonoPairs = Take[Reverse[Sort[BestOfMidCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

$\rho = 0.08$

```
resamplingfactor = 10;
```

```
ReSampledTherapy1SurvivalDistribution =
```

```
Reverse[Sort[Flatten[Table[RandomSample[Therapy1SurvivalDistribution, Length[Therapy2SurvivalDistribution]], {resamplingfactor}]]];
```

```
ReSampledTherapy2SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy2SurvivalDistribution, {resamplingfactor}]]];
```

(\* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.08 \*)

```
amountofrankrandomization = 53000;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
  {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
BestOfLowCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
```

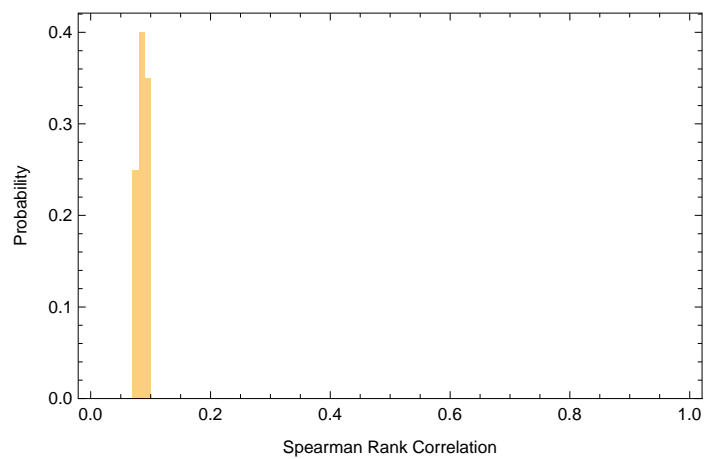
```
0.0897829
```

```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.08 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 53000;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
    , {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

Mean response correlation = 0.087



(\* after generating the distribution of survival times predicted by independent drug action, we can remove the 'resampling' to plot the results. With a resampling factor of 10, this is achieved by sorting the distribution and keeping every 10th entry \*)

```
SubSampledBestOfLowCorrelatedMonoPairs = Take[Reverse[Sort[BestOfLowCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

$\rho = 0.48$

```
resamplingfactor = 10;
```

```
ReSampledTherapy1SurvivalDistribution =
```

```
Reverse[Sort[Flatten[Table[RandomSample[Therapy1SurvivalDistribution, Length[Therapy2SurvivalDistribution]], {resamplingfactor}]]];
```

```
ReSampledTherapy2SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy2SurvivalDistribution, {resamplingfactor}]]];
```

(\* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.48 \*)

```
amountofrankrandomization = 8700;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
```

```
{i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
```

```
ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
BestOfHighCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy2Distribution[[i, 2]]},
```

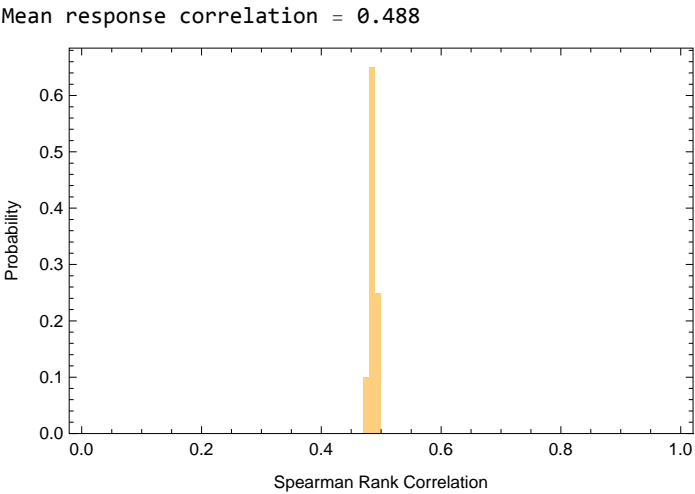
```
{i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
```

```
0.485207
```

```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.48 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 8700;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy2Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy2SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy2SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy2Distribution[[All, 2]]
    , {20}];

Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame -> True, FrameLabel -> {"Spearman Rank Correlation", "Probability"}]
```



```
(* after generating the distribution of survival times predicted by independent drug action,
we can remove the 'resampling' to plot the results. With a resampling factor of 10,
this is acheived by sorting the distribution and keeping every 10th entry *)
SubSampledBestOfHighCorrelatedMonoPairs = Take[Reverse[Sort[BestOfHighCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

Computing median PFS for each condition: the observed individual therapies, the observed combination, and the simulated effects with high, medium, or low response correlation (respectively,  $\rho = 0.48, 0.28, 0.08$ )

