October 27, 2014

OUTPERFORM

Reason for report:

INITIATION

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CALITHERA BIOSCIENCES, INC.

Experienced Team, First-in-Class Compounds -- Initiate With OP

• **Bottom Line: We are initiating coverage of CALA with an Outperform rating and a price target of $13.** CALA is an early clinical-stage biotechnology company developing novel, potentially first-in-class agents for cancer by exploiting dysregulated metabolism of tumor cells and host immune response.

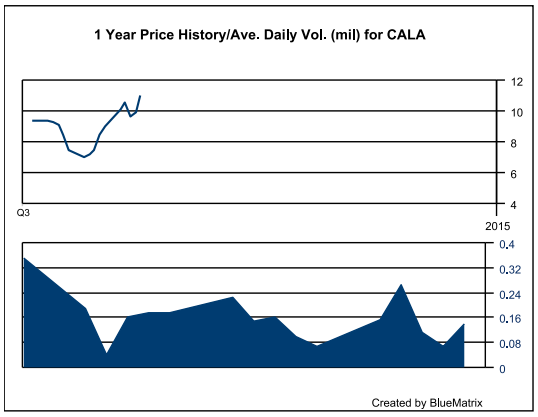
• **We believe targeting cancer metabolism is an important new area of exploration for cancer therapeutics.** We believe the rationale for targeting cancer metabolism is strong, given the elevated metabolic need as a hallmark of cancer and importantly altered metabolic pathways compared to normal cells. CALA's lead compound CB-839 (Phase I) is a specific inhibitor of glutaminase, thereby interfering with increased glutamine metabolism seen in cancer cells. Based on preclinical data and biological rationale, glutaminase inhibitors could be especially interesting for settings where a high unmet need exists such as triple negative breast cancer as well as patients with ras and myc mutations.

• **The effectiveness of a glutaminase inhibitor is likely context-dependent – patient selection and combinations could be key to success.** Glutaminase clearly remains to be validated clinically as a target. Feedback we received is mixed, and a concern about targeting glutaminase and perhaps metabolism in general is that cancer cells could potentially switch to a low-growth state and therefore these agents may not be cytotoxic but rather cytostatic. Data for CB-839 show that for at least some cells, CB-839 is cytotoxic. MEDACorp cancer biology specialists point out that the susceptibility to a glutaminase inhibitor varies considerably among different tumor cells; therefore patient selection will likely need to be integral to development.

• **Potential for a sustained pipeline.** In addition to CB-839, CALA has an interesting preclinical immuno-oncology program in targeting arginase which has similarities to IDO (indoleamine-2,3-dioxygenase) inhibitors which have drawn considerable attention recently. The management's proven track record with Kyprolis (AMGN, MP) bodes well, in our view, for a sustainable pipeline.

Key Stats:	**(NASDAQ:CALA)**
S&P 600 Health Care Index:	**1,336.04**
Price:	**$11.04**
Price Target:	$13.00
Methodology:	DCF analysis, 10% discount rate
52 Week High:	$11.70
52 Week Low:	$6.51
Shares Outstanding (mil):	17.9
Market Capitalization (mil):	$197.6
Book Value/Share:	$0.00
Cash Per Share:	$6.15
Dividend (ann):	$0.00
Dividend Yield:	0.0%

Shares Outstanding (mil): Cash Per Share: Calculated on a pro forma basis



Dec Yr	1Q	2Q	3Q	4Q	FY Rev	1Q	2Q	3Q	4Q	FY EPS	P/E
2014E	0.0	0.0	0.0	0.0	0.0	($0.60)	($0.60)	($0.49)	($0.28)	($1.78)	NM
2015E	--	--	--	--	0.0	--	--	--	--	($1.10)	NM
2016E	--	--	--	--	0.0	--	--	--	--	($1.52)	NM

Source: Company Information and Leerink Partners LLC Research
1H:14 results available but 1Q and 2Q were not broken out separately.

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CALITHERA: INITIATING WITH OUTPERFORM

OCT. 27, 2014

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INVESTMENT THESIS

- **We are initiating coverage of CALA with an Outperform rating and a price target of $13.** CALA is an early clinical-stage biotechnology company developing novel, potentially first-in-class agents for cancer by exploiting dysregulated metabolism of tumor cells and host immune response.
- **We believe targeting cancer metabolism is an important new area of exploration for cancer therapeutics.** We believe the rationale for targeting cancer metabolism is strong, given the elevated metabolic need as a hallmark of cancer and importantly altered metabolic pathways compared to normal cells. CALA's lead compound CB-839 (Phase I) is a specific inhibitor of glutaminase, thereby interfering with increased glutamine metabolism seen in cancer cells. Based on preclinical data and biological rationale, glutaminase inhibitors could be especially interesting for settings where a high unmet need exists such as triple negative breast cancer as well as patients with ras and myc mutations.
- **The effectiveness of a glutaminase inhibitor is likely context-dependent – patient selection and combinations could be key to success.** Glutaminase clearly remains to be validated clinically as a target. Feedback we received is mixed, and a concern about targeting glutaminase and perhaps metabolism in general is that cancer cells could potentially switch to a low-growth state and therefore these agents may not be cytotoxic but rather cytostatic. Data for CB-839 show that for at least some cells, CB-839 is cytotoxic. MEDACorp cancer biology specialists point out that the susceptibility to a glutaminase inhibitor varies considerably among different tumor cells; therefore patient selection will likely need to be integral to development.
- **Potential for a sustained pipeline.** In addition to CB-839, CALA has an interesting preclinical immuno-oncology program in targeting arginase which has similarities to IDO (indoleamine-2,3-dioxygenase) inhibitors which have drawn considerable attention recently. The management's proven track record with Kyprolis (AMGN, MP) bodes well, in our view, for a sustainable pipeline.

VALUATION

- Our price target for CALA of $13 a share is based on DCF analysis and probability-weighted sales for CB-839 in triple-negative breast cancer (TNBC) and multiple myeloma (MM) (10% probability), with a 10% discount rate. We believe this discount rate is appropriate as we use probability-weighted sales for the products.

RISKS TO VALUATION

- **Early stage of development.** Lead candidate is still in Phase I, and both efficacy and safety data remain limited.
- **Novel targets that have not been validated clinically.** As a potentially first in class agent, lead compound CB-839 targets an enzyme (glutaminase) that is still unproven as a target either clinically with a drug or genetically through mutation linkage. The broader approach of targeting cancer metabolism is also a new approach that does not have extensive validation.
- **Financing risks.** CALA's current balance of cash or equivalent (of ~$110M) is expected to support operations through 2017 but additional financing will likely be needed before the company turns profitable.

CALITHERA OVERVIEW

- Calithera is a clinical stage oncology company developing novel small molecule drugs inhibiting **tumor metabolic pathways** and against **tumor immunological** targets
- An early pipeline of internally discovered compounds is under development. The most advanced compound CB-839 is currently being evaluated in Phase I trials.
- CB-839 is a glutaminase inhibitor, an enzyme critical for metabolic processes in a tumor cell. It is currently being assessed in 3 Phase I trials, namely CX-839-001 in solid tumors, including triple negative breast cancer, renal cell carcinoma, non-small cell lung cancer and mesothelioma), CX-839-002 in liquid tumors, including multiple myeloma, non-Hodgkin's lymphoma) and CX-839-003 in acute lymphocytic leukemia and acute myeloid leukemia)
- Phase I data from single agent trials are expected in **mid:15** and for Phase Ib combination trials in **YE:15.**
- Second candidate is an arginase inhibitor that is expected to enter the clinic in 2015. It inhibits arginase, thereby preventing the depletion of arginine and inactivation of cytotoxic T cells, and this mechanism of action has similarities to IDO inhibitors.
- In addition, the company has an active undisclosed R&D pipeline focused toward tumor metabolism and immunology.
- Key members of the management team were previously at Proteolix acquired by Onyx which was in turn acquired by Amgen. Proteolix team discovered and successfully developed Kyprolis through registration trials.
- CALA has full commercial rights for CB-839 and a matter of composition patent until beyond **2032.**
- Key financials: Total cash at the end of July 2014 was **~$110M**.

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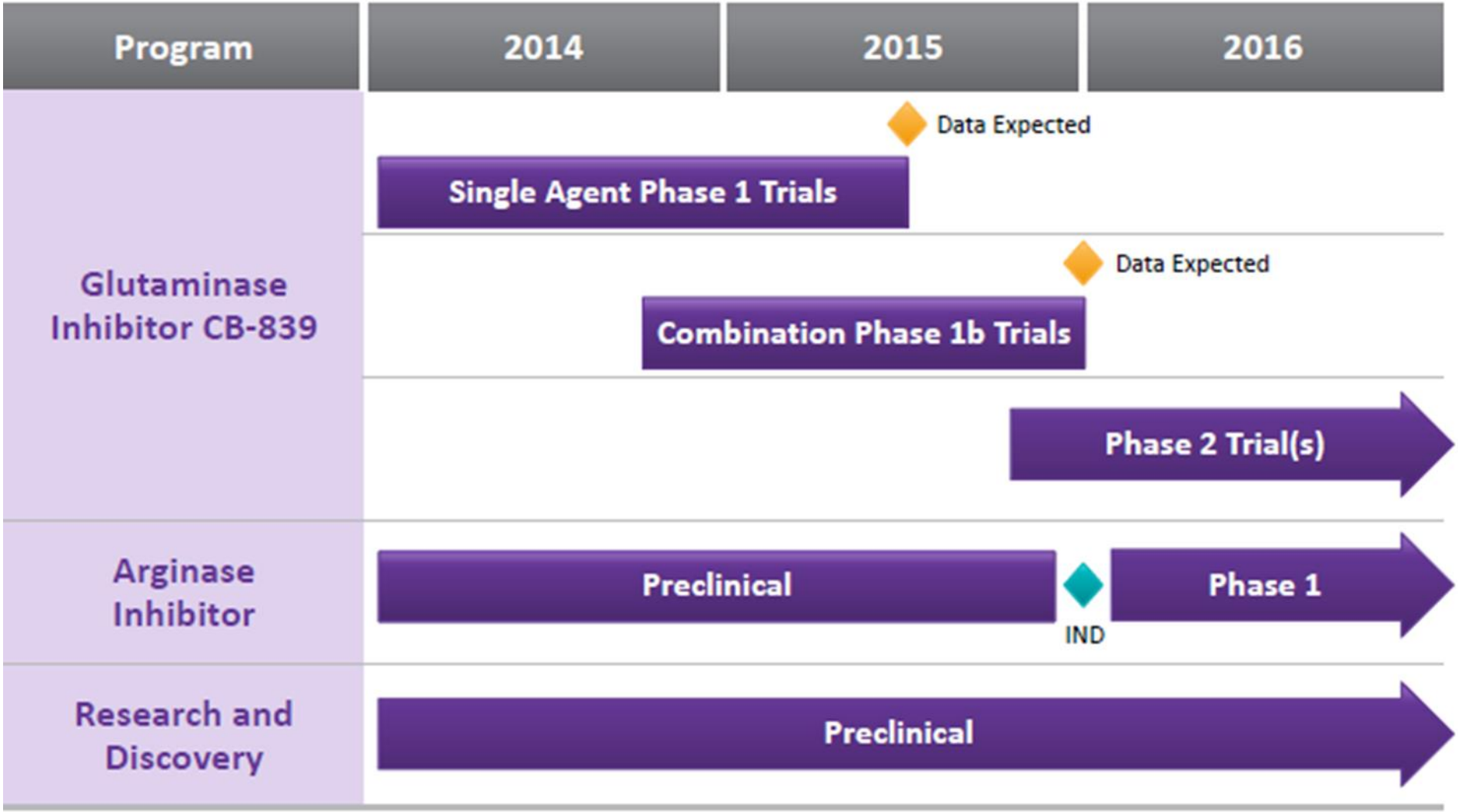
CALA HAS A PIPELINE OF POTENTIALLY FIRST IN CLASS AGENTS TARGETING MAJOR TUMORS



.Source: Company reports

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CLINICAL DEVELOPMENT PLAN FOR THE LEAD AGENT CB-839

Study Type	Trial and Indications	2014	2015	2016
Phase 1 Single Agent	**CX-839-001** Solid Tumors (including triple-negative breast cancer)	Dose Escalation / Dose Expansion		
	CX-839-002 Multiple Myeloma Non-Hodgkin's Lymphoma	Dose Escalation / Dose Expansion		
	CX-839-003 Acute Lymphocytic Leukemia Acute Myeloid Leukemia	Dose Escalation / Dose Expansion		
Phase 1b Combination	Triple-negative Breast Cancer		CB-839 + paclitaxel	
	Multiple Myeloma		CB-839 + pomalidomide + dex	
Phase 2	To be determined based on Phase 1/1b results			→

- Expect to treat ~130 patients in Phase 1/1b

NHL = Non-Hodgkin's Lymphoma
ALL = Acute Lymphocytic Leukemia
AML = Acute Myeloid Leukemia
Source: Company Reports

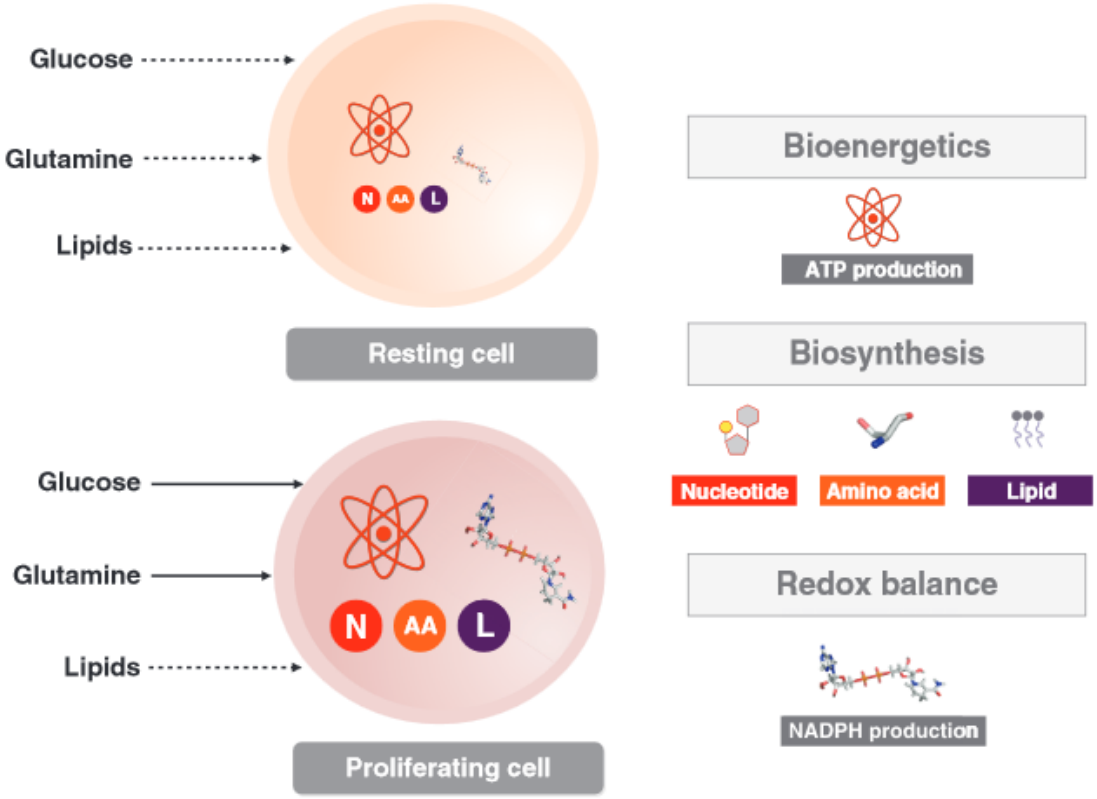
2015 COULD BE AN EVENTFUL YEAR FOR CALITHERA

Drug	Timing	Description
CB-839	4Q:14	Complete dose escalation of three Phase I trials
	4Q:14	Initiate dose expansion studies in all three Phase I trials
	mid:15	Phase I data solid tumors (TNBC)
	mid:15	Phase I data in MM and NHL
	mid:15	Phase I data in ALL and AML
	YE:15	Data from combination Phase 1b with placitaxel in TNBC
	YE:15	Data from combination Phase 1b with pomolidomide in MM
Arginase inhibitors	YE:15	Submit IND with the FDA

Source: Company reports and Leerink Partners Research

Targeting Aberrant Tumor Metabolism Is a New Area for Developing Novel Cancer Therapeutics

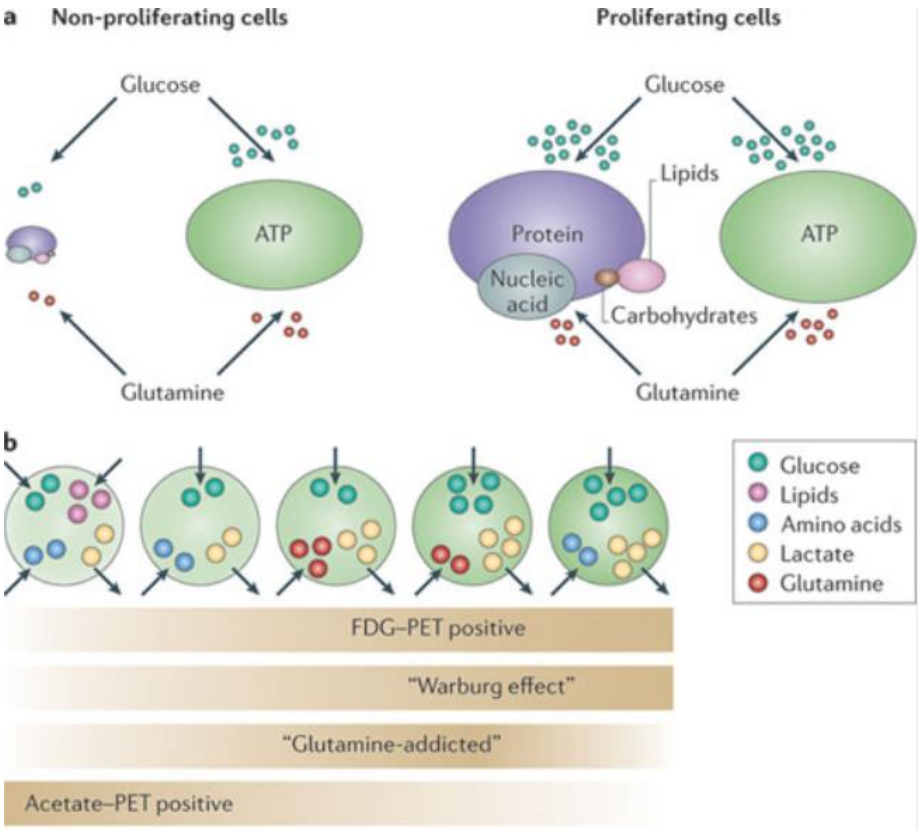
CANCER CELLS HAVE INCREASED BIOENERGETIC NEEDS



- Normal resting cells use a catabolic metabolism to satisfy the energetic requirements of homeostasis. This demand is met through fatty acid oxidation and the oxidative metabolism of glucose.
- Proliferating cells, however, must rewire their metabolic program to not only meet various energetic requirements, but to also satisfy the anabolic demands of macromolecular biosynthesis (nucleotides, lipids, and proteins). Upon growth factor–mediated stimulation, proliferating cells increase their uptake of **glucose** and **glutamine**, which are the two primary substrates that fuel cell growth.

