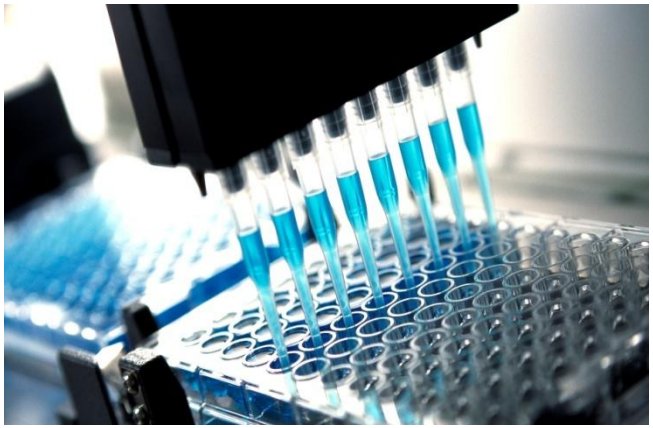


Imagen Biotech
See more than images

Imagen Biotech
See more than images

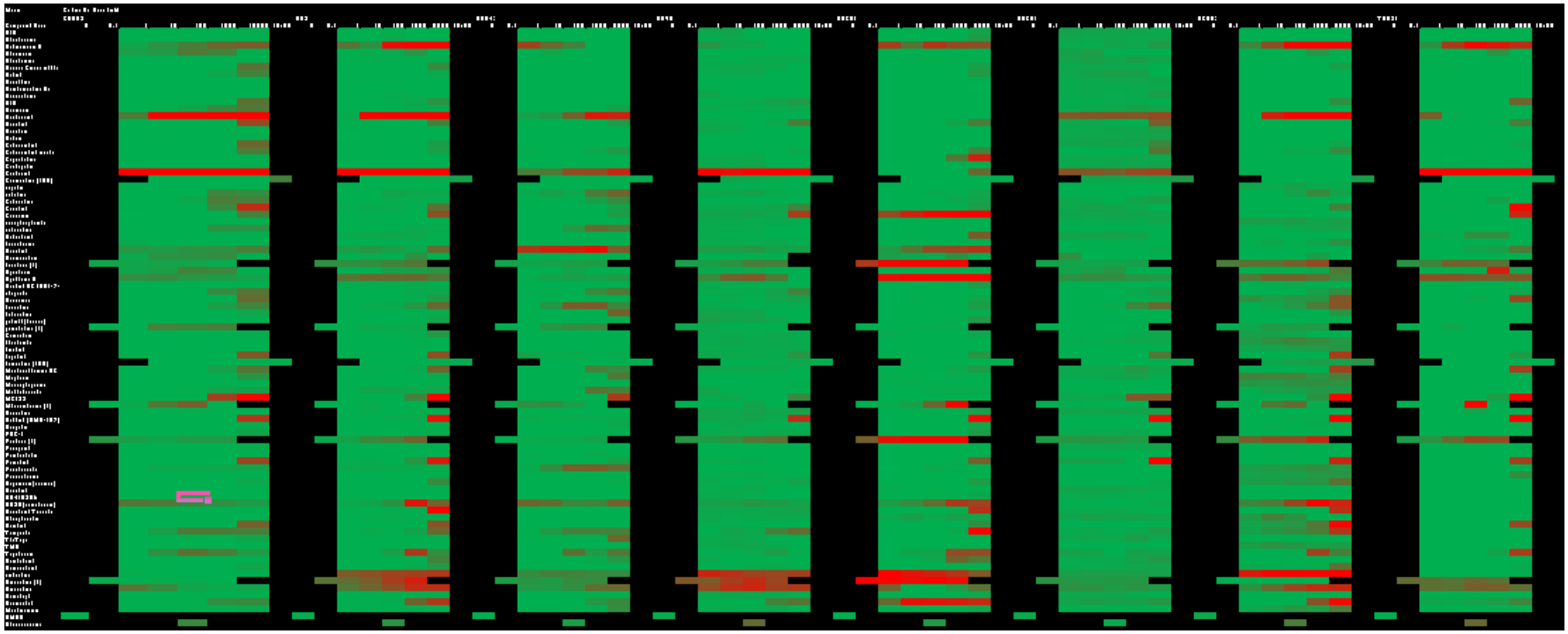
Typical data produced by Genetic Analysis

Cell line	Genotype 20 genes (alterations in sequence and putative copy number for Akt1/2/3, ARID1A, BRCA1/2, BRAF, C11ORF30, CCNE1, CTNNB1, ErbB2, KRAS, MAP2K4, MYC, NF1, Notch3, PIK3CA, PTEN, Rb1, TP53)
KURAMOCH	Akt2/3 gain, ARID1A gain, BRAF gain, BRCA1 hetloss, BRCA2 mut (ns), CCNE1 gain, CTNNB1 hetloss, ErbB2 hetloss, KRAS amp, MYC amp, NF1 homdel, Notch3 hetloss, PTEN hetloss, TP53 mut (ms)
OVSAHO	Akt1/3 gain, BRAF gain, BRCA2 homdel, CCNE1 gain, MAP2K4 hetloss, MYC gain, Notch3 gain, PIK3CA gain, PTEN gain, Rb1 homdel, TP53 mut (ns) and hetloss
SNU119	Akt1 hetloss, Akt2/3 gain, BRAF gain, BRCA2 hetloss, C11ORF30 gain, CTNNB1 hetloss, KRAS gain, MAP2K4 hetloss, MYC mut (ms) and amp, NF1 homdel, Notch3 gain, PIK3CA gain, PTEN hetloss, Rb1 amp, TP53 mut (ms) and hetloss
COV362	ARID1A hetloss, BRAF gain, BRCA1 mut (ss and fs) and hetloss, BRCA2 hetloss, C11ORF30 gain, ErbB2 hetloss, MAP2K4 hetloss, MYC amp, NF1 hetloss, PTEN gain, Rb1 homdel, TP53 mut (ms) and hetloss
OVCAR4	Akt2/3 gain, BRAF gain, BRCA1/2 hetloss, CCNE1 gain, CTNNB1 hetloss, ErbB2 hetloss, MAP2K4 hetloss, MYC gain, NF1 hetloss, Notch3 gain, PTEN gain, Rb1 hetloss, TP53 mut (ms) and hetloss
COV318	Akt1/2/3 gain, ARID1A gain, BRAF gain, C11ORF30 gain, CCNE1 amp, CTNNB1 hetloss, KRAS hetloss, MAP2K4 hetloss, PIK3CA gain, TP53 mut (ms) and hetloss
JHOS4	Akt2/3 gain, ARID1A hetloss, BRAF gain, BRCA2 gain, C11ORF30 gain, CCNE1 gain, MAP2K4 hetloss, MYC mut (ms) and gain, NF1 hetloss, Notch3 gain, PIK3CA gain, PTEN gain, Rb1 gain, TP53 mut (ms) and hetloss
TYKNU	Akt3 gain, BRAF gain, KRAS hetloss, MYC gain, TP53 mut (ms)
OVKATE	Akt3 gain, BRCA1 hetloss, C11ORF30 gain, CTNNB1 hetloss, ErbB2 hetloss, KRAS gain, MAP2K4 hetloss, NF1 hetloss, PIK3CA amp, PTEN hetloss, TP53 mut (ms) and hetloss
CAOV4	Akt2 gain, Akt3 amp, ARID1A gain, BRAF gain, CCNE1 gain, KRAS gain, MYC amp, NF1 gain, PIK3CA gain, TP53 mut (ms)
OAW28	Akt1/3 gain, ARID1A hetloss, BRAF gain, BRCA1 hetloss, C11ORF30 gain, KRAS amp, MAP2K4 homdel, MYC gain, PIK3CA amp, Rb1 hetloss, TP53 mut (fs) and hetloss
JHOS2	Akt2/3 hetloss, BRCA1 mut (ms), C11ORF30 gain, CTNNB1 gain, MAP2K4 hetloss, MYC gain, NF1 mut (ms), PIK3CA gain, TP53 mut (ss) and hetloss
CAOV3	Akt1/2 gain, BRAF gain, BRCA1 hetloss, BRCA2 gain, C1130ORF gain, CTNNB1 hetloss, ErbB2 hetloss, KRAS hetloss, MAP2K4 hetloss, NF1 hetloss, PIK3CA amp, PTEN gain, Rb1 hetloss, TP53 mut (ns) and hetloss
59M	Akt3 hetloss, KRAS gain, Rb1 gain, TP53 mut (fs)
ONCODG1	Akt2 amp, ARID1A hetloss, BRCA1/2 hetloss, C11ORF30 amp, CCNE1 amp, ErbB2 hetloss, KRAS amp, MYC gain, NF1 gain, Notch3 hetloss, PIK3CA gain, Rb1 hetloss, TP53 mut (ms) and hetloss
FUOV1	Akt1/2 gain, ARID1A hetloss, BRCA1 gain, CCNE1 amp, CTNNB1 hetloss, ErbB2 gain, KRAS gain, NF1 muts (ms and ns) and homdel, MAP2K4 hetloss, MYC amp, Notch3 hetloss, PIK3CA gain, Rb1 hetloss, TP53 mut (ms)
NIHOVCAR3	Akt2 amp, ARID1A hetloss, BRCA1/2 hetloss, C11ORF30 amp, CCNE1 amp, ErbB2 hetloss, KRAS gain, MYC gain, NF1 gain, Notch3 hetloss, PIK3CA gain, Rb1 hetloss, TP53 mut (ms) and hetloss
ES2	Akt2 hetloss, BRAF mut (ms) and gain, BRCA2 hetloss, CCNE1 hetloss, KRAS hetloss, MAP2K4 gain, MYC gain, Rb1 hetloss, TP53 mut (ms)
JHOM2B	BRAF mut (ms) and gain, BRCA1 homdel, BRCA2 gain, ErbB2 homdel, MAP2K4 homdel, MYC gain, NF1 homdel, Rb1 mut (ns), TP53 mut (ms)
SNU8	Akt1/2/3 gain, BRAF gain, BRCA1 gain, BRCA2 hetloss, CCNE1 amp, CTNNB1 hetloss, ErbB2 gain, KRAS mut (ms), MAP2K4 hetloss, NF1 gain, Notch3 hetloss, PTEN hetloss, Rb1 hetloss, TP53 mut (fs) and hetloss
COV504	Akt1/2 hetloss, BRAF gain, BRCA1 hetloss, CCNE1 hetloss, CTNNB1 hetloss, ErbB2 gain, MAP2K4 hetloss, MYC gain, NF1 amp, Notch3 hetloss, PIK3CA gain, TP53 mut (fs) and hetloss
OV90	Akt2 gain, BRAF gain, CCNE1 gain, CTNNB1 hetloss, MAP2K4 hetloss, Notch3 hetloss, TP53 mut (ms)
RMUGS	Akt2 gain, ARID1A hetloss, BRAF hetloss, CCNE1 gain, CTNNB1 hetloss, MAP2K4 hetloss, Notch3 hetloss, PTEN hetloss, TP53 mut (ms) and hetloss
JHOM1	Akt1 gain, BRAF hetloss, C11ORF30 amp, CCNE1 mut (ms), KRAS gain, MYC gain, Notch3 hetloss, PTEN mut (fs), Rb1 mut (ms), TP53 mut (ns)
HS578T	Akt1/3 gain, BRCA1 gain, CTNNB1 mut (ms), ErbB2 gain, KRAS gain, MAP2K4 gain, MYC gain, NF1 gain, TP53 mut (ms) and gain
OVCAR8	Akt3 gain, ARID1A hetloss, C11ORF30 gain, CCNE1 gain, CTNNB1 mut (ms), ErbB2 mut (ms), KRAS mut (ms), MYC gain, TP53 mut (ss)
COV644	Akt1 homdel, BRAF gain, BRCA2 hetloss, C11ORF30 gain, MAP2K4 mut (ms) and hetloss, Notch3 hetloss, PTEN hetloss, TP53 hetloss
EFO21	Akt3 gain, BRCA2 hetloss, C11ORF30 gain, CCNE1 gain, CTNNB1 hetloss, ErbB2 gain, KRAS hetloss, MYC gain, NF1 homdel, Notch3 gain, PIK3CA gain, Rb1 homdel
JHOC5	Akt3 gain, ARID1A gain, BRCA1 amp, BRCA2 hetloss, CCNE1 gain, CTNNB1 hetloss, ErbB2 gain, KRAS gain, MAP2K4 hetloss, MYC gain, NF1 gain, Notch3 hetloss, PTEN hetloss, Rb1 hetloss, TP53 hetloss
SNU840	Akt1/3 gain, ARID1A hetloss, BRAF hetloss, MAP2K4 hetloss, MYC gain, Notch3 hetloss, PIK3CA mut (ms), TP53 hetloss
COLO704	Akt2 gain, Akt3 homdel, BRAF gain, CCNE1 gain, MYC gain, Notch3 gain, PTEN mut (ns), Rb1 mut (fs)
OVISE	Akt2 gain, ARID1A mut (fs), BRAF hetloss, BRCA1 gain, BRCA2 hetloss, C11ORF30 hetloss, CCNE1 gain, CTNNB1 hetloss, ErbB2 gain, MAP2K4 hetloss, MYC gain, NF1 gain, PIK3CA gain, Rb1 hetloss, TP53 hetloss
OAW42	Akt3 gain, ARID1A mut (fs) and gain, BRCA1 gain, ErbB2 gain, KRAS hetlos, MYC gain, PIK3CA mut (ms) and gain, PTEN hetloss
OVTOKO	C11ORF30 gain
OVMANA	Akt2 gain, ARID1A muts (ns and ns), BRCA1 gain, BRCA2 mut (ms), CCNE1 gain, ErbB2 gain, KRAS gain, MAP2K4 hetloss, NF1 gain, PIK3CA mut (ms) and gain, TP53 hetloss
RMGI	Akt1/2 gain, Akt3 hetloss, BRCA1 gain, BRCA2 hetloss, CCNE1 homdel, ErbB2 amp, MAP2K4 homdel, Rb1 gain, TP53 homdel
HEYA8	BRAF1 mut (ms) and hetloss, C11ORF30 gain, KRAS mut (ms) and gain, MYC gain, NF1 hetloss, PIK3CA gain
MCAS	KRAS mut (ms) and gain, PIK3CA mut (ms), PTEN gain
COV434	ARID1A mut (ms)
OV56	ARID1A mut (fs), BRAF hetloss, KRAS mut (ms), MYC gain, PTEN mut (ms)
SKOV3	ARID1A mut (ns), BRAF hetloss, CTNNB1 hetloss, ErbB2 amp, KRAS gain, MAP2K4 hetloss, NF1 mut (ms), PIK3CA mut (ms), PTEN hetloss, TP53 hetloss
A2780	Akt3 gain, ARID1A muts (ns and fs), BRAF mut (ms), Notch3 mut (ms), PIK3CA mut (ms), PTEN mut (del)
IGROV1	ARID1A muts (fs and fs), BRCA1 mut (fs), BRCA2 mut (ms), Notch3 mut (ms), PIK3CA muts (ms and nonstop), PTEN muts (ms and fs), TP53 mut (ms)
OVK18	Akt3 gain, ARID1A mut (fs), KRAS mut (ms), PTEN muts (ms, ms and fs) and gain, TP53 mut (fs)
EFO27	ARID1A muts (fs and ns), ErbB2 mut (ms), MYC mut (ms), NF1 mut (ms), PIK3CA mut (ms), PTEN mut (fs), TP53 muts (ms and ss)
OC316	Akt1 gain, ARID1A muts (ns and ns), BRAF mut (ms) and gain, BRCA2 mut (fs) and hetloss, CTNNB1 gain, PIK3CA mut (ms), Rb1 gain
TOV21G	ARID1A muts (fs and fs), CTNNB1 mut (fs), KRAS mut (ms), PIK3CA mut (ms), PTEN muts (fs and fs) and gain