```
Mono1Median = Round[Median[Therapy1SurvivalDistribution], 0.01]
Mono2Median = Round[Median[Therapy2SurvivalDistribution], 0.01]
ComboMedian = Round[Median[ComboSurvivalDistribution], 0.01]
Sim1Median = Round[Median[SubSampledBestOfHighCorrelatedMonoPairs], 0.01]
Sim2Median = Round[Median[SubSampledBestOfMidCorrelatedMonoPairs], 0.01]
Sim3Median = Round[Median[SubSampledBestOfLowCorrelatedMonoPairs], 0.01]

7.59

4.15

4.18

8.71

9.55

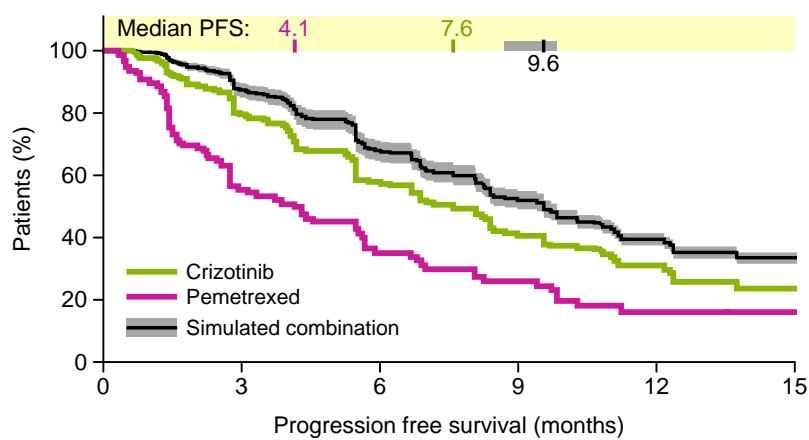
9.84
```

## Plotting the observed and simulated survival functions

```
(*legend offset*)
lo = -0.05;
(* legend horizontal offset *)
ho = -0;

Plot[{
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfLowCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfMidCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfHighCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[Therapy1SurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[Therapy2SurvivalDistribution]][x]
}, {x, 0, 16}, PlotRange -> {{0, 15.0}, {0, 1.11}}, Exclusions -> None,
PlotStyle -> {Directive[Opacity[0], AbsoluteThickness[1.8]], Directive[Black, AbsoluteThickness[1.8]],
  Directive[Opacity[0], AbsoluteThickness[1.8]], Directive[ColorData[3, 4], AbsoluteThickness[3]],
  Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[3]], Directive[ColorData[3, 6], AbsoluteThickness[3]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 12}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.015}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.015}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)", Style["Patients (%)"]]},
Prolog -> {Gray, Thickness[Medium], Lighter[Yellow, 0.75], EdgeForm[None], Rectangle[{0, 1}, {15, 1.11}],
  Black, AbsoluteThickness[1.8], GrayLevel[0.65], Rectangle[{Sim1Median, 1}, {Sim3Median, 1.03}], Black, Opacity[1],
  Line[{Sim2Median, 1}, {Sim2Median, 1.03}], Text["Median PFS:", {0.3, 1.03}, {-1, -1}], Darker[ColorData[3, 4], 0.1],
  Text["7.6", {Mono1Median, 1.03}, {-0.25, -1}], RGBColor[0.8, 0.1, 0.6], Text["4.1", {Mono2Median, 1.03}, {0, -1}],
  Black, Text["9.6", {Sim2Median, 1.0}, {0, 1}], AbsoluteThickness[2], Darker[ColorData[3, 4], 0.1],
  Line[{Mono1Median, 1}, {Mono1Median, 1.03}], RGBColor[0.8, 0.1, 0.6], Line[{Mono2Median, 1}, {Mono2Median, 1.03}], ColorData[3, 6]},
AspectRatio -> 1 / 2, Filling -> {1 -> {3}}, FillingStyle -> Directive[GrayLevel[0.65], Opacity[1]],
ImageSize -> {{1000}, {250}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 500,
Epilog -> {EdgeForm[Directive[Black, Thickness[Medium]]], White, Opacity[1], EdgeForm[None], CapForm["Butt"], AbsoluteThickness[3],
  AbsolutePointSize[8], ColorData[3, 4], Line[{0.5 + ho, 0.34 + lo}, {1.6 + ho, 0.34 + lo}], RGBColor[0.8, 0.1, 0.6],
  Line[{0.5 + ho, 0.26 + lo}, {1.6 + ho, 0.26 + lo}], Opacity[1], GrayLevel[0.65], Rectangle[{0.5 + ho, 0.13 + lo}, {1.6 + ho, 0.19 + lo}],
  Black, Opacity[1], AbsoluteThickness[1.8], Line[{0.5 + ho, 0.16 + lo}, {1.6 + ho, 0.16 + lo}], FontFamily -> "Arial",
  FontSize -> 11, Text[Style["Crizotinib", FontSize -> 11], {1.8 + ho, 0.34 + lo}, {-1, 0}], Text[Style["Pemetrexed", FontSize -> 11],
  {1.8 + ho, 0.26 + lo}, {-1, 0}], Text[Style["Simulated combination", FontSize -> 11], {1.8 + ho, 0.16 + lo}, {-1, 0}]}]