Source: Cantor et al., Cancer Discovery 2012

CANCER CELLS HAVE MARKEDLY ELEVATED METABOLIC NEEDS



- Metabolic requirements of cancer cells for glucose/ glutamine are elevated as they are important for facilitating their proliferation and survival
- Alterations in the metabolic pathways utilized by cancer cells to derive energy were first observed by Warburg. Studies in carcinoma slices from rats and humans suggested that cancer cells prefer glycolytic breakdown of glucose for energy rather than mitochondrial oxidative phosphorylation, also known as the Warburg effect
- The Warburg effect is defined as the increased utilization of glucose via aerobic glycolysis leading to the production of lactate.

Source: Vander Heiden et al et al., Nat Rev Imm., 2011

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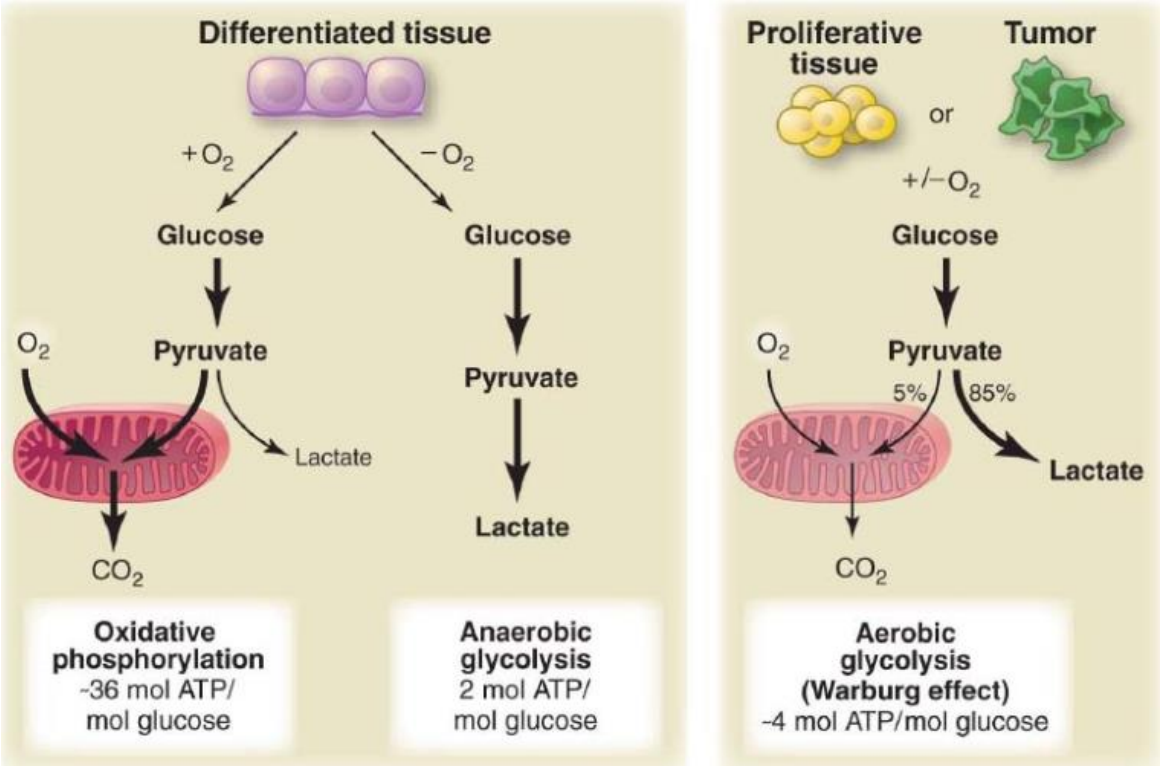
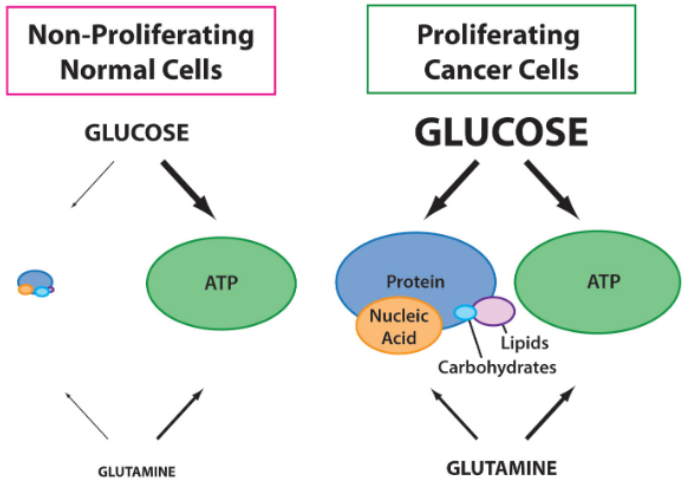
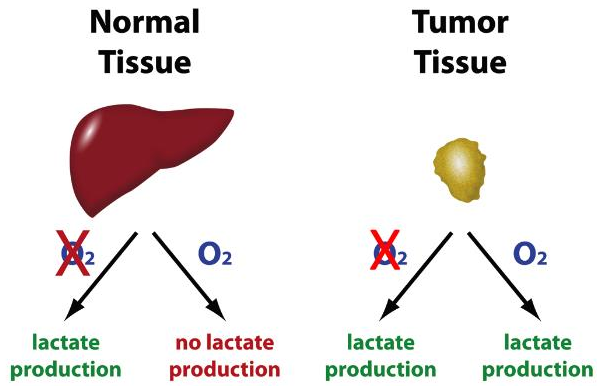
UNCONTROLLED GROWTH AND PROLIFERATION FORCE CANCER CELLS TO RE-WIRE THEIR METABOLIC MACHINERY



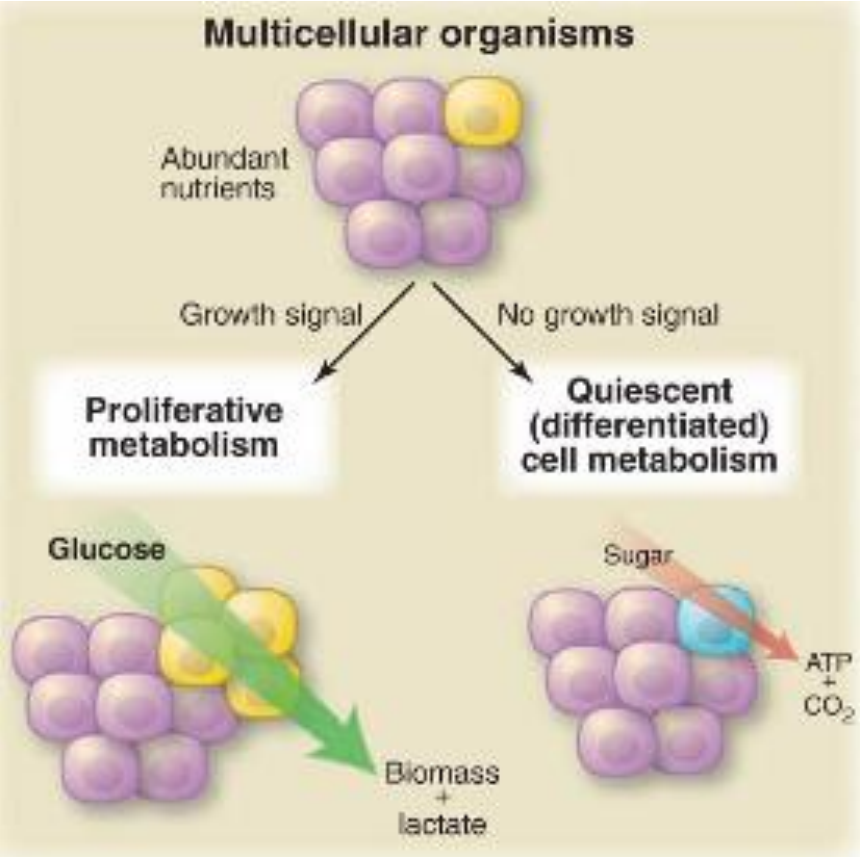




- Most normal tissue metabolize glucose to pyruvate and lactate in the presence and absence of oxygen, respectively
- However, Warburg observed that cancer cells tended to convert their glucose to lactate even in the presence of oxygen
- This altered metabolic mechanism is the hallmark of many cancer cells and presents an opportunity to target tumors via components of the metabolic pathway
- One such enzyme is glutaminase; it facilitates the use of the alternative metabolic pathways abetting proliferation of tumor cells

Source: Koong et al., Int. J. Radiat. Oncol. Biol. Phys., 2000

PROLIFERATING CELLS SWITCH TO AN ALTERED, LESS EFFICIENT METABOLISM



- The metabolism of glucose to lactate only generates 2 ATPs per molecule compared to 36 ATPs upon complete oxidation of one molecule of glucose
- Initially the reason for this shift toward a low energy (ATP) producing pathway was not well understood.
- However, recent studies have provided initial insights on the reasons for altered metabolism

  (i)- Metabolic requirements of cancer cells extend beyond ATP, and possibly the excessive lactate produced allows faster incorporation of carbon into biomass and as a result supporting the proliferative needs of a tumor cell.

  (ii)- Aerobic glycolysis leads to energy production more rapidly in comparison to oxidative phosphorylation.

ATP= Adenosine triphosphate

Source: Vander Heiden et al., Science 2009

METABOLIC ALTERATIONS LEAD TO GLUTAMINE ADDICTION IN CANCER CELLS

- Changes to the glycolytic pathway in turn lead to an increase in the glutamine needs of cancer cells
- This increased dependence can be seen as a compensatory mechanism through which cancer cells meet their bioenergetic and biosynthetic requirements to support proliferation and growth
- Glutamine is hydrolyzed to glutamate by an enzyme Glutaminase (GLS) and subsequently to α-ketoglutarate, which in turn helps maintain the output of the citric acid cycle in cancer cells
- The role of glutamine in offsetting the aberrations as a result of the Warburg effect has been demonstrated by metabolic flux experiments using NMR studies. These studies show that in cancer cells with altered glycolytic pathways, the citric acid cycle remains intact leading to production of key metabolic intermediates.
- This dependence on glutamine by cancer cells is often referred to as "**glutamine addiction**"

NMR=Nuclear magnetic resonance

Source: Erickson et al., Oncotarget 2010

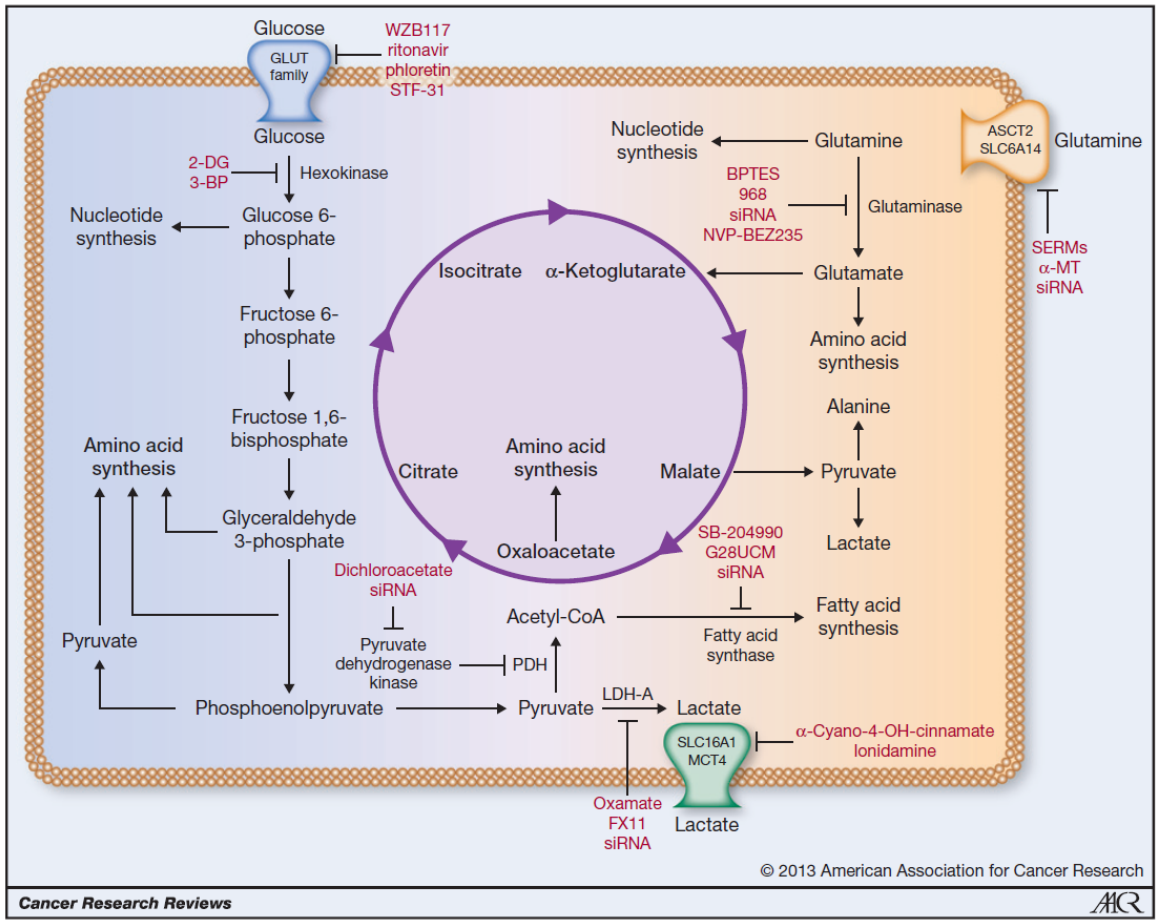
TARGETING CANCER METABOLISM AS A THERAPEUTIC APPROACH

- Aberrations in metabolism may influence cancer initiation and progression
- Studies have shown that metabolism could potentially improve existing therapeutic approaches
- In addition, oncogenes and transcription factors, such as AKT, C-MYC, RAS, p53, and HIF1 have also been shown to regulate various components of the metabolic pathways
- The genetic and epigenetic changes in a cancer cell that contribute to the glycolytic phenotype also contribute to the progressive development of resistance to chemotherapeutics that in part may be a consequence of increased glucose catabolism.
- Previous studies have demonstrated the utility of caloric restriction in inducing chemosensitization to a wide range of chemotherapeutics. It was shown that starvation induced sensitization to radio- or chemotherapy and led to extended survival in an in vivo glioma model

Source: Bronte et al., Nat. Rev. Imm., 2005

A WIDE RANGE OF OPPORTUNITIES EXIST FOR TARGETING CANCER METABOLISM

- Glucose and glutamine are metabolized into intermediates for cell growth such as amino acid, nucleotide, and fatty acid.
- Disruption of these metabolic networks can reduce drug resistance and make tumors more susceptible to drugs.