- In just these 20 genes the combinations of mutations, copy number changes is vast.
- In order to make use of these complex data one needs to create a statistical model based on a clinical training data set.
- **Genotypic signatures cannot be trained to recognise drugs that are never used in the clinic to treat a particular cancer.**
- The degrees of freedom in the statistical model make it very prone to over fitting the training set.

Imagen Biotech
See more than images

Our data set is measuring cell death directly so much easier to interpret.



We only have one parameter in our data set that needs calibrating against clinical response, using a clinical training set, and that is *in vitro* drug dose.

Imagen Biotech
See more than images

A 3D Cell Death Assay

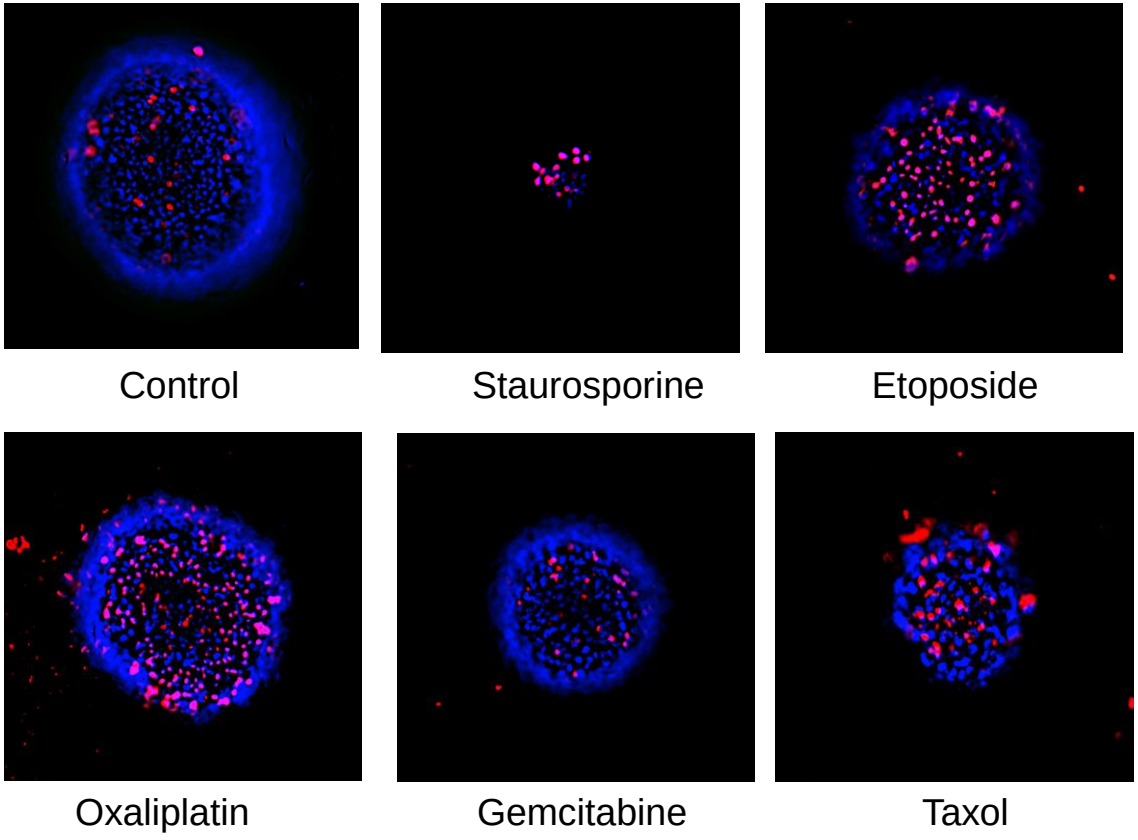
Originally developed using InSphero's GravityTRAP™ specifically designed for scaffold-free microtissue culture.

- 3D Liver model for toxicity
- 3D Tumour microtissues for anti-cancer drug testing

- HCA allows measurement of both tissue shrinkage and cell death within the tissue.
- Analysis in 96 well plates increases throughput allowing dose responses to be performed or the number of compounds tested increased.