Export[NotebookDirectory[] <> "Figure 5D, crizotinib plus pemetrexed.pdf", %, "PDF"];
```



## Second, simulating the combination of Crizotinib plus Docetaxel

$\rho = 0.28$

```
Length[Therapy1SurvivalDistribution]
Length[Therapy3SurvivalDistribution]
1703
1703

(* how many repeats of the complete data set to merge together
(for purpose of minimizing variance between individual repeats of the 'rank randomization' process) *)
resamplingfactor = 10;
ReSampledTherapy1SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy1SurvivalDistribution, {resamplingfactor}]]]];
ReSampledTherapy3SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy3SurvivalDistribution, {resamplingfactor}]]]];
```

```
(* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.28 *)
```

```
amountofrankrandomization = 15 000;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],  
{i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy3Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],  
ReSampledTherapy3SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy3SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
BestOfMidCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy3Distribution[[i, 2]]}],  
{i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy3Distribution[[All, 2]]]
```

```
0.274479
```

```
(* Repeating the randomization procedure 20 times to show that
```

```
response correlation is tightly distributed around the targeted value of 0.28 *)
```

```
TableOfCorrelationsFromRepeats = Table[
```

```
amountofrankrandomization = 15 000;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],  
{i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy3Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],  
ReSampledTherapy3SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy3SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy3Distribution[[All, 2]]]
```

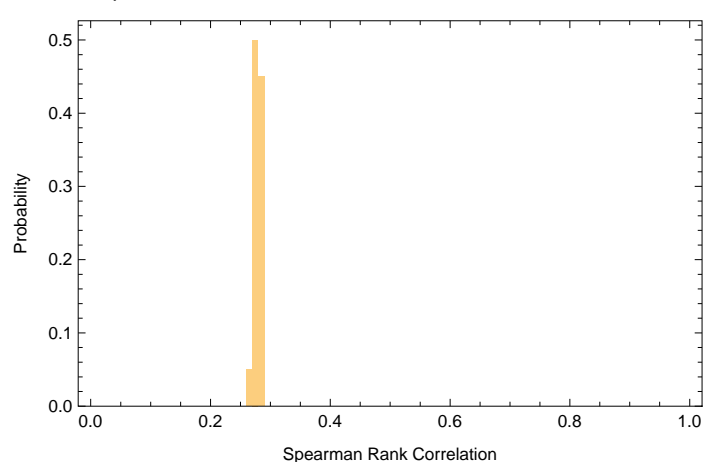
```
, {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
```

```
"Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

```
Mean response correlation = 0.28
```



```
(* after generating the distribution of survival times predicted by independent drug action,
```

```
we can remove the 'resampling' to plot the results. With a resampling factor of 10,
```

```
this is achieved by sorting the distribution and keeping every 10th entry *)
```

```
SubSampledBestOfMidCorrelatedMonoPairs = Take[Reverse[Sort[BestOfMidCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

$\rho = 0.08$

```
resamplingfactor = 10;
```

```
ReSampledTherapy1SurvivalDistribution =
```

```
Reverse[Sort[Flatten[Table[RandomSample[Therapy1SurvivalDistribution, Length[Therapy3SurvivalDistribution]], {resamplingfactor}]]]]];
```

```
ReSampledTherapy3SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy3SurvivalDistribution, {resamplingfactor}]]]]];
```

```
(* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.08 *)
```

```
amountofrankrandomization = 53 000;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],  
{i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy3Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],  
ReSampledTherapy3SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy3SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
BestOfLowCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy3Distribution[[i, 2]]}],  
{i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy3Distribution[[All, 2]]]
```

