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In vitro assessment of Avoca 95 capsule and Avoca-95 liquid in a standard propidium based 2D monolayer assay in a panel of 42 cancer cell lines followed by a COMPARE Analysis

Study Report

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1 Authorisation

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2 Summary

In the present study, the *in vitro* anti-tumor activity of two different Avoca 95 formulas from Herbal Home SDN BHD was assessed in a standard panel of 42 cell lines. Avoca 96 was supplied i) as capsules and ii) in the form of liquid oils. Capsules were broken and the content was dissolved in DMSO. The oily Avoca 95 liquid was extracted 1:1 with DMSO and the DMSO phase used for the treatment of the cells. These two formulas were applied to the cells at 10 concentrations in half-log dilution steps in duplicate up to 0.3 %(v/v) (Avoca 95 liquid) or 30 µg/mL (Avoca 95 capsule) and efficacy was assessed after a treatment period of 72 h using a propidium iodide based 2D monolayer assay. Anti-tumor activity is expressed as absolute and relative IC_{50} values, calculated by non-linear regression analysis. In addition, a Compare Analysis was done by correlation of the individual IC_{50}/IC_{70} values of the test compound as obtained in this study with the corresponding IC_{50}/IC_{70} values for 307 standard anticancer agents historically determined at Charles River Freiburg for these 42 cell lines. These standard agents represent the main mode of actions (MoAs) for current anticancer drugs.

Avoca 95 liquid showed concentration dependent inhibition of tumor cell growth in all cell lines tested. Avoca 95 liquid exhibited a geomean relative (absolute) IC_{50} value of 0.015% v/v (0.015% v/v) with significant activity (T/C<50%) in 3/42 cell lines at a concentration of 0.0095% v/v, in 34/42 cell lines at 0.03% v/v and in 42/42 cell lines at 0.095% v/v and 0.3% v/v. Above average activity (individual absolute IC_{50} of a cell line below ½ mean IC_{50} value) of Avoca 95 liquid was detected in the melanoma cell lines MEXF 1341 (abs. IC_{50} of 0.003% v/v) and MEXF 276 (0.004% v/v), as well as in the pancreatic cancer cell line PAXF 1657 (0.003% v/v).

Avoca 95 capsule exhibited a geomean relative (absolute) IC_{50} of 21.349µg/ml (21.784µg/ml) but in most cell lines significant activity was only achieved at the highest test concentration of 30 µg/ml. However, similar to Avoca 95 liquid, the melanoma cell lines MEXF 1341 and MEXF 276 responded particular well to Avoca 95 capsule and individual absolute IC_{50} values of 1.99 µg/ml (MEXF 276) and 2.25 µg/ml (MEXF 1341) were achieved in these cell lines. Furthermore, above-average activity was detected in the pancreatic cancer cell line PAXF 1657 and colon cancer cell line DiFi.

Compare Analysis of the activity profile of the two formulations with 307 standard agents did not give a clear indication on the probable mode of action of the test articles. For both formulations maximum Spearman correlation coefficients were around rho=0.4 or lower. For a Compare positive results, rho>0.6 should be achieved to indicate the same mode of action as the corresponding standard agent. Possibly the mode of action was not represented by these 307 reference compounds. However, due to the weak selectivity of the test articles the significance of this Compare Analysis was somewhat limited.

3 Introduction

Herbal Home is currently developing natural medical therapeutics, such as different formulations of their dietary supplement Avoca 95, for the treatment of cancer. In the present study the *in vitro* anti-tumor activity of Avoca 95 supplied in two different formulations was assessed in 42 established human tumor cell lines in an in vitro 2D monolayer assay. Avoca 95 was either tested as a powder isolated from capsules (Avoca 95 capsule) or as a DMSO extract prepared from a liquid oily formulation (Avoca 95 liquid) as supplied by the Sponsor. Both were tested at 10 concentrations in half-log dilution steps up to 30 µg/ml (Avoca 95 capsule) or 0.3% v/v (Avoca 95 liquid), respectively. Efficacy of the test articles was assessed after 72 h treatment using a propidium iodide based 2D monolayer assay. Anti-tumor activity was expressed as absolute and relative IC_{50} values, calculated by non-linear regression analysis. In addition, a Compare Analysis was performed by correlation of the individual IC_{50}/IC_{70} values of the test articles as obtained in this study with the corresponding IC_{50}/IC_{70} values for 307 standard anticancer agents as historically determined for these 42 cell lines and available in Charles Rivers Data Warehouse. These standard agents represent the main mode of actions (MoAs) for current anticancer drugs.

Charles River Laboratories Germany has established a large collection of human tumor explants that were directly transplanted from patients to nude mice and are passaged subcutaneously. Such patient-derived tumor xenografts (PDXs) retain most of the characteristics of the parental patient tumors including histology and sensitivity to anti-cancer drugs. Studies have shown that PDXs passaged in nude mice correctly replicate the response of the donor tumor to standard cytotoxic anti-cancer drugs in >90% of cases and that PDX models also enable the identification of predictive biomarkers [1,2].

In addition, Charles River's proprietary tumor cell line panel comprises more than 70 cell lines established at Charles River from these patient-derived tumor xenografts (PDX). Most of these cell lines have a low passage number and exhibit relatively slow proliferation *in vitro*. Nude mouse xenografts derived from these cell lines tend to resemble the original tumor xenografts in both histology and chemosensitivity [3,4]. Furthermore, the Charles River cell line repository consist of more than 270 publicly available cell lines, including cell lines derived from haematological malignancies and from cancers of Asian patients. In the present study, publicly available cell lines as well as PDX-derived cell lines from the Charles River proprietary cell line repository were used.

In the propidium iodide (PI) based 2D monolayer assay in vitro anti-tumor activity of test compounds is determined as their capacity to inhibit the survival and/or proliferation of tumor cell lines [5].

4 Objective

4.1 Study Outline

In the present study, the *in-vitro* anti-tumor activity of two formulations of Avoca 95 was assessed in a standard panel of 42 human cancer cell lines for IC_{50} determination. Cells were treated for a period of 72 h followed by a PI based 2D monolayer assay. In addition, an IC_{50}/IC_{70} Compare Analysis with 307 reference compounds was performed to identify a possible mode of action of the test articles.

4.2 Changes to or Deviations from the Study Protocol

Due to limited solubility, the Avoca 95 capsule formulation could not be tested up to 300 µg/ml

as agreed in the SOW. The highest soluble DMSO stock solution was 10 mg/ml, allowing to use 30 µg/ml as the highest concentration in the assay corresponding to a final DMSO concentration of 0.3%.
The oily liquid formulation of Avoca 95 was insoluble in water or cell culture media and could not be applied directly in the assay. It was used as solvent extraction in DMSO. For this a 1:1 mixture of the oily liquid and DMSO was prepared and agitated. When both components are separated again, the DMSO phase was used in the assay up to a top concentration of 0.3% v/v.

There were no other changes to or deviations from the study protocol.

5 Abbreviations

Table 1: List of abbreviations

ATCC	American Type Culture Collection
BXF	Bladder cancer
CE curve	Concentration-effect curve
CNS	Central nervous system
CNXF	Cancer of the CNS, Caucasian ethnicity
CRL	Charles River Laboratories
CXF	Colon cancer
DNA	Deoxyribonucleic acid
DMSO	Dimethyl sulfoxide
DSMZ	Deutsche Sammlung von Mikroorganismen und Zellkulturen (German collection of microorganisms and cell cultures)
ECACC	European Collection of Authenticated Cell Cultures
FCS	Fetal calf serum
FU	Fluorescence unit
GXA	Gastric cancer, Asian ethnicity
GXF	Gastric cancer, Caucasian ethnicity
HNXF	Head & neck cancer, Caucasian ethnicity
IC_{50} / IC_{70}	50% / 70% inhibitory concentration
JCRB	Japanese Collection of Research Biosources
KCLB	Korean Cell Line Bank
LIXAH	Hepatocellular carcinoma, Asian ethnicity
LXFA	Adeno lung cancer, Caucasian ethnicity
LXFL	Large cell lung cancer, Caucasian ethnicity
MAXFTN	Triple negative breast cancer, Caucasian ethnicity
MEXF	Melanoma, Caucasian ethnicity
MoA	Mode of action
MW	Molecular weight
n.a.	Not available, not analyzed
NCI	National Cancer Institute
n.e.	Not evaluated
OVXF	Ovarian cancer, Caucasian ethnicity
PAXF	Pancreatic cancer, Caucasian ethnicity
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
PDX	Patient-derived Xenograft
PI	Propidium iodide
PXF	Pleuramesothelioma
PRXF	Prostate cancer, Caucasian ethnicity
RPMI	Roswell Park Memorial Institute
RXF	Renal carcinoma, Caucasian ethnicity
SXFO, SXFS	Osteosarcoma, soft tissue sarcoma, Caucasian ethnicity
STR	Short tandem repeats
T/C-value	Test versus control value
UXF	Uterine cancer, Caucasian ethnicity

6 Materials and Methods

6.1 Compounds

Avoca 95 was supplied as two different formulations.

Avoca 95 capsule: 12 bottles containing 60 capsules, each capsule with 500 mg powder content. They were shipped at ambient temperature on 27 July 2023. After arrival, the material was stored at ambient temperature. The powder was composed of figs germ powder (300 mg), olive germ powder (150 mg), turmeric powder (30 mg), star anis powder (10 mg), and rock salt (10 mg).

Avoca 95 liquid: oily liquid supplied in 10 bottles with 20 grams each. Avoca 95 liquid was shipped at ambient temperature on 02 August 2023. After arrival, the vials were stored at ambient temperature. The oily liquid contained extracted oil from botanical sources as follows: figs germ oil (55 %), olive germ oil (22 %), olive oil (5 %), propolis (10 %), and turmeric oil (8 %).

Details about the compound are given in Table 2.

Table 2: Designation of test articles

Name (delivery date)	Supplier, order no. (batch no.)	Storage at CRL	MW [g/mol]	Amount delivered	Test concentration
Avoca 95 capsules (27 Jul 2023)	Herbal Home (23080001)	ambient	n.k.	360 g	0.00095 – 30 µg/ml half-log dilutions
Avoca 95 liquid (02 Aug 2023)	Herbal Home (23080001)	ambient	n.k.	200 g	0.0000095 – 0.3 % (v/v) half-log dilutions

6.2 Compound Handling

Avoca 95 capsule: The content of the Avoca 95 capsule was prepared as a stock solution in DMSO at a concentration of 10 mg/ml. First, serial half-log dilutions of the DMSO stock solution were prepared in DMSO. These dilutions were then diluted 1:22 into cell culture medium in an intermediate dilution plate. Finally, 10 µl taken from the intermediate dilution plate were transferred to 140 µl / well of the final assay plate, resulting in a 330-fold dilution of the DMSO stock. The final concentration of DMSO was the same in all conditions and did not exceed 0.3%. The highest concentration of Avoca 95 capsule was 30 µg/ml.

Avoca 95 liquid: a direct testing the oily liquid material on the cells did not work, because the oily Avoca 95 liquid was completely insoluble in any aqueous media. As an alternative, a further extraction step was implemented by preparation of 1:1 mixture of the oily liquid mixture with DMSO followed by agitation using a Vortex Mixer. Few minutes later, both components separated spontaneously again and the ingredients of the oil appeared to migrate into the DMSO phase (The DMSO phase took the brown color of the oils). For the assays, this DMSO phase was used and serially diluted in half-log increments. These dilutions were then diluted 1:22 into cell culture medium in an intermediate dilution plate. Finally, 10 µl taken from the intermediate dilution plate were transferred to 140 µl / well of the final assay plate, resulting in a 330-fold dilution of the DMSO extract. The final concentration of DMSO was the same in all conditions and did not exceed 0.3%. The highest test concentration of Avoca 95 liquid was 0.3% v/v, related to the DMSO extraction phase.

6.3 Tumor Cell Lines

The cell lines used in the study were derived from solid tumors and comprised most clinical relevant human tumor histotypes, namely bladder (BXF, n=3), colorectal (CXF, 5), gastric (GXA, 1,

GXF, 1), head and neck (HNXF, 1), liver (LIXFC, 1), non-small cell lung (LXFA lung adeno, 3; LXFL large cell, 3), breast (MAXF, 3), ovarian (OVXF, 2), pancreatic (PAXF, 3), prostate (PRXF, 4), renal (RXF, 3), and uterus (UXF, 1) cancer as well as melanoma (MEXF, 3), pleuramesothelioma (PXF, 3) and sarcoma (SXF, 2).
The origin of the xenografts has been described previously [6].
Publicly available tumor cell lines were obtained from American Type Culture Collection (ATCC, Rockville, MD, USA), Cell line Services (CLS, Heidelberg, Germany), Deutsche Sammlung von Mikroorganismen und Zellkulturen (DSMZ, Braunschweig, Germany), European Collection of Authenticated Cell Cultures (ECACC, Salibury, UK), Japanese Collection of Research Biosources (JCRB, Osaka, Japan), Korean Cell Line Bank (KCLB, Seoul, Korea) or National Cancer Institute (NCI, Bethesda, MD, USA).

Authenticity of cell lines was proven at the DSMZ by STR (short tandem repeat) analysis, a PCR based DNA-fingerprinting methodology [7,8].

6.4 Cultivation of Cell Lines

Cell lines were routinely passaged once or twice weekly and maintained in culture for up to 20 passages. Cells were grown at 37°C in a humidified atmosphere with 5% CO_2 in RPMI 1640 medium supplemented with 10% (v/v) fetal calf serum and 50 µg/ml gentamicin. The percentage of viable cells was determined using a CASY Cell Counter Model TT.

6.5 2D Monolayer Assay (PI Assay)

A modified propidium iodide (PI)-based 2D monolayer assay was used to assess the anti-cancer activity of the compounds. Briefly, cells were harvested from exponential phase cultures, counted and plated in 96-well flat-bottom microtiter plates at a cell density depending on the cell line’s growth rate. The individual seeding density for each cell line ensured exponential growth conditions over the whole or at least the bigger part of the treatment period. After a 24 h recovery period, to allow the cells to resume exponential growth, compounds were added as described in Chapter 6.2 and cells were treated for a period of 72 h. Every plate included six untreated control wells and drug-treated groups in duplicate wells. After three days of treatment, cells were washed with 200 µl PBS to remove dead cells and debris, then 200 µl of a solution containing 10 µg/mL propidium iodide (PI) (Genaxxon Germany, #M3181.0025) and 0.1% (v/v) Triton X-100 were added. After an incubation period of 2 hours at room temperature, fluorescence (FU) was measured using the Enspire Multimode Plate Reader (excitation λ = 530 nm, emission λ = 620 nm) to quantify the amount of attached viable cells.