Source: Butler et al, Cancer Research, 2013

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DYSREGULATED CELLULAR METABOLISM IS LINKED TO DRUG RESISTANCE IN CANCER THERAPY

- Dysregulated metabolic pathways usually cause resistance against chemotherapy by protecting cancer cells against oxidative damage
- Multiple studies have shown that inhibitors against metabolic targets can re-sensitize cancer cells toward therapies they had shown resistance toward
- In addition, glutamine metabolism helps cancer cells overcome redox stress caused by chemotherapeutic agents. Thus, inhibiting glutaminase may sensitize cancer cells further toward chemotherapy
- Inhibiting glutaminolysis appears to have a similar sensitizing effect to the reduction of the mTOR signaling in cancer cells

mTOR =Mammalian target of rapamycin

Source: Butler et al., AACR 2013

CELLULAR METABOLISM TARGETS THAT IMPROVE CHEMOTHERAPY OUTCOMES

Target	Target action	Targeted by	Sensitivity or synergy	Cancer types	Tested as combined agent	Compound notes
GLUT1	Glucose transport	WZB117	Synergy with cisplatin and paclitaxel	Lung cancer	Animal models	Low toxicity, higher efficacy in cancer cells, mild weight loss
GLUT1	Glucose transport	STF-31	None reported / not yet tested	Renal cell carcinoma	Animal models	No reported toxicity, no effect in VHL wild type cells
GLUT1	Glucose transport	Phloretin	Induces daunorubicin sensitivity	Colon carcinoma, breast cancer	*In vitro*	High concentrations necessary to effect non-hypoxic cells
GLUT4	Glucose transport	Ritonavir	Induces doxorubicin sensitivity	Multiple myeloma	Patient samples and clinical trials	FDA approved
ASCT2	Glutamine transport	siRNA	None reported / not yet tested	Hepatocellular carcinoma	*In vitro*	Requires siRNA based delivery system
ASCT2	Glutamine transport	Tamoxifen or raloxifen	None reported / not yet tested	Estrogen independent breast cancer	*In vitro*	FDA approved
SLC6A14	Glutamine transport	α-MT	Synergy with autophagy inhibitors	Breast cancer	Animal models and clinical trials	No toxicity in observed in animal models, high selectivity
Hexokinase	Glycolysis	2-DG	Synergy with adriamycin, paclitaxel, and BCL-2 antagonists; induces trastuzumab sensitivity	Alveolar rhabdomyosarcoma, hypoxic tumors, osteosarcoma, non-small cell lung cancer, breast cancer, leukemia	Animal models and clinical trials	Requires large quantities to produce effect as solo agent
Hexokinase	Glycolysis	3-BP	Induces sensitivity to oxaliplatin, 5-fluorouracil, daunorubicin, and mitoxantrone	Myeloma, myelogenous leukemia, liver carcinoma	Animal models	No toxicity, but high concentrations required to produce effect as solo agent
PKM2	Glycolysis	TLN-232	Helps overcome hypoxia induced resistance	Melanoma, breast cancer, prostate carcinoma, colon carcinoma, and promyelocytic leukemia	Animal models and clinical trials	No toxicity, highly selective in cell lines and animal models, small transient weight loss *in vivo*, effective at low doses

Source: Butler et al., AACR 2013

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CELLULAR METABOLISM TARGETS THAT IMPROVE CHEMOTHERAPY OUTCOMES

Glutaminase	Glutamine catabolism	BPTES or siRNA	None reported / not yet tested	glioblastoma	*In vitro*	Non-glutamine analog, possible lead compound for development
Glutaminase	Glutamine catabolism	968	None reported / not yet tested	lymphoma	Animal models	No reported toxicity, no effect *in vitro* on normal cells
Glutaminase	Glutamine catabolism	NVP-BEZ235	Induces vincristine sensitivity	leukemia	Patient samples and clinical trials	Low toxicity, good oral bioavailability, minimal effects on normal cells *in vitro*
MCT1	Lactate export	Lonidamine or CHC	Induces radiosensitivity	Lung adenocarcinoma, colorectal adenocarcinoma	Animal models and clinical trials	Mild toxicity in patients, not suitable for IV delivery
LDHA	Lactate synthesis	FX11	Synergy with FK866	Pancreatic cancer, lymphoma	Animal models	Solubility limiting, no weight loss in animals treated with more soluble analog
LDHA	Lactate synthesis	Oxamate or siLDHA	Induces paclitaxel and trastuzumab sensitivity	Breast cancer	Animal models	Low toxicity
Mitochondrial respiratory chain complex I	Electron transport chain	metformin	Induces cisplatin, gemcitabine, and trastuzumab sensitivity	Ovarian cancer, pancreatic ductal adenocarcinoma, HER2 amplified breast cancer	Animal models and clinical trials	FDA approved
PDK	Inhibits pyruvate metabolism	DCA	Synergy with omeprazole, temozolomide	Alveolar carcinoma, breast cancer, fibrosarcoma, colon carcinoma	Animal models and clinical trials	High concentrations required to produce effect as solo agent
ACLY	Fatty acid synthesis	SB-204990	None reported / not yet tested	Alveolar carcinoma, pancreatic carcinoma	Animal models	No toxicity in animal models, stability may be low, good oral bioavailability
FASN	Fatty acid synthesis	G28UCM or siFASN	Synergy with trastuzumab, lapatinib, erlotinib, and gefitinib	Breast cancer	Animal models	Avoids common FASN inhibitor side effects: no anorexia or weight loss observed in aminal models

Source: Butler et al., AACR 2013

PROMISING METABOLIC TARGETS FOR CANCER THERAPY

Targets	Pathways	Agents or approaches (company)*	Development stage	Observations
Bioenergetic metabolism				
CPT1	β-oxidation	• Etomoxir • Oxfenicine • Perhexiline • RNAi	Perhexiline is approved for use as an anti-angina agent in Asia, Australia and New Zealand	Inhibition of CPT1 exerts anticancer effects *in vitro* and *in vivo*, yet it remains unclear whether these stem from the blockade of β-oxidation
Complex I	Mitochondrial respiration	• Metformin • Phenformin	Metformin is prescribed for the treatment of type 2 diabetes	The antineoplastic activity of metformin is independent of glycaemia and may reflect its capacity to inhibit mitochondrial respiration
GLUT1	Glycolysis	• WZB117 • RNAi	Preclinical data	Pharmacological or genetic inhibition of GLUT1 exerts antineoplastic effects, both *in vitro* and *in vivo*
GLS1	Glutamine metabolism	• 968 • BPTES • RNAi	Preclinical data	Malignant cells expressing mutant IDH1 may be particularly sensitive to GLS1-targeting agents
Hexokinases	Glycolysis	• 2-DG • 3-BP • Lonidamine • Methyl jasmonate • RNAi	The clinical development of 2-DG, 3-BP and lonidamine has been discontinued	It remains to be determined whether the anticancer effects of 3-BP and lonidamine stem from the inhibition of hexokinases
MCT1	Krebs cycle	• AR-C155858 • AR-C117977 • AZD3965 (AstraZeneca) • CHC • RNAi	AZD3965 is in clinical development	AZD3965 is currently being tested in a Phase I clinical trial enrolling patients with advanced solid tumours; these agents may be incompatible with the use of MCT1-transported drugs such as 3-BP
PDK1	Krebs cycle	• DCA	DCA is a prescription drug for the treatment of lactic acidosis	DCA is well tolerated by patients with glioblastoma multiforme and provokes profound mitochondrial defects in cancer cells
PKM2	Glycolysis	• TLN-232 (Thallion) • RNAi	The clinical development of TLN-232 has been discontinued	Inhibition of PKM2 reverses the Warburg effect (at least in some tumour models), yet it may favour anabolism

Source: Galluzzi et al., Nat. Rev Drug Discovery 2013

PROMISING METABOLIC TARGETS FOR CANCER THERAPY

Targets	Pathways	Agents or approaches (company)*	Development stage	Observations
Anabolic metabolism				
Choline kinase	Lipid biosynthesis	• CK37 • TCD-717 (TCD Pharma) • RNAi	TCD-717 is in clinical development	The safety and therapeutic profile of TCD-717 is currently being tested in patients with advanced solid tumours
HMGCR	Mevalonate pathway	• Statins	Statins are prescription drugs that are used to treat hypercholesterolaemia	The antineoplastic potential of statins is being investigated in multiple prospective clinical trials
IDHs	Lipid biosynthesis	• AGI-5198 (Xcessbio) • AGI-6780 (Xcessbio) • RNAi	Preclinical data	Inhibition of both wild-type and mutant IDH results in multipronged antineoplastic effects, presumably reflecting a decrease in 2-HG levels as well as an interference with glutamine metabolism
MGLL	Lipid biosynthesis	• JZL184 • RNAi	Preclinical data	MGLL promotes the migration, invasion and survival of malignant cells, as well as *in vivo* tumour growth
PGAM1	Pentose phosphate pathway	• PGMI-004A • RNAi	Preclinical data	Pharmacological or genetic inhibition of PGAM1 attenuates tumour growth *in vitro* and *in vivo*, presumably owing to the 3PG-mediated inhibition of the pentose phosphate pathway
PHGDH	Anaplerosis	• RNAi	Preclinical data	PHGDH inhibition fails to affect serine availability, yet limits that of multiple intermediates of the Krebs cycle
PKM2	Pentose phosphate pathway	• TEPP-46 • SAICAR • Serine	Preclinical data	PKM2 activators reportedly limit the diversion of glucose toward the pentose phosphate pathway, hence mediating antitumour effects

Source: Galluzzi et al., Nat. Rev Drug Discovery 2013

PROMISING METABOLIC TARGETS FOR CANCER THERAPY

Targets	Pathways	Agents or approaches (company)*	Development stage	Observations
Other metabolic circuitries				
HIF1	Hypoxic responses	• Acriflavine • PX-478	Preclinical data	Most, if not all, HIF1-targeting agents have failed (or never reached) clinical development
IDO	Tryptophan metabolism	• RNAi	Preclinical data	IDO-derived kynurenine promotes tumour progression via cell-intrinsic and cell-extrinsic mechanisms
mTOR	Cell growth, autophagy	• Rapalogues • Torins	Rapalogues are prescription drugs for the treatment of graft rejection and several tumours	Although mTOR inhibitors may limit tumour growth, they may also favour chemoresistance or neocarcinogenesis
PTGS2, AMPK?	Cell growth, autophagy	• Aspirin	Over-the-counter non-steroidal anti-inflammatory drug	Although aspirin has been shown to activate AMPK, its antineoplastic activity appears to stem from on-target effects

Source: Galluzzi et al., Nat. Rev Drug Discovery 2013

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THE DIFFERENT METABOLIC TARGETS IN DEVELOPMENT FOR THE TREATMENT OF CANCER

Company	Compound	Mechanism	Indication	Stage of development
Agios	AG-221	IDH2 mutation	IDH2 mutated hematologic malignancies	Phase I
	AG-120	IDH1 mutation	IDH1 mutated hematologic malignancies and solid tumor	Phase I
Advanced cancer therapeutics	PFK158	PFKFB3	advanced malignancies	Phase I
Cornerstone Pharmaceuticals	CPI-613	pyruvate dehydrogenase/ a-KG dehydrogenase	pancreatic cancer	Phase I/II
3-V Biosciences	FASN inhibitor	fatty acid synthase (FASN)	multiple tumor types (including breast, prostate and pancreatic cancers)	Phase I
AZN/ Cancer Research UK	AZD3965	monocarboxylate transporter 1	Solid tumors, prostate cancer, gastric cancer and DLBCL	Phase I

DLBCL = Diffused Large B-Cell Lymphoma
Source: Biomedtracker, and company reports

CALA Has a Potentially First-in-Class Specific Glutaminase Inhibitor

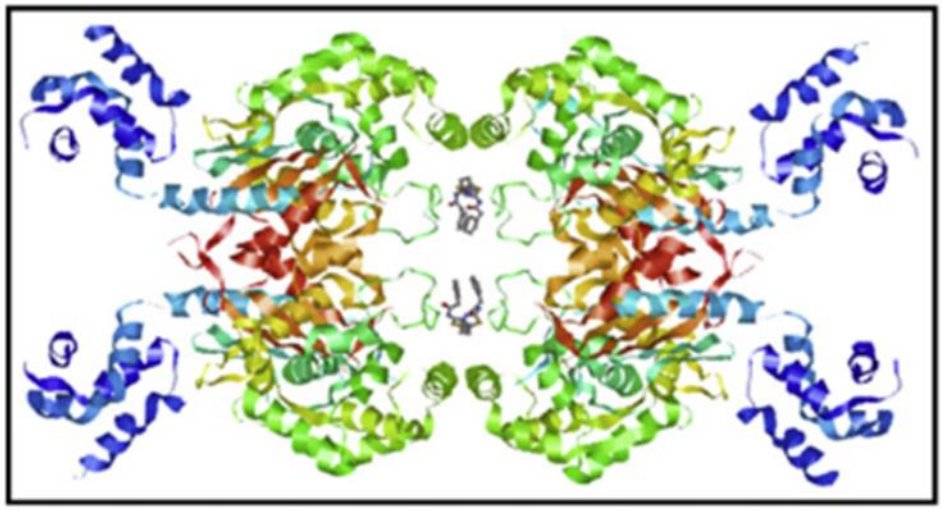
CB-839 A GLUTAMINASE INHIBITOR – LEAD CANDIDATE

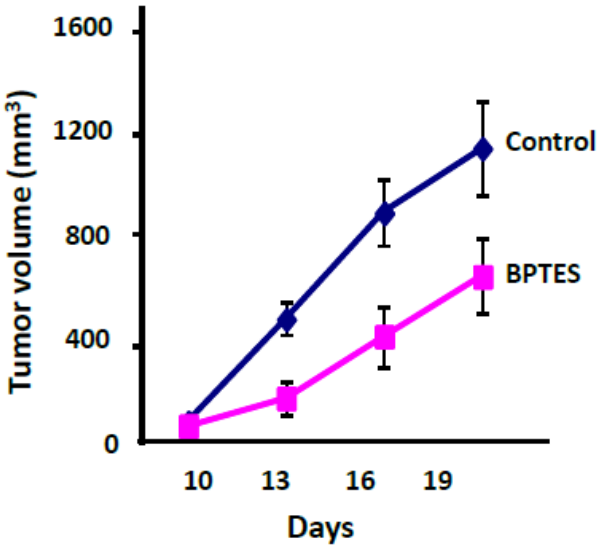
- CB-839 is an oral inhibitor of both splice variants (KGA and GAC) and the kidney and brain forms of the glutaminase encoded by the GLS1 gene.
- No activity against the liver form of the glutaminase, encoded by the GLS2 gene
- CB-839 inhibits glutaminase by binding to an allosteric site (distinct from the glutamine binding site) thereby stabilizing the inactive conformation (the dimer) and preventing the formation of the active conformation (the tetramer)
- Pre-clinically, CB-839 has shown anti-proliferative activity across numerous cancer cell types
- In addition, it has exhibited synergy with standard of care chemotherapeutic agents in TNBC and IMiDs in MM disease models
- In Feb. 2014, Calithera initiated three Phase I trials in various solid and liquid tumor types to assess the safety and tolerability of CB-839. The first trial CX-839-001 is a two part trial in solid tumors (TNBC, NSCLC, RCC [renal cell carcinoma] and mesothelioma), where part I is a dose escalation study. In part 2 dose expansion phase, the safety, pharmacokinetics, pharmcodynamics, biomarkers and tumor response will be evaluated. The other two trials, CX-839-002 in liquid tumors (including multiple myeloma, non-Hodgkin's lymphoma) and CX-839-003 in acute lymphocytic leukemia and acute myeloid leukemia) are also two part trials assessing the same criteria as CX-839-001 trial. Data from all the three trials are expected in mid: 2015.

IMiDs= Immunomodulatory drugs

Source: Company Reports

BIS-2-[5-PHENYLACETAMIDO-1,2,4-THIADIAZOL-2-YL] ETHYL SULFIDE (BPTES) HAS BEEN THE LEAD GLUTAMINASE INHIBITOR

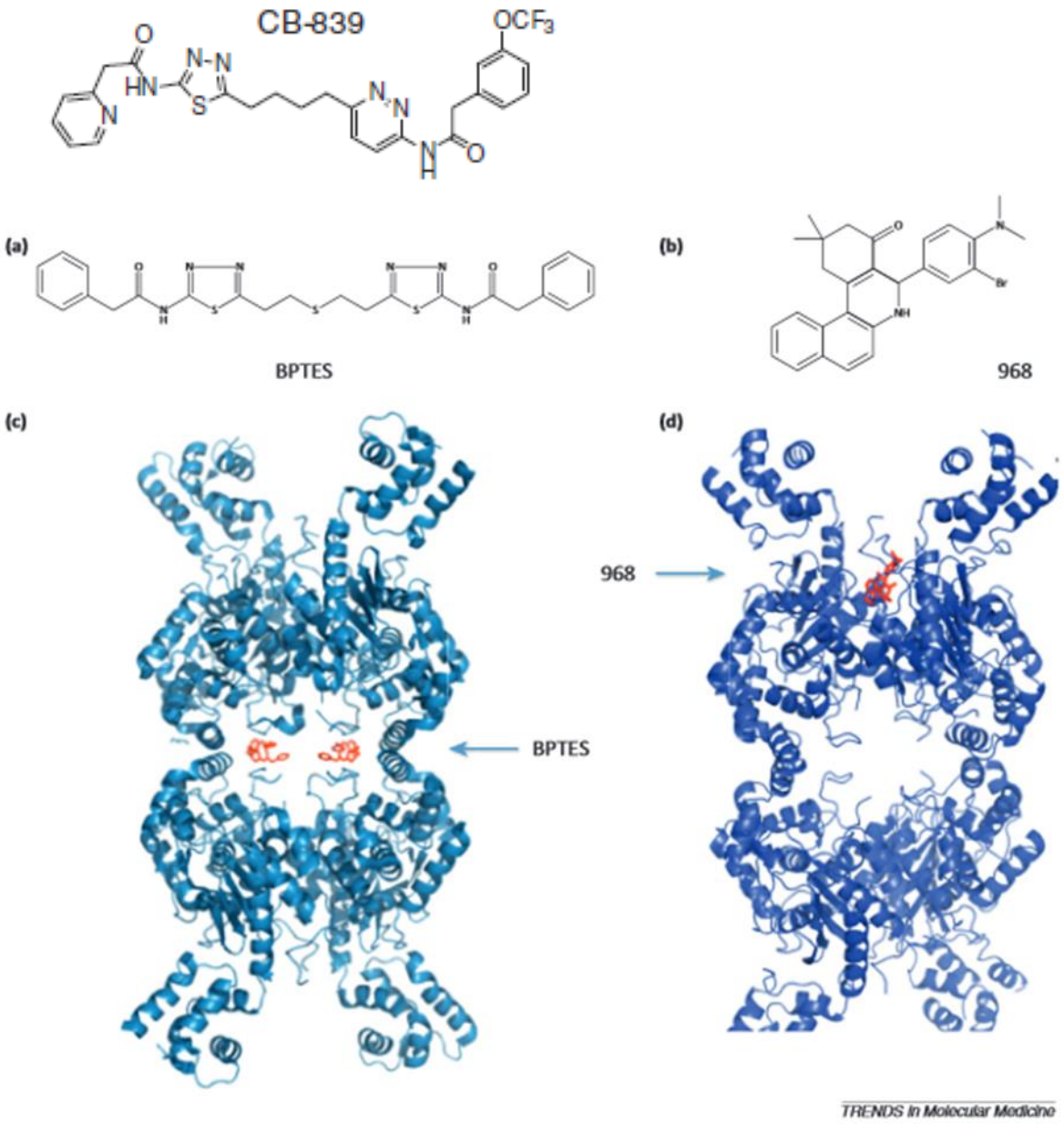




- BPTES is an allosteric glutaminase inhibitor active against both splice variants of the GLS gene, GAC and KGA
- The allosteric mechanism for BPTES (and BPTES analogs) inhibits glutaminase activity through the binding of two inhibitor molecules at the interface between a pair of homodimers
- Several studies have reported the antitumor activity for BPTES in lymphoma, breast, glioma, pancreatic, lung, and renal tumor types
- CALA and AGIO have developed analogs of BPTES for their anti-tumorigenic effects in various cancer types