```
0.0762624
```

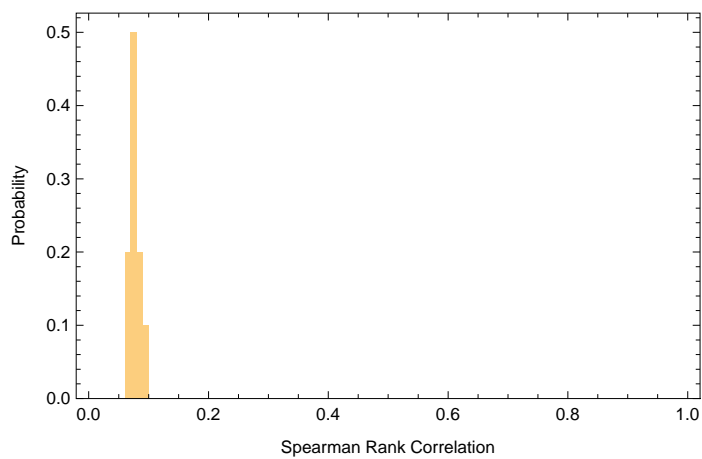


```
(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.08 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 53000;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
    {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy3Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy3SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy3SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy3Distribution[[All, 2]]
, {20}];
```

```
Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
```

```
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame → True, FrameLabel → {"Spearman Rank Correlation", "Probability"}]
```

```
Mean response correlation = 0.077
```



```
(* after generating the distribution of survival times predicted by independent drug action,
we can remove the 'resampling' to plot the results. With a resampling factor of 10,
this is achieved by sorting the distribution and keeping every 10th entry *)
```

```
SubSampledBestOfLowCorrelatedMonoPairs = Take[Reverse[Sort[BestOfLowCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];
```

$\rho = 0.48$

```
resamplingfactor = 10;
```

```
ReSampledTherapy1SurvivalDistribution =
```

```
Reverse[Sort[Flatten[Table[RandomSample[Therapy1SurvivalDistribution, Length[Therapy3SurvivalDistribution]], {resamplingfactor}]]];
```

```
ReSampledTherapy3SurvivalDistribution = Reverse[Sort[Flatten[Table[Therapy3SurvivalDistribution, {resamplingfactor}]]];
```

```
(* this is the amount of rank randomization that produces Spearman Rank Correlation of approximately 0.48 *)
```

```
amountofrankrandomization = 8700;
```

```
SlightlyRandomizedTherapy1Distribution =
```

```
Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]],
  {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
SlightlyRandomizedTherapy3Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
  ReSampledTherapy3SurvivalDistribution[[i]], {i, 1, Length[ReSampledTherapy3SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
```

```
BestOfHighCorrelatedMonoPairs = Table[Max[{SlightlyRandomizedTherapy1Distribution[[i, 2]], SlightlyRandomizedTherapy3Distribution[[i, 2]]},
  {i, 1, Length[SlightlyRandomizedTherapy1Distribution]}];
```

```
SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy3Distribution[[All, 2]]
```

```
0.496309
```

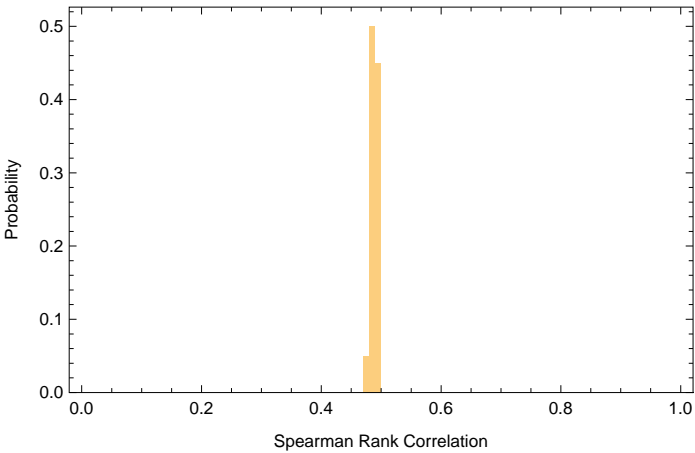
```

(* Repeating the randomization procedure 20 times to show that
response correlation is tightly distributed around the targeted value of 0.48 *)
TableOfCorrelationsFromRepeats = Table[
  amountofrankrandomization = 8700;
  SlightlyRandomizedTherapy1Distribution =
    Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}], ReSampledTherapy1SurvivalDistribution[[i]]},
      {i, 1, Length[ReSampledTherapy1SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SlightlyRandomizedTherapy3Distribution = Sort[Table[{i + RandomReal[{- amountofrankrandomization, amountofrankrandomization}],
    ReSampledTherapy3SurvivalDistribution[[i]]}, {i, 1, Length[ReSampledTherapy3SurvivalDistribution]}], #1[[1]] < #2[[1]] &];
  SpearmanRho[SlightlyRandomizedTherapy1Distribution[[All, 2]], SlightlyRandomizedTherapy3Distribution[[All, 2]]
    , {20}];