6.6 Data Evaluation for Efficacy Assessment

An assay was considered fully evaluable if the following quality control criteria were fulfilled:

- control/background ratio >3.0
- Z’-factor calculated within the assay plate $\geq$0.5 [9]
- coefficient of variation in the growth control wells $\leq$30%
- the positive reference compound staurosporine (at 1 µM) must cause a reduction of signal to <50% of the growth control

Drug effects were expressed in terms of the percentage of the fluorescence signal, obtained by comparison of the mean signal in the treated wells with the mean signal of the untreated controls (expressed by the test-versus-control value, T/C-value [%]):

$$\frac{T}{C}\,(\%) = \frac{mean\ signal_{treated\ group}}{mean\ signal_{control\ group}} * 100$$

Sigmoidal concentration-response curves were fitted through the data points obtained for each tumor model using 4 parameter non-linear curve fit (Charles River Discovery Research Services Germany Data-Warehouse Software). IC_{50} values are reported as relative and/or absolute IC_{50} values. The relative IC_{50} value is the concentration of test compound that gives a response half-way between the top and bottom plateau of the sigmoidal concentration-response curve (inflection point of the curve). The absolute IC_{50} value is determined as the concentration at the intersection of the concentration effect curve with T/C = 50%.

The overall potency of a compound was expressed by the geometric mean IC_{50} value of all individual IC_{50} values. If an IC_{50} value could not be determined within the examined dose range (because a compound was either too active or lacked activity), the lowest or highest concentration studied was used for calculation of the geometric mean value. In the heat map presentation of IC_{50} values, the distribution of IC_{50} values obtained for a test compound in the individual tumor models is given in relation to the geometric mean IC_{50} value, obtained over all tumors tested. The individual IC_{50} values are highlighted in colors ranging from dark blue (≤1/32-fold geometric mean IC_{50}, equal to very potent compound activity or high tumor sensitivity) to dark red (≥32-fold geometric mean IC_{50}, equal to lack of compound activity or tumor resistance). The heat map presentation, therefore, represents an anti-proliferative “fingerprint” profile of a test compound.

6.7 Compare Analysis

The Compare Analysis uses *in vitro* activity data to obtain indications about a possible mode of action of a test compound. Individual IC values of a test compound obtained in the 42 cell line panel using the 2D monolayer assay were correlated to the corresponding IC values for 307 standard agents. Efficacy data for these standard agents, which represent the main mode of actions of current anti-cancer drugs, are available in a proprietary database. For a list of standard agents used for the Compare Analysis please refer to Table 14 in the Appendix. Similarities between the sensitivity pattern of a test compound and those of standard agents were expressed quantitatively as Spearman correlation coefficients. A high correlation ($\rho>0.6$) between the sensitivity pattern of a test compound and a cluster of profiles of standard agents with the same mode of action (referred to as “Compare-positive”) were indicative of a similar mode of action. Low correlations between the sensitivity profile of a test compound and the profiles of all standard agents (referred to as “Compare-negative”) might indicate that the mode of action of the test compound was not represented by the selected standard agents. Of note, if a test compound exhibits a low selectivity across the 42 cell line panel, correlations to the reference compounds might be calculated by chance, making the significance of this Compare Analysis questionable.

7 Results and Discussion

The *in-vitro* anti-tumor activity of two formulations of Avoca 95 was assessed in a standard panel of 42 human cancer cell lines for IC_{50} determination. Avoca 95 was supplied i) as capsules and ii) in the form of liquid oils. Capsules were broken and the content was dissolved in DMSO. The oily Avoca 95 was extracted 1:1 with DMSO and the DMSO phase was used for the treatment of the cells. These two formulas were applied to the cells at 10 concentrations in half-log dilution steps in duplicate up to 0.3 %(v/v) (Avoca 95 liquid) or 30 µg/mL (Avoca 95 capsule) and efficacy was assessed after a treatment period of 72 h using a propidium iodide based 2D monolayer assay. Anti-tumor activity is expressed as absolute and relative IC_{50} values, calculated by non-linear regression analysis. In addition, a Compare Analysis was done by correlation of the individual IC_{50}/IC_{70} values of the test compound as obtained in this study with the corresponding IC_{50}/IC_{70} values for 307 standard anticancer agents historically determined at Charles River Freiburg for these 42 cell lines. These standard agents represent the main mode of actions (MoAs) for current anticancer drugs. Results are summarized in Tables 3-5 (heatmaps of IC_{50} and IC_{70} values), Tables 6 and 7 (T/C values at each test concentration), Figures 1 and 2 (concentration-effect curves) and Tables 8 and 9 (Compare Analysis).

Both formulations showed concentration-dependent activity in many of the tested cell lines with absolute geomean IC_{50} values across the 42 cell lines of 0.015% v/v for Avoca 95 liquid and 21.784 µg/ml for Avoca 95 capsule. However, a direct comparison of the activity is not possible, because the preparation of these test articles was completely different. The content (powder) of the Avoca 95 capsule was dissolved in DMSO at a concentration of 10 mg/ml allowing a top concentration of 30 µg/ml which corresponds to 0.3% DMSO in the assay. The oily Avoca 95 liquid was prepared by solvent extraction with DMSO and then the DMSO phase was used for the assays resulting in 0.3% (v/v) as the top concentration in the assay

Avoca 95 liquid showed concentration dependent inhibition of tumor cell growth in all cell lines tested. Avoca 95 liquid exhibited a geomean relative (absolute) IC_{50} value of 0.015% v/v (0.015% v/v) with significant activity (T/C<50%) in 3/42 cell lines at a concentration of 0.0095% v/v, in 34/42 cell lines at 0.03% v/v and in 42/42 cell lines at 0.095% v/v and 0.3% v/v. Above average activity (individual absolute IC_{50} of a cell line below ½ mean IC_{50} value) of Avoca 95 liquid was detected in the melanoma cell lines MEXF 1341 (abs. IC_{50} of 0.003% v/v) and MEXF 276 (0.004% v/v), as well as in the pancreatic cancer cell line PAXF 1657 (0.03% v/v). Individual absolute IC50 values were in the range from 0.003% v/v (MEXF 1341 and PAXF 1657) and 0.079% v/v, corresponding to a 26-fold difference between the most sensitive and most resistant cell line.

Avoca 95 capsule exhibited a geomean relative (absolute) IC_{50} of 21.349µg/ml (21.784µg/ml) and in most cell lines significant activity was only achieved at the highest test concentration of 30 µg/ml. However, similar to Avoca 95 liquid, the melanoma cell lines MEXF 1341 and MEXF 276 responded particular well to Avoca 95 capsule and individual absolute IC_{50} values of 1.99 µg/ml (MEXF 276) and 2.25 µg/ml (MEXF 1341) were achieved in these cell lines. Furthermore, the colon cancer cell line DiFi (T/C of 68% at 9.5 µg/ml) and PAXF 1657 (T/C of 61% at 9.5 µg/ml) responded quite well to Avoca 95 capsule. For all other cell lines no activity was detected at a concentration of 9.5 µg/ml. Individual absolute IC_{50} values were between 1.99 µg/ml (MEXF 276) and >30 µg/ml (several cell lines), corresponding to a 15-fold difference.

Compare Analysis of the activity profile of the two formulations with 307 standard agents did not give a clear indication on the probable mode of action of the test articles. Regarding Compare Analysis for Avoca 95 liquid based on absolute IC_{50} values, a correlation coefficient of rho>0.6 was not achieved for any reference compound. The highest correlation was detected for Avoca 95 capsule (rho=0.430). For all standard agents rho<0.4 was detected. Similarly, Compare Analysis based on relative IC_{50} values and absolute IC_{70} values could not indicate the mode of action for Avoca 95 liquid. The same picture was given for Avoca 95 capsule, with a Spearman correlation coefficient rho not significantly higher than 0.4 for any of the reference compounds. For a Compare positive result, rho>0.6 should be achieved to indicate the same mode of action as the corresponding standard agent. Possibly the mode of action was not represented by these 307 reference compounds. However, due to the weak selectivity of the test articles, in particular for Avoca 95 capsule, the significance of this Compare Analysis was somewhat limited.

Table 3: *In vitro* activity of Avoca 95 capsules and Avoca 95 liquid in 42 cancer cell lines (Heatmap presentation of absolute IC_{50} values)

P1113A Tumor model		Passage	Exp. no.		Capsule (µg/mL)		Liquid (%, v/v)
BXF	1218	30N15	XA0998-P2615266-3		21,465		0,014
BXF	1352	17N11	XA0948-P2613238-3		28,459		0,023
BXF	T24	23N11	XA0985-P2615237-3		28,646		0,014
CXF	269	13N3	XA0949-P2613600-3	>	30,000		0,014
CXF	DiFi	16N4	XA0989-P2615444-3		10,122		0,012
CXF	HCT 116	24N11	XA0986-P2615421-3		11,281		0,017
CXF	HT-29	24N8	XA0921-P2612813-3		20,533		0,037
CXF	RKO	22N8	XA0922-P2611825-3	>	30,000	>	0,032
GXA	MKN45	38N6	XA0923-P261282A-3	>	30,000	>	0,040
GXF	251	32N8	XA0924-P2612836-3	>	30,000		0,039
HNXF	CAL-27	15N3	XA0951-P2613617-3		13,134		0,016
LIXAH	575	28N5	XA0990-P2615243-3	>	30,000		0,012
LXFA	289	37N5	XA0997-P2615846-3	>	30,000		0,013
LXFA	526	33N11	XA0925-P2612233-3	>	30,000		0,079
LXFA	629	29N12	XA0926-P2612842-3	>	30,000		0,047
LXFL	1121	20N3	XA0954-P2613623-3		22,470		0,013
LXFL	529	29N17	XA1037-P2619206-3		25,747		0,013
LXFL	NCI-H460	23N4	XA0918-P2611021-3		17,481		0,011
MAXFLB	MCF7	15N2	XA0955-P2613830-3		27,375		0,011
MAXFTN	401	46N8	XA0928-P261224A-3	>	30,000	>	0,033
MAXFTN	MDA-MB-231	19N10	XA0987-P2615616-3	>	30,000		0,012
MEXF	1341	12N8	XA0930-P2611050-3		2,252		0,003
MEXF	276	32N8	XA0931-P2611067-3		1,991		0,004
MEXF	462	21N3	XA0956-P2613801-3		23,686		0,011
OVXF	899	23N3	XA0991-P2615823-3	>	30,000		0,025
OVXF	OVCAR-3	21N3	XA0958-P2613646-3	>	30,000		0,013
PAXF	1657	22N6	XA0932-P2611831-3		11,027		0,003
PAXF	546	19N2	XA0959-P2614002-3		23,168		0,016
PAXF	PANC-1	15N3	XA0960-P2613066-3	>	30,000		0,017
PRXF	22Rv1	15N7	XA0992-P2615622-3		27,958		0,011
PRXF	DU-145	31N5	XA0988-P2615438-3		27,113		0,013
PRXF	LNCaP	27N4	XA1000-P2615272-3		20,374		0,010
PRXF	PC-3M	19N2	XA0936-P261108A-3	>	30,000		0,015
PXF	1118	24N5	XA0993-P2615450-3	>	30,000		0,012
PXF	1752	34N5	XA0994-P261583A-3	>	30,000		0,014
PXF	698	13N3	XA0965-P2613072-3	>	30,000		0,011
RXF	1781	17N6	XA0933-P2612865-3		18,619		0,033
RXF	393	26N4	XA0995-P261525A-3	>	30,000		0,019
RXF	486	20N3	XA0967-P2613089-3		26,100		0,010
SXFO	Saos-2	20N4	XA0996-P2615467-3		21,816		0,014
SXFS	TE671	16N3	XA0969-P2614031-3		20,655		0,014
UXF	1138	31N6	XA0934-P2611073-3	>	30,000		0,019
Geomean abs. IC50:					**21,784**		**0,015**

1/32	1/16	1/8	1/4	1/2	1	2	4	8	16	32	-fold mean IC
sensitive tumor models						resistant tumor models					

Top, Bot.: top, bottom plateau of the concentration-effect curve

Table 4: *In vitro* activity of Avoca 95 capsules and Avoca 95 liquid in 42 cancer cell lines (Heatmap presentation of relative IC_{50} values)

P1113A Tumor model		Passage	Exp. no.		Capsule (µg/mL)		Liquid (%, v/v)
BXF	1218	30N15	XA0998-P2615266-3		20.306		0.013
BXF	1352	17N11	XA0948-P2613238-3		26.652		0.023
BXF	T24	23N11	XA0985-P2615237-3		27.851		0.014
CXF	269	13N3	XA0949-P2613600-3		28.673		0.014
CXF	DiFi	16N4	XA0989-P2615444-3		9.803		0.012
CXF	HCT 116	24N11	XA0986-P2615421-3		10.723		0.017
CXF	HT-29	24N8	XA0921-P2612813-3		11.435		0.036
CXF	RKO	22N8	XA0922-P2611825-3	>	30.000	>	0.033
GXA	MKN45	38N6	XA0923-P261282A-3	>	30.000	>	0.040
GXF	251	32N8	XA0924-P2612836-3	>	30.000		0.038
HNXF	CAL-27	15N3	XA0951-P2613617-3		11.855		0.015
LIXAH	575	28N5	XA0990-P2615243-3	>	30.000		0.012
LXFA	289	37N5	XA0997-P2615846-3	>	30.000		0.013
LXFA	526	33N11	XA0925-P2612233-3	>	30.000		0.079
LXFA	629	29N12	XA0926-P2612842-3	>	30.000		0.047
LXFL	1121	20N3	XA0954-P2613623-3		20.993		0.013
LXFL	529	29N17	XA1037-P2619206-3		18.288		0.013
LXFL	NCI-H460	23N4	XA0918-P2611021-3		16.991		0.011
MAXFLB	MCF7	15N2	XA0955-P2613830-3		27.538		0.011
MAXFTN	401	46N8	XA0928-P261224A-3	>	30.000	>	0.033
MAXFTN	MDA-MB-231	19N10	XA0987-P2615616-3		28.531		0.012
MEXF	1341	12N8	XA0930-P2611050-3		3.157		0.003
MEXF	276	32N8	XA0931-P2611067-3		4.798		0.005
MEXF	462	21N3	XA0956-P2613801-3		22.864		0.011
OVXF	899	23N3	XA0991-P2615823-3	>	30.000		0.024
OVXF	OVCAR-3	21N3	XA0958-P2613646-3	>	30.000		0.013
PAXF	1657	22N6	XA0932-P2611831-3		11.352		0.003
PAXF	546	19N2	XA0959-P2614002-3		20.825		0.016
PAXF	PANC-1	15N3	XA0960-P2613066-3	>	30.000		0.016
PRXF	22Rv1	15N7	XA0992-P2615622-3		26.570		0.010
PRXF	DU-145	31N5	XA0988-P2615438-3		22.642		0.012
PRXF	LNCaP	27N4	XA1000-P2615272-3		18.399		0.010
PRXF	PC-3M	19N2	XA0936-P261108A-3	>	30.000		0.015
PXF	1118	24N5	XA0993-P2615450-3	>	30.000		0.011
PXF	1752	34N5	XA0994-P261583A-3	>	30.000		0.014
PXF	698	13N3	XA0965-P2613072-3		29.638		0.011
RXF	1781	17N6	XA0933-P2612865-3		17.921		0.033
RXF	393	26N4	XA0995-P261525A-3	>	30.000		0.019
RXF	486	20N3	XA0967-P2613089-3		25.089		0.010
SXFO	Saos-2	20N4	XA0996-P2615467-3		19.342		0.013
SXFS	TE671	16N3	XA0969-P2614031-3		21.491		0.013
UXF	1138	31N6	XA0934-P2611073-3	>	30.000		0.020
Geomean rel. IC50:					**21.349**		**0.015**