Source: Seltzer et al., Cancer Research, 2010

DIFFERENT STRATEGIES FOR INHIBITING GLUTAMINASE INHIBITORS

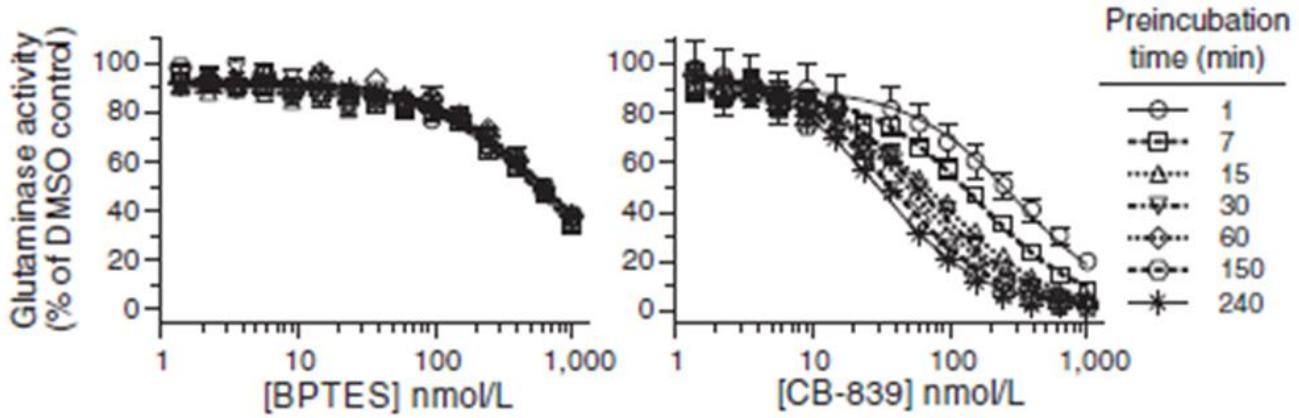


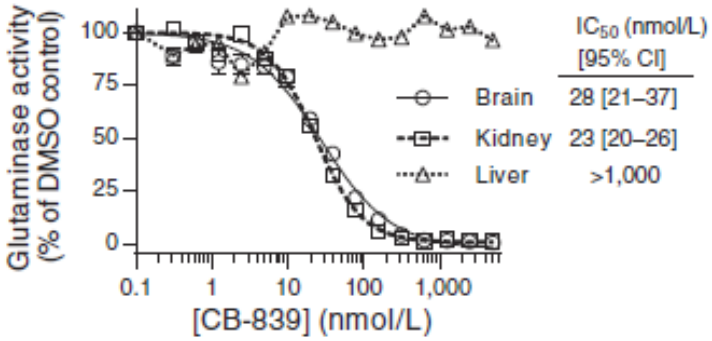
- CALA's CB-839 and AGIO's glutaminase inhibitors are analogs of BPTES. They bind to inactive dimers of glutaminase, which prevents the formation of active glutaminase tetramers
- Another compound 968, discovered at Cornell University, is an allosteric inhibitor of glutaminase that binds to the active form of the enzyme
- One key difference between the two glutaminase inhibitors BPTES (and BPTES analogs) and 968 is that BPTES can bind to glutaminase in all cells vs. 968 which preferentially binds to glutaminase in cancer cells

Source: Wang et al., Cancer cell, 2010

LEERINK

CB-839 IS A SPECIFIC GLUTAMINASE INHIBITOR THAT IS MORE POTENT THAN BPTES

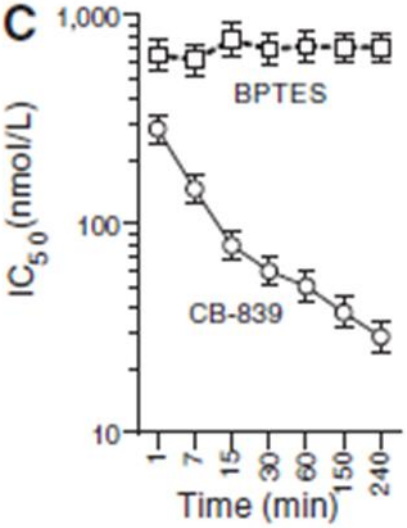


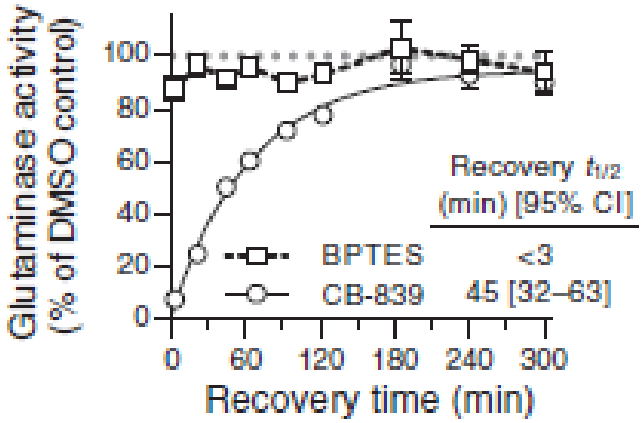


- Although CB-839 and BPTES have a similar allosteric binding mechanism and selectivity profile, CB-839 appears more potent than BPTES

Source: Gross et al (2014) Mol Cell Thera.

CB-839 BEHAVES DIFFERENTLY AS COMPARED TO BPTES





- Unlike BPTES, CB-839 potency is dependent on the incubation time
- After the withdrawal of CB-839, the recovery of glutaminase activity is much slower compared to BPTES
- In addition, CB-839 potency is independent of glutamine concentration, unlike BPTES which has greater potency with increasing glutamine concentration

Source: Gross et al (2014) Mol Cell Thera.

GLUTAMINASE COMPETITIVE LANDSCAPE

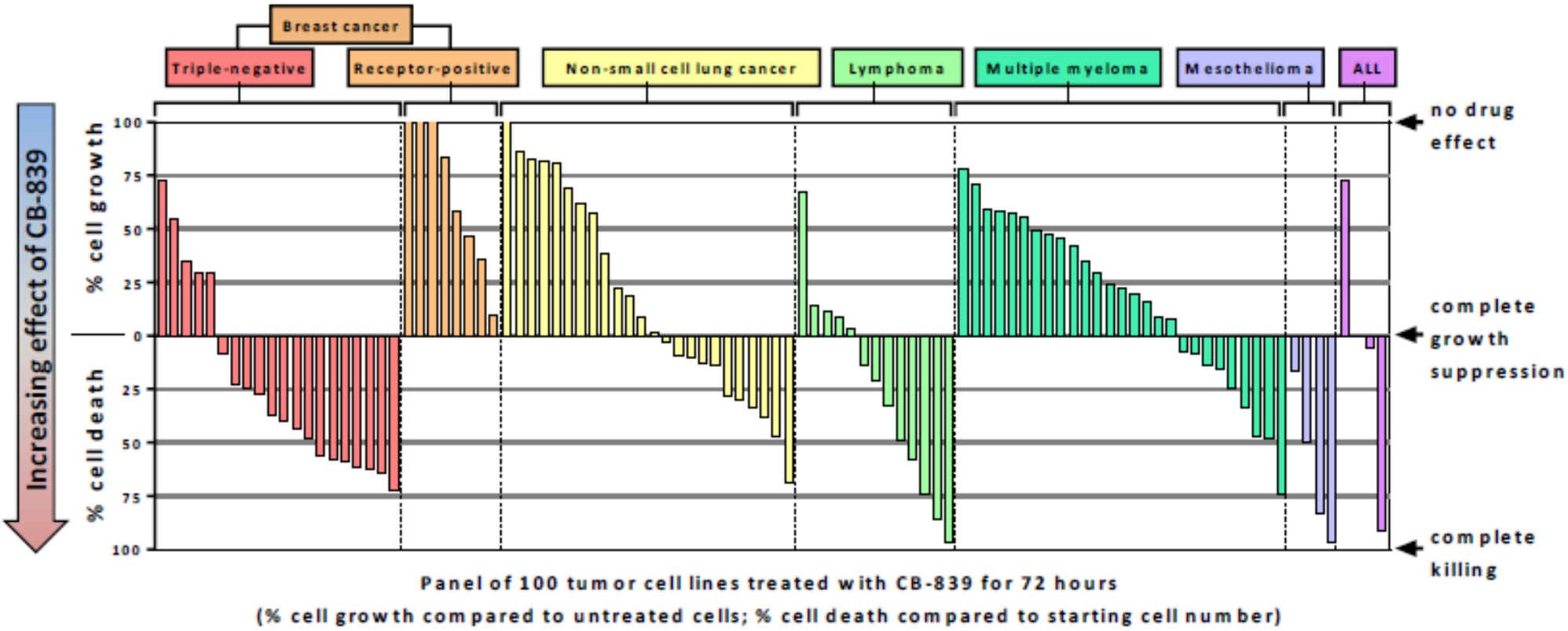
Company	Compound	Indication	Stage of development
Calithera	CB-839	TNBC, MM, NHL, ALL and AML	Phase I
Agios	inhibitor of GLS1	not known	Pre-clinical*
Johns Hopkins University	BPTES	pancreatic cancer/ Burkitt lymphoma	Pre-clinical**
Cornell University	968	breast cancer/ B-cell lymphoma	Pre-clinical**

Note: * not clear if it is under active development; ** appear to be laboratory compounds not being developed as drugs. Abbreviations: TNBC-triple-negative breast cancer, MM- multiple myeloma, NHL- non-Hodgkin's lymphoma, ALL-Acute lymphoblastic leukemia and AML- Acute myeloid leukemia

Source: Le et al., Cell , 2011 and Wang et al., Cancer cell, 2010

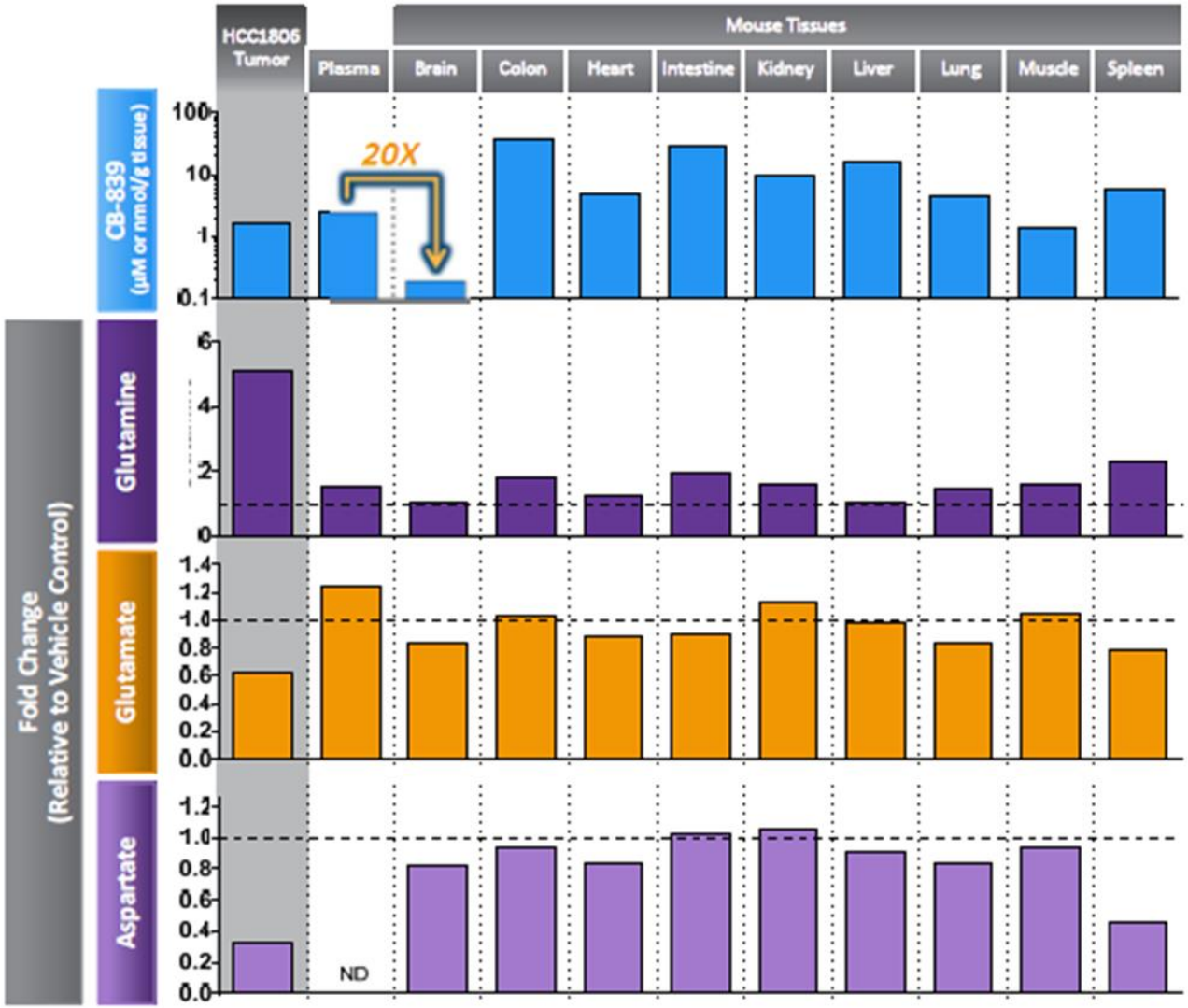
LEERINK

CB-839 KILLS AND SUPPRESSES PROLIFERATION OF CANCER CELLS OF MULTIPLE TYPES



Source: Company Reports

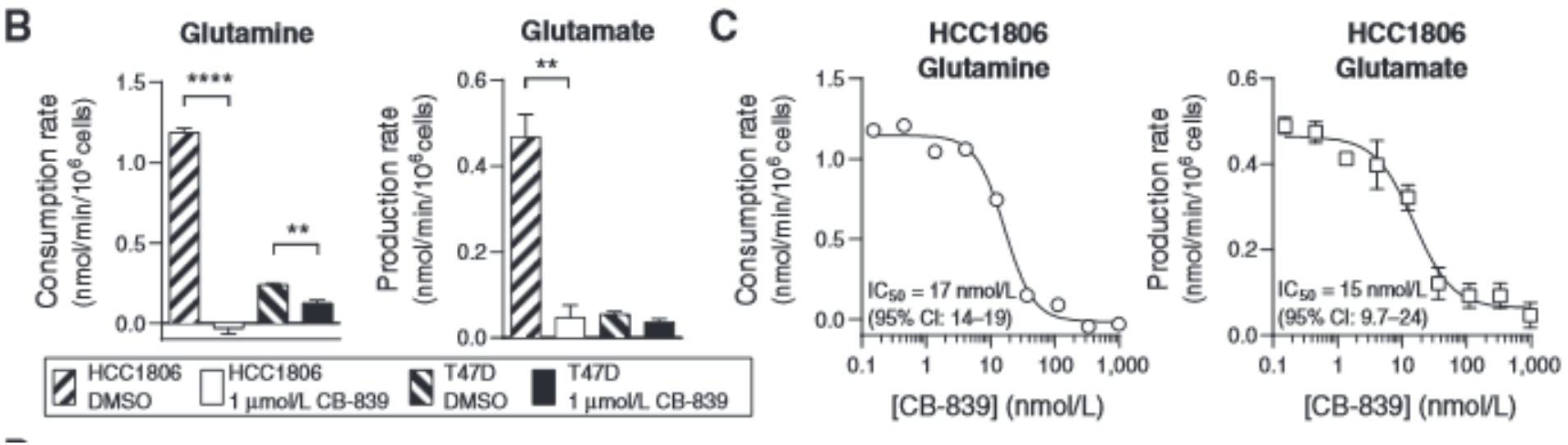
CB-839 HAS SIGNIFICANTLY REDUCED EXPOSURE IN THE BRAIN



- Except in the brain where exposure was >7-fold lower than tumor or other tissues.
- This may be desirable given the involvement of Gln/Glu in the brain
- Changes in tissue metabolites after a dose of CB-839 were the highest in HCC1806, TNBC cell line

Source: Company Reports

GLUTAMINE CONSUMPTION IS REDUCED UPON TREATMENT WITH CB-839 in TNBC CELL LINES

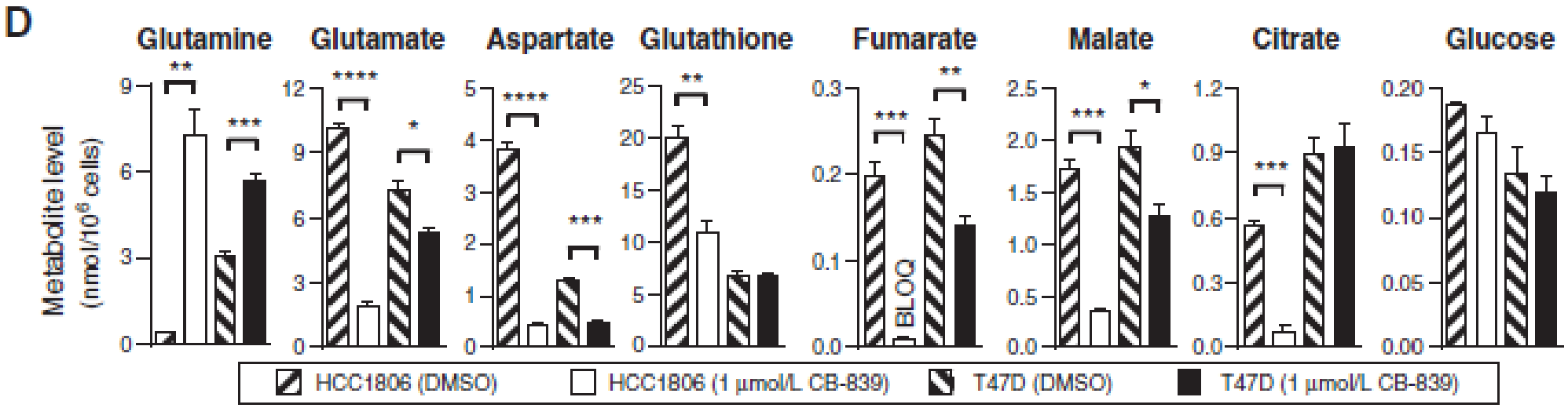


- CB-839 reduced the rates of glutamine consumption for both lines.
- The consumption rate exhibited by HCC1806 cells was completely inhibited by CB-839 demonstrating the absolute requirement of glutaminase activity vs. in the T47D cells suggesting that these cells are capable of metabolizing glutamine through glutaminase-independent pathways
- In addition, the glutamate production rates were reduced in HCC1806 cells after CB-839 treatment.