Print["Mean response correlation = " <> ToString[Round[Mean[TableOfCorrelationsFromRepeats], 0.001]]]
Histogram[TableOfCorrelationsFromRepeats, {0., 1.0, 0.01},
  "Probability", Frame -> True, FrameLabel -> {"Spearman Rank Correlation", "Probability"}]

```

Mean response correlation = 0.489



```

(* after generating the distribution of survival times predicted by independent drug action,
we can remove the 'resampling' to plot the results. With a resampling factor of 10,
this is acheived by sorting the distribution and keeping every 10th entry *)
SubSampledBESTOfHighCorrelatedMonoPairs = Take[Reverse[Sort[BESTOfHighCorrelatedMonoPairs]], 1 ;; -1 ;; resamplingfactor];

```

Computing median PFS for each condition: the observed individual therapies, the observed combination, and the simulated effects with high, medium, or low response correlation (respectively,  $\rho = 0.48, 0.28, 0.08$ )

```

Mono1Median = Round[Median[Therapy1SurvivalDistribution], 0.01]
Mono2Median = Round[Median[Therapy3SurvivalDistribution], 0.01]
ComboMedian = Round[Median[ComboSurvivalDistribution], 0.01]
Sim1Median = Round[Median[SubSampledBESTOfHighCorrelatedMonoPairs], 0.01]
Sim2Median = Round[Median[SubSampledBESTOfMidCorrelatedMonoPairs], 0.01]
Sim3Median = Round[Median[SubSampledBESTOfLowCorrelatedMonoPairs], 0.01]

7.59

2.53

4.18

8.08

8.21

8.28

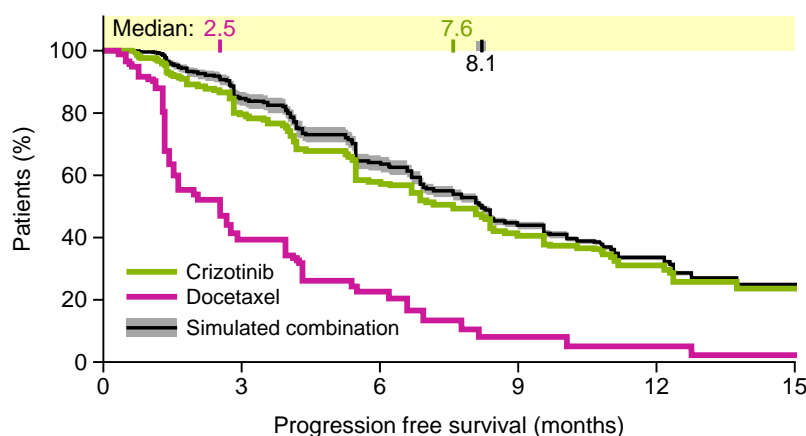
```

## Plotting the observed and simulated survival functions

```
(*legend offset*)
lo = -0.05;
(* legend horizontal offset *)
ho = -0;