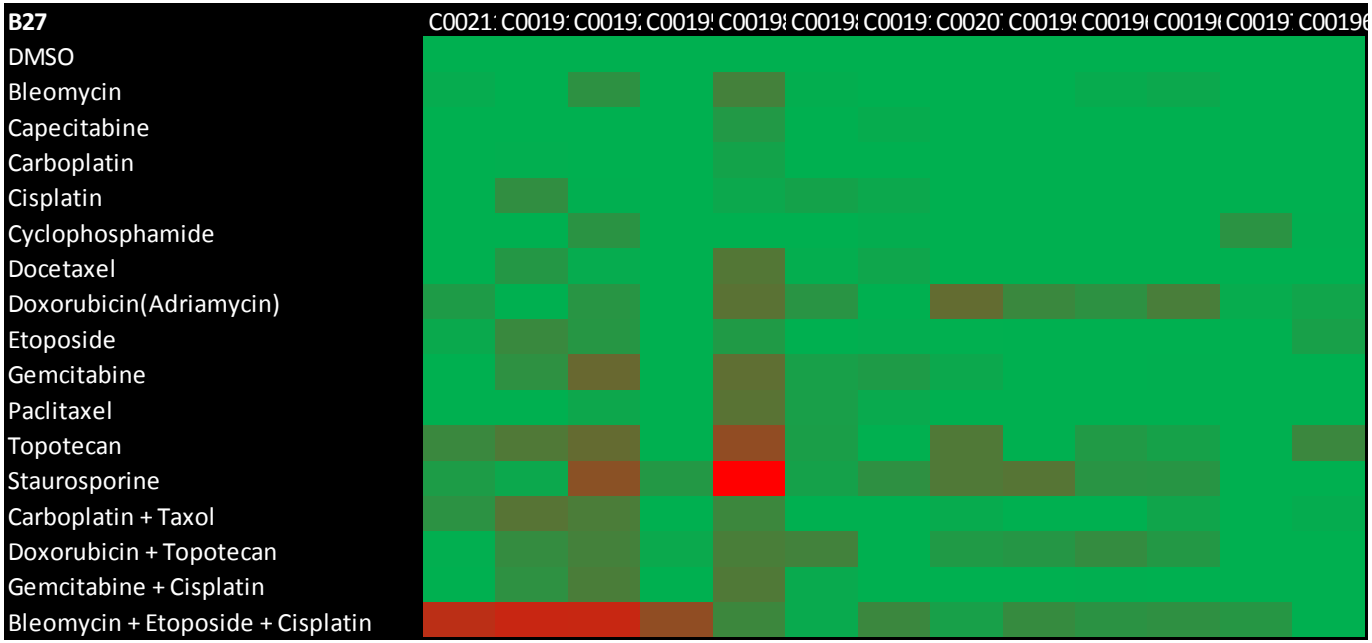
- Blue- Nuclei staining
- Red- permeability stain

HepG2 microtissues exposed to 10uM compounds for 7 Days



Summary of Ovarian Screen in Standard DMEM in IB Media

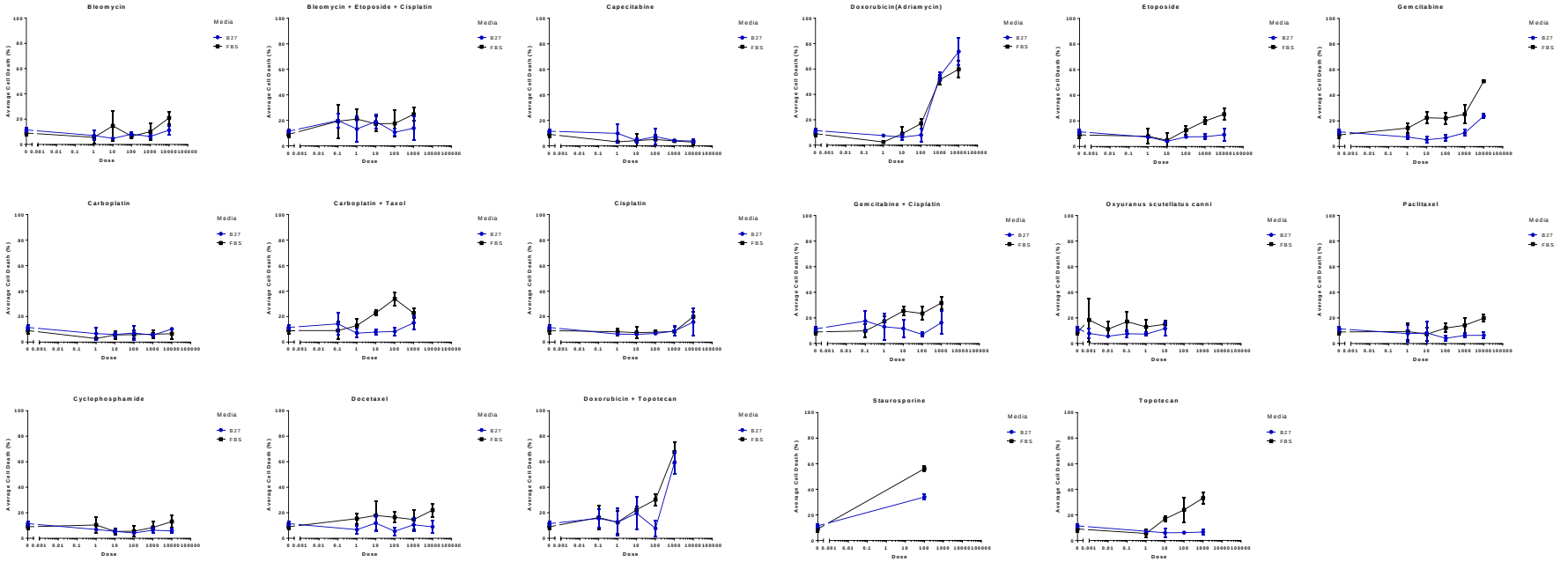
<51 Percentile = Green & > highest value = Red



- Response is highly patient-dependent with some patients sensitive to the majority of treatments others highly insensitive to all treatment.
- Background cell death is a critical factor when looking at these particular heatmaps of multiple patients together.
- Background cell death is low in FBS, but in the selective media it can vary suggesting a subpopulation of ‘normal’ cells are being eliminated.

Imagen Biotech
See more than images

Patient 1995T1Fa



- Sensitive to Doxorubicin
- Gemcitabine
- Topotecan (in FBS only)
- First example of how we could improve our growth media to make the assay more predictive.

Imagen Biotech
See more than images

Patient response matchup with assay prediction

Green- Correct prediction
Pink - Incorrect

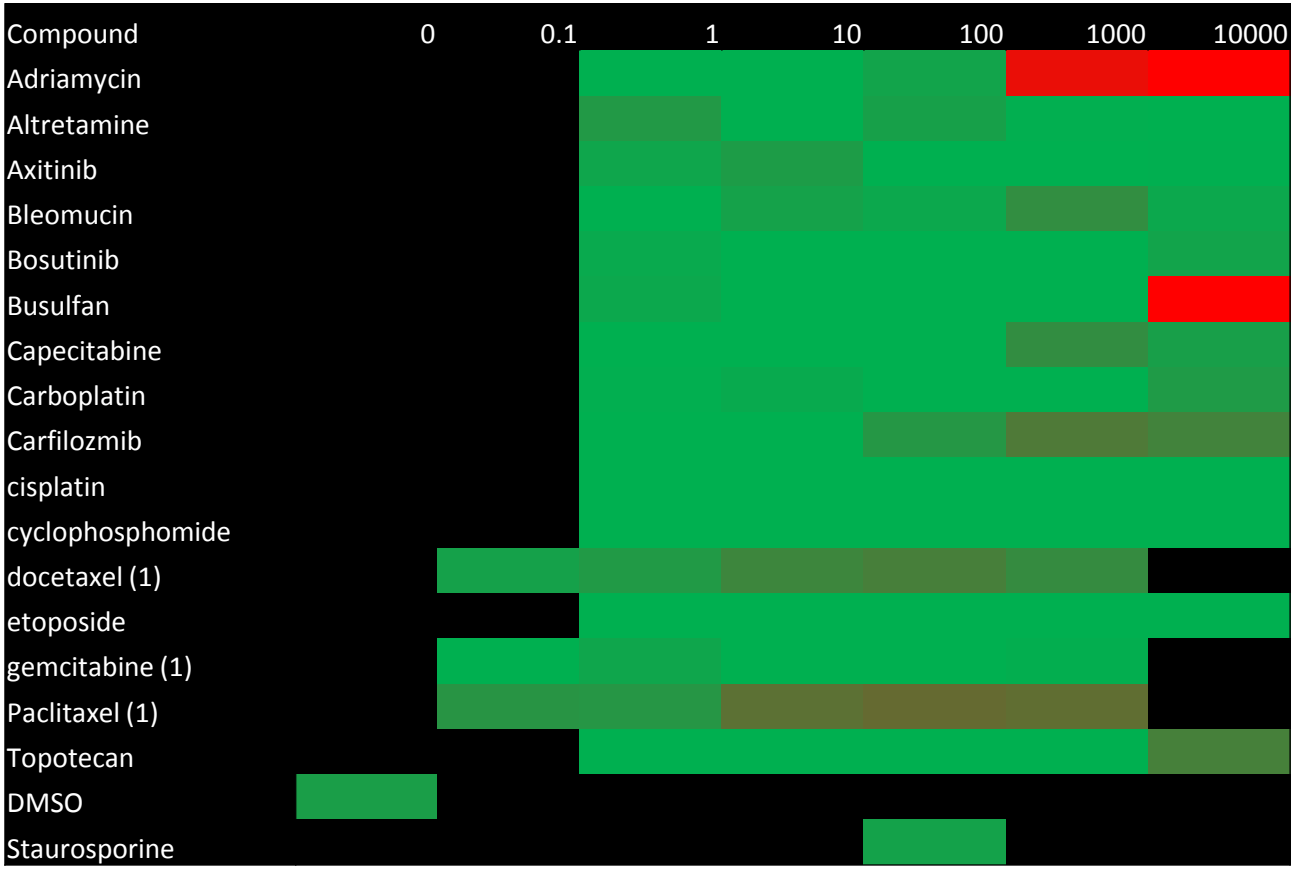
Blue highlights represent actual clinical responders

Responder?	Identifier	Type	When Sample was taken	Response?	Prediction correct?
	1901	Stage IIIa high grade endometrioid adenocarcinoma of ovarian type	post treatment	N	Y
	1987	stage 3c high grade serous	Pre treatment	N	Y
	2170	poorly differentiated carcinoma of ovarian origin with omental mets	Pre treatment	N	Y
	2175	Stage 4, mixed endometrioid and	Pre treatment	N	Y
	2218	Colon,Metastatic sigmoid cancer	Post treatment	N	Y
	1980T1(B27)	Ovarian	Pre treatment	N	Y
	2115T1	Stage 3c/4 high grade serous adenocarcinoma of ovarian or primary peritoneal origin	Post treatment	N	Y
	C001952	Stage 3c primary peritoneal/ovarian	Post treatment	N	Y
	C001962T2AFa	Psammocarcinoma of ovarian	Post treatment	N	Y
	C002075 T1AFa	Stage 3c/4 adenocarcinoma of primary ovarian	Post treatment	N	Y
	C002138 T1AFa	Unknown origin	Pre treatment	N	Y
	C002220 T1AFa	Stage 4 ovarian/peritoneal cancer	Pre treatment	N	Y
	C002254 T2AFa	Stage 3c High grade serious ovarian/ fallopian tubes/ primary peritoneal carcinoma	Pre treatment	N	Y
	C002272	Stage 3/4 Low grade serous carcinoma	Pre treatment	N	Y
	C002284T1	Stage 3c ovarian high grade serous carcinoma	Post treatment	N	Y
	C002287T1AFa	High grade serous ovarian adenocarcinoma	Pre treatment	N	Y
	C002346T1AFa	Primary tumour stage 4 ovarian cancer,	post treatment	N	Y
	C002375T1AFa	Stage 3c low grade serous ovarian carcinoma	Mid treatment	N	Y
	C002393T1AFb	Relapsed stage 3C high	Mid treatment	N	Y
	C002406 T1	Recurrent high serous carcinoma	Post treatment	N	Y
Y	2122	High Grade serous adenocarcinoma,	Pre treatment	Y	Y
Y	C001874T1AFa	Stage IIIc ovarian cancer	Pre treatment	Y	Y
Y	C001926	Carcinosarcoma of the ovary, at least stage 3c	Mid treatment	Y	Y
Y	C002222T1AFa	Primary Peritoneal Cancer/Ovarian Stage 3c, poorly differentiated high grade adenocarcinoma	Pre treatment	Y	Y
Y	C002307	poorly differenciated carcinoma	Pre treatment	Y	N
Y	C002350T1AFa	Poorly differentiated carcinoma of the ovary	Pre treatment	Y	Y
Y	C002385T1AFa (naive)	Stage 3C high grade serous carcinoma	Pre treatment	Y	Y
Y	C002401T1AFb	High grade serous adenocarcinoma FIGO stage 3c	Pre treatment	Y	Y