1/32 1/16 1/8 1/4 1/2 1 2 4 8 16 32 -fold mean IC value

sensitive cell lines resistant cell lines

Top, Bot.: top, bottom plateau of the concentration-effect curve

Table 5: *In vitro* activity of Avoca 95 capsules and Avoca 95 liquid in 42 cancer cell lines (Heatmap presentation of absolute IC_{70} values)

P1113A		Passage	Exp.		Capsule		Liquid
Tumor model			**no.**		**(µg/mL)**		**(%, v/v)**
BXF	1218	30N15	XA0998-P2615266-3		25,484		0,017
BXF	1352	17N11	XA0948-P2613238-3	>	30,000		0,038
BXF	T24	23N11	XA0985-P2615237-3	>	30,000		0,017
CXF	269	13N3	XA0949-P2613600-3	>	30,000		0,018
CXF	DiFi	16N4	XA0989-P2615444-3		11,003		0,013
CXF	HCT 116	24N11	XA0986-P2615421-3		12,564		0,017
CXF	HT-29	24N8	XA0921-P2612813-3	>	30,000		0,039
CXF	RKO	22N8	XA0922-P2611825-3	>	30,000	>	0,035
GXA	MKN45	38N6	XA0923-P261282A-3	>	30,000	>	0,045
GXF	251	32N8	XA0924-P2612836-3	>	30,000		0,045
HNXF	CAL-27	15N3	XA0951-P2613617-3		15,699		0,018
LIXAH	575	28N5	XA0990-P2615243-3	>	30,000		0,013
LXFA	289	37N5	XA0997-P2615846-3	>	30,000		0,015
LXFA	526	33N11	XA0925-P2612233-3	>	30,000		0,103
LXFA	629	29N12	XA0926-P2612842-3	>	30,000		0,059
LXFL	1121	20N3	XA0954-P2613623-3	>	30,000		0,017
LXFL	529	29N17	XA1037-P2619206-3	>	30,000		0,016
LXFL	NCI-H460	23N4	XA0918-P2611021-3		21,033		0,014
MAXFLB	MCF7	15N2	XA0955-P2613830-3	>	30,000		0,012
MAXFTN	401	46N8	XA0928-P261224A-3	>	30,000	>	0,035
MAXFTN	MDA-MB-231	19N10	XA0987-P2615616-3	>	30,000		0,014
MEXF	1341	12N8	XA0930-P2611050-3		4,054		0,004
MEXF	276	32N8	XA0931-P2611067-3		8,408		0,006
MEXF	462	21N3	XA0956-P2613801-3	>	30,000		0,012
OVXF	899	23N3	XA0991-P2615823-3	>	30,000		0,027
OVXF	OVCAR-3	21N3	XA0958-P2613646-3	>	30,000		0,014
PAXF	1657	22N6	XA0932-P2611831-3		15,223		0,003
PAXF	546	19N2	XA0959-P2614002-3	>	30,000		0,021
PAXF	PANC-1	15N3	XA0960-P2613066-3	>	30,000		0,021
PRXF	22Rv1	15N7	XA0992-P2615622-3	>	30,000		0,012
PRXF	DU-145	31N5	XA0988-P2615438-3	>	30,000		0,015
PRXF	LNCaP	27N4	XA1000-P2615272-3	>	30,000		0,011
PRXF	PC-3M	19N2	XA0936-P261108A-3	>	30,000		0,020
PXF	1118	24N5	XA0993-P2615450-3	>	30,000		0,015
PXF	1752	34N5	XA0994-P261583A-3	>	30,000		0,017
PXF	698	13N3	XA0965-P2613072-3	>	30,000		0,012
RXF	1781	17N6	XA0933-P2612865-3		27,655		0,036
RXF	393	26N4	XA0995-P261525A-3	>	30,000		0,023
RXF	486	20N3	XA0967-P2613089-3	>	30,000		0,011
SXFO	Saos-2	20N4	XA0996-P2615467-3	>	30,000		0,017
SXFS	TE671	16N3	XA0969-P2614031-3		28,483		0,017
UXF	1138	31N6	XA0934-P2611073-3	>	30,000		0,026
Geomean abs. IC70:					**25,319**		**0,018**

1/32	1/16	1/8	1/4	1/2	1	2	4	8	16	32	-fold mean IC

sensitive tumor models — resistant tumor models

Top, Bot.: top, bottom plateau of the concentration-effect curve

Table 6: In vitro activity of Avoca 95 liquid (T/C values at each test concentration)

Avoca 95 liquid		Passage	Exp.	Test/Control (%) at Drug Concentratio (%(v/v))									
Tumor model			no.	9E-06	3E-05	9E-05	0.0003	0.0009	0.003	0.0095	0.03	0.0949	0.3
BXF	1218	30N15	XA0998-P2615266-5	103	108	113	103	104	96	82	7	3	4
BXF	1352	17N11	XA0948-P2613238-5	97	101	102	105	100	98	82	41	4	2
BXF	T24	23N11	XA0985-P2615237-5	101	108	109	106	105	107	92	6	2	5
CXF	269	13N3	XA0949-P2613600-5	111	107	114	116	109	105	91	7	2	5
CXF	DiFi	16N4	XA0989-P2615444-5	95	109	106	108	101	113	97	6	8	10
CXF	HCT 116	24N11	XA0986-P2615421-5	87	104	107	100	89	105	101	1	3	2
CXF	HT-29	24N8	XA0921-P2612813-5	105	102	106	99	102	113	102	98	1	1
CXF	RKO	22N8	XA0922-P2611825-5	88	81	85	80	72	85	90	63	-2	0
GXA	MKN45	38N6	XA0923-P261282A-5	108	100	101	100	106	102	90	90	2	2
GXF	251	32N8	XA0924-P2612836-5	102	103	104	108	103	103	100	82	2	2
HNXF	CAL-27	15N3	XA0951-P2613617-5	104	114	115	118	119	119	107	4	1	0
LIXAH	575	28N5	XA0990-P2615243-5	103	115	105	104	101	106	99	9	13	11
LXFA	289	37N5	XA0997-P2615846-5	100	103	94	89	91	83	75	3	1	2
LXFA	526	33N11	XA0925-P2612233-5	93	99	101	99	102	104	103	96	36	2
LXFA	629	29N12	XA0926-P2612842-5	100	103	99	99	96	96	94	84	8	2
LXFL	1121	20N3	XA0954-P2613623-5	101	110	106	112	109	107	83	6	1	5
LXFL	529	29N17	XA1037-P2619206-5	103	109	101	100	99	102	82	3	1	1
LXFL	NCI-H460	23N4	XA0918-P2611021-5	100	104	106	101	95	94	67	1	0	1
MAXFLB	MCF7	15N2	XA0955-P2613830-5	97	99	97	96	93	106	81	10	13	11
MAXFTN	401	46N8	XA0928-P261224A-5	106	101	104	109	102	99	96	85	-1	1
MAXFTN	MDA-MB-231	19N10	XA0987-P2615616-5	105	110	107	98	94	97	79	3	0	5
MEXF	1341	12N8	XA0930-P2611050-5	86	85	81	79	72	54	1	5	2	1
MEXF	276	32N8	XA0931-P2611067-5	79	84	88	70	68	61	12	1	4	3
MEXF	462	21N3	XA0956-P2613801-5	102	100	93	95	85	86	74	1	5	2
OVXF	899	23N3	XA0991-P2615823-5	90	92	91	93	91	105	96	16	7	7
OVXF	OVCAR-3	21N3	XA0958-P2613646-5	95	86	98	101	91	95	89	3	3	3
PAXF	1657	22N6	XA0932-P2611831-5	92	101	92	89	99	77	1	0	0	5
PAXF	546	19N2	XA0959-P2614002-5	97	101	102	96	96	93	85	13	3	4
PAXF	PANC-1	15N3	XA0960-P2613066-5	110	115	108	99	109	106	96	11	3	3
PRXF	22Rv1	15N7	XA0992-P2615622-5	98	104	109	106	106	103	79	6	7	11
PRXF	DU-145	31N5	XA0988-P2615438-5	114	125	121	119	119	113	92	3	3	2
PRXF	LNCaP	27N4	XA1000-P2615272-5	105	99	96	94	96	101	67	7	12	13
PRXF	PC-3M	19N2	XA0936-P261108A-5	100	99	98	92	96	93	76	13	0	0
PXF	1118	24N5	XA0993-P2615450-5	102	101	100	97	96	97	72	13	11	14
PXF	1752	34N5	XA0994-P261583A-5	100	108	101	100	94	100	94	6	6	5
PXF	698	13N3	XA0965-P2613072-5	108	114	113	105	108	111	92	9	12	18
RXF	1781	17N6	XA0933-P2612865-5	105	102	99	94	101	93	93	69	-1	-1
RXF	393	26N4	XA0995-P261525A-5	89	87	85	93	93	91	89	16	11	10
RXF	486	20N3	XA0967-P2613089-5	95	100	103	98	97	89	82	0	0	4
SXFO	Saos-2	20N4	XA0996-P2615467-5	102	98	99	111	98	93	82	15	16	11
SXFS	TE671	16N3	XA0969-P2614031-5	99	102	105	106	101	92	83	4	1	1
UXF	1138	31N6	XA0934-P2611073-5	94	92	96	91	98	94	83	23	-3	1

Color code (T/C, %): ≥ 100 70 50 0

Table 7: *In vitro* activity of Avoca 95 capsule (T/C values at each test concentration)

Avoca 95 capsule		Passage	Exp.	Test/Control (%) at Drug Concentratio (µg/mL)									
Tumor model			no.	0.0009	0.003	0.0095	0.03	0.0949	0.3	0.9487	3	9.4868	30
BXF	1218	30N15	XA0998-P2615266-3	113	119	111	116	116	109	122	109	111	17
BXF	1352	17N11	XA0948-P2613238-3	108	106	110	106	105	112	104	103	96	47
BXF	T24	23N11	XA0985-P2615237-3	110	108	112	112	119	117	124	122	117	38
CXF	269	13N3	XA0949-P2613600-3	113	115	121	114	116	124	123	118	110	56
CXF	DiFi	16N4	XA0989-P2615444-3	104	110	112	101	105	110	119	119	68	8
CXF	HCT 116	24N11	XA0986-P2615421-3	104	120	109	110	117	119	136	119	88	10
CXF	HT-29	24N8	XA0921-P2612813-3	112	108	113	106	118	110	110	116	101	50
CXF	RKO	22N8	XA0922-P2611825-3	115	112	114	98	100	98	103	99	84	80
GXA	MKN45	38N6	XA0923-P261282A-3	102	99	108	102	101	107	103	101	93	67
GXF	251	32N8	XA0924-P2612836-3	109	113	118	110	112	116	111	113	107	97
HNXF	CAL-27	15N3	XA0951-P2613617-3	110	114	111	116	118	122	119	118	101	20
LIXAH	575	28N5	XA0990-P2615243-3	114	115	118	114	121	126	117	124	113	96
LXFA	289	37N5	XA0997-P2615846-3	106	106	106	104	111	110	111	108	100	74
LXFA	526	33N11	XA0925-P2612233-3	92	99	94	97	98	99	101	97	90	94
LXFA	629	29N12	XA0926-P2612842-3	107	106	103	103	105	106	110	103	107	109
LXFL	1121	20N3	XA0954-P2613623-3	107	107	110	103	108	107	110	101	89	36
LXFL	529	29N17	XA1037-P2619206-3	106	111	111	110	111	111	112	110	97	44
LXFL	NCI-H460	23N4	XA0918-P2611021-3	104	107	110	107	108	107	105	107	99	8
MAXFLB	MCF7	15N2	XA0955-P2613830-3	97	101	102	95	99	96	106	98	93	44
MAXFTN	401	46N8	XA0928-P261224A-3	100	106	105	99	106	103	111	111	101	90
MAXFTN	MDA-MB-231	19N10	XA0987-P2615616-3	108	113	117	118	119	124	125	116	104	56
MEXF	1341	12N8	XA0930-P2611050-3	80	73	86	77	78	72	64	45	4	2
MEXF	276	32N8	XA0931-P2611067-3	74	80	76	78	67	65	56	55	22	16
MEXF	462	21N3	XA0956-P2613801-3	103	100	107	104	107	107	101	103	91	37
OVXF	899	23N3	XA0991-P2615823-3	104	113	106	101	114	114	108	116	113	115
OVXF	OVCAR-3	21N3	XA0958-P2613646-3	100	108	110	100	109	106	105	97	98	57
PAXF	1657	22N6	XA0932-P2611831-3	98	100	99	89	97	95	103	87	61	4
PAXF	546	19N2	XA0959-P2614002-3	109	109	107	103	114	111	106	100	84	40
PAXF	PANC-1	15N3	XA0960-P2613066-3	102	106	110	111	114	111	119	111	113	70
PRXF	22Rv1	15N7	XA0992-P2615622-3	107	101	112	101	107	112	114	104	101	45
PRXF	DU-145	31N5	XA0988-P2615438-3	110	126	126	121	128	127	129	121	108	44
PRXF	LNCaP	27N4	XA1000-P2615272-3	112	106	105	117	111	112	110	107	86	32
PRXF	PC-3M	19N2	XA0936-P261108A-3	100	104	100	94	98	96	101	98	94	74
PXF	1118	24N5	XA0993-P2615450-3	110	109	113	108	113	119	111	103	99	59
PXF	1752	34N5	XA0994-P261583A-3	111	109	100	106	111	114	111	111	114	95
PXF	698	13N3	XA0965-P2613072-3	104	112	112	109	112	120	116	113	104	55
RXF	1781	17N6	XA0933-P2612865-3	100	105	105	101	107	110	107	93	85	26
RXF	393	26N4	XA0995-P261525A-3	98	106	107	108	118	120	114	119	113	71
RXF	486	20N3	XA0967-P2613089-3	100	102	104	103	96	106	102	104	91	43
SXFO	Saos-2	20N4	XA0996-P2615467-3	110	113	107	112	118	115	109	113	93	33
SXFS	TE671	16N3	XA0969-P2614031-3	97	89	95	92	92	100	100	93	86	27
UXF	1138	31N6	XA0934-P2611073-3	115	113	113	108	116	115	109	109	100	82