Plot[{
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfLowCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfMidCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[SubSampledBestOfHighCorrelatedMonoPairs]][x],
  SurvivalFunction[EmpiricalDistribution[Therapy1SurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[Therapy3SurvivalDistribution]][x]
}, {x, 0, 16}, PlotRange -> {{0, 15.0}, {0, 1.11}}, Exclusions -> None,
PlotStyle -> {Directive[Opacity[0], AbsoluteThickness[1.8]], Directive[Black, AbsoluteThickness[1.8]],
  Directive[Opacity[0], AbsoluteThickness[1.8]], Directive[ColorData[3, 4], AbsoluteThickness[3]],
  Directive[RGBColor[0.8, 0.1, 0.6], AbsoluteThickness[3]], Directive[ColorData[3, 6], AbsoluteThickness[3]]},
BaseStyle -> {FontFamily -> "Arial", FontSize -> 12}, FrameStyle -> Directive[Black, Thickness[Medium]], Frame -> {{True, False}, {True, False}},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.015}}, {i, 0, 1, 1 / 5}], None}, {Table[{i, i, {0, 0.015}}, {i, 0, 60, 3}], None}},
FrameLabel -> {Style["Progression free survival (months)", Style["Patients (%)"]]},
Prolog -> {Gray, Thickness[Medium], Lighter[Yellow, 0.75], EdgeForm[None], Rectangle[{0, 1}, {15, 1.11}],
  Black, AbsoluteThickness[1.8], GrayLevel[0.65], Rectangle[{Sim1Median, 1}, {Sim3Median, 1.03}], Black, Opacity[1],
  Line[{Sim2Median, 1}, {Sim2Median, 1.03}], Text["Median:", {0.2, 1.03}, {-1, -1}], Darker[ColorData[3, 4], 0.1],
  Text["7.6", {Mono1Median, 1.03}, {-0.25, -1}], RGBColor[0.8, 0.1, 0.6], Text["2.5", {Mono2Median, 1.03}, {0, -1}],
  Black, Text["8.1", {Sim2Median, 1.0}, {0, 1}], AbsoluteThickness[2], Darker[ColorData[3, 4], 0.1],
  Line[{Mono1Median, 1}, {Mono1Median, 1.03}], RGBColor[0.8, 0.1, 0.6], Line[{Mono2Median, 1}, {Mono2Median, 1.03}], ColorData[3, 6]},
AspectRatio -> 1 / 2, Filling -> {1 -> {3}}, FillingStyle -> Directive[GrayLevel[0.65], Opacity[1]],
ImageSize -> {{1000}, {250}}, ImagePadding -> {{60, 10}, {60, 10}},
PlotPoints -> 500,
Epilog -> {EdgeForm[Directive[Black, Thickness[Medium]]], White, Opacity[1], EdgeForm[None], CapForm["Butt"], AbsoluteThickness[3],
  AbsolutePointSize[8], ColorData[3, 4], Line[{0.5 + ho, 0.34 + lo}, {1.6 + ho, 0.34 + lo}], RGBColor[0.8, 0.1, 0.6],
  Line[{0.5 + ho, 0.26 + lo}, {1.6 + ho, 0.26 + lo}], Opacity[1], GrayLevel[0.65], Rectangle[{0.5 + ho, 0.13 + lo}, {1.6 + ho, 0.19 + lo}],
  Black, Opacity[1], AbsoluteThickness[1.8], Line[{0.5 + ho, 0.16 + lo}, {1.6 + ho, 0.16 + lo}], FontFamily -> "Arial", FontSize -> 11,
  Text[Style["Crizotinib", FontSize -> 11], {1.8 + ho, 0.34 + lo}, {-1, 0}], Text[Style["Docetaxel", FontSize -> 11], {1.8 + ho, 0.26 + lo}, {-1, 0}],
  Text[Style["Simulated combination", FontSize -> 11], {1.8 + ho, 0.16 + lo}, {-1, 0}]}]

Export[NotebookDirectory[] <> "Figure 5D, crizotinib plus docetaxel.pdf", %, "PDF"];
```



## Supplementary Figure I, fitting log-normal distribution to clinically observed distributions of Progression Free Survival

### Importing survival data as tabulated in 'Table of survival distributions.xlsx' :

```
SupplementaryFigure1RawData = Import[NotebookDirectory[] <> "Table of survival distributions.xlsx", "XLSX"][[12]
(* the twelfth tab of this spreadsheet contains progression free survival data for trastuzumab in HER2-amplified breast cancer,
and for vemurafenib in BRAF-mutant melanoma *) ];

TrastuzumabSurvivalDistribution =
  Select[SupplementaryFigure1RawData[[8 ;;, 2(* column 2 of this spreadsheet contains PFS data for trastuzumab*)]], NumberQ];
VemurafenibSurvivalDistribution = Select[SupplementaryFigure1RawData[[8 ;;, 3
(* column 3 of this spreadsheet contains PFS data for vemurafenib*)]], NumberQ];

(* custom frame ticks for log-scale *)
logframeticks = Join[Table[{x, ToString[10^x], {0, 0.025}}, {x, Log[10, {0.1, 0.3, 1, 3, 10, 30, 100}]}],
  Flatten[Table[Table[{Log[10, x], "", {0, 0.015}}, {x, 1 * 10^y, 9 * 10^y, 1 * 10^y}], {y, -5, 5, 1}], 1]];


```

### HER2-amplified breast cancer response to trastuzumab

```
Print["Coefficient of variation in Trastuzumab PFS = " <>
  ToString[Round[StandardDeviation[TrastuzumabSurvivalDistribution] / Mean[TrastuzumabSurvivalDistribution] * 100]] <> "%"]
```

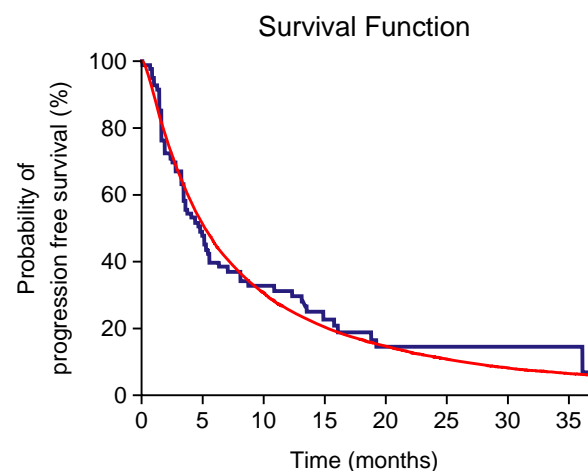
Coefficient of variation in Trastuzumab PFS = 116%

## Fitting a log - normal distribution