Cancer of unknown primary

Imagen Biotech
See more than images

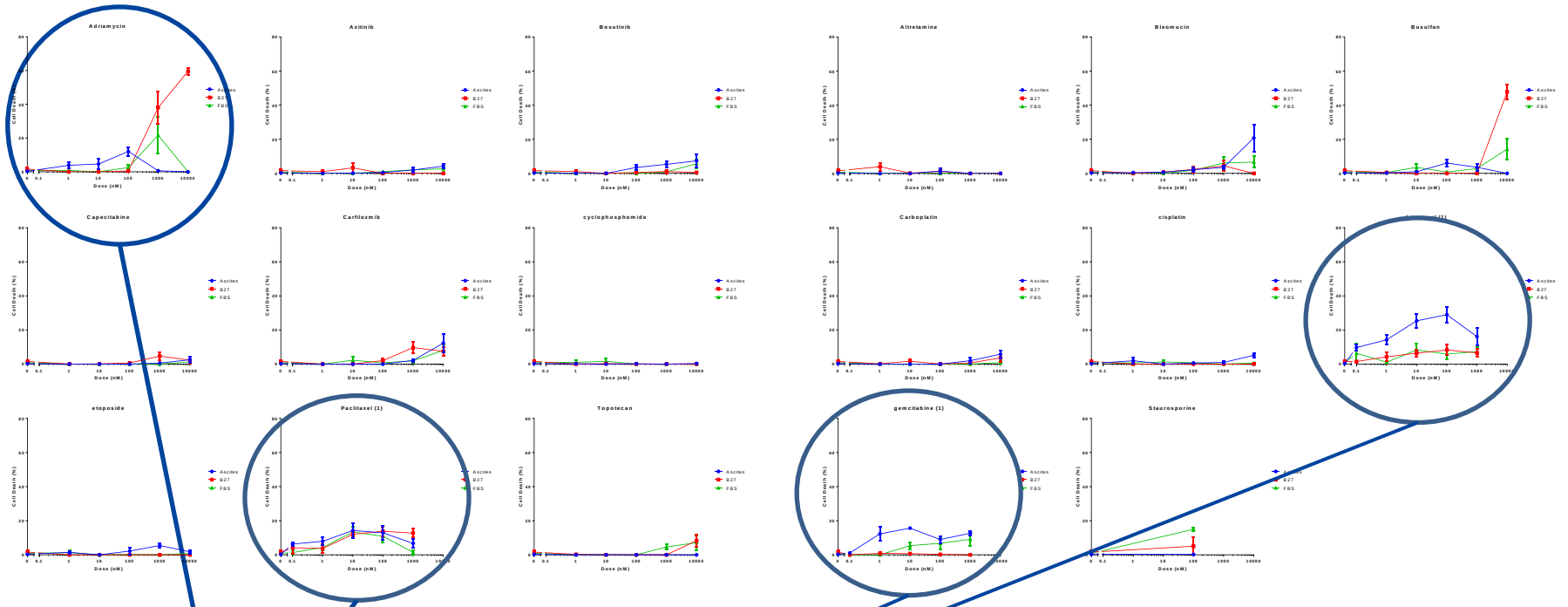
Patient 2138 Cancer of Unknown Primary



Cancer very resistant to standard chemotherapies

Imagen Biotech
See more than images

Patient 2138 Cancer of Unknown Primary

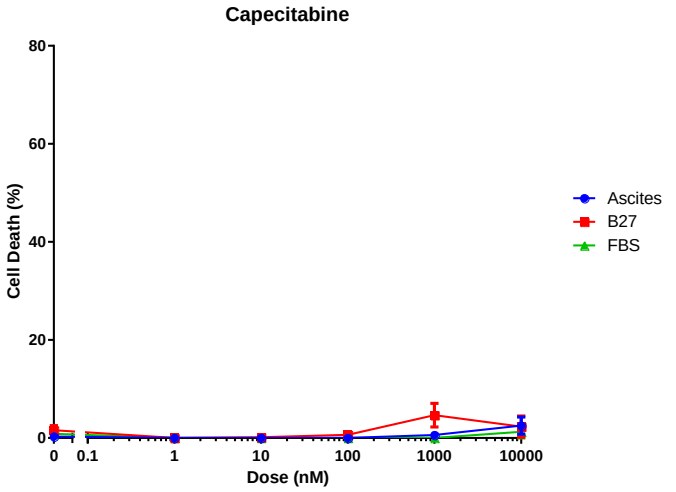


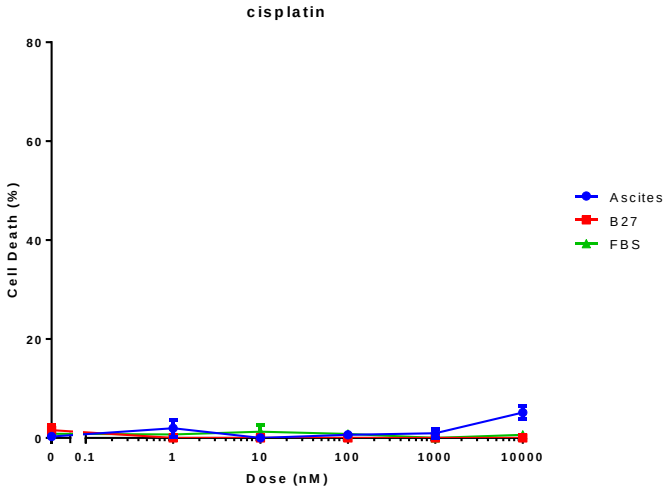
- This patient was analysed early in our development when we were comparing different culture media.
- Red line response is our own proprietary media. Cancer appears to respond to Adriamycin but only at high doses.
- Cancer may also be sensitive to docetaxel, gemcitabine and paclitaxel.

Imagen Biotech
See more than images

Patient 2138 Received

(Epirubicin, Oxaliplatin & Capecitabine) 16/06/2014 - 03/10/2014





Patient passed away 22/10/2014

Imagen Biotech
See more than images

Summary of Assay Predictive Rate

- **28 samples – 27 correct predictions (overall prediction 96%)**
- All predictions indicating positive response were correct (**7/7 – 100% specificity**)
- Only 1 prediction indicating no response was incorrect
- The rest were correct (7/8 – **88%** sensitivity)

Why do we out perform earlier *in vitro* cell death assay studies?

Growth medium: Our data demonstrates cells grown in FBS have a lower prediction rate of *in vivo* tumour response.

Timing: The assay needs to be performed immediately.

Sample C002287: Our assay showed correctly there would be no response. Stable cell line derived after several months in FBS showed incorrectly it would respond. This satisfies the strongly held position that cells change when you grow them on plastic long term.

Assay: We measure cell death directly not a surrogate marker of cell count.

Overall the 1990s data did show prediction of response but not improvement in survival (PM is only as good as the best drug you have available to treat the patient)

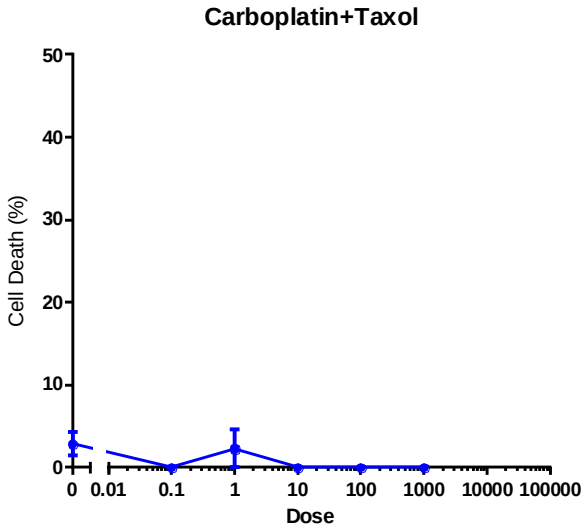
Imagen Biotech
See more than images

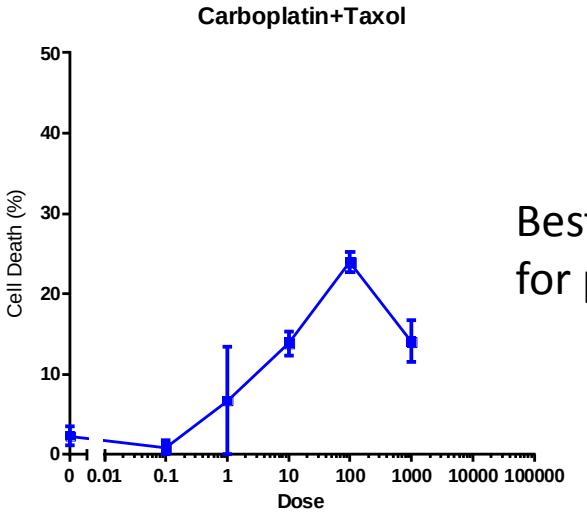
Our Contention

If you used our assay with standard licensed therapies then you will not have the statistical power to see significant shift on overall survival curves and this is the mistake that was made in the 1990s.