Figure 1: *In vitro* **activity of Avoca 95 liquid (concentration-effect curves)**

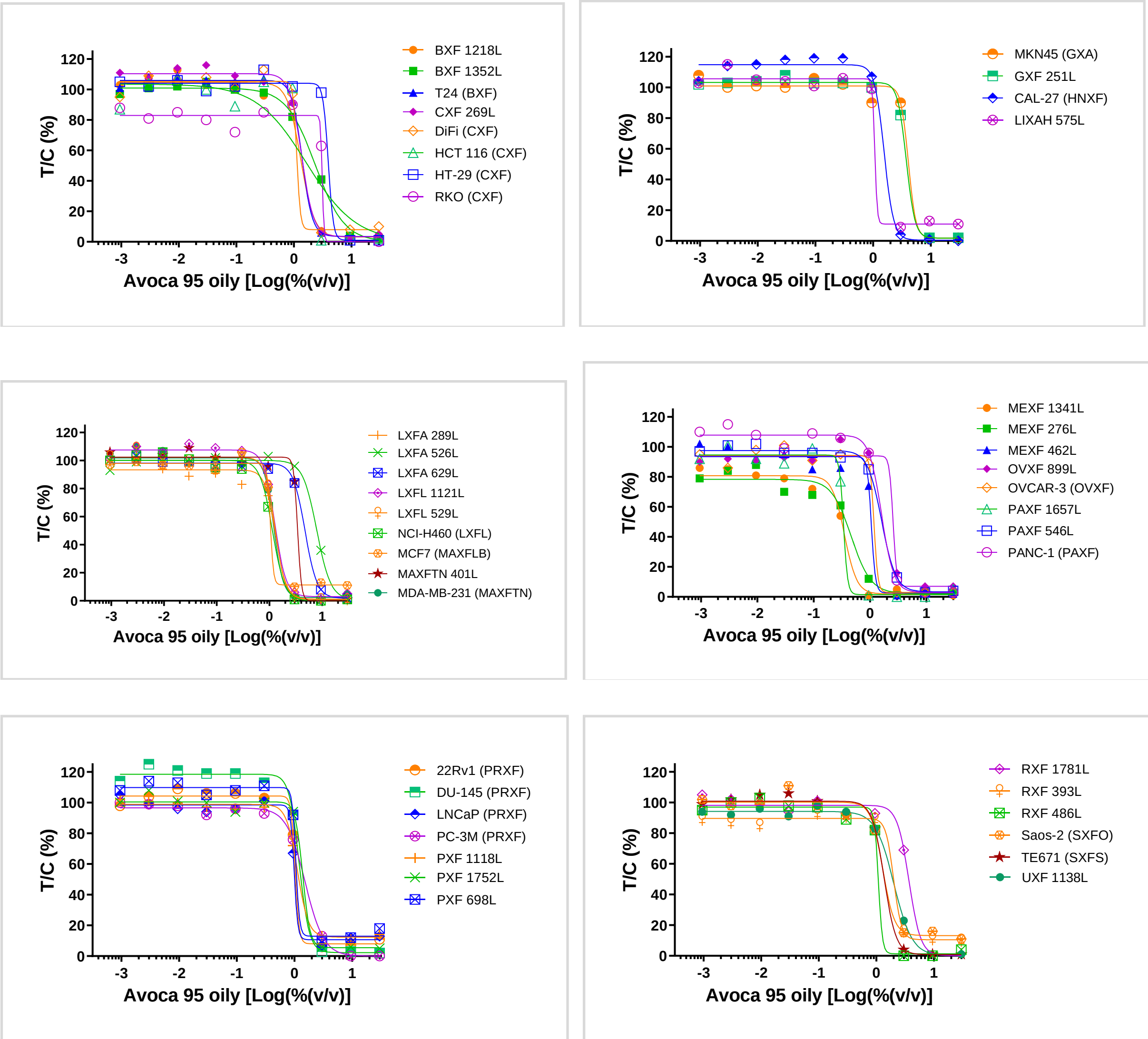

Figure 2: *In vitro* activity of Avoca 95 capsule (concentration-effect curves)

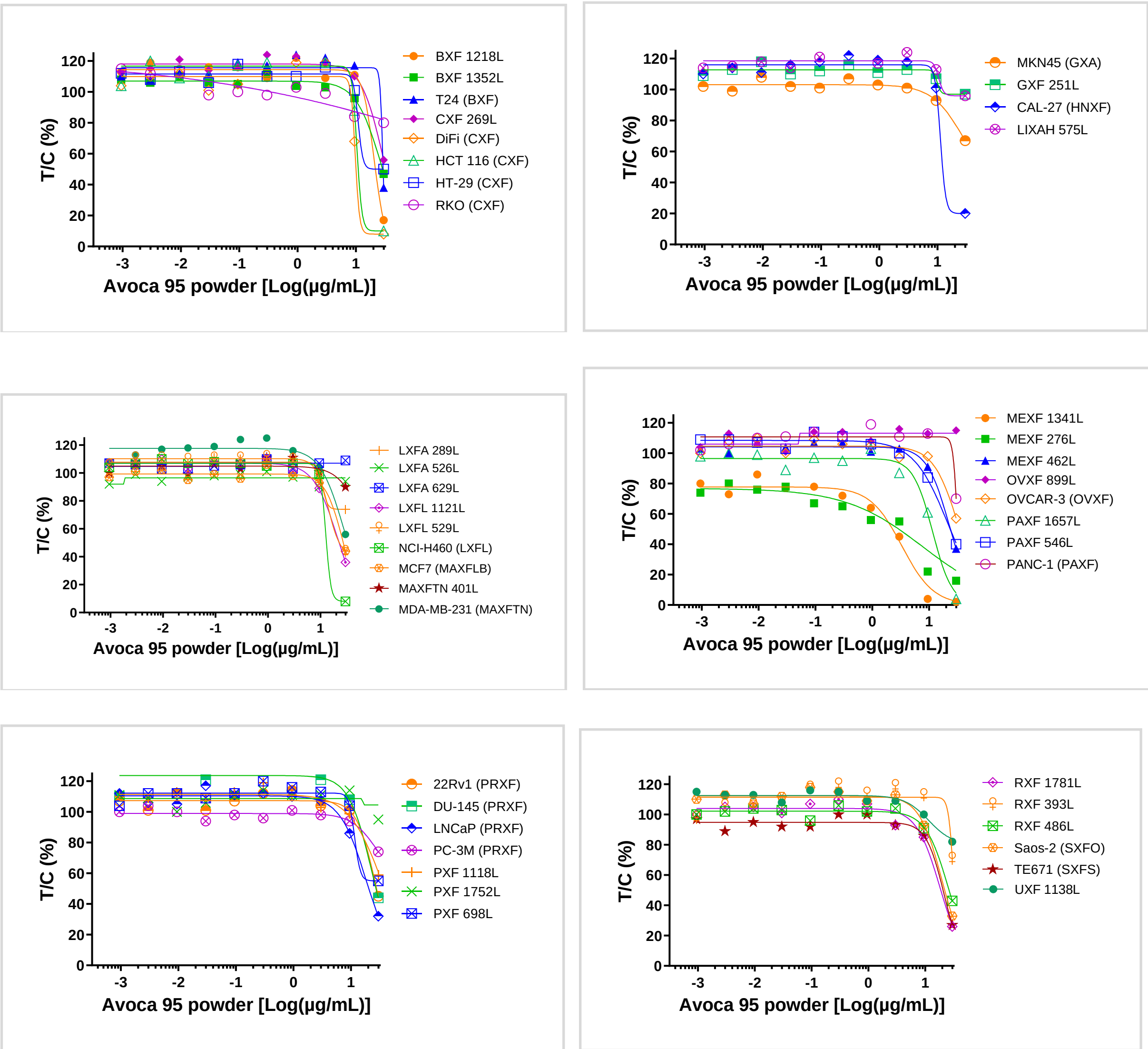

Table 8: Compare Analysis for Avoca 95 liquid

A. Based on absolute IC_{50} values

Compound to compare: Avoca 95 liquid (99

Export: Export to Excel

Compound	Mode of Action	Spearman	N	Geom. Mean	<1/2	<1/2
Avoca 95 liquid (99624)		**1.000**	**42**	**0.015 %(v/v)**	**3/42**	**7.1 %**
Avoca 95 capsule (99543)		0.430	42	21.612 µg/mL	3/42	7.1 %
LY-294,002 HCl (16010)	PI3K	0.366	42	14.921 µM	6/42	14.3 %
BGT226, Maleic acid salt (23961)	PI3K/mTOR	0.345	42	0.01 µM	13/42	31 %
ZSTK474, free base (23981)	PI3K	0.308	42	0.889 µM	8/42	19 %
AZD1480 (38071)	JAK2	0.297	41	4.766 µM	9/41	22 %
Entinostat (16803)	HDAC	0.294	41	0.814 µM	7/41	17.1 %
Dactolisib (11726)	PI3K/mTOR	0.281	42	0.061 µM	17/42	40.5 %
YH239-EE (35946)	p53/MDM2	0.265	41	12.059 µM	1/41	2.4 %
Suberic bis-hydroxamic acid (17854	HDAC	0.265	42	23.251 µM	6/42	14.3 %
Alectinib (25503)	ALK	0.263	42	23.674 µM	2/42	4.8 %
INC280, free base (23963)	c-Met	0.255	42	40.373 µM	9/42	21.4 %
CUDC-101, free base (23979)	Multikinase (HDAC,	0.248	42	0.433 µM	7/42	16.7 %
Ipatasertib (14670)	AKT1/2/3	0.242	42	15.979 µM	8/42	19 %
Vorinostat (18214)	HDAC	0.238	42	1.6 µM	6/42	14.3 %
AZD5363 (25502)	AKT	0.236	42	21.071 µM	10/42	23.8 %
LEE011 (17061)	CDK4/6	0.236	40	11.564 µM	9/40	22.5 %
MI-773 (36025)	MDM2	0.228	42	5.9 µM	12/42	28.6 %
M344 (16079)	HDAC	0.227	42	0.838 µM	5/42	11.9 %
Sabutoclax (38065)	Bcl-2/xL, Mcl-1, Bfl-	0.225	41	0.359 µM	13/41	31.7 %
Droxinostat (20970)	HDAC3/6/8	0.222	42	24.549 µM	3/42	7.1 %
PFI-1 (38243)	BRD4	0.218	41	14.659 µM	8/41	19.5 %
Lomustine (15985)	Alkylating agent	0.215	42	53.954 µM	5/42	11.9 %
PI-103 (23965)	PI3K/mTOR	0.212	42	0.934 µM	15/42	35.7 %
Tofacitinib Citrate (36006)	JAK3	0.209	41	95.443 µM	1/41	2.4 %
SB-505124 (25521)	ALK	0.204	42	4.297 µM	10/42	23.8 %
MK-2461 (23967)	c-Met	0.204	42	14.608 µM	9/42	21.4 %

A correlation coefficient of rho>0.6 was not achieved for any reference compound. The highest correlation was detected for Avoca 95 Capsule (rho=0.430). For all standard agents rho<0.4 was detected. Overall, this Compare Analysis could not indicate the mode of action for Avoca 95 liquid.

B. Based on relative IC_{50} values

Compound to compare: Avoca 95 liquid (99

Export: Export to Excel

Compound	Mode of Action	Spearman	N	Geom. Mean	<1/2	<1/2
Avoca 95 liquid (99624)		**1.000**	**42**	**0.015 %(v/v)**	**3/42**	**7.1 %**
Avoca 95 capsule (99543)		0.460	42	21.232 µg/mL	3/42	7.1 %
BGT226, Maleic acid salt (23961)	PI3K/mTOR	0.405	42	0.008 µM	14/42	33.3 %
AZD1480 (38071)	JAK2	0.367	41	3.506 µM	8/41	19.5 %
LY-294,002 HCl (16010)	PI3K	0.366	42	13.28 µM	6/42	14.3 %
Entinostat (16803)	HDAC	0.322	41	0.761 µM	6/41	14.6 %
Dactolisib (11726)	PI3K/mTOR	0.314	42	0.039 µM	13/42	31 %
ZSTK474, free base (23981)	PI3K	0.302	42	0.559 µM	6/42	14.3 %
AZD5363 (25502)	AKT	0.301	42	19.046 µM	12/42	28.6 %
SB-505124 (25521)	ALK	0.300	42	3.268 µM	10/42	23.8 %
LEE011 (17061)	CDK4/6	0.299	40	6.817 µM	11/40	27.5 %
CPI-203 (38103)	BRD4	0.292	41	0.417 µM	14/41	34.1 %
OTX015, free base (36023)	BET	0.282	42	0.631 µM	13/42	31 %
PFI-1 (38243)	BRD4	0.270	41	11.795 µM	8/41	19.5 %
CUDC-101, free base (23979)	Multikinase (HDAC,	0.268	42	0.402 µM	7/42	16.7 %
GS-0387 (33144)	JAK	0.268	42	4.042 µM	5/42	11.9 %
Ipatasertib (14670)	AKT1/2/3	0.266	42	10.838 µM	10/42	23.8 %
Lomustine (15985)	Alkylating agent	0.266	42	52.658 µM	5/42	11.9 %
Doxorubicin HCl (12707)	TopoII	0.263	42	0.044 µM	13/42	31 %
Tofacitinib Citrate (36006)	JAK3	0.262	41	87.883 µM	4/41	9.8 %
Teniposide (17976)	TopoII	0.250	40	0.108 µM	7/40	17.5 %
Droxinostat (20970)	HDAC3/6/8	0.242	42	23.809 µM	3/42	7.1 %
Amsacrine HCl (11123)	Alkylating agent	0.241	42	0.18 µM	6/42	14.3 %
YH239-EE (35946)	p53/MDM2	0.237	41	11.687 µM	1/41	2.4 %
MS436 (36024)	BET	0.237	41	14.747 µM	9/41	22 %
TG101348 (19516)	JAK2	0.232	42	2.448 µM	2/42	4.8 %
Sabutoclax (38065)	Bcl-2/xL, Mcl-1, Bfl-	0.229	41	0.341 µM	13/41	31.7 %

A correlation coefficient of rho>0.6 was not achieved for any reference compound. The highest correlation was detected for Avoca 95 Capsule (rho=0.460) and PI3K/mTOR inhibitor BGT226 (rho=0.405). For all other drugs rho<0.4 was detected. Overall, this Compare Analysis could not indicate the mode of action for Avoca 95 liquid.