Source: Gross et al., Mol Cancer Ther; 13(4); 890–901. 2014

LEERINK

CB-839 REDUCED THE CONCENTRATION OF A NUMBER OF KEY METABOLITES DOWNSTREAM OF GLUTAMATE

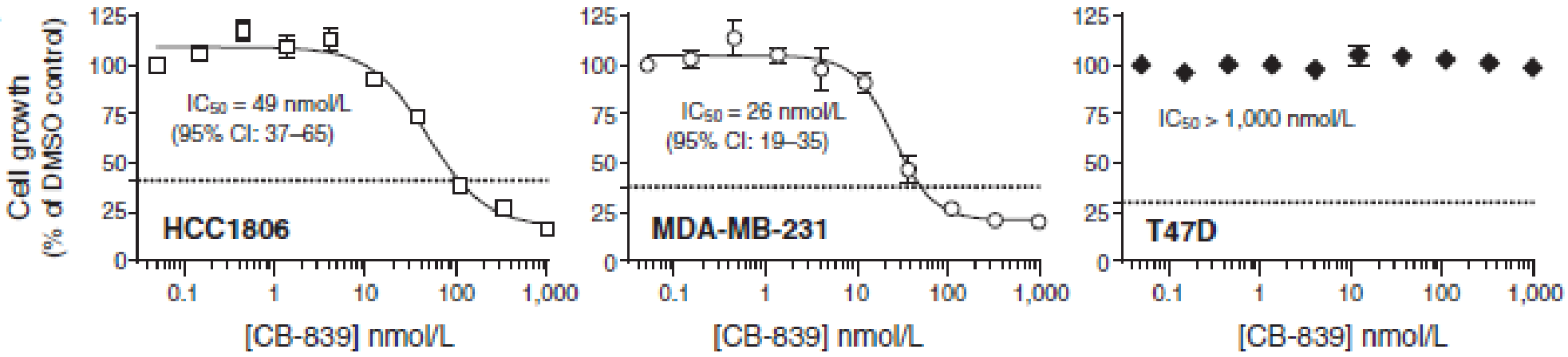


- Among the downstream metabolites downregulated by CB-839 were: aspartate, glutathione, and the TCA cycle intermediates fumarate, malate, and citrate)
- As expected no changes in the glucose levels were observed

Source: Gross et al., Mol Cancer Ther; 13(4); 890–901. 2014

CB-839 EXHIBITS ANTI-PROLIFERATIVE ACTIVITY IN TNBC CELL LINES

A



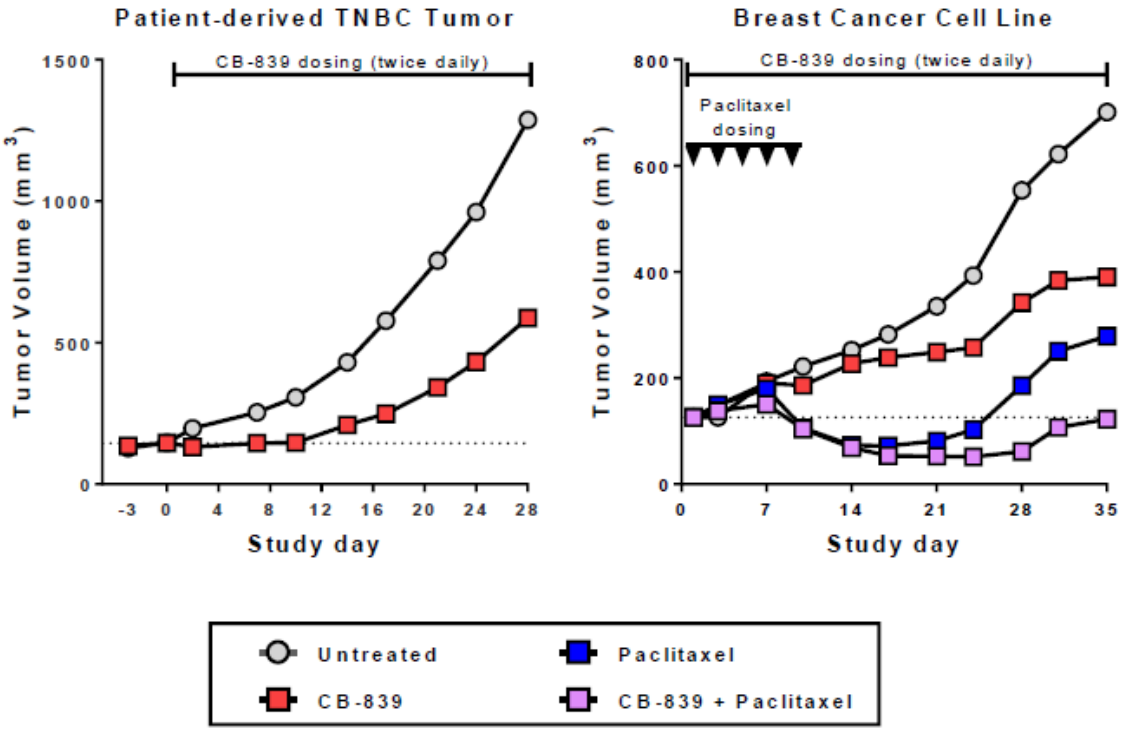
TNBC CELL LINES

ER+/ HER2- CELL LINE

- CB-839 treatment had a potent effect on the proliferation of the two TNBC cell lines (IC_{50} of 20–55 nmol/L associated with cell loss at >100 nmol/L) but no effect on the viability of T47D cells, which is a estrogen receptor positive cell line.
- These results suggest that CB-839 specifically targets TNBC cell lines

Source: Gross et al., Mol Cancer Ther; 13(4); 890–901. 2014

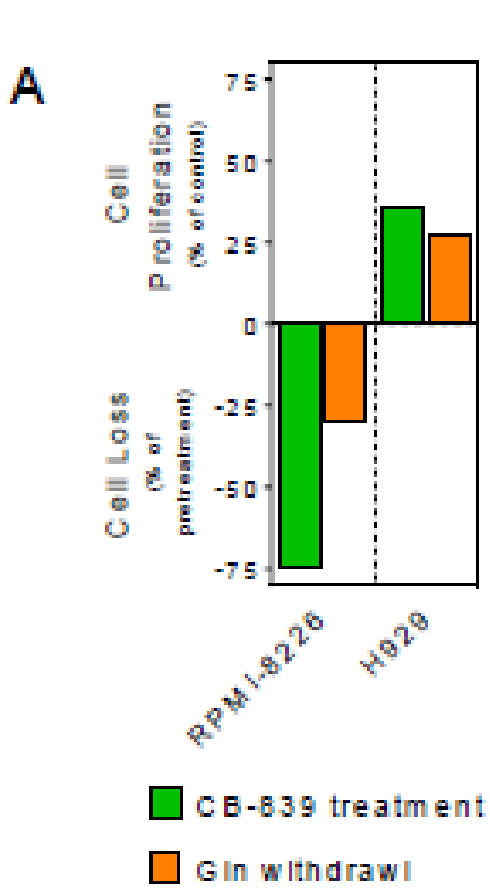
CB-839 EXHIBITS ACTIVITY IN TNBC BOTH AS A SINGLE AGENT AND IN COMBINATION WITH STANDARD OF CARE

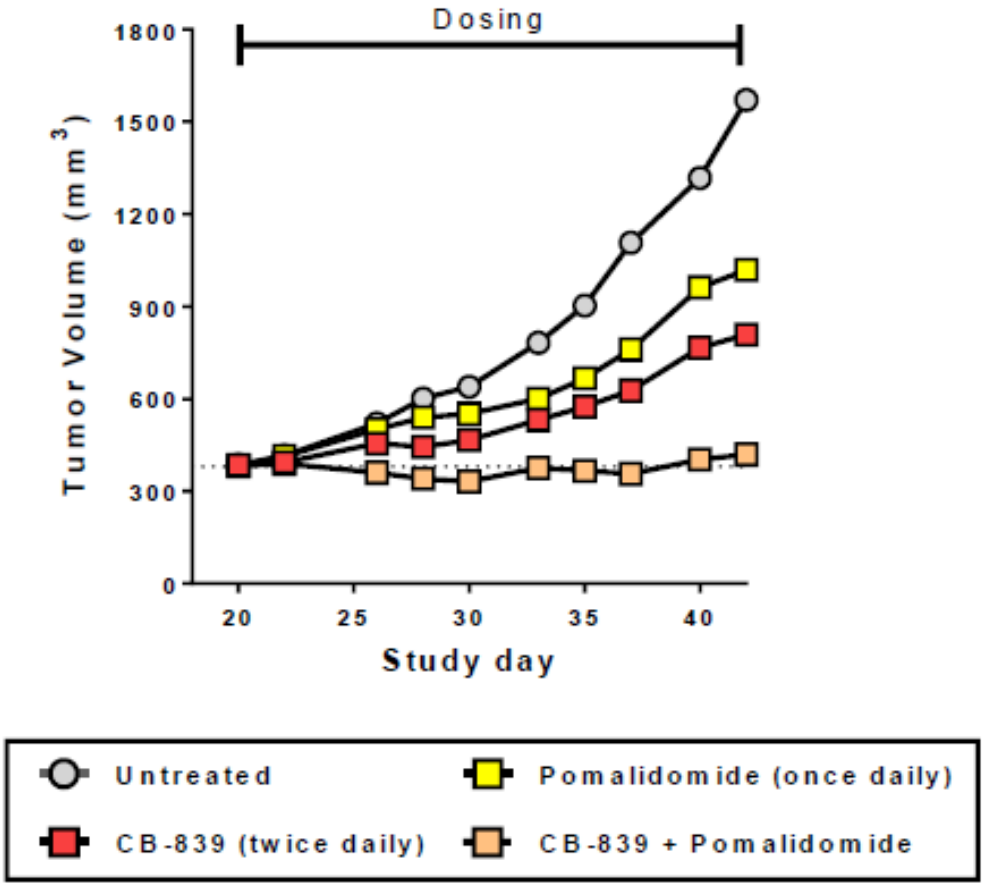


- CB-839 as a single agent suppressed tumor growth by 61% relative to vehicle control
- In the JIMT-1 xenograft model, the antitumor efficacy was evaluated by treating established tumors with CB-839 both as a single agent and in combination with paclitaxel (standard-of-care chemotherapeutic agent).
- Combination of CB-839 with paclitaxel largely suppressed the regrowth of the tumors resulting in a tumor growth inhibition (TGI) relative to vehicle control of 100% at the end of study

Source: Gross et al., Mol Cancer Ther; 13(4); 890–901. 2014 and Company Reports

CB-839 ACTS SYNERGISTICALLY WITH IMMUNOMODULATORY AGENTS IN MM MODELS





- RPMI-8266 multiple myeloma cell line but not H929 multiple myeloma cell line is sensitive to CB-839 treatment and glutamine withdrawal
- In myeloma cells in culture, CB-839 was synergistic with lenalidomide (Revlimid) and pomalidomide, two approved immunomodulatory drugs used to treat myeloma.

Source: Tareen et al., AACR 2014, Yang wt al., Nat. Biotechnol. 2008

CLINICAL DEVELOPMENT STRATEGY FOR CB-839

Indication	Treatment	Rationale
Triple-negative Breast Cancer (TNBC)	• Single agent • Combo with Paclitaxel	• Large market • Unmet need • Potential CB-839 biomarker identified
Multiple Myeloma (MM)	• Single agent • Combo with Pomalidomide/Dex	• Large market • Preclinical synergy with standard of care drugs • Potential CB-839 biomarker identified
Rare Cancers (with TCA cycle driver mutations)	• Single agent	• Ultra-orphan indication(s) • Genetic identification of patients • No approved therapies • Potential for rapid approval

- **Plans to evaluate CB-839 as a single agent and in combination with existing treatment options**

TCA cycle= tricarboxylic acid cycle
Source: Company Reports

CB-839 PHASE I PRELIMINARY EFFICACY

- **Dose escalation** in all three Phase 1 trials is ongoing and as of Jul. 25, 2014, **24** patients were enrolled
- Patients enrolled in these trials have relapsed and are refractory to all approved therapies and have received on average ~5 prior lines therapy.
- Of the 24 patients enrolled, 5 were colorectal cancer patients, 5 were TNBC patients, 2 were RCC patients and 1 each were cholangiocarcinoma, sarcoma, and mesothelioma patients. In the liquid tumor trial, 3 MM patients enrolled. In the third Phase I trial, 5 AML patients and 1 ALL patient.
- Of these 24 patients, the best response as of July 25, 2014 was **stable disease (n=4)**, observed in 1 mesothelioma patient, 2 MM patients, and 1 TNBC patient.
- 1 mesothelioma patient's and 2 multiple myeloma patients' disease progressed after more than five cycles of dosing with CB-839. The TNBC patient was actively progressing disease at the time of enrollment and is continuing treatment with CB-839 with no ongoing adverse events (AEs) at 250 mg TID, showing a 13% decrease in tumor size at the end of three cycles of treatment with CB-839.

Source: Company Reports

PRELIMINARY CLINICAL SAFETY OF CB-839

- As of July 25, 2014, 21 Grade 1 adverse events (AEs), 2 Grade 2 AEs, and 2 Grade 3 AEs have been reported and are potentially related to CB-839
- The most common Grade 1 AEs were **nausea**, **vomiting,** and **fatigue**. They were observed across all three trials.
- Grade 2 **anemia** was observed in 1 patient with MM who already had Grade 1 anemia at baseline. Grade 2 worsening **fatigue** occurred also in 1 MM patient.
- Grade 3 **reduced white blood cell count** occurred in 1 RCC patient who had Grade 2 reduced white blood cell count at baseline. A Grade 3 **increase in creatinine** was seen in another colorectal cancer patient receiving 250 mg TID who had preexisting diabetic nephropathy and severe proteinuria.
- Increase of creatinine levels at 250 mg was noted as a dose limiting toxicity (DLT), as the patient required hospitalization as a precaution and for hydration. After CB-839 discontinuation and hydration, the patient's creatinine levels returned to normal.
- There have **been no further DLTs, and the trial has proceeded to the next higher dose level of 400 mg TID. So far no other drug-related** AEs due to a creatinine increase in patients have been reported.