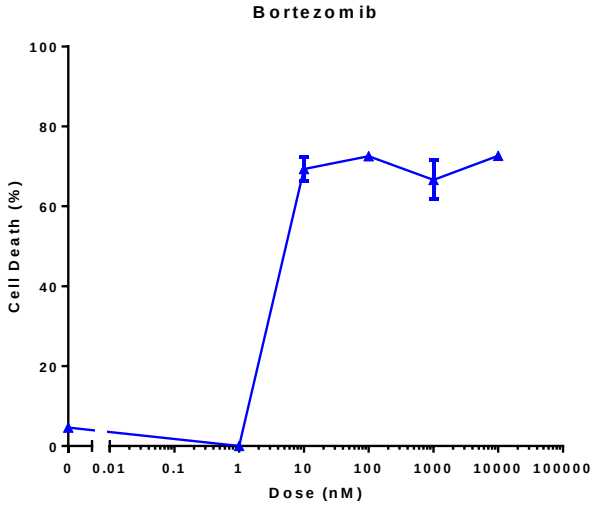
Imagen Biotech
See more than images

Responder versus non responder





Best licensed chemotherapy for patient G



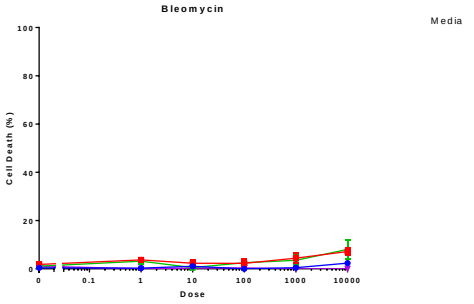
Best response in larger 56 chemotherapy screen for patient Y

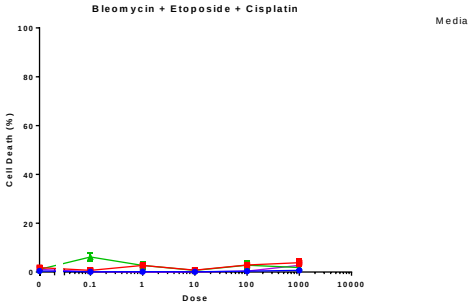
Imagen Biotech
See more than images

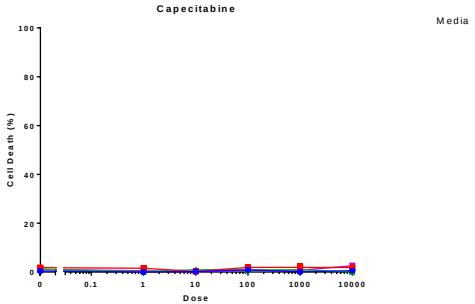
The Drugs Don't Work they just make you worse … (The Verve, 1997)

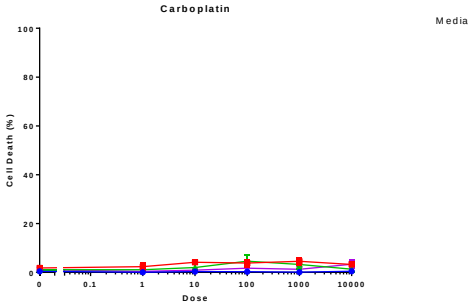
Patient X

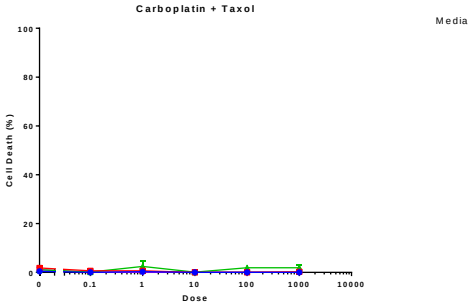
Drain 2

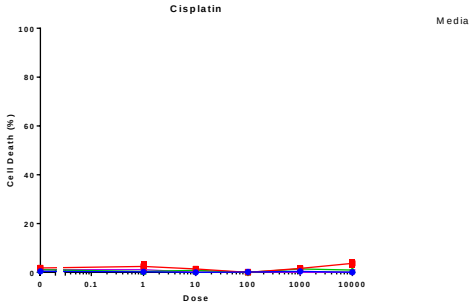


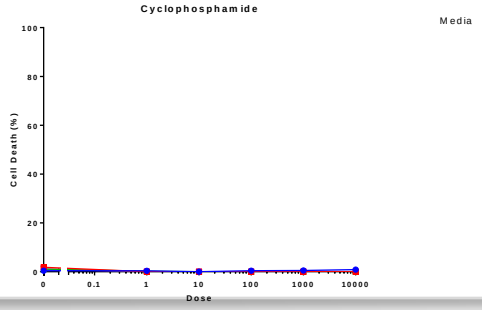


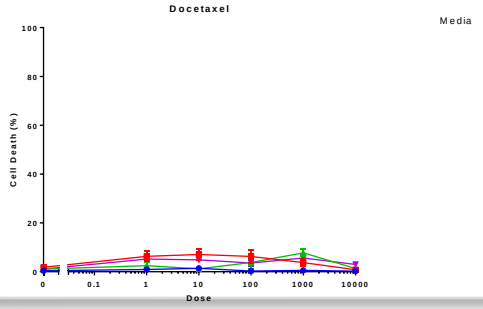












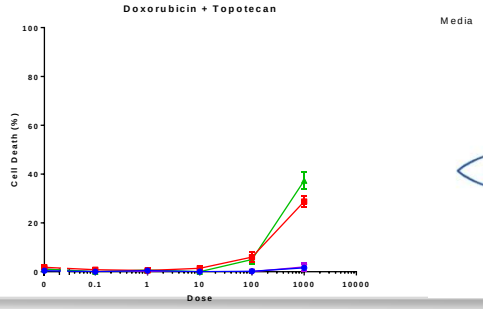


Imagen Biotech
See more than images

The Drugs Don't Work they just make you worse … (The Verve, 1997)

Patient X

Drain 4

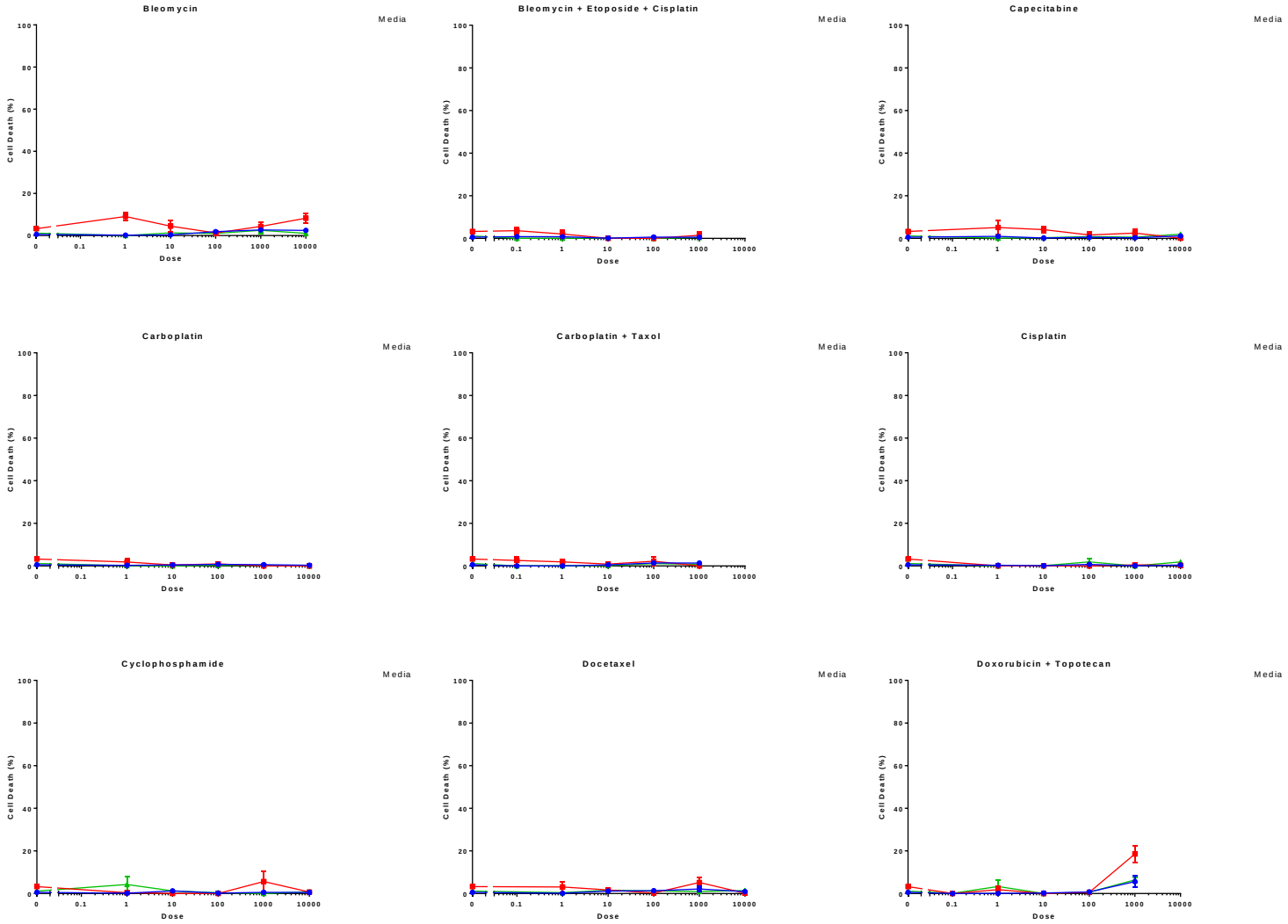
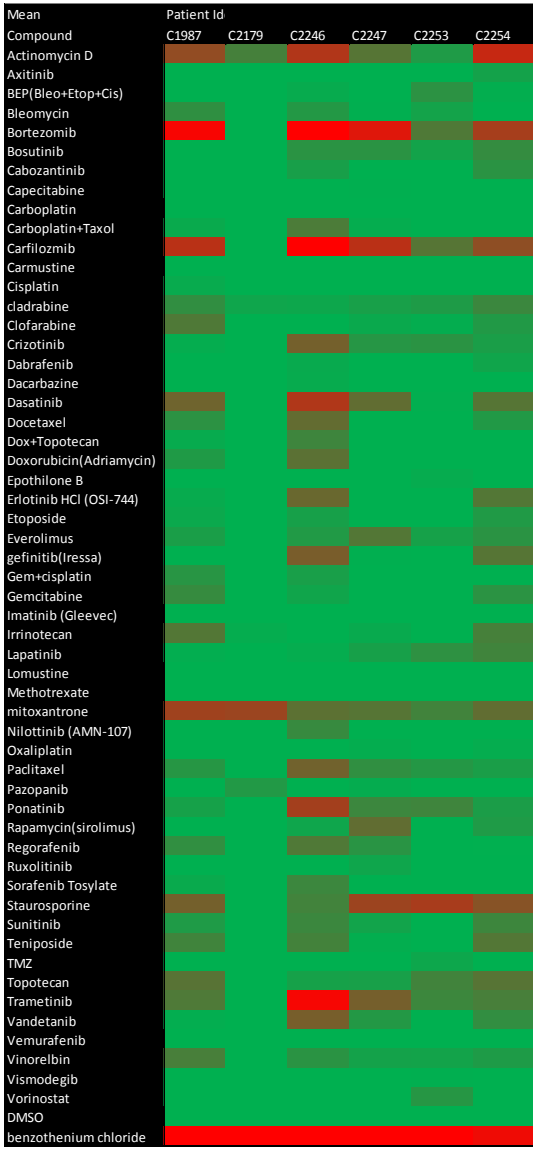