C. Based on absolute IC_{70} values

Compound to compare: Avoca 95 liquid (99▾

Export: Export to Excel

Compound	Mode of Action	Spearman	N	Geom. Mean	<1/2	<1/2
Avoca 95 liquid (99624)		**1.000**	**42**	**0.018 %(v/v)**	**3/42**	**7.1 %**
Suberic bis-hydroxamic acid (17854)	HDAC	0.349	42	43.754 µM	6/42	14.3 %
Dactolisib (11726)	PI3K/mTOR	0.325	42	0.199 µM	20/42	47.6 %
Entinostat (16803)	HDAC	0.320	41	1.584 µM	8/41	19.5 %
Avoca 95 capsule (99543)		0.313	42	25.225 µg/mL	4/42	9.5 %
M344 (16079)	HDAC	0.292	42	1.502 µM	6/42	14.3 %
MK-2461 (23967)	c-Met	0.284	42	22.334 µM	3/42	7.1 %
Vorinostat (18214)	HDAC	0.276	42	3.128 µM	6/42	14.3 %
LY-294,002 HCl (16010)	PI3K	0.274	42	29.133 µM	3/42	7.1 %
ZSTK474, free base (23981)	PI3K	0.263	42	3.428 µM	16/42	38.1 %
CUDC-101, free base (23979)	Multikinase (HDAC,	0.252	42	0.779 µM	9/42	21.4 %
BGT226, Maleic acid salt (23961)	PI3K/mTOR	0.251	42	0.033 µM	16/42	38.1 %
AZD8055 (21001)	mTOR	0.250	42	0.252 µM	18/42	42.9 %
Apicidin (11219)	HDAC	0.249	42	0.55 µM	6/42	14.3 %
KU0063794 (18892)	mTOR	0.243	42	4.25 µM	19/42	45.2 %
AZD5363 (25502)	AKT	0.236	42	49.986 µM	5/42	11.9 %
Dacinostat (20968)	HDAC	0.234	42	0.058 µM	4/42	9.5 %
Droxinostat (20970)	HDAC3/6/8	0.232	42	36.678 µM	3/42	7.1 %
Ibrutinib (25120)	Btk	0.215	41	14.586 µM	4/41	9.8 %
Tofacitinib Citrate (36006)	JAK3	0.214	41	99.016 µM	0/41	0 %
PI-103 (23965)	PI3K/mTOR	0.209	42	2.17 µM	13/42	31 %
Silmitasertib (38126)	CK2	0.200	42	13.764 µM	0/42	0 %
Erismodegib, free base (25508)	Smo	0.198	42	33.316 µM	2/42	4.8 %
MI-773 (36025)	MDM2	0.184	42	8.765 µM	12/42	28.6 %
Lomustine (15985)	Alkylating agent	0.183	42	83.1 µM	4/42	9.5 %
ON-01910 (23964)	PLK1	0.177	42	0.625 µM	25/42	59.5 %
Idelalisib (21021)	PI3K	0.177	42	26.257 µM	2/42	4.8 %

A correlation coefficient of rho>0.6 was not achieved for any reference compound. For all standard agents rho<0.4 was detected. Overall, this Compare Analysis could not indicate the mode of action for Avoca 95 liquid.

Table 9: Compare Analysis for Avoca 95 capsule

A. Based on absolute IC_{50} values

Compound to compare: Avoca 95 capsule (

Export: Export to Excel

Compound	Mode of Action	Spearman	N	Geom. Mean	<1/2	<1/2
Avoca 95 capsule (99543)		**1.000**	**42**	**21.612 µg/mL**	**3/42**	**7.1 %**
Entinostat (16803)	HDAC	0.439	41	0.814 µM	7/41	17.1 %
Avoca 95 liquid (99624)		0.430	42	0.015 %(v/v)	3/42	7.1 %
Pimasertib (21000)	MEK1/2	0.362	42	0.888 µM	17/42	40.5 %
CI-1040 (18890)	MEK1/2	0.340	42	2.349 µM	9/42	21.4 %
AZD5363 (25502)	AKT	0.333	42	21.071 µM	10/42	23.8 %
Aurora A inhibitor I (20962)	Aurora A	0.323	42	1.089 µM	8/42	19 %
RO5126766 (38263)	B-Raf, MEK	0.318	41	4.863 µM	16/41	39 %
TAK-632 (20440)	B-Raf, C-Raf	0.314	42	1.821 µM	7/42	16.7 %
Bortezomib (12078)	Proteasome	0.297	42	0.014 µM	8/42	19 %
Selumetinib (11443)	MEK1/2	0.289	42	6.454 µM	16/42	38.1 %
Trametinib (21861)	MEK1/2	0.282	42	0.067 µM	16/42	38.1 %
Erlotinib HCl (12886)	EGFR	0.279	39	19.648 µM	11/39	28.2 %
PD318088 (21860)	MEK1/2	0.271	42	2.118 µM	12/42	28.6 %
Tenovin-1 (25528)	SIRT1, SIRT2	0.265	42	14.845 µM	13/42	31 %
PIK-90, free base (20901)	PI3K	0.261	42	2.434 µM	13/42	31 %
Pazopanib, free base (18861)	Multikinase (VEGFR1	0.258	42	32.432 µM	18/42	42.9 %
CPI-203 (38103)	BRD4	0.256	41	1.003 µM	17/41	41.5 %
Binimetinib (22119)	MEK1/2	0.252	42	6.236 µM	16/42	38.1 %
AZD8330 (21859)	MEK1/2	0.251	42	0.352 µM	18/42	42.9 %
TAK-733 (18923)	MEK1/2	0.250	42	0.453 µM	18/42	42.9 %
Manumycin A (16538)	FTase	0.249	40	7.195 µM	3/40	7.5 %
PD0325901 (18891)	MEK1/2	0.246	42	0.961 µM	20/42	47.6 %
Dabrafenib (23179)	B-Raf, C-Raf	0.244	42	23.178 µM	3/42	7.1 %
6-Thioguanine (10623)	Anti-metabolite	0.242	42	1.372 µM	10/42	23.8 %
GDC-0623 (35945)	MEK1	0.240	42	0.595 µM	18/42	42.9 %
Dactolisib (11726)	PI3K/mTOR	0.240	42	0.061 µM	17/42	40.5 %

A correlation coefficient of rho>0.6 was not achieved for any reference compound. The highest correlation was detected for HDAC inhibitor Etinostat (rho=0.439) and for Avoca 95 liquid (rho=0.430). For all other drugs rho<0.4 was detected. Overall, this Compare Analysis could not indicate the mode of action for Avoca 95 Capsule.

B. Based on relative IC_{50} values

Compound to compare: Avoca 95 capsule (9

Export: Export to Excel

Compound	Mode of Action	Spearman	N	Geom. Mean	<1/2	<1/2
Avoca 95 capsule (99543)		**1.000**	**42**	**21.232 µg/mL**	**3/42**	**7.1 %**
Avoca 95 liquid (99624)		0.460	42	0.015 %(v/v)	3/42	7.1 %
Entinostat (16803)	HDAC	0.453	41	0.761 µM	6/41	14.6 %
GDC-0623 (35945)	MEK1	0.390	42	0.33 µM	22/42	52.4 %
CI-1040 (18890)	MEK1/2	0.380	42	2.234 µM	8/42	19 %
RO5126766 (38263)	B-Raf, MEK	0.375	41	2.482 µM	14/41	34.1 %
Trametinib (21861)	MEK1/2	0.373	42	0.044 µM	19/42	45.2 %
Binimetinib (22119)	MEK1/2	0.368	42	4.033 µM	15/42	35.7 %
Pimasertib (21000)	MEK1/2	0.364	42	0.677 µM	16/42	38.1 %
TAK-733 (18923)	MEK1/2	0.354	42	0.307 µM	19/42	45.2 %
PD318088 (21860)	MEK1/2	0.354	42	1.705 µM	12/42	28.6 %
AZD8330 (21859)	MEK1/2	0.342	42	0.181 µM	20/42	47.6 %
PD0325901 (18891)	MEK1/2	0.337	42	0.301 µM	20/42	47.6 %
Selumetinib (11443)	MEK1/2	0.329	42	5.606 µM	15/42	35.7 %
Bortezomib (12078)	Proteasome	0.311	42	0.014 µM	8/42	19 %
Aurora A inhibitor I (20962)	Aurora A	0.298	42	1.113 µM	7/42	16.7 %
Ixazomib (19001)	Proteasome	0.292	39	0.175 µM	6/39	15.4 %
AZD5363 (25502)	AKT	0.283	42	19.046 µM	12/42	28.6 %
Erlotinib HCl (12886)	EGFR	0.273	39	11.234 µM	9/39	23.1 %
Lestaurtinib (25549)	RTK	0.253	42	0.366 µM	11/42	26.2 %
CUDC-101, free base (23979)	Multikinase (HDAC,	0.250	42	0.402 µM	7/42	16.7 %
TAK-632 (20440)	B-Raf, C-Raf	0.250	42	1.359 µM	5/42	11.9 %
PFI-1 (38243)	BRD4	0.244	41	11.795 µM	8/41	19.5 %
Oprozomib (38043)	Proteasome	0.233	41	0.072 µM	7/41	17.1 %
MG132 (16665)	Proteasome	0.231	42	0.243 µM	6/42	14.3 %
I-BET151 (37964)	BET	0.225	40	1.184 µM	13/40	32.5 %
Alisertib, free base (20969)	Aurora A	0.220	42	0.616 µM	19/42	45.2 %

A correlation coefficient of rho>0.6 was not achieved for any reference compound. The highest correlation was detected for Avoca 95 liquid (rho=0.460). Among the standard agents a Spearman correlation coefficient of rho=0.453 was detected for HDAC inhibitor Entinostat. For all other drugs rho<0.4 was detected. Overall, this Compare Analysis could not indicate the mode of action for Avoca 95 Capsule.

C. Based on absolute IC_{70} values

Compound to compare: Avoca 95 capsule (

Export: Export to Excel

Compound	Mode of Action	Spearman	N	Geom. Mean	<1/2	<1/2
Avoca 95 capsule (99543)		**1.000**	**42**	**25.225 µg/mL**	**4/42**	**9.5 %**
RO5126766 (38263)	B-Raf, MEK	0.415	41	12.403 µM	8/41	19.5 %
CI-1040 (18890)	MEK1/2	0.378	42	4.826 µM	10/42	23.8 %
Ixazomib (19001)	Proteasome	0.377	39	0.255 µM	12/39	30.8 %
Actinomycin D (10999)	DNA	0.359	42	0.002 µM	9/42	21.4 %
Echinomycin A (12814)	DNA	0.348	42	0.001 µM	7/42	16.7 %
TAK-733 (18923)	MEK1/2	0.344	42	1.244 µM	16/42	38.1 %
Selumetinib (11443)	MEK1/2	0.337	42	18.563 µM	12/42	28.6 %
Pimasertib (21000)	MEK1/2	0.337	42	3.283 µM	16/42	38.1 %
Trametinib (21861)	MEK1/2	0.331	42	0.185 µM	14/42	33.3 %
Dabrafenib (23179)	B-Raf, C-Raf	0.322	42	59.924 µM	2/42	4.8 %
Binimetinib (22119)	MEK1/2	0.321	42	18.397 µM	13/42	31 %
TAK-632 (20440)	B-Raf, C-Raf	0.313	42	4.898 µM	9/42	21.4 %
Avoca 95 liquid (99624)		0.313	42	0.018 %(v/v)	3/42	7.1 %
AZD8330 (21859)	MEK1/2	0.302	42	1.139 µM	15/42	35.7 %
Bortezomib (12078)	Proteasome	0.282	42	0.018 µM	7/42	16.7 %
PD318088 (21860)	MEK1/2	0.279	42	4.49 µM	9/42	21.4 %
Entinostat (16803)	HDAC	0.279	41	1.584 µM	8/41	19.5 %
Manumycin A (16538)	FTase	0.275	40	11.774 µM	3/40	7.5 %
GSK1059615 (20976)	PI3K	0.273	42	1.811 µM	8/42	19 %
Romidepsin (12598)	HDAC	0.258	42	0.002 µM	12/42	28.6 %
Aurora A inhibitor I (20962)	Aurora A	0.252	42	2.017 µM	5/42	11.9 %
ONX-0914 (38063)	Proteasome	0.247	39	0.492 µM	4/39	10.3 %
AZD5363 (25502)	AKT	0.246	42	49.986 µM	5/42	11.9 %
GDC-0623 (35945)	MEK1	0.246	42	2.658 µM	18/42	42.9 %
6-Thioguanine (10623)	Anti-metabolite	0.236	42	2.706 µM	12/42	28.6 %
BI-847325 (36184)	MEK1/2, Aurora A/C	0.233	41	0.337 µM	11/41	26.8 %
AT9283 (20974)	Aurora A/B	0.231	42	0.742 µM	13/42	31 %

A correlation coefficient of rho>0.6 was not achieved for any reference compound. The highest correlation was detected for BRAF/MEK inhibitor RO5126766 (rho=0.415). For all other drugs rho<0.4 was detected. Overall, this Compare Analysis could not indicate the mode of action for Avoca 95 Capsule.