Source: Company Reports

PLANS TO EVALUATE BIOMARKERS FOR BETTER IDENTIFICATION OF PATIENT POPULATIONS

- Calithera plans to evaluate numerous biomarkers during the Phase I clinical trials, potentially facilitating the identification of patients most likely to respond upon treatment with CB-839

- These biomarker analyses will measure the activity of glutaminase in response to CB-839 in TNBC and other tumor cell lines. Immunohistochemistry will be used for evaluating glutaminase expression levels in newly biopsied and old tumor samples from all patients in Phase 1 trials

- In addition, the expression of approximately 40 genes related to glutamine uptake and metabolism will be assessed by measuring mRNA levels

- Advanced imaging technologies such as positron emission tomography (PET) metabolic imaging will be used to identify responsive patients in the Phase I studies

Source: Company Reports

Glutaminase as a Target: Not Yet Fully Validated – Patient Selection and Combination Strategies May Be Important

GLUTAMINASE IS CRITICAL FOR THE EXPANSION OF CANCER CELLS

- Glutamine plays an important role in cell growth and energy metabolism
- Glutaminolysis is a two step process (i) - conversion of glutamine to glutamate by glutaminase (GLS)

  (ii) - subsequent conversion of glutamate to α-ketoglutarate (α-KG)

- GLS can be expressed as isoforms GLS1 (kidney glutaminase) and GLS2 (liver glutaminase); GLS1 can be expressed as variants GAC and KGA. GAC is the predominant GLS1 variant in Non-small cell lung cancer (NSCLC)
- Removal of glutamine leads to a substantial reduction in cell growth and can also induce cell death in glutamine dependent cells
- Cancer cells exhibit higher levels of glutaminase mRNA compared to normal cells
- Pre-clinical studies have identified glutaminase for being critical in facilitating the utilization of glutamine in cancer cells.
- However, it is a novel target that still requires clinical validation for its potential anti-tumoregenic activity

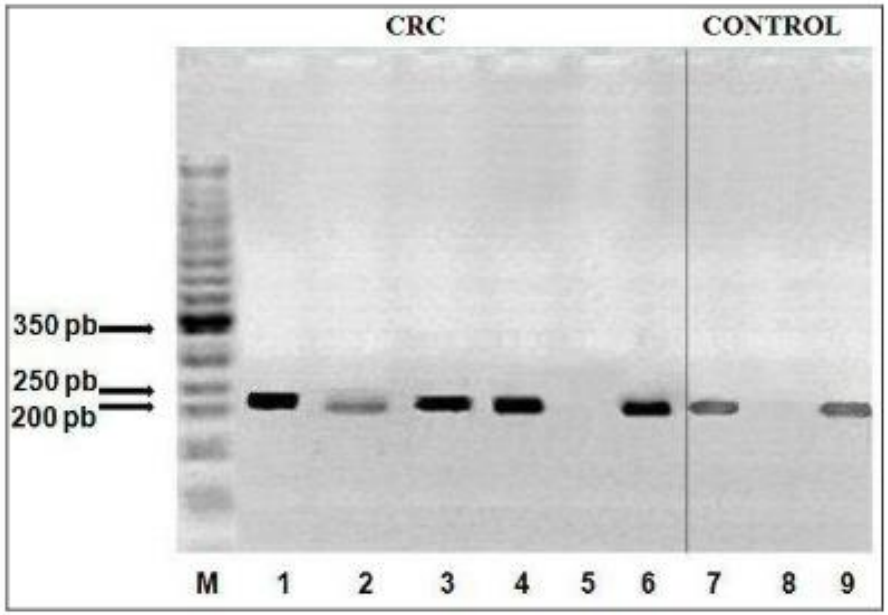
Source: Bronte et al., Nat. Rev. Imm., 2005

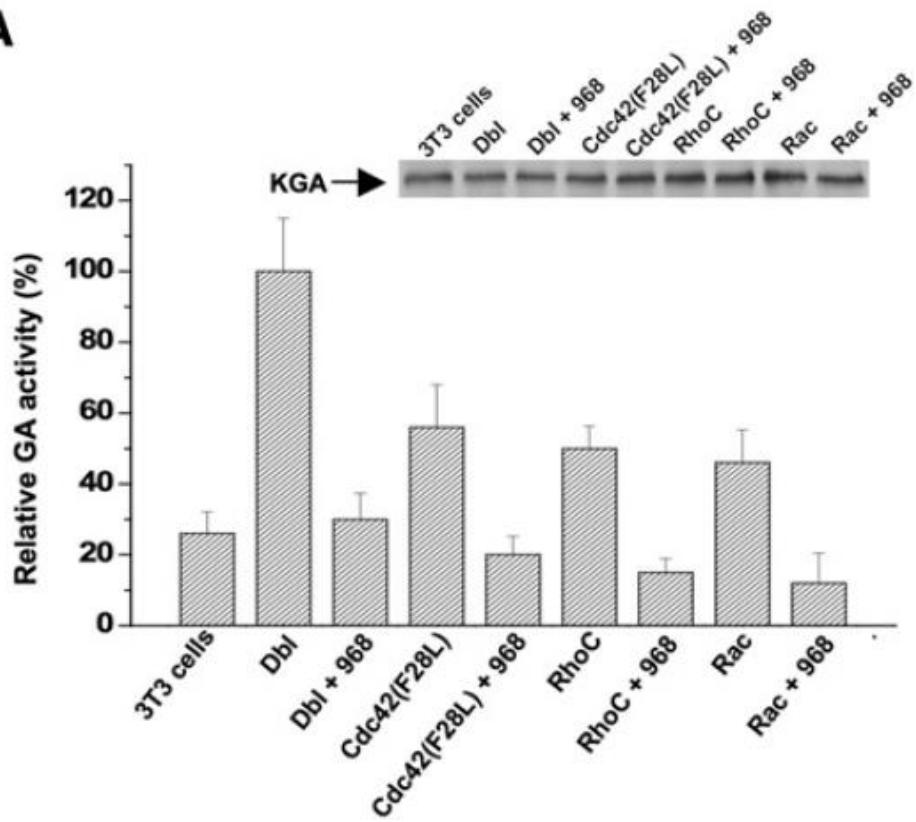
FEEDBACK FROM MEDACORP CANCER BIOLOGY SPECIALISTS ON GLUTAMINASE AS A TARGET

LEERINK

- MEDACorp specialists had mixed opinions on glutaminase as a target. Most of the MEDACorp cancer biologists we spoke to believe glutaminase is a good target or at least should be explored, while one of them was cautious citing the lack of genetic association (i.e., cancer-associated mutations) and lack of effectiveness of a glutaminase inhibitor in some preclinical models.
- One question raised is whether a glutaminase inhibitor could be cytotoxic to tumor cells or just cytostatic as tumor cells could alter its metabolism, go to a low-growth state and therefore become no longer dependent on glutaminase. We note that experimentally CB-839 is cytotoxic at least to some tumor cells.
- The MEDACorp cancer biologists we spoke to agreed that the susceptibility of a glutaminase inhibitor is highly dependent on the cell type. There does not yet appear to be a generally agreed-upon strategy for patient selection although the presence of some driver mutations upstream of the metabolic pathways such as ras and myc was noted to be a potential patient selection scheme.
- They argued for rational combinations and believed that synergistic combinations would effectively kill tumor cells.

GLUTAMINASE ACTIVITY IS ELEVATED IN CANCER CELLS

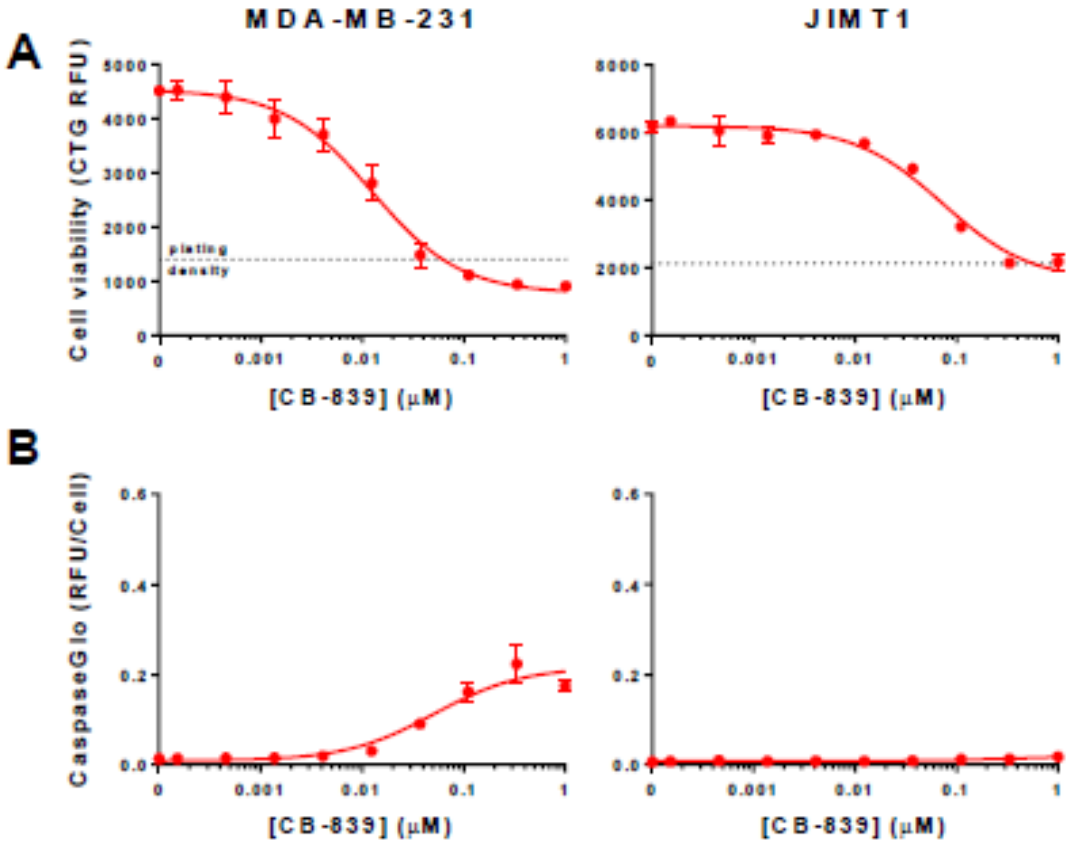




- Glutaminase isoforms are more highly expressed in primary human colorectal cancer cells compared to normal human cells
- Glutaminase activity can be lowered using a glutaminase inhibitor (968)

Source: Otto-Ślusarczyk et al., JMB (year unknown) and Wang et al., Cancer Cell, 2010

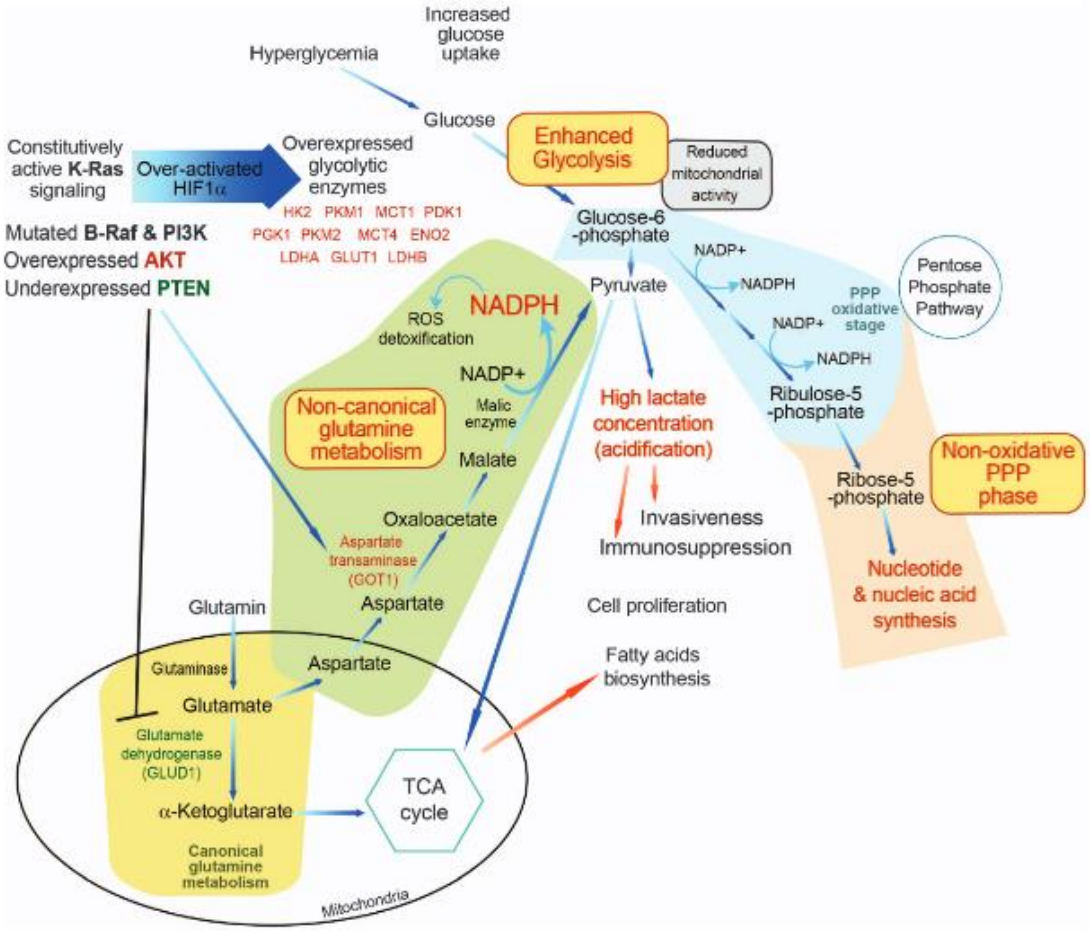
CB-839 INDUCES APOPTOSIS AND GROWTH ARREST



- Pre-clinically, CB-839 causes both cell cycle arrest and apoptotic cell death in triple-negative cancer cell lines, MDA-MB-231, and JIMT1 after treatment with CB-839 for 72 hours
- Changes in cell proliferation were measured using a luminescent cell viability assay, Celltiter-Glo
- Cell death via apoptosis was measured using caspase 3/7

Source: : Demo et al., AACR 2013, #5604

MUTATIONS IN ONCOGENES ALTER METABOLIC MACHINERY OF TUMOR CELLS AND MAY SERVE AS POTENTIAL DIAGNOSTIC MARKERS

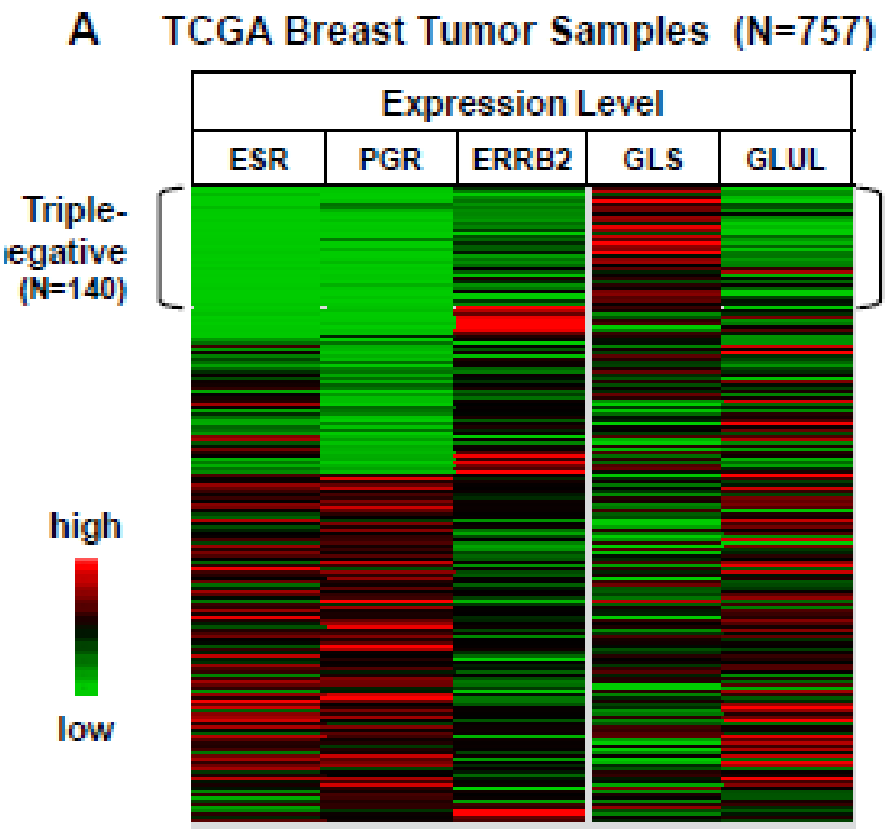


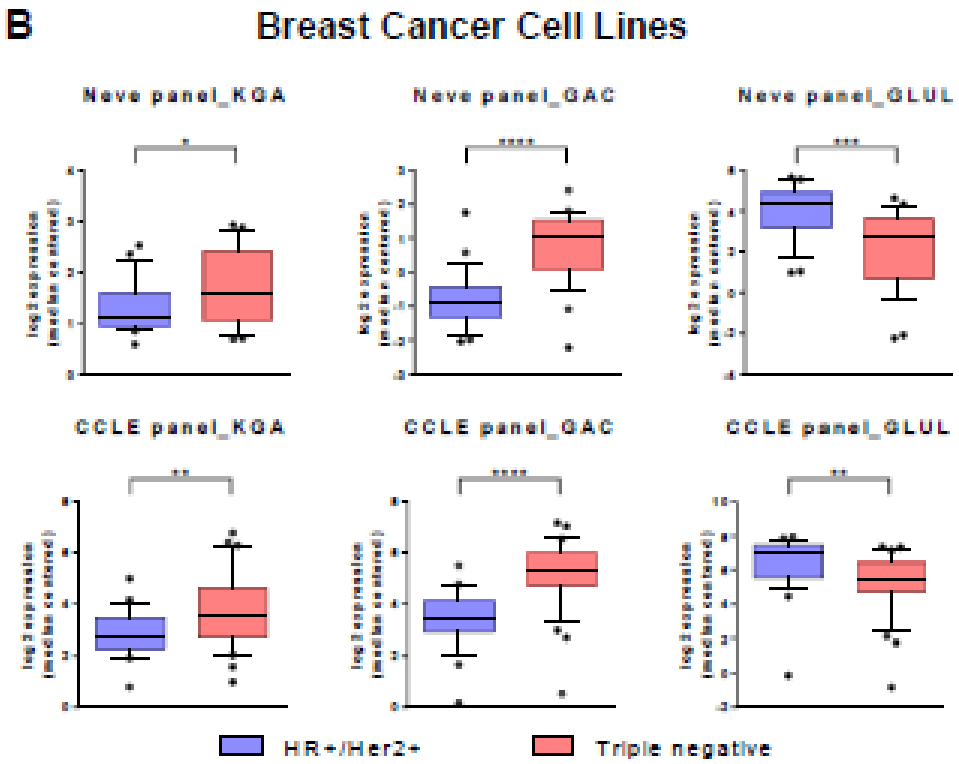
- Given the complex nature of metabolic pathways and their possible alterations in tumor cells, a single approach is unlikely to successfully treat different metabolic aberrations in tumor cells
- In order to specifically target tumors most likely to respond to a therapy, patients must be pre-screened for the specific metabolic aberration
- Furthermore, KOLs we spoke with believe that therapies directed against glutamine metabolism will be most effective in tumors that display glutamine dependence
- Studies have shown that oncogenes such as MYC, PI3K, RAS, and AKT alter the metabolism of cancer cells to aerobic glycolysis and glutamine dependence
- Given this, these oncogenes can be used as biomarkers for pre-screening patients most likely to have high levels of glutaminase