Imagen Biotech
See more than images

Larger Screen with 54 chemotherapies

Proprietary Culture Media A

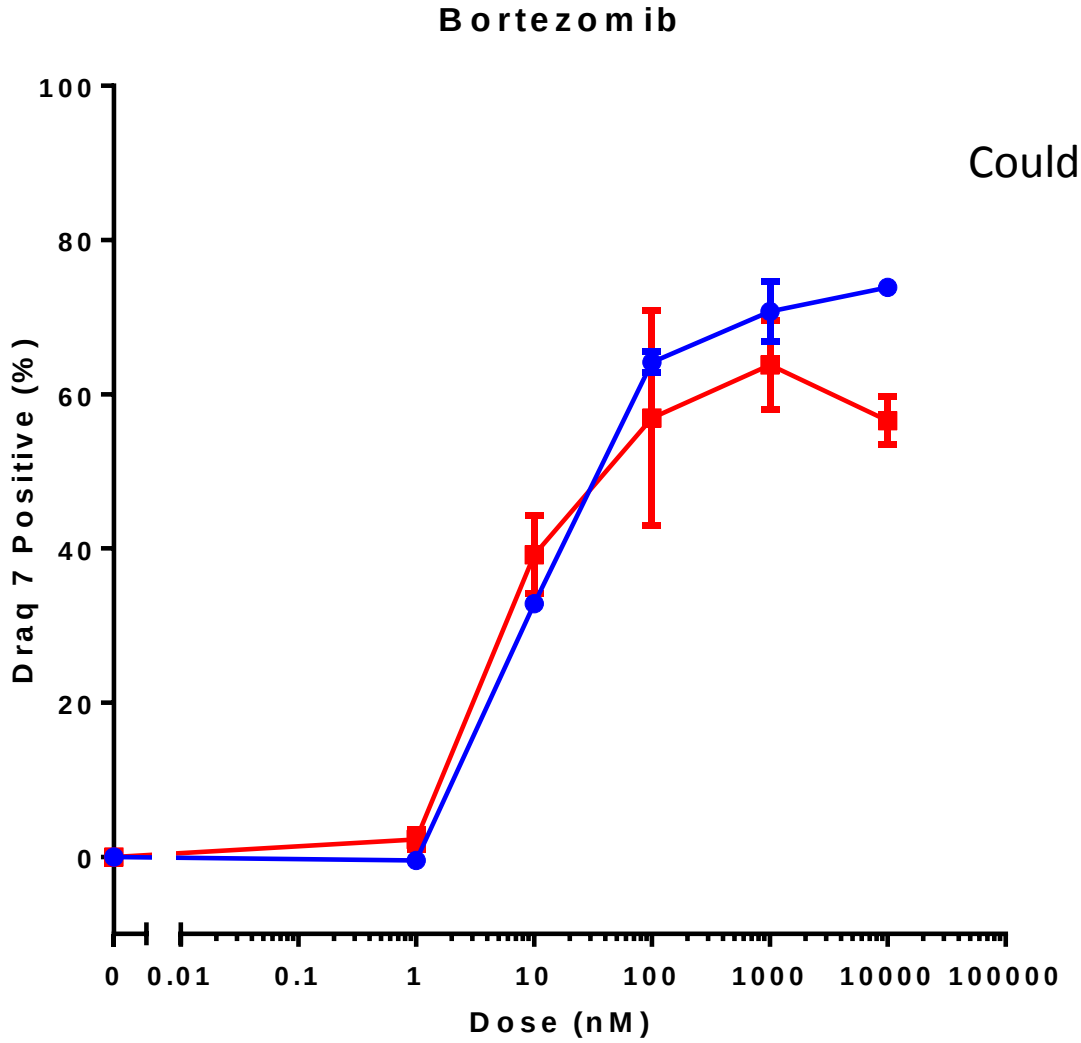


- 2D measure is % cell death.
- Each block represents the mean response across a log scale dose response curve.
- **Heat map code:**
  1. Green = all data where death is below the 50 percentile.
  2. Red = all data where death is above the 97 percentile.
  3. 51-97 percentile coded in green/red colour mixtures proportional to the percentile value.

Imagen Biotech
See more than images

Patient X Response to Bortezomib

Patient X



Could this be an assay false positive?

Imagen Biotech
See more than images

Background Dose Response Curves for 6 patients

- Can use the data set a group of patients to address the question of *in vitro* assay false positives. If heterogeneous responses are observed for a particular drug in different patients then this suggests the assay is picking up true patient differences in chemosensitivity profiles for the particular drug under study (as shown below).

- Disturbingly these data predict that Bortezomib will work in only a subset of ovarian patients so how this will translate in a clinical trial is uncertain.

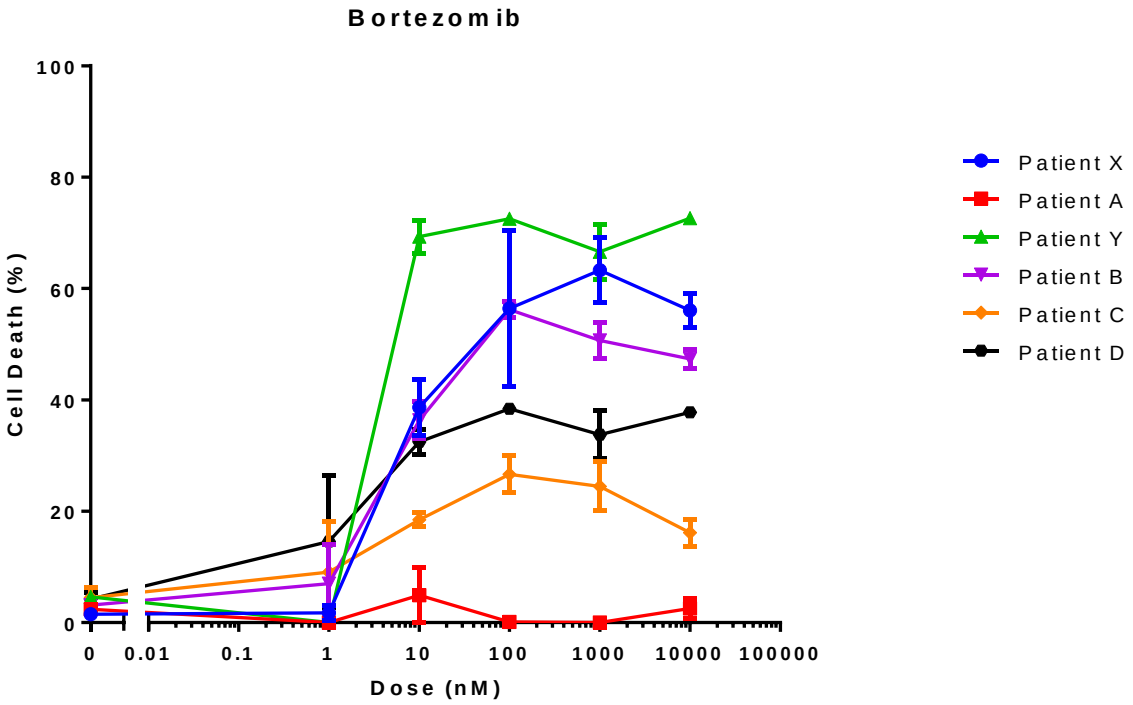


Imagen Biotech
See more than images

Phase I Clinical Trial – Bortezomib with Carboplatin

VOLUME 23 · NUMBER 25 · SEPTEMBER 1 2005

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Phase I Trial of Bortezomib and Carboplatin in Recurrent Ovarian or Primary Peritoneal Cancer

C. Aghajanian, D.S. Dizon, P. Sabbatini, J.J. Raizer, J. Dupont, and D.R. Spriggs

From the Developmental Chemotherapy Service, Memorial Sloan-Kettering Cancer Center, New York, NY; The Program in Women's Oncology, Women & Infants' Hospital, Brown Medical School, Providence, RI; and Department of Neurology, Northwestern University, Feinberg School of Medicine, Chicago, IL.

Submitted February 14, 2005; accepted May 9, 2005.

Supported by grant No. 5RD1 CA84009 from the National Cancer Institute (Bethesda, MD).

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Carol Aghajanian, MD, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021; e-mail: aghajanc@mskcc.org.

0732-183X/05/2325-5943/$20.00

DOI: 10.1200/JCO.2005.16.006

A B S T R A C T

Purpose
To determine the maximum-tolerated dose, pharmacodynamics, and safety of the combination of bortezomib and carboplatin in recurrent ovarian cancer.

Patients and Methods
Fifteen patients were treated with a fixed dose of carboplatin (area under the curve [AUC] 5) and increasing doses of bortezomib (0.75, 1, 1.3, and 1.5 mg/m²/dose). Patients must have received upfront chemotherapy and up to two prior chemotherapy regimens for recurrent disease. Neurologic evaluation was performed at baseline and after every two cycles by the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group neurotoxicity questionnaire and examination by an attending neurologist. All patients received carboplatin alone in cycle 1 to establish baseline pharmacodynamics for nuclear factor-kappa B (NF-kB). Starting with cycle 2, patients were treated with carboplatin on day 1 and bortezomib on days 1, 4, 8, and 11.

Results
Diarrhea, rash, neuropathy, and constipation (with colonic wall thickening on computed tomography) were dose-limiting toxicities, occurring in the two patients treated at the 1.5 mg/m²/dose level. The Functional Assessment of Cancer Therapy/Gynecologic Oncology Group neurotoxicity questionnaire was helpful in guiding the need for dose reductions. Neurotoxicity was manageable through six cycles, with appropriate dose reductions. Carboplatin had no effect on bortezomib pharmacodynamics as measured by percent inhibition of the 20S proteasome. Bortezomib decreased carboplatin-induced NF-kB. The overall response rate to this combination was 47%, with two complete responses (CR) and five partial responses, including one CR in a patient with platinum-resistant disease.