Personnel Involved

Dr. Gerhard Kelter	Head of tumor test laboratory I (monolayer assay)
Jutta Fehr	Lab assistant, tumor test laboratory I (monolayer assay)
Isabel Disch	Lab assistant, tumor test laboratory I (monolayer assay)
Margitta Bolanz-Eismann	Scientist, data management & reporting

8 Appendix

8.1 Tumor Models

Table 10: Tumor cell lines tested in the present study (42 cell line panel)

Tumor Designation	Tumor Number	Cancer Type	Source
BXF	1218	bladder cancer	PDX-derived
BXF	1352	bladder cancer	PDX-derived
BXF	T24	bladder cancer	ATCC
CXF	269	colon cancer (caucasian, Europe)	PDX-derived
CXF	DiFi	colon cancer (caucasian, Europe)	n.a.
CXF	HCT 116	colon cancer (caucasian, Europe)	NCI
CXF	HT-29	colon cancer (caucasian, Europe)	NCI
CXF	RKO	colon cancer (caucasian, Europe)	ATCC
GXA	MKN45	gastric cancer (asian)	JCRB
GXF	251	gastric cancer (caucasian)	PDX-derived
HNXF	CAL-27	head & neck cancer (caucasian)	DSMZ
LIXFC	575	liver cancer (caucasian, Cholangiocarcinoma)	PDX-derived
LXFA	289	NSCLC (caucasian, adenocarcinoma subtype)	PDX-derived
LXFA	526	NSCLC (caucasian, adenocarcinoma subtype)	PDX-derived
LXFA	629	NSCLC (caucasian, adenocarcinoma subtype)	PDX-derived
LXFL	529	NSCLC (caucasian, large cell subtype)	PDX-derived
LXFL	1121	NSCLC (caucasian, large cell subtype)	PDX-derived
LXFL	NCI-H460	NSCLC (caucasian, large cell subtype)	NCI
MAXFLB	MCF7	breast cancer (luminal B)	DSMZ
MAXFTN	401	breast cancer (triple negative)	PDX-derived
MAXFTN	MDA-MB-231	breast cancer (triple negative)	ATCC
MEXF	276	melanoma	PDX-derived
MEXF	462	melanoma	PDX-derived
MEXF	1341	melanoma	PDX-derived
OVXF	899	ovarian cancer (caucasian)	PDX-derived
OVXF	OVCAR-3	ovarian cancer (caucasian)	NCI
PAXF	546	pancreatic cancer (caucasian)	PDX-derived
PAXF	1657	pancreatic cancer (caucasian)	PDX-derived
PAXF	PANC-1	pancreatic cancer (caucasian)	CLS
PRXF	22Rv1	prostate cancer	DSMZ
PRXF	DU-145	prostate cancer	NCI
PRXF	LNCaP	prostate cancer	DSMZ
PRXF	PC-3M	prostate cancer	NCI
PXF	698	pleuramesothelioma	PDX-derived
PXF	1118	pleuramesothelioma	PDX-derived
PXF	1752	pleuramesothelioma	PDX-derived
RXF	393	renal cancer (caucasian)	PDX-derived
RXF	486	renal cancer (caucasian)	PDX-derived
RXF	1781	renal cancer (caucasian)	PDX-derived
SXFO	Saos-2	osteosarcoma (caucasian)	DSMZ
SXFS	TE671	soft tissue sarcoma (caucasian)	ECACC
UXF	1138	uterus cancer	PDX-derived

Table 11: Abbreviation of tumor model designation

Tumor designation	Histotype		Tumor designation	Histotype
ACXF	Adrenocortical		LXFL	Lung (NSCLC, large cell)
AHS	Hematopoietic stem cells		LXFS	Lung (SCLC)
ATFR	Animal tumor (Freiburg, GER)		LYXF	Lymphoma (Undefined)
ATNC	Animal tumor (Morrisville, NC, USA)		LYXFDLBC	Lymphoma (DLBCL)
AXF	Anal		LYXFH	Lymphoma (Hodgkin)
BXF	Bladder		LYXFNH	Lymphoma (Non-Hodgkin)
CEXA	Cervix (Asian)		MAXFHER	Breast, HER2-enriched
CEXF	Cervix (Caucasian)		MAXFLB	Breast, luminal B
CNXF	Central nervous system, glioblastoma		MAXFTN	Breast, triple negative
CXA	Colon (Asian)		MEXF	Melanoma
CXF	Colon (Caucasian)		MMXF	Multiple Myeloma
GIXF	Stomach, gastrointestinal stromal tumor (GIST)		NBXF	Neuroblastoma
GXA	Stomach/gastric (Asian)		OEXF	Oesophagus
GXF	Stomach/gastric (Caucasian)		OVXF	Ovary (Freiburg, GER)
HNXA	Head & Neck (Asian)		OVXNC	Ovary (Morriville, NC, USA)
HNXF	Head & Neck (Caucasian)		PAXA	Pancreas (Asian)
LEXFAL	Leukemia (ALL)		PAXF	Pancreas (Caucasian)
LEXFAM	Leukemia (AML)		PRXF	Prostate
LEXFCL	Leukemia (B-CLL)		PXF	Pleuramesothelioma
LEXFCM	Leukemia (CML)		RXA	Kidney/renal (Asian)
LEXFCN	Leukemia (chronic neutrophil)		RXF	Kidney/renal (Caucasian)
LEXFPLL	Leukemia (B-prolymphocytic)		SKXF	Epidermal
LEXFU	Leukemia (undefined subtype)		SXA	Sarcoma (Asian)
LIXAH	Liver, hepatocellular (Asian)		SXFE	Sarcoma, Ewing sarcoma (Caucasian)
LIXFC	Liver, cholangiocellular		SXFO	Sarcoma, osteosarcoma (Caucasian)
LIXFH	Liver, hepatocellular (Caucasian)		SXFS	Sarcoma, soft tissue sarcoma (Caucasian)
LXA	Lung (Asian)		THXF	Thyroid (Freiburg, GER)
LXAA	Lung (NSCLC, adeno, Asian)		THXNC	Thyroid (Morrisville, NC, USA)
LXF	Lung (Undefined)		TXF	Testis
LXFA	Lung (NSCLC, adeno)		UXF	Uterus
LXFE	Lung (NSCLC, squamous cell)		VXF	Vulva

8.2 *In vitro* activity of Avoca 95 capsule and Avoca 95 liquid in 42 human cancer cell lines (relative and absolute $IC_{50/70}$ values)

Table 12: Avoca 95 capsule

Avoca 95 capsule Tumor model		Passage	Exp. no.	Top (%)	Bot. (%)	Unit	Rel. IC50	Rel. IC70	Abs. IC50	Abs. IC70
BXF	1218	30N15	XA0998-P2615266-3	114	0	µg/mL	20.306	24.452	21.465	25.484
BXF	1352	17N11	XA0948-P2613238-3	107	0	µg/mL	26.652	> 30.000	28.459	> 30.000
BXF	T24	23N11	XA0985-P2615237-3	116	0	µg/mL	27.851	> 30.000	28.646	> 30.000
CXF	269	13N3	XA0949-P2613600-3	118	0	µg/mL	28.673	> 30.000	> 30.000	> 30.000
CXF	DiFi	16N4	XA0989-P2615444-3	110	8	µg/mL	9.803	10.572	10.122	11.003
CXF	HCT 116	24N11	XA0986-P2615421-3	113	10	µg/mL	10.723	11.772	11.281	12.564
CXF	HT-29	24N8	XA0921-P2612813-3	112	50	µg/mL	11.435	12.604	20.533	> 30.000
CXF	RKO	22N8	XA0922-P2611825-3			µg/mL	> 30.000	> 30.000	> 30.000	> 30.000
GXA	MKN45	38N6	XA0923-P261282A-3			µg/mL	> 30.000	> 30.000	> 30.000	> 30.000
GXF	251	32N8	XA0924-P2612836-3			µg/mL	> 30.000	> 30.000	> 30.000	> 30.000
HNXF	CAL-27	15N3	XA0951-P2613617-3	116	20	µg/mL	11.855	13.260	13.134	15.699
LIXAH	575	28N5	XA0990-P2615243-3			µg/mL	> 30.000	> 30.000	> 30.000	> 30.000
LXFA	289	37N5	XA0997-P2615846-3			µg/mL	> 30.000	> 30.000	> 30.000	> 30.000
LXFA	526	33N11	XA0925-P2612233-3			µg/mL	> 30.000	> 30.000	> 30.000	> 30.000
LXFA	629	29N12	XA0926-P2612842-3			µg/mL	> 30.000	> 30.000	> 30.000	> 30.000
LXFL	1121	20N3	XA0954-P2613623-3	107	0	µg/mL	20.993	> 30.000	22.470	> 30.000
LXFL	529	29N17	XA1037-P2619206-3	110	25	µg/mL	18.288	25.465	25.747	> 30.000
LXFL	NCI-H460	23N4	XA0918-P2611021-3	107	0	µg/mL	16.991	20.600	17.481	21.033
MAXFLB	MCF7	15N2	XA0955-P2613830-3	99	0	µg/mL	27.538	> 30.000	27.375	> 30.000
MAXFTN	401	46N8	XA0928-P261224A-3			µg/mL	> 30.000	> 30.000	> 30.000	> 30.000
MAXFTN	MDA-MB-231	19N10	XA0987-P2615616-3	118	0	µg/mL	28.531	> 30.000	> 30.000	> 30.000
MEXF	1341	12N8	XA0930-P2611050-3	77	0	µg/mL	3.157	5.070	2.252	4.054
MEXF	276	32N8	XA0931-P2611067-3	75	0	µg/mL	4.798	15.261	1.991	8.408
MEXF	462	21N3	XA0956-P2613801-3	104	0	µg/mL	22.864	> 30.000	23.686	> 30.000
OVXF	899	23N3	XA0991-P2615823-3			µg/mL	> 30.000	> 30.000	> 30.000	> 30.000
OVXF	OVCAR-3	21N3	XA0958-P2613646-3	105	0	µg/mL	> 30.000	> 30.000	> 30.000	> 30.000
PAXF	1657	22N6	XA0932-P2611831-3	96	0	µg/mL	11.352	15.542	11.027	15.223
PAXF	546	19N2	XA0959-P2614002-3	108	0	µg/mL	20.825	> 30.000	23.168	> 30.000
PAXF	PANC-1	15N3	XA0960-P2613066-3	111	0	µg/mL	> 30.000	> 30.000	> 30.000	> 30.000
PRXF	22Rv1	15N7	XA0992-P2615622-3	107	0	µg/mL	26.570	> 30.000	27.958	> 30.000
PRXF	DU-145	31N5	XA0988-P2615438-3	124	0	µg/mL	22.642	> 30.000	27.113	> 30.000
PRXF	LNCaP	27N4	XA1000-P2615272-3	111	0	µg/mL	18.399	29.024	20.374	> 30.000
PRXF	PC-3M	19N2	XA0936-P261108A-3			µg/mL	> 30.000	> 30.000	> 30.000	> 30.000
PXF	1118	24N5	XA0993-P2615450-3	112	0	µg/mL	> 30.000	> 30.000	> 30.000	> 30.000
PXF	1752	34N5	XA0994-P261583A-3			µg/mL	> 30.000	> 30.000	> 30.000	> 30.000
PXF	698	13N3	XA0965-P2613072-3	112	0	µg/mL	29.638	> 30.000	> 30.000	> 30.000
RXF	1781	17N6	XA0933-P2612865-3	104	0	µg/mL	17.921	26.890	18.619	27.655
RXF	393	26N4	XA0995-P261525A-3	111	0	µg/mL	> 30.000	> 30.000	> 30.000	> 30.000
RXF	486	20N3	XA0967-P2613089-3	102	2	µg/mL	25.089	> 30.000	26.100	> 30.000
SXFO	Saos-2	20N4	XA0996-P2615467-3	112	2	µg/mL	19.342	28.675	21.816	> 30.000
SXFS	TE671	16N3	XA0969-P2614031-3	95	0	µg/mL	21.491	29.299	20.655	28.483
UXF	1138	31N6	XA0934-P2611073-3			µg/mL	> 30.000	> 30.000	> 30.000	> 30.000
Geometric mean							**21.349**	**24.957**	**21.784**	**25.319**