Source: Blum et al., Cell Death and Disease 2014

LEERINK

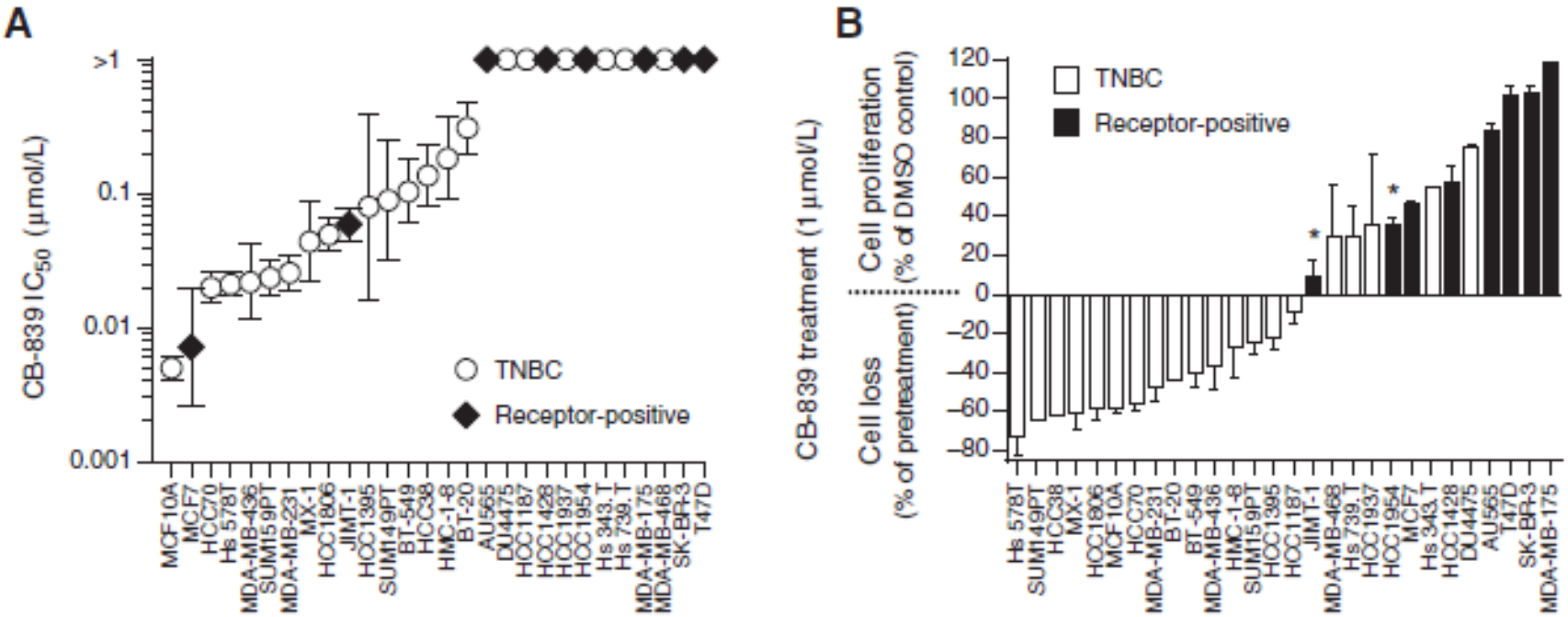
TRIPLE-NEGATIVE BREAST CANCER HAS HIGH GLUTAMINASE EXPRESSION RELATIVE TO RECEPTOR POSITIVE BREAST CANCER





Source: Demo et al., AACR 2013, #5604

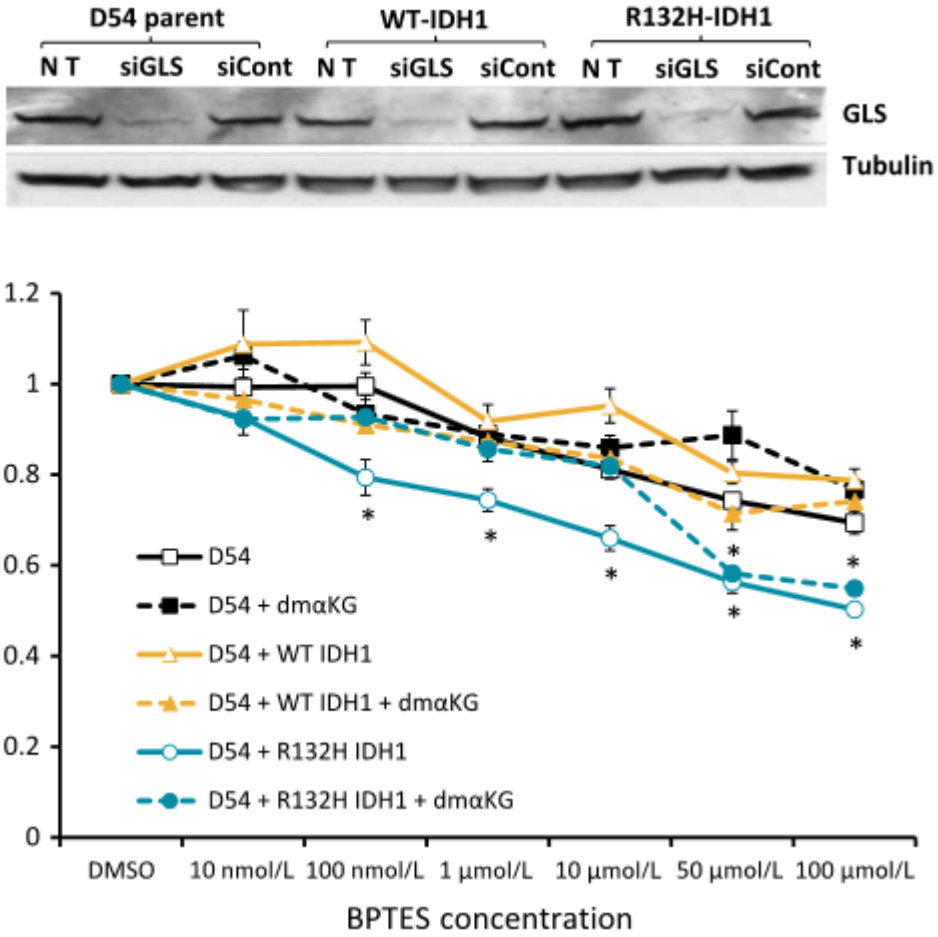
CB-839 APPEARS TO BE ESPECIALLY ACTIVE IN TRIPLE-NEGATIVE BREAST CANCER



- Anti-proliferative activity of CB-839 was evaluated in 28 breast cancer cell lines(20TNBC, 4 ER+/HER2,and 4 ER-/HER2+)
- Potent anti-proliferative IC50 values for CB-839 (2–300 nmol/L) were observed in majority of TNBC cell lines compared to most receptor-positive breast cancer lines which had an IC50 > 1 mmol/L, with the exception of two receptor positive cell lines
- Similarly, the TNBC cell lines also showed greater cell loss when compared to receptor positive cell lines following treatment with 1 mmol/L CB-839 for 72 hours
- These experiments suggest that TNBC is more sensitive to CB-389 treatment compared to receptor positive breast cancer cell lines

Source: Gross et al., Mol Cancer Ther; 13(4); 890–901. 2014

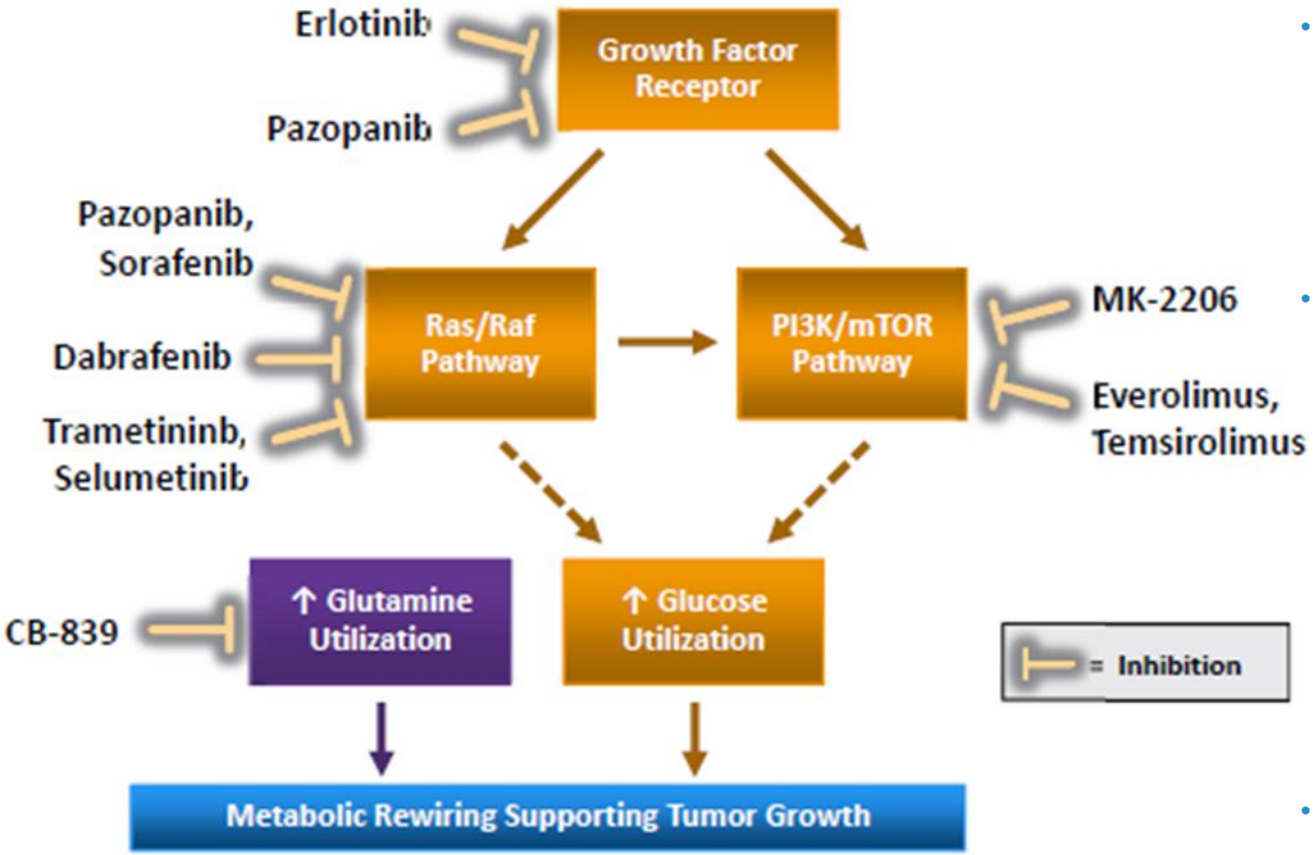
GLUTAMINASE INHIBITORS HAVE SHOWN ACTIVITY IN CELLS WITH TCA CYCLE MUTATIONS



- IT has also been shown that inhibition of GLS by siRNA (short interfering RNA) slows growth of cancer cells with an isocitrate dehydrogenase 1 (IDH1) mutation.

Source: Seltzer et al., Cancer Research, 2010

COMBINATION STRATEGIES COULD IMPROVE THE EFFICACY OF GLUTAMINASE INHIBITORS



- Potential drugs that can be combined with CB-839 for the treatment of RCC, NSCLC, sarcoma, and melanoma
- KOLs we spoke with believe that CB-839 could potentially be more effective if combined with the right compound, as in their opinion CB-839 is most likely to weaken the cell via glutamine starvation and another agent may be required to kill the tumor cells
- Given the glutaminase inhibitor mechanism of action, its combination with DNA metabolites that are cytotoxic and cause redox stress is likely to exhibit synergy

Source: Hudis et al., Oncologist 2011

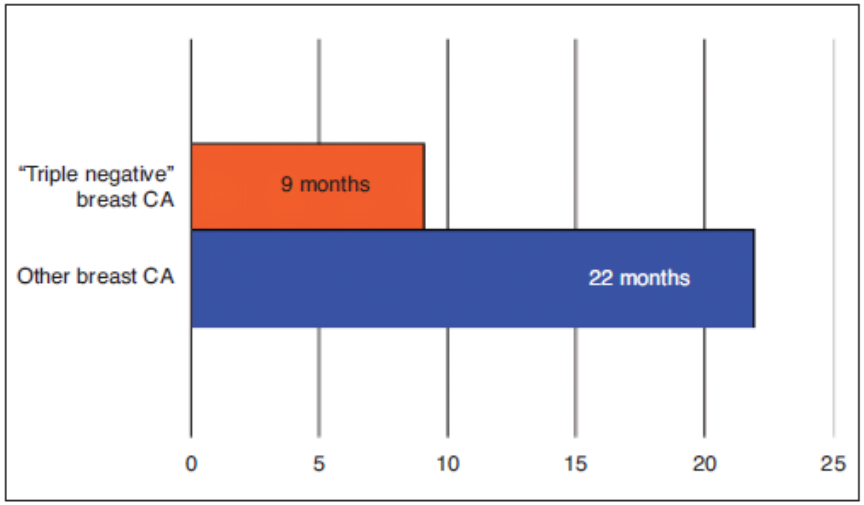
Background Triple Negative Breast Cancer and Multiple Myeloma

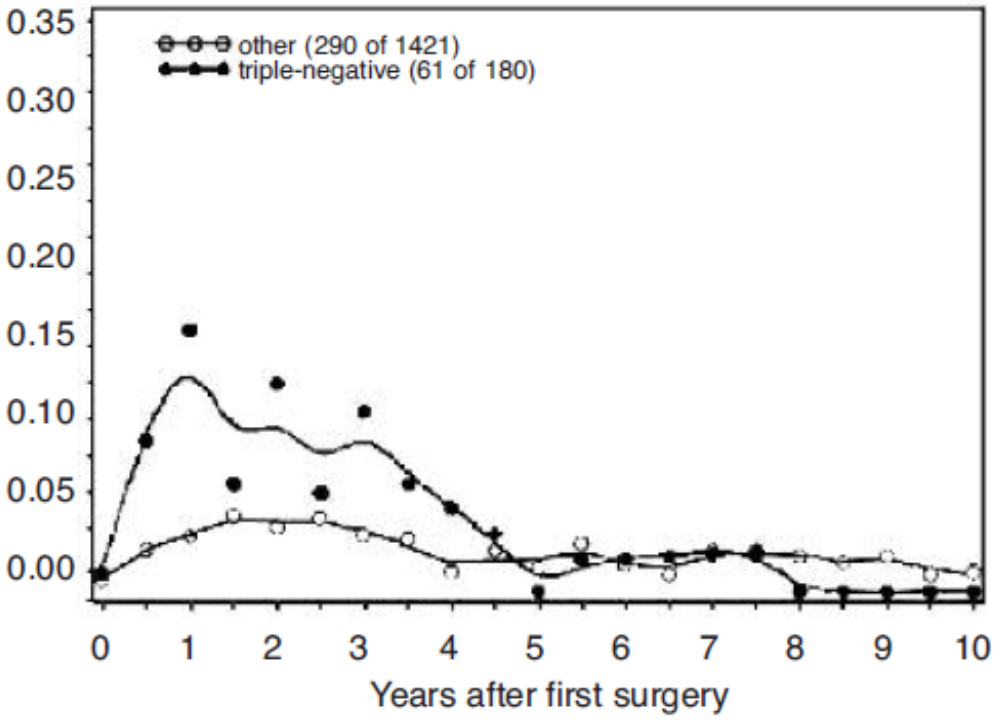
TRIPLE-NEGATIVE BREAST CANCER (TNBC)

- The types of breast cancers that do not express the estrogen receptor (ER), progesterone receptor (PR,) and Her2 genes
- According to the American Cancer Society statistics over 230,000 women will be diagnosed with invasive forms of breast cancer in the US and nearly 40,000 will die from it in 2014
- It is estimated that ~10-20% of the newly diagnosed breast cancers are of the triple-negative subtype
- Epidemiology studies show higher rates of TNBC in younger woman that may express the BRCA1 gene
- Current treatments for triple-negative disease include anthracyclines, taxanes, ixabepilone, platinum agents, and biologics
- Despite the development of therapies in other breast cancer sub-types, TNBC still remains very challenging to treat as it lacks adequate treatment options
- Overall, TNBC is difficult to treat and represents a large unmet need for effective targeted therapies

Source: Hudis et al., Oncologist 2011

TRIPLE-NEGATIVE BREAST CANCER (TNBC) HAS A HIGHER PROBABILITY OF RELAPSE AFTER TREATMENT AND SURGERY





- TNBC patients survive approximately only 9 months after the recurrence of their disease vs. other breast cancer patients that can live up to 22 months
- TNBC patients have an increased likelihood of distant recurrence and death with 5 years of diagnosis