- 47% response rate
- 2 out of 15 complete responders
- 1 in platinum sensitive 1 in platinum resistant group

Conclusion of study is very positive and recommends progression to phase 2 trial

"The preclinical activity of bortezomib makes it a promising agent for combination therapy in overcoming chemotherapy resistance. The CR seen in this study in a platinum-resistant patient is also encouraging."

Imagen Biotech
See more than images

Phase 2 Clinical Trial – Bortezomib with Doxirubicin

ORIGINAL STUDY

An Open-Label Phase 2 Study of Twice-Weekly Bortezomib and Intermittent Pegylated Liposomal Doxorubicin in Patients With Ovarian Cancer Failing Platinum-Containing Regimens

Gabriella Parma, MD, Rosanna Mancari, MD,* Gianluca Del Conte, MD,† Giovanni Scambia, MD,‡ Angiolo Gadducci, MD,§ Dagmar Hess, MD,|| Dionyssios Katsaros, MD,¶ Cristiana Sessa, MD,# Andrea Rinaldi, PhD,# Francesco Bertoni, MD,# Andrea Vitali, ScD,** Carlo Vittorio Catapano, MD, PhD,# Silvia Marsoni, MD,** Helgi van de Velde, MD, PhD,†† and Nicoletta Colombo, MD*‡‡*

Background: Pegylated liposomal doxorubicin (PLD) is an established treatment for relapsed ovarian cancer. Preclinical and clinical evidences in other tumor types suggest that the proteasome inhibitor bortezomib can act synergistically with PLD.

Methods: Patients with relapsed ovarian cancer (N = 58), previously treated with platinum (100%) and taxane (95%), received bortezomib, 1.3 mg/m^2 intravenous (days 1, 4, 8, and 11), and PLD, 30 mg/m^2 intravenous (day 1), every 3 weeks. Tumor responses were assessed using Response Evaluation Criteria In Solid Tumors and Gynecologic Cancer Intergroup criteria. An optimal 2-stage design was implemented. Gene expression profiling in peripheral blood was characterized before and during treatment in 10 platinum-sensitive patients enrolled in stage 2 of the study.

Results: Median number of bortezomib-PLD cycles was 3.5. Of 38 patients in the platinum-sensitive group, 9 responses were observed (median duration, 4.8 months). The platinum-resistant group was closed at stage 1 owing to lack of response. Toxicity was moderate and

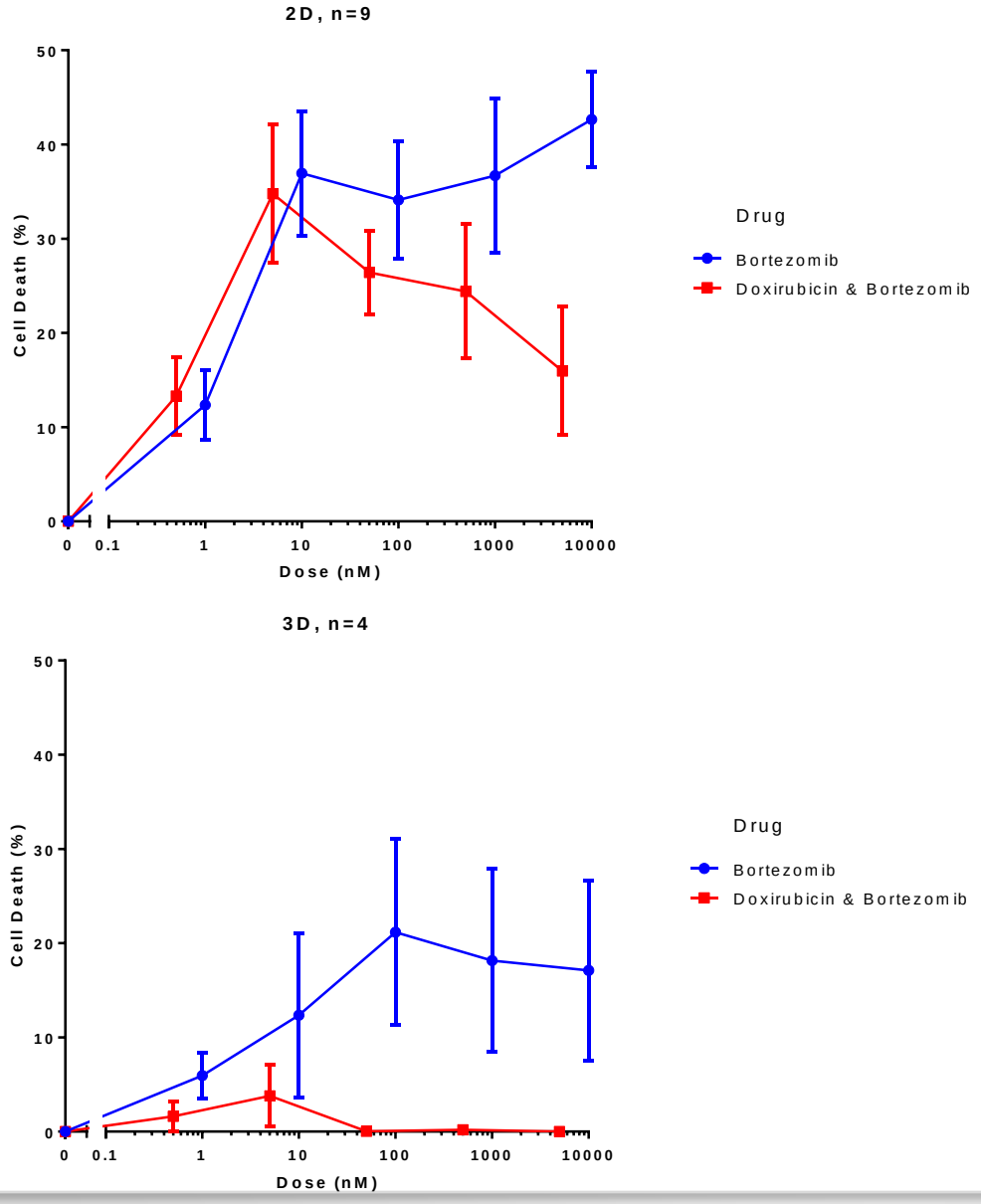
Overall conclusion response rate no different from doxirubicin on its own so did not recommend further use.

"Conclusions: The combination of bortezomib and PLD was well tolerated, but the antitumor activity is insufficient to warrant further investigation in ovarian cancer."

Our data suggests that bortezomib does not work as well when combined with doxorubicin.

Imagen Biotech
See more than images

In Vitro results of Bortezomib versus Bortezomib & Doxirubicin

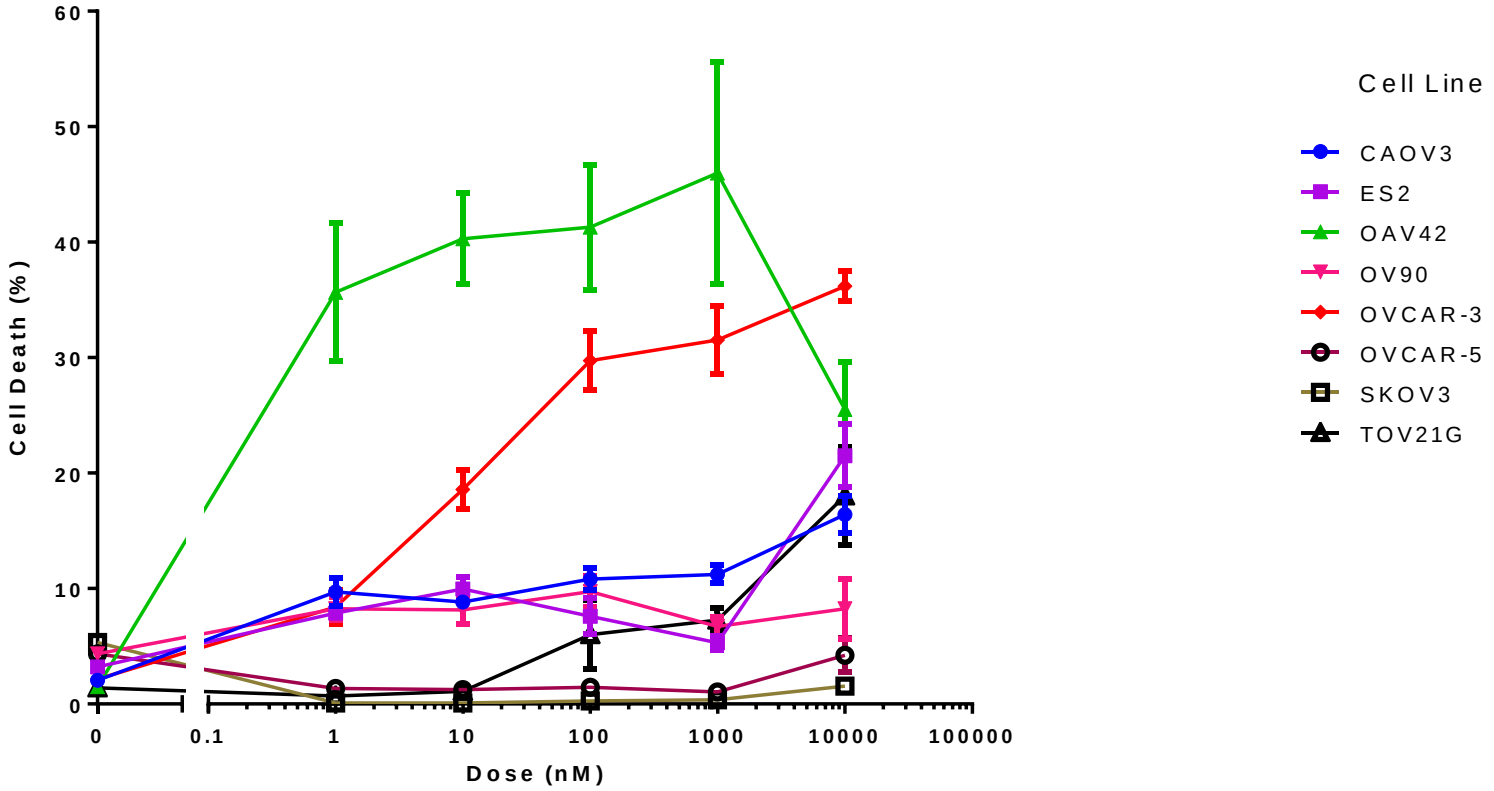


- Large error bars in 2D and 3D bortezomib because of the heterogeneous response of different patients to bortezomib (see slide 14 for example)
- In all 3D samples bortezomib and doxrubicin never worked better than bortezomib on its own.
- Both 2D and 3D data suggests that it is naïve to assume that drug combinations will never interfere with each other.