1/32 1/16 1/8 1/4 1/2 1 2 4 8 16 32 -fold mean IC value

sensitive cell lines resistant cell lines

Table 13: Avoca 95 liquid

Avoca 95 liquid Tumor model		Passage	Exp. no.	Top (%)	Bot. (%)	Unit		Rel. IC50		Rel. IC70		Abs. IC50		Abs. IC70
BXF	1218	30N15	XA0998-P2615266-5	105	3	%(v/v)		0.013		0.016		0.014		0.017
BXF	1352	17N11	XA0948-P2613238-5	101	0	%(v/v)		0.023		0.037		0.023		0.038
BXF	T24	23N11	XA0985-P2615237-5	106	4	%(v/v)		0.014		0.016		0.014		0.017
CXF	269	13N3	XA0949-P2613600-5	110	3	%(v/v)		0.014		0.017		0.014		0.018
CXF	DiFi	16N4	XA0989-P2615444-5	105	8	%(v/v)		0.012		0.012		0.012		0.013
CXF	HCT 116	24N11	XA0986-P2615421-5	99	2	%(v/v)		0.017		0.017		0.017		0.017
CXF	HT-29	24N8	XA0921-P2612813-5	104	1	%(v/v)		0.036		0.039		0.037		0.039
CXF	RKO	22N8	XA0922-P2611825-5	83	0	%(v/v)	>	0.033	>	0.036	>	0.032	>	0.035
GXA	MKN45	38N6	XA0923-P261282A-5	101	1	%(v/v)	>	0.040	>	0.045	>	0.040	>	0.045
GXF	251	32N8	XA0924-P2612836-5	103	2	%(v/v)		0.038		0.044		0.039		0.045
HNXF	CAL-27	15N3	XA0951-P2613617-5	115	1	%(v/v)		0.015		0.018		0.016		0.018
LIXAH	575	28N5	XA0990-P2615243-5	105	11	%(v/v)		0.012		0.012		0.012		0.013
LXFA	289	37N5	XA0997-P2615846-5	94	1	%(v/v)		0.013		0.016		0.013		0.015
LXFA	526	33N11	XA0925-P2612233-5	100	0	%(v/v)		0.079		0.103		0.079		0.103
LXFA	629	29N12	XA0926-P2612842-5	98	2	%(v/v)		0.047		0.059		0.047		0.059
LXFL	1121	20N3	XA0954-P2613623-5	108	3	%(v/v)		0.013		0.016		0.013		0.017
LXFL	529	29N17	XA1037-P2619206-5	102	1	%(v/v)		0.013		0.015		0.013		0.016
LXFL	NCI-H460	23N4	XA0918-P2611021-5	100	0	%(v/v)		0.011		0.014		0.011		0.014
MAXFLB	MCF7	15N2	XA0955-P2613830-5	98	11	%(v/v)		0.011		0.012		0.011		0.012
MAXFTN	401	46N8	XA0928-P261224A-5	102	0	%(v/v)	>	0.033	>	0.034	>	0.033	>	0.035
MAXFTN	MDA-MB-231	19N10	XA0987-P2615616-5	102	2	%(v/v)		0.012		0.014		0.012		0.014
MEXF	1341	12N8	XA0930-P2611050-5	81	2	%(v/v)		0.003		0.004		0.003		0.004
MEXF	276	32N8	XA0931-P2611067-5	78	3	%(v/v)		0.005		0.006		0.004		0.006
MEXF	462	21N3	XA0956-P2613801-5	93	3	%(v/v)		0.011		0.012		0.011		0.012
OVXF	899	23N3	XA0991-P2615823-5	94	7	%(v/v)		0.024		0.027		0.025		0.027
OVXF	OVCAR-3	21N3	XA0958-P2613646-5	94	3	%(v/v)		0.013		0.014		0.013		0.014
PAXF	1657	22N6	XA0932-P2611831-5	95	1	%(v/v)		0.003		0.003		0.003		0.003
PAXF	546	19N2	XA0959-P2614002-5	98	3	%(v/v)		0.016		0.021		0.016		0.021
PAXF	PANC-1	15N3	XA0960-P2613066-5	108	3	%(v/v)		0.016		0.020		0.017		0.021
PRXF	22Rv1	15N7	XA0992-P2615622-5	105	8	%(v/v)		0.010		0.011		0.011		0.012
PRXF	DU-145	31N5	XA0988-P2615438-5	118	2	%(v/v)		0.012		0.014		0.013		0.015
PRXF	LNCaP	27N4	XA1000-P2615272-5	99	11	%(v/v)		0.010		0.011		0.010		0.011
PRXF	PC-3M	19N2	XA0936-P261108A-5	97	0	%(v/v)		0.015		0.020		0.015		0.020
PXF	1118	24N5	XA0993-P2615450-5	99	12	%(v/v)		0.011		0.014		0.012		0.015
PXF	1752	34N5	XA0994-P261583A-5	101	6	%(v/v)		0.014		0.016		0.014		0.017
PXF	698	13N3	XA0965-P2613072-5	110	13	%(v/v)		0.011		0.012		0.011		0.012
RXF	1781	17N6	XA0933-P2612865-5	98	0	%(v/v)		0.033		0.036		0.033		0.036
RXF	393	26N4	XA0995-P261525A-5	90	10	%(v/v)		0.019		0.022		0.019		0.023
RXF	486	20N3	XA0967-P2613089-5	97	1	%(v/v)		0.010		0.011		0.010		0.011
SXFO	Saos-2	20N4	XA0996-P2615467-5	100	14	%(v/v)		0.013		0.015		0.014		0.017
SXFS	TE671	16N3	XA0969-P2614031-5	101	1	%(v/v)		0.013		0.016		0.014		0.017
UXF	1138	31N6	XA0934-P2611073-5	94	0	%(v/v)		0.020		0.027		0.019		0.026
Geometric mean								**0.015**		**0.018**		**0.015**		**0.018**

1/32 1/16 1/8 1/4 1/2 1 2 4 8 16 32 -fold mean IC value

sensitive cell lines resistant cell lines

8.3 Reference Compounds Used for Compare Analysis

Table 14: List of Reference compounds

#	Drug Name	Aliases	Target
1	(+)-JQ1		BET
2	4-Hydroperoxy-cyclophosphamide	4-HC; CYACT; D-18864; Perfosfamide	Alkylating agent
3	4-Hydroperoxy-ifosfamide	D-18851; IFOACT	Alkylating agent
4	5-Fluoro-2-deoxyuridine	2'-Deoxy-5-fluorouridine; 5-FUDR; FLOXURINE; Floxuridine	Anti-metabolite
5	5-Fluorouracil	5-FU; 5FU; ADM1; EX 59/1, GT2002 1207, KULTURFILTRATEXTRAKT	Anti-metabolite
6	6-Diazo-5-oxo-L-norleucine	(S)-2-Amino-6-diazo-5-oxocaproic acid; DON	Glu synthase
7	6-Mercaptopurine	6-MP; MERCAPTOPURIN; PURINETHOL; Purinethol	Anti-metabolite
8	6-Thioguanine	2-amino-6-mercaptopurine; 6-TG	Anti-metabolite
9	7-Ethyl-10-hydroxy-camptothecin	SN38; irinotecan, active metabolite	TopoI
10	ABT-263	Navitoclax	Bcl-2
11	ABT-737		Bcl-2
12	AMG-208		c-Met
13	AMG-458		c-Met
14	AMG925		Flt-3, CDK4
15	ARQ 621		Eg5
16	AS-605240	AS605240	PI3K
17	AT-101	(R)-(-)-Gossypol acetic acid; (R)-Gossypol acetic acid	Bcl-2
18	AT7519		CDK1/2/4/6/9
19	AT7867	AT-7867	AKT, p70S6K
20	AT9283	AT-9283	Aurora A/B
21	AUY922	CCT018159; NVP-AUY922; VER-52296	HSP90
22	AZ 3146		Mps1
23	AZ628		B-Raf, C-Raf
24	AZD1080		GSK2-alpha/beta
25	AZD1480		JAK2
26	AZD3463		ALK
27	AZD5363	AZD-5363; Capivasertib	AKT
28	AZD5438		CDK1/2/9
29	AZD6738	AZ13386215; Ceralasertib	ATR
30	AZD8055		mTOR
31	AZD8330	ARRY-424704; ARRY-704	MEK1/2
32	Abemaciclib sulfate	LY2835219 sulfate	CDK4/6
33	Actinomycin D	ACD; Actinomycin C1; Actinomycin IV; DACT; Dactinomycin	DNA
34	Afatinib, free base	BIBW-2992; BIBW2992; Tomtovok; Tovok	EGFR, HER2
35	Afuresertib	GSK2110183	AKT1/2/3
36	Alectinib	AF-802; CH-5424802; RG-7853; RO5424802	ALK
37	Alisertib, free base	MLN8237; MNL-8237	Aurora A
38	Alsterpaullone		CDK1
39	Alvespimycin HCl	17-DMAG; 17-Dimethyl-aminopropyl-geldanamycin; 17DMAG	HSP90
40	Amsacrine HCl	Amsacrin; Amsacrine hydrochloride; M-AMSA	Alkylating agent
41	Anguidine	12,13-Epoxytrichothec-9-ene-3,4,15-triol-4,15-diacetate; 4β,15-Diacetoxy-3α-hydroxy-12,13 epoxy-trichothec-9-ene; Diacetoxyscirpenol	Protein synthesis
42	Apicidin	Cyclo[(2S)-2-amino-8-oxodecanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinexcarbonyl]; OSI-2040	HDAC
43	Apigenin	4â€²,5,7-Trihydroxyflavone	PKC, MAPK
44	Aurora A inhibitor I		Aurora A
45	BGT226, Maleic acid salt	NVP-BGT226, Maleic acid salt	PI3K/mTOR
46	BI 2536	NYC424409	PLK1
47	BI 6727 3HCl	ML00693955; ML00693955-058-B	PLK1
48	BI-847325		MEK1/2, Aurora A/C
49	BIBR1532	BIBR 1532; BIBR-1532	Telomerase

#	Drug Name	Aliases	Target
50	BIIB021	CNF2024	HSP90
51	BIRB796	NYC405346, Doramapimod	p38 MAPK
52	BIX02188	BIX 02188	MEK5
53	BIX02189	BIX 02189	MEK5
54	BMS 777607		Multikinase (c-Met, AXL, RON, Tyro3)
55	BMS-265246		CDK1/2
56	BV-6		cIAP
57	Bexarotene	LG100069; LGD-1069; SR-11247; Targretin; Targretyn; Targrexin	RXR
58	Binimetinib	ARRY-162; ARRY-438162; MEK162; NVP-MEK162-NX-2	MEK1/2
59	Bleomycin sulfate	BLM; Blenoxane; Bleo; Bleomedac	DNA
60	Bortezomib	MLN-341; PS-341; VELCADE	Proteasome
61	Bosutinib, free base	SKI-606	Bcr-Abl
62	Brefeldin A	Ascotoxin; BFA; Cyanein; Decumbin; Nectrolide; Synergisidin	ATPase
63	Brigatinib	AP-26113	ALK, ROS1, Flt-3, EGFR
64	Buparlisib	BKM120; LY2Q1005; NVP-BKM-120	PI3K
65	CEP-32496		B-Raf, C-Raf
66	CH5138303		HSP90
67	CHIR-98014		GSK3-alpha/beta
68	CHIR-99021	CT99021, CT-99021, CHIR99021	GSK3
69	CI-1040	PD-184352, free base	MEK1/2
70	CPI-203		BRD4
71	CUDC-101, free base		Multikinase (HDAC, EGFR, HER2)
72	CYC116	CYC12116	Aurora A/B, VEGFR2
73	Cabozantinib	BMS-907351; XL184, free base	Multikinase (VEGFR2, c-Met, Ret, c-Kit, Flt-3, Tie2, AXL)
74	Camptothecin		TopoI
75	Canertinib, dihydrochloride	CI-1033; PD183805	EGFR, HER2/3/4
76	Carboplatin	CARBOPLA; CARBOPLAT; CBDCA; JM-8; cis-Diammine(1,1-cyclobutanedicarboxylato) platinum	DNA
77	Carfilzomib	PR-171, Kyprolis	Proteasome
78	Cediranib free base	AZD2171, Recentin	VEGFR2
79	Ceritinib	LDK378	ALK
80	Cisplatin	CDDP; CISPLATIN; DDP; PLAT; PLATIBLASTIN; PLATINEX; cis-Diamminedichloroplatinum; cis-Patinum II; cis-dichlorodiammineplatinum(II)	DNA
81	Clofarabine, free base	CAFdA; CHEBI:120185; Cl-F-Ara-A; Clolar; Evoltra	Anti-metabolite
82	Crizotinib, free base	PF02341066	c-Met, ALK
83	Cyclo(RGDyK)		aVb3 integrin
84	Cyclocytidine HCl	2,2â€-Anhydro-(1-Î²-D-arabinofuranosyl)cytosine hydrochloride; Ancitabine HCl; Ancitabine hydrochloride; O2,2â€-Cyclocytidine	Anti-metabolite
85	Cyclopamine, free base	11-Deoxyjervine	Smo
86	Cyclopentenyl cytosin		Anti-metabolite
87	Cytarabine	ARAC; Ara-C; Cytosar; Cytosine arabinoside; Cytosine ß-D-arabinofuranoside; MSC 63878; U19920	Anti-metabolite
88	D4476	D-4476	CK1
89	DMXAA	5,6-MeXAA; ASA404; NSC-640488; Vadimezan	VDA
90	DUP 785	BPQ; BREQUINAR SODIUM; DUP-785	Anti-metabolite
91	Dabrafenib	GSK2118436	B-Raf, C-Raf
92	Dacinostat	LAQ824; NVP-LAQ824	HDAC
93	Dactolisib	BEZ-235; BEZ235, free base; NVP-BEZ235	PI3K/mTOR
94	Danusertib	PHA-739358	Aurora A/B/C, Bcr-Abl
95	Dasatinib monohydrate	BMS-354825; SPRYCEL	Multikinase (Bcr-Abl, Src, c-Kit)
96	Daunorubicin HCl	DAUNOBLASTIN; DNR; Dauno; Daunomycin hydrochloride; Daunorubicin hydrochloride; Rubidomycin	TopoII
97	Dinaciclib	SCH727965	CDK1/2/5/9
98	Docetaxel	DTX; TAXOTERE; TXT	Tubulin
99	Dovitinib, free base	CHIR-258; LY2Q0814; TKI-258	Multikinase (Flt-3, c-Kit, FGFR1/3, VEGFR1/2/3/4)