```
CenterOfDistribution = 5.1; (*months*)
StDevOfDistribution = 0.56; (* standard deviation on log scale *)
lognormallydistributedtimes = 10^RandomVariate[NormalDistribution[Log[10, CenterOfDistribution], StDevOfDistribution], 10000];
```

```
Plot[{
  SurvivalFunction[EmpiricalDistribution[TrastuzumabSurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[lognormallydistributedtimes]][x]
}, {x, 0, 36.5}, Exclusions -> None, PlotRange -> {{0, 36.5}, {0, 1}},
PlotRangePadding -> None, Frame -> {{True, False}, {True, False}}, Axes -> False, PlotStyle ->
{Directive[ColorData[3, 7], AbsoluteThickness[2]], Directive[Red, AbsoluteThickness[1.5]], Directive[Orange, AbsoluteThickness[1.5]]},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 2 / 10}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 36, 5}], None}},
FrameStyle -> Directive[Black, Thickness[Medium]], BaseStyle -> {FontFamily -> "Arial", FontSize -> 12},
FrameLabel -> {"Time (months)", "Probability of\nprogression free survival (%)"}, PlotLabel -> Style["Survival Function", Black],
AspectRatio -> 3 / 4, ImagePadding -> {{70, 10}, {50, 10}}, ImageSize -> {{1000}, {250}}]
```

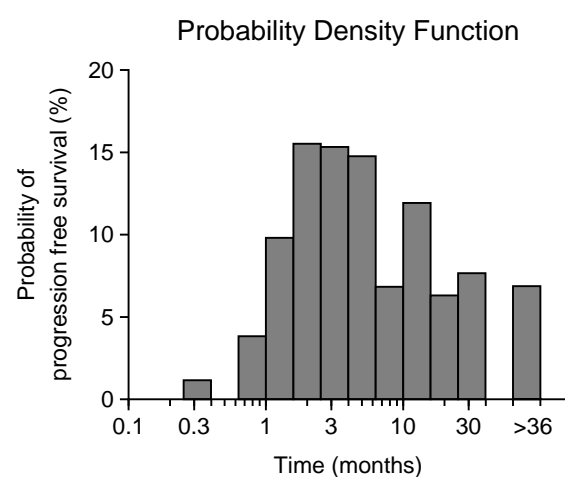
```
Export[NotebookDirectory[] <> "Supplementary Figure 1A, survival function.pdf", %, "PDF"];
```



```
(* pre-processing: values smaller than 10-0.5 (<10 days) are rounded up to 10 days so as not to be absent from the logarithmic plot range;
and the portion of probability density that is still 'progression free' at the end of the data
(>36 months) is shifted to larger value in order to be shown in a separate column labelled as ">36 months" *)
plotdata = Map[Max[{-0.5, #}] &, Log[10, TrastuzumabSurvivalDistribution]] /. {Log[37.] / Log[10] -> Log[10, 70]};
```

```
Histogram[plotdata, {-1, 3, 0.2}, PlotRange -> {{-1, 2.2}, {0, 20 / 100 * Length[TrastuzumabSurvivalDistribution]}},
PlotRangePadding -> None, Frame -> {{True, False}, {True, False}}, Axes -> False,
ChartStyle -> Directive[GrayLevel[0.5], EdgeForm[Directive[Black, Opacity[1], Thickness[Medium]]]], FrameTicks ->
{{Table[{i, 100 * i / Length[TrastuzumabSurvivalDistribution], {0, 0.02}}, {i, 0, 2000, Length[TrastuzumabSurvivalDistribution] / 10 / 2}],
None}, {Join[Select[logframeticks, #[[1]] ≤ Log[10, 40] &], {{1.9, " >36", {0, 0}}, {1.8, , {0, 0.015}}, {2.0, , {0, 0.015}}}], None}},
FrameStyle -> Directive[Black, Thickness[Medium]], BaseStyle -> {FontFamily -> "Arial", FontSize -> 12},
FrameLabel -> {"Time (months)", "Probability of\nprogression free survival (%)"}, PlotLabel -> Style["Probability Density Function", Black],
AspectRatio -> 3 / 4, ImagePadding -> {{70, 10}, {50, 10}}, ImageSize -> {{1000}, {250}}]
```