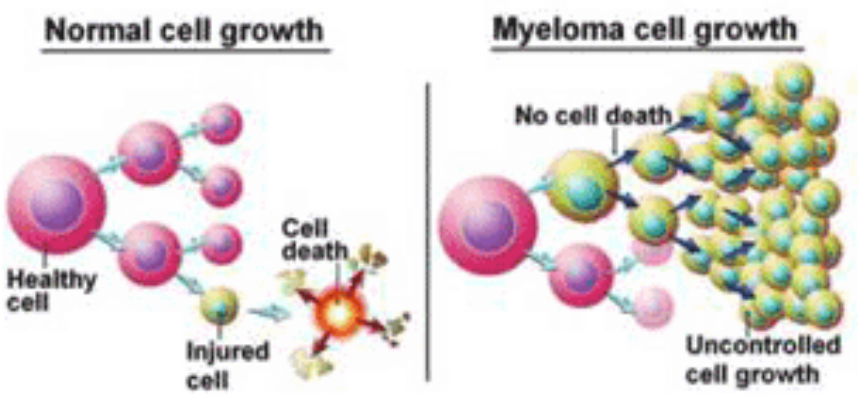
Source: Rastelli et al., Tumori 2010

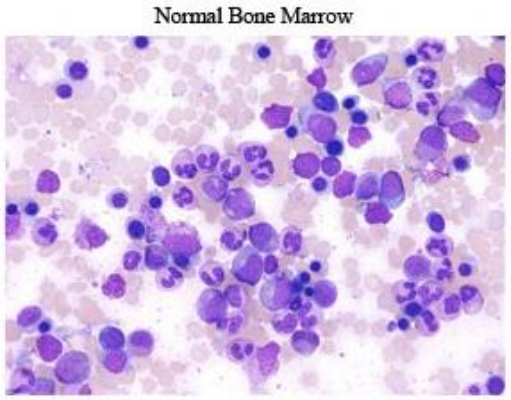
OTHER TARGETS FOR TRIPLE-NEGATIVE BREAST CANCER

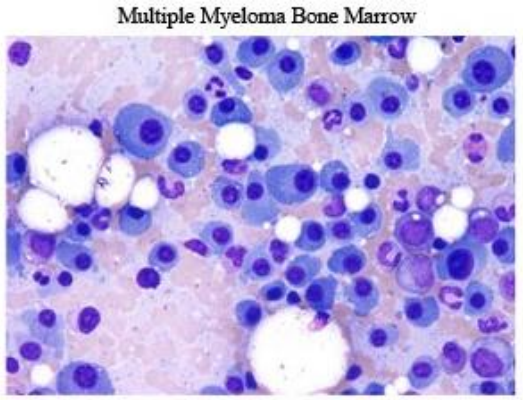
Target	Agent/approach	Initial outcomes
DNA repair pathways	Poly(ADP-ribose) polymerase inhibitors (BSI-201, olaparib, AG014699, ABT-888), trabectedin	
Vascular endothelial growth factor receptor	Sunitinib	Overall response rate = 15% (Burstein et al. [33])
Angiogenesis	Endo TAG-1, metronomic chemotherapy	
Src kinase	Dasatinib	Clinical benefit rate = 9.3% (Finn et al. [34])
Checkpoint kinase 1	UCN-01	
mTOR	RAD001, everolimus, temsirolimus	
Androgen receptor	Bicalutamide	
TRAIL	Lexatumumab	
TGF-beta	GC1008, AP 12009, LY2157299	
PDGFR, c-KIT	Imatinib	

Source: Biomedtracker, and company reports

MULTIPLE MYELOMA





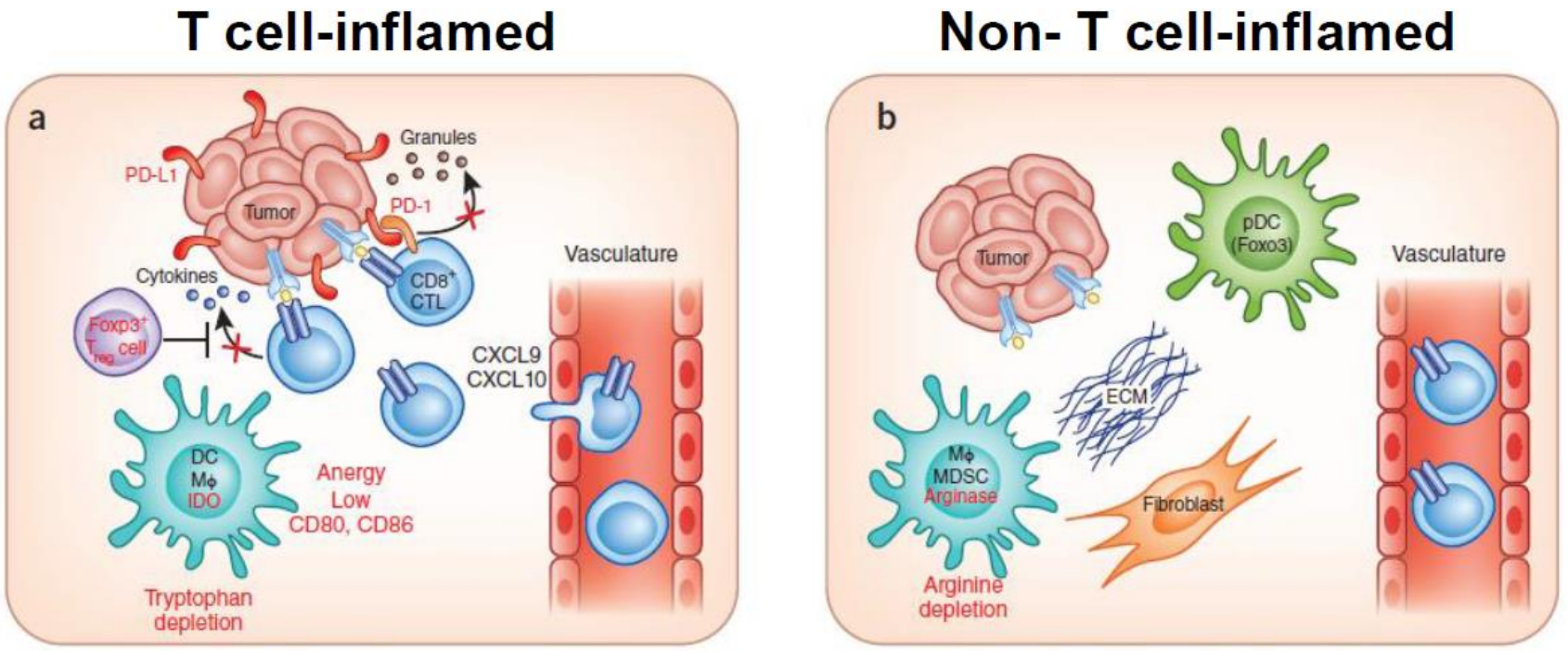


- Multiple Myeloma is a hematological malignancy caused by the proliferation of monoclonal plasma cells in the bone marrow
- The median age at diagnosis is 65-74 years and according the American Cancer Society there will be ~24,050 new cases of myeloma diagnosed in the US in 2014
- The current treatment paradigm for MM includes chemotherapy or a combination of drugs that includes bortezomib, thalidomide or lenalidomide and dexamethasone

Source: Biomedtracker, and company reports

Tumor Immunology Program

IMMUNOBIOLOGY OF T CELLS IN INFLAMED AND NON-INFLAMED TUMORS

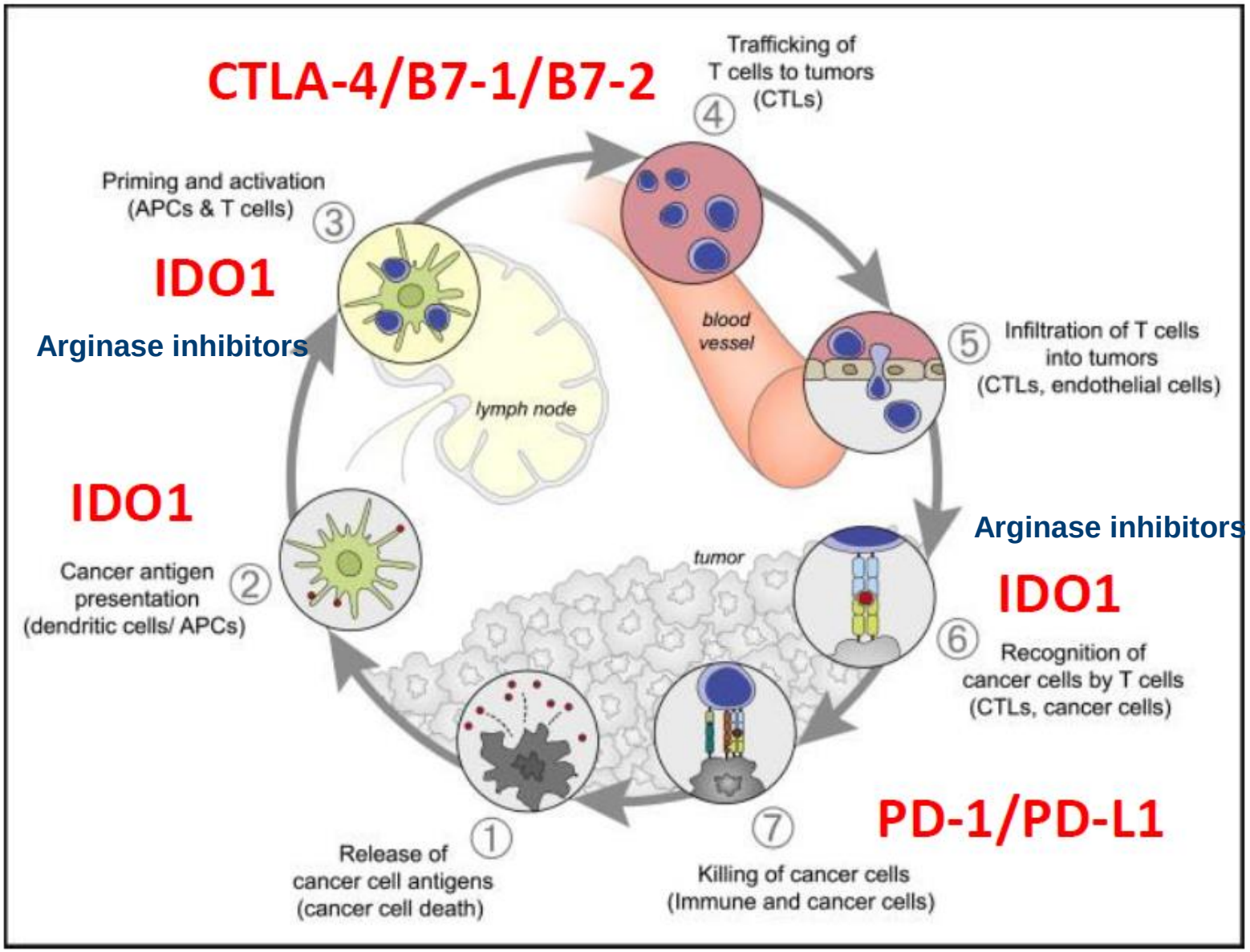


- Majority of immunotherapy responders have inflamed T cells
- In non-T cell-inflamed tumors, there is a lack of T cell infiltration but also minimal presence of defined immune inhibitory pathways, and as a result these tumors evade the immune system
- However, now there is some evidence that this lack of T cell infiltration could be in part a result of T cell anergy
- Inhibition of an enzyme, indoleamine-2,3-dioxygenase (IDO) that leads to the depletion of tryptophan (an amino acid) can rescue this T cell dysfunction

Source: Bronte et al., Nat. Rev. Imm., 2005

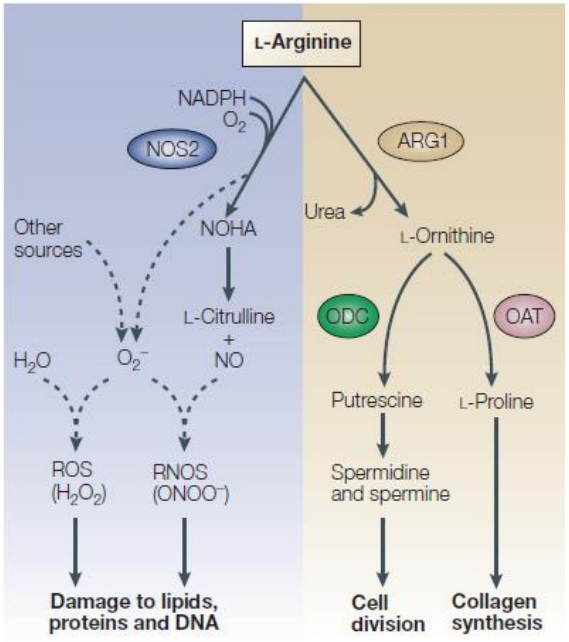
LEERINK

POTENTIAL PATHWAYS THAT TUMOR IMMUNOLOGY ENZYMES AND CHECKPOINT INHIBITORS MAY ALTER



Source: Bronte et al., Nat. Rev. Imm., 2005

L-ARGININE PLAYS A ROLE IN CELL DIVISION AND DIFFERENTIATION

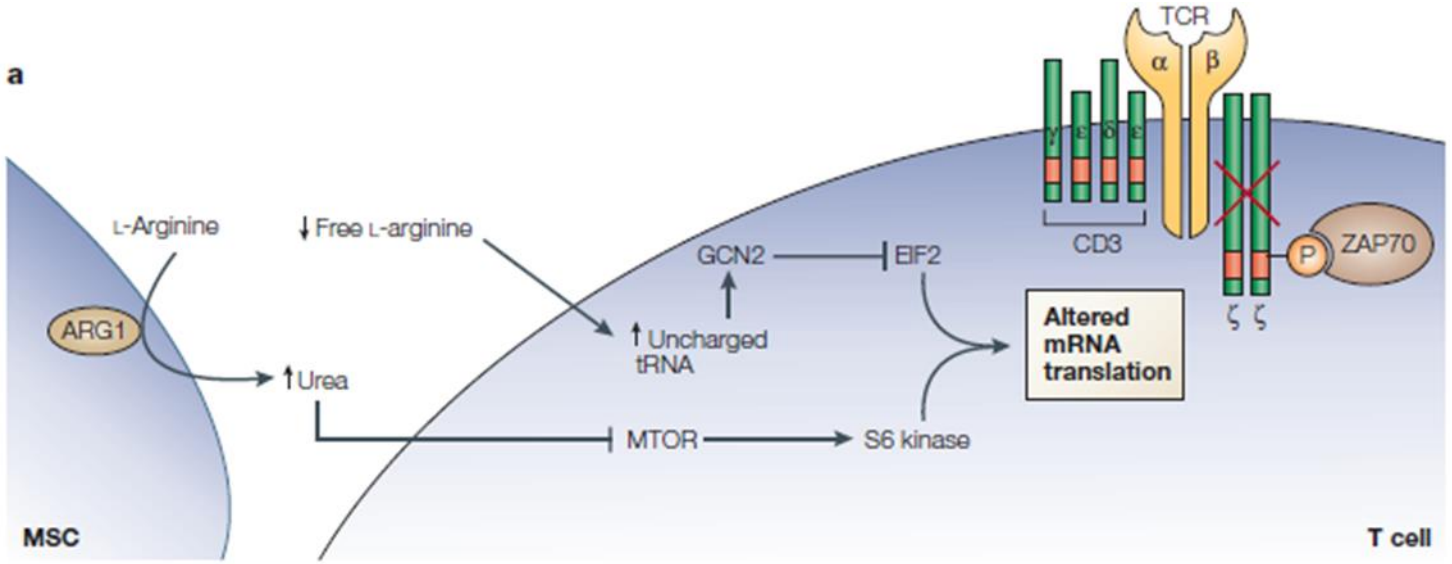


- L-Arginine is a conditionally essential amino acid, i.e., it may have to supplemented through diet under conditions where requirement exceeds production, such as pregnancy, sepsis and trauma
- L-Arginine is a component of proteins such as creatine and agmatine
- It is primarily metabolized by the enzymes Arginase and nitric oxide synthase to produce urea and L-ornithine, and nitric acid and L-citrulline, respectively
- Furthermore, L-ornithine is a precursor to polyamines, which are involved cell growth and differentiation

Source: Bronte et al., Nat. Rev. Imm., 2005

LEERINK

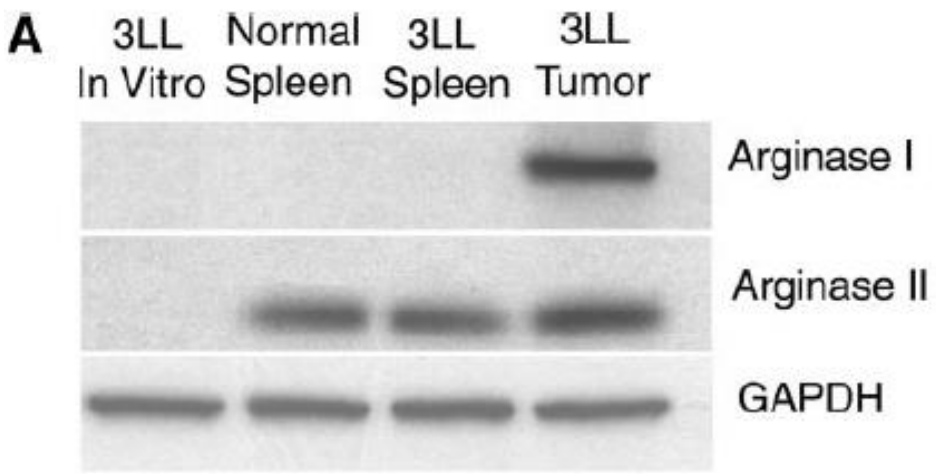
DEPLETION OF ARGININE BY MYELOID-DERIVED SUPPRESSOR CELLS (MDSC) INHIBITS T CELL ACTIVATION