#	Drug Name	Aliases	Target
100	Doxorubicin HCl	ADM; ADR; ADRIABLASTIN; ADRIAMYCIN; ADRIMEDAC; DX	TopoII
101	Droxinostat		HDAC3/6/8
102	ENMD-2076	ENMD-981693, ENMD2076	Aurora A
103	Echinomycin A	Levomycin; Quinomycin A	DNA
104	Elmustine	HECNU; Hemustine; Hydroxy-ethyl-CNU	Alkylating agent
105	Entinostat	BYK276536/3/10; MS 275-27; MS-27-275; MS-275; MS275; SNDX-275; SNDX-275	HDAC
106	Enzastaurin HCl	LSN436881	PKC
107	Epothilone A		Tubulin
108	Epothilone B, free base	EPO-906; EPO906; EPOTHILONE B; EpoB; PATUPILONE	Tubulin
109	Epothilone D	Epothilone D, Desoxyepothilone B, Epo D, KOS 862, NSC 703147	Tubulin
110	Epoxomicin, synthetic		Proteasome
111	Erismodegib, free base	LDE-225; LDE225; NVP-LDE-225; NVP-LDE225; Sonidegib, free base	Smo
112	Erlotinib HCl	CP-358,774; ERLOTINIB; Erlotinib Hydrochloride; NYC409736; OSI-774; RO0508231; RO0508231-001; SFI0002; TARCEVA	EGFR
113	Etoposide	ETO CS 100MG; ETO GRY 100MG; ETO-CELL; VP-16; VP-16-213; VP16	TopoII
114	FLLL32		JAK2, STAT3
115	Fascaplysin, synthetic		CDK4
116	Flavopiridol HCl	Alvocidib HCl; DB03496; HMR-1275; L86-8275; MDL 107826A; NSC 649890	CDK2/4/7
117	Foretinib, free base	EXEL-2880; GSK-1363089; GSK089; XL-880	c-Met, VEGFR2
118	Ftorafur	Citofur; Fluorofur	Anti-metabolite
119	GDC-0152, free base	GDC 0152; GDC0152	cIAP, XIAP, ML-IAP
120	GDC-0623	GDC 0623; GDC0623	MEK1
121	GDC-0879	GDC 0879; GDC0879	B-Raf
122	GS-0387	Momelotinib, CYT387	JAK
123	GSK1059615	GSK-1059615	PI3K
124	GSK1324726A	GSK-726A; GSK726A; I-BET726	BET
125	GSK1904529A		IGF-1R
126	GSK461364A	NYC466383	PLK1
127	GSK503	GSK-503; GSK2635503C	EZH2
128	GSK690693		AKT
129	Gefitinib	AZ10027436; IRESSA; NYC315761; RO 33-2843; RO0332843-000; ZD1839	EGFR
130	Gemcitabine HCl	GEM; GEMZAR; Gemedac; LY188011; dFdC; dFdCyd	Anti-metabolite
131	Glesatinib	MGCD-265	c-Met, VEGFR1/2/3
132	Golvatinib	E7050	c-Met, VEGFR2
133	Hepsulfam	1,7-Heptanediyl ester; Sulfamic acid	Alkylating agent
134	Homoharringtonine		Protein synthesis
135	Hydroxyurea	HU; Hydroxycarbamid; Hydroxyharnstoff; LITALIR	RNR
136	I-BET151	GSK1210151A	BET
137	INC280, free base	INCB-28060; INCB28060; NVP-INC280-AA, Capmatinib	c-Met
138	IWR-1		Wnt
139	Ibrutinib	PCI-32765	Btk
140	Idarubicin	DMDR; IDA; Imi 30	TopoII
141	Idelalisib	CAL-101; CAL101; GS-1101	PI3K
142	Imatinib, mesylate	CGP057148B; CGP57148B; STI571	Bcr-Abl
143	Infigratinib	BGJ-398; NVP-BGJ398	FGFR1/2/3
144	Iniparib	BSI-201; IND-71677; SAR240550	PARP1
145	Ipatasertib	G-035608, GDC-0068; GDC 0068; GDC0068	AKT1/2/3
146	Ispinesib, mesylate	CK-0238273; NYC410248; SB-715992	Eg5
147	Ixazomib	MLN2238; MLN3	Proteasome
148	JNJ-7706621		CDK1/2, Aurora A/B
149	KU0063794	Ku-0063794	mTOR
150	LCL-161		cIAP, XIAP
151	LDC1267		AXL, Mer, Tyro3
152	LEE011	LEE-011, NVP-LEE011-BBA, Ribociclib	CDK4/6
153	LRRK2-IN-1		LRRK2
154	LY-294,002 HCl	2-(4-Morpholinyl)-8-phenyl-1(4H)-benzopyran-4-one hydrochloride; LY-294,002 hydrochloride	PI3K
155	LY2090314		GSK3
156	LY2784544	LSN 2784544; LY1Q0906	JAK2
157	Lapatinib, free base	GW-2016; GW-572016; LAPATINIB,FREE BASE; NYC405493	EGFR, HER2
158	Lestaurtinib	CEP-701; KT-5555	RTK
159	Lomustine	CCNU; CeeNU	Alkylating agent

#	Drug Name	Aliases	Target
160	M344	D237	HDAC
161	MG132	MG-132; Z-LEU-LEU-LEU-AL	Proteasome
162	MI-773	SAR405838	MDM2
163	MK-2206, dihydrochlorid	LY2Q1003; MK2206	AKT1/2/3
164	MK-2461		c-Met
165	MK-8745		Aurora A
166	MLN0128	INK128	mTOR
167	MLN4924, Hydrochlorid	ML00644507; ML644507; MLN4924-001; MLN4924-003	NAE
168	MS436		BET
169	MST-312	Telomerase Inhibitor 9; Telomerase Inhibitor IX	Telomerase
170	Manumycin A		FTase
171	Masitinib, free base	AB-1010	c-Kit, PDGFR-alpha/beta
172	Methotrexat Hydrat	4-Amino-10-methylfolic acid hydrate; Antifolan hydrate; L-4-Amino-N10-methylpteroylglutamic acid hydrate; L-Amethopterin hydrate; MTX hydrate; MTXK; Methotrexate hydrate; Methylaminopterin hydrate	Anti-metabolite
173	Methyl-GAG	Guanylhydrazone; M-GAG; Methyl GAG dihydrochloride; Methylglyoxal bis(guanylhydrazone) dihydrochloride hydrate; Mitoguazone; methyl-glyoxal-bis(guanylhydrazone)	Polyamine synthesis
174	Mithramycin A	Aureolic acid; Plicamycin	DNA
175	Mitomycin C	MITO; MMC	Alkylating agent
176	Mitoxantron 2HCl	MOX; Mitoxantrone dihydrochloride; NOVA; NOVANTRON	DNA
177	Monastrol		Eg5
178	NMS-E973		HSP90
179	NMS-P937	NMS1286937	PLK1
180	NPS-1034		c-Met, AXL
181	NU7441	KU-57788	DNA-PK
182	Nilotinib HCl	AMN107; NVP-AMN107-AA; Tasigna	Bcr-Abl
183	Nutlin-3a		p53/MDM2
184	ON-01910	Estybon; Novonex; Rigosertib	PLK1
185	ONX-0914	PR-957	Proteasome
186	OSI-027, HCl	OSI027	mTOR
187	OSI-930	OSI930	c-Kit, VEGFR2
188	OSU-03012, HCl		PDK-1
189	OTX015, free base		BET
190	Obatoclax mesylate	GX15-070; GX15-070MS; Obatoclax, methanesulfonate salt	Bcl-2
191	Olaparib	AZD-2281; AZD2281; KU-0059436; Lynparza	PARP1/2
192	Oprozomib	ONX 0912	Proteasome
193	Osimertinib	AZ13552748-020; AZ35; AZD9291; AZD9291 free base; Mereletinib	EGFR
194	Oxaliplatin	ACT-078; ELOXATIN; LOHP; OXPLAT; SR96669; SR96670	DNA
195	PAC-1		Procaspase-3
196	PD0166285		Wee1, Chk1
197	PD0325901	PD 325901	MEK1/2
198	PD168393		EGFR
199	PD318088		MEK1/2
200	PF-04217903		c-Met
201	PF-04691502	PF04691502	PI3K/mTOR
202	PF-477736		Chk1
203	PFI-1	PF-6405761	BRD4
204	PHA-665752		c-Met
205	PHA-680632	PHA680632	Aurora A/B/C
206	PHA-767491		CDC7, CDK9
207	PI-103		PI3K/mTOR
208	PIK-90, free base		PI3K
209	PKI-587	PF-05212384	PI3K/mTOR

#	Drug Name	Aliases	Target
210	PLX-4720	MSC2357264A; PLX4720	B-Raf
211	PQ 401		IGF-1R
212	PX-866	DJM-166; DJM-2-166	PI3K
213	Paclitaxel	PTX; Paclitaxel; TAXOL; Taxol	Tubulin
214	Pacritinib	SB1518	JAK2
215	Palbociclib HCl	PD-0332991; PF-0332991; PF-332991; PF0332991	CDK4/6
216	Panobinostat, free base	Faridak; LBH-589; LBH589; NVP-LBH-589; Panobinostat; SD2107	HDAC
217	Pazopanib, free base	Armala; GW-786034; Votrient	Multikinase (VEGFR1/2/3, PDGFR-alpha/beta, c-Kit)
218	Peficitinb	ASP015K, JNJ-54781532	JAK
219	Pelitinib	CID6445562; D05399; EKB569; NYC404065; WAY-172569; WAY-EKB 569	EGFR
220	Pemetrexed, dinatrium	ALIMTA; LY231514; MTA	Anti-metabolite
221	Perifosine	D-21266; KRX-0401; NKA17; NSC639966	AKT
222	Pictilisib, free base	GDC 0941; GDC-0941; GDC0941; LY2Q1006; PI-103; PI103; RG7321	PI3K
223	Pimasertib	AS-703026; AS703026; MSC1936369B; PGS-1156a	MEK1/2
224	Plinabulin	BPI-2358; NPI-2358; NPI2358	VDA
225	Purvalanol A	2-(1R-Isopropyl-2-hydroxyethylamino)-6-(3-chloroanilino)-9-isopropylpurine; NG-60	CDK1/2/4/5
226	Pyrazoloacridine		TopoII
227	RAF265	CHIR-265	B-Raf, VEGFR2
228	RG-7112		MDM2
229	RO5126766	CH5126766	B-Raf, MEK
230	Raltitrexed	TOMUDEX; ZD-1694	Anti-metabolite
231	Rapamycin	Antibiotic AY 22989; Sirolimus	mTOR
232	Regorafenib, free base	BAY73-4506	Multikinase (VEGFR2, Ret, C-Raf)
233	Rifamycin SV sodium	Rifocin	RNA polymerase
234	Riviciclib HCl	H-101; P276-00, P276	CDK1/4/9
235	Ro3280		PLK1
236	Rociletinib	CO-1686, AVL-301	EGFR
237	Romidepsin	Depsipeptide; FK228; FR901228; Istodax; NSC630176	HDAC
238	Rucaparib phosphate	AG-014447; AG-014699; PF-01367338; Rubraca	PARP1
239	S-Trityl-L-cysteine	Tritylcystein	Eg5
240	SB-202190		p38 MAPK
241	SB-505124		ALK
242	SB216763		GSK3
243	SB525334		TGF-betaRI
244	SB590885	GSK2118436	B-Raf
245	SGI-7079		AXL
246	SMI-4a	(5Z)-5-[[3-(Trifluoromethyl)phenyl]methylene]-2,4-thiazolidinedione; (Z)-5-(3-Trifluoromethylbenzylidene)thiazolidine-2,4-dione	PIM1
247	SNS-032	BMS-387032	CDK2/7/9
248	SP 600125		JNK
249	SU11274	PKI-SU11274	c-Met
250	SU9516		CDK2
251	Sabutoclax		Bcl-2/xL, Mcl-1, Bfl-1
252	Satraplatin	Poplat	DNA
253	Selumetinib	ARRY-142886; ARRY-886; ARRY142886; AZ12252244; AZD-6244; AZD6244	MEK1/2
254	Silmitasertib	CX-4945	CK2
255	Sorafenib, free base	BAY43-9006; NEXAVAR	Multikinase (B-Raf, C-Raf, c-Kit, Flt-3, VEGFR2/3, PDGFR-beta)
256	Staurosporine	STS; antibiotic AM-2282	PKC
257	Suberic bis-hydroxamic acid	SBHA; Suberic Bishydroxamate; Suberoyl Bishydroxamic Acid	HDAC
258	Sunitinib malate	SU-11248; SUTENT	Multikinase (VEGFR1/2/3, PDGFR-alpha/beta, c-Kit, Ret, Flt-3)

#	Drug Name	Aliases	Target
259	TAE684	NVP-TAE684; TAE-684	ALK
260	TAK-632	PGS-1134; T'632; T-3109632	B-Raf, C-Raf
261	TAK-733	SYR-733; SYR144733	MEK1/2
262	TDZD-8		GSK3
263	TG101348		JAK2
264	TH287		MTH1
265	TIC10		AKT, ERK
266	TP-0903		AXL
267	TW-37		Bcl-2/xL, Mcl-1
268	TWS119		GSK3-beta
269	Tandutinib, free base	CT53518; D06005; MLN0518	Flt-3
270	Taselisib	GDC 0032; GDC-0032; GDC0032; PF-06739138	PI3K
271	Temsirolimus	CCI-779; MSC2214504A-A; Torisel	mTOR
272	Teniposide	PTG; VM-26; Vehem; Vumon	TopoII
273	Tenovin-1		SIRT1, SIRT2
274	Tetrandrine	(1Î²)-6,6â€,7,12-Tetramethoxy-2,2â€-dimethylberbaman; Fanchinine; Hanfangchin A; d-Tetrandrine	Ca2+ channel
275	Tetraplatin		DNA
276	Thiotepa	TESPA; TSPA	Alkylating agent
277	Tivantinib	ARQ-197	c-Met
278	Tofacitinib Citrate	CP-690550	JAK3
279	Topotecan HCl	BAY92S; TOPO	TopoI
280	Trametinib	EX00100636; EX100636; GS-646643; GSK1120212; GSK212; JTP-74057	MEK1/2
281	Treosulfan	OVASTAT; TREO	Alkylating agent
282	UNC-2025		Mer, Flt-3
283	UNC2250		Mer
284	VE-821		ATR
285	VE-822	Berzosertib; M6620; VX970	ATR
286	VER-49009	NYC456375	HSP90
287	VER155008		HSP70
288	VR23		Proteasome
289	VX-680	LYRB2A; MK-0457; NYC336556; Tozasertib	Aurora A/B
290	Vandetanib	ZD6474; Zactima	VEGFR2/3, EGFR
291	Vatalanib, free base	CGP-79787, ZK-222584; NYC406262; PTK-787; PTK/ZK	VEGFR2, PDGFR-beta
292	Vemurafenib	LY1Q1107; LY3045247; PLX-4032; PLX4032; R7204; RG7204; RO518426; Zelboraf	B-Raf
293	Venetoclax	ABT-199; GDC 0199; GDC-0199; GDC0199	Bcl-2
294	Vinblastine sulfate	N67; VBL; VELBE; VINBLAST; VLB; Vincaleukoblastine sulfate	Tubulin
295	Vincristine sulfate	22-Oxovincaleukoblastine sulfate; Leurocristine sulfate; VCR	Tubulin
296	Vindesin sulfate hydrate	3-(Aminocarbonyl)-O4-deacetyl-3-de(methoxycarbonyl)vincaleukoblastine sulfate; Desacetylvinblastine amide sulfate; ELDISINE; VDS; VIND	Tubulin
297	Vinflunine, di-tartrate	BMS-710485; Javlor	Tubulin
298	Vinorelbine bistartrate	3â€²,4â€²-Didehydro-4â€²-deoxy-Câ€²-norvincaleukoblastine [R-(R*,R*)-2-3-dihydroxybutanedioate (1:2)salt]; 5â€²-Noranhydrovinoblastine tartrate; KW-2307; NVB; Navelbine tartrate; VNL; VRL	Tubulin
299	Vismodegib, free base	Erivedge; GDC 0449; GDC-0449; GDC0449; HhAntag691	Smo
300	Vorinostat	MRLB-70652; SAHA	HDAC
301	WP1066		JAK2, STAT3
302	XL888		HSP90
303	YH239-EE		p53/MDM2
304	ZM 336372		C-Raf
305	ZSTK474, free base		PI3K
306	Zelavespib	PU-H71	HSP90
307	trans-HR22C16	NYC320681	Eg5

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