```
Export[NotebookDirectory[] <> "Supplementary Figure 1A, probability density function.pdf", %, "PDF"];
```



## BRAF V600(E/K) melanoma response to vemurafenib

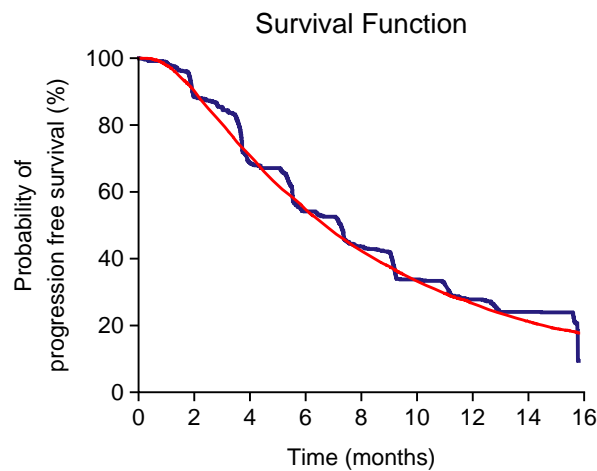
```
Print["Coefficient of variation in Vemurafenib PFS = " <>
ToString[Round[StandardDeviation[VemurafenibSurvivalDistribution] / Mean[VemurafenibSurvivalDistribution] * 100]] <> "%"]
Coefficient of variation in Vemurafenib PFS = 65%
```

## Fitting a log - normal distribution

```
CenterOfDistribution = 6.6; (*months*)
StDevOfDistribution = 0.4; (* standard deviation on log scale *)
lognormallydistributedtimes = 10^RandomVariate[NormalDistribution[Log[10, CenterOfDistribution], StDevOfDistribution], 10000];
```

```
Plot[{
  SurvivalFunction[EmpiricalDistribution[VemurafenibSurvivalDistribution]][x],
  SurvivalFunction[EmpiricalDistribution[lognormallydistributedtimes]][x]
}, {x, 0, 15.8}, Exclusions -> None, PlotRange -> {{0, 16}, {0, 1}},
PlotRangePadding -> None, Frame -> {{True, False}, {True, False}}, Axes -> False, PlotStyle ->
{Directive[ColorData[3, 7], AbsoluteThickness[2]], Directive[Red, AbsoluteThickness[1.5]], Directive[Orange, AbsoluteThickness[1.5]]},
FrameTicks -> {{Table[{i, 100 * i, {0, 0.02}}, {i, 0, 1, 2 / 10}], None}, {Table[{i, i, {0, 0.02}}, {i, 0, 16, 2}], None}},
FrameStyle -> Directive[Black, Thickness[Medium]], BaseStyle -> {FontFamily -> "Arial", FontSize -> 12},
FrameLabel -> {"Time (months)", "Probability of\nprogression free survival (%)"}, PlotLabel -> Style["Survival Function", Black],
AspectRatio -> 3 / 4, ImagePadding -> {{70, 10}, {50, 10}}, ImageSize -> {{1000}, {250}}]
```

```
Export[NotebookDirectory[] <> "Supplementary Figure 1B, survival function.pdf", %, "PDF"];
```



```
Histogram[Select[Log[10, VemurafenibSurvivalDistribution], # > -1 &], {-1, 2, 0.2},
PlotRange -> {{-1, Log[10, 30]}, {0, 25 / 100 * Length[VemurafenibSurvivalDistribution]}},
PlotRangePadding -> None, Frame -> {{True, False}, {True, False}}, Axes -> False,
ChartStyle -> Directive[GrayLevel[0.5], EdgeForm[Directive[Black, Opacity[1], Thickness[Medium]]]],
FrameTicks -> {{Table[{i, 100 * i / 702, {0, 0.02}}, {i, 0, 2000, 702 / 10 / 2}], None}, {logframeticks, None}},
FrameStyle -> Directive[Black, Thickness[Medium]], BaseStyle -> {FontFamily -> "Arial", FontSize -> 12},
FrameLabel -> {"Time (months)", "Probability of\nprogression free survival (%)"}, PlotLabel -> Style["Probability Density Function", Black],
AspectRatio -> 3 / 4, ImagePadding -> {{70, 10}, {50, 10}}, ImageSize -> {{1000}, {250}}]
```

```
Export[NotebookDirectory[] <> "Supplementary Figure 1B, probability density function.pdf", %, "PDF"];
```