Imagen Biotech
See more than images

Targeted Therapeutics- Another example of a personalised response

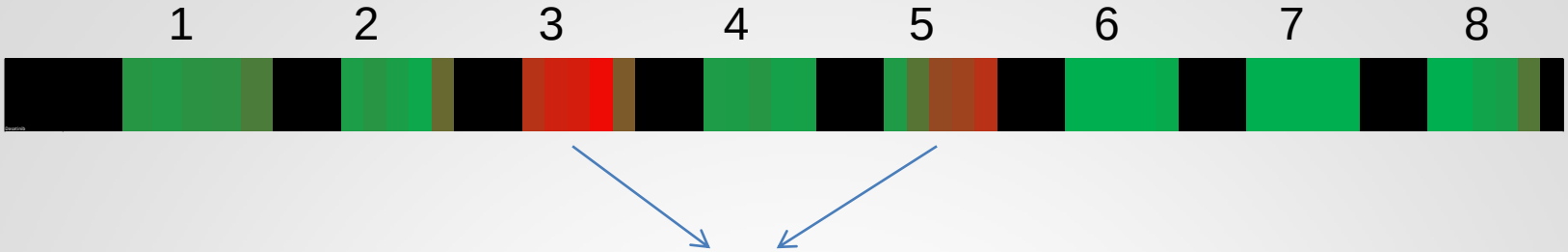
Dasatanib tested in an 8 Ovarian cell line panel



- 6 non-responders, 1 medium responder and 1 super responder.
- Would this pattern repeat in ovarian patients?

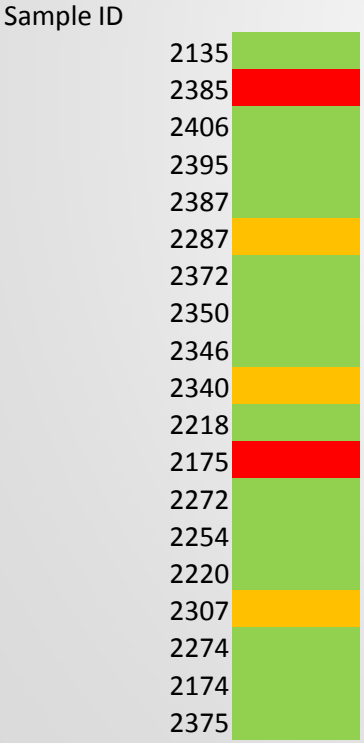
Imagen Biotech
See more than images

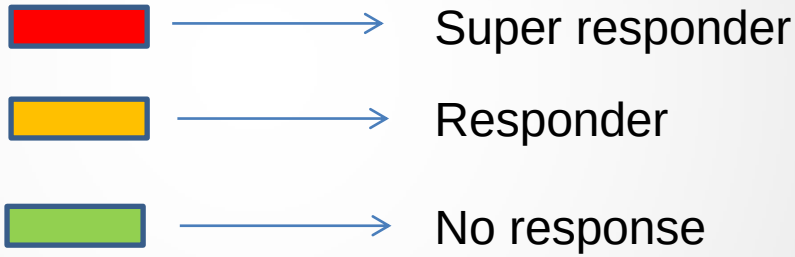
Ovarian cell lines treated with Dasatinib* (a BCR/Abl and Src inhibitor)



2 responders from 8 cell lines

We therefore hypothesized that we would get some responders in our Ovarian Panel from patients





There are clearly a subpopulation of patients that could benefit greatly from this drug, however they never receive them or if they do it is simply a calculated guess

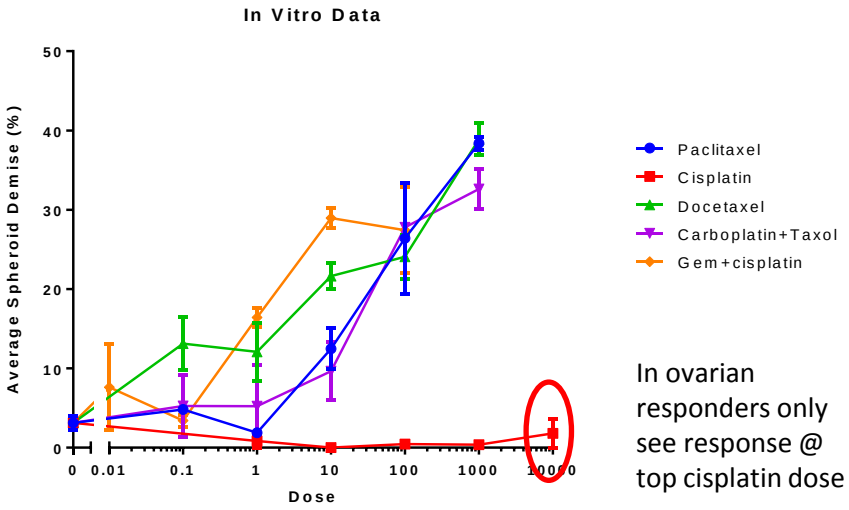
* Bristol-Myers Squibb and sold under the trade name Sprycel. Dasatinib is an oral multi-**BCR/Abl and Src family tyrosine kinase inhibitor** approved for first line use in patients with chronic myelogenous leukemia (CML)[1] and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL).

Initial PDX Match Work

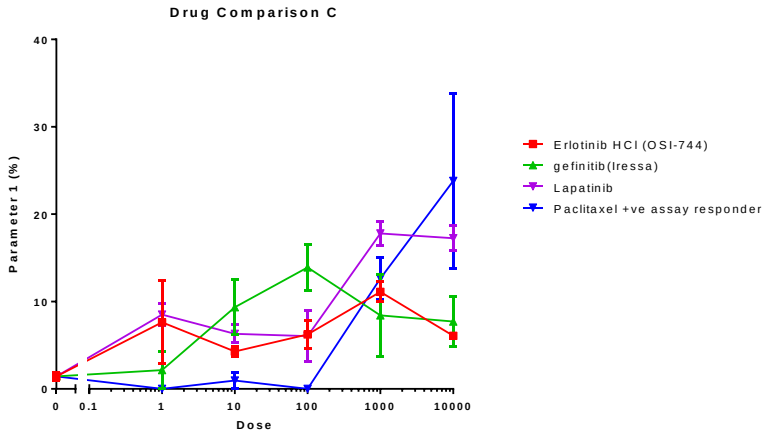
- Have received two frozen samples from a large company that specialised in PDX models.
- The first did not work, from the second we produced a good data set of 56 different chemotherapies.
- The second sample had been frozen for 8 years.
- Our match up with the PDX response was good.
- We will continue to work with this company hopefully moving towards a prospective treatment study where our data is used to directly influence the chemotherapy treatment of the mice.

Imagen Biotech
See more than images

Initial PDX Match Work



In ovarian responders only see response @ top cisplatin dose



	Drug	Dose (mg/kg)	Route	Schedule	% TGI
	Paclitaxel	20 mg/kg	iv	q4dx3	33
	Cisplatin	1.5 mg/kg	ip	qdx5	20
	Docetaxel	20 mg/kg	iv	q7dx3	78
	Docetaxel	5 mg/kg	iv	q7dx3	59
	Paclitaxel	25 mg/kg	iv	q7dx3	44
	Carboplatin	30 mg/kg	ip	q7dx3	
	Cisplatin	1.5 mg/kg	ip	qdx5	79
	Gemcitabine	40 mg/kg	ip	q3dx4	
NT	Carboplatin	30 mg/kg	ip	q7dx3	79
	Paclitaxel	25 mg/kg	iv	q7dx3	
	Bevacizumab	5 mg/kg	ip	q3dx8	
NT	Pemetrexed	200 mg/kg	ip	qdx5x2	0
	Erlotinib	50 mg/kg	po	qdx28	66
	Paclitaxel	10 mg/kg	iv	q4dx6	13
	Cisplatin	7.5 mg/kg	ip	q7dx4	58
	Erlotinib	35 mg/kg	po	qdx23	61

Complete Matchup

Reasonable Matchup

Possible Mismatch

Imagen Biotech
See more than images

Next Steps

- We want to publish the data with our clinical colleagues as co-authors as soon as possible. Part this process will involve working closely with them to audit our matchup data and try to, as best we can mimic Recist categories even though these patients were not part of a formal clinical trial.

- We now want to expand quickly into other cancers especially finalising an upstream workflow for the collection of solid tissue from theatre.

- Work with a few surgeons in the MRI to tweak upstream workflow of tissue collection from theatre to Imagen Biotech.

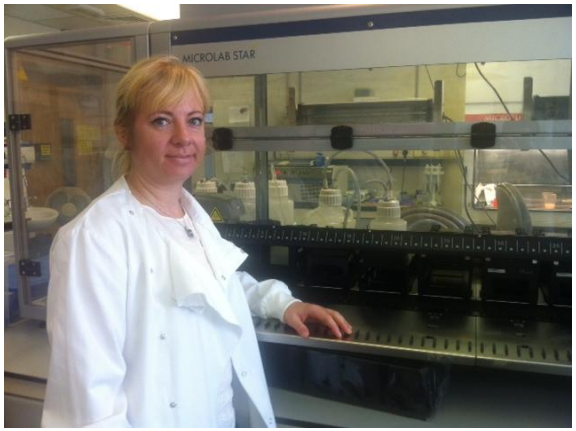
- The next cancers we want to look at in order of preference are:

    1. Solid ovarian cancer (so we can compare data with ascites source).
    2. Malignant melanoma (because of the BRAF hyper-responder mutation).
    3. Cancer of Unknown Primary (CUP) because it does not have a clear chemotherapy protocol for treatment.
    4. Breast Cancer

- A prospective PDX animal study to validate our assay's off-license predictive power.

Imagen Biotech
See more than images

Acknowledgements



Asia & Hal

Roderick Benson

Gareth & the VTI

Deniz Beyit & Mat Milner

With thanks to …

Dr Brian Bigger
Mr Kenny Yu
Mr Omar Pathmanaban
Mr Ian Kamaly
Ms Jane Rogan (**MCRC Biobank**)
Dr Andrew Clamp
Dr Sacha Howell
Professor Gordon Jayson

University of Manchester

Christie Biobank

ThermoScientific

Imagen Biotech
See more than images

Address: 3F68, The Biohub at Alderley Park
Mereside, Alderley Edge, Cheshire
SK10 4TG
Phone: 01625 238-785
Email: info@imagen-biotech.com
Web Address: www.imagen-biotech.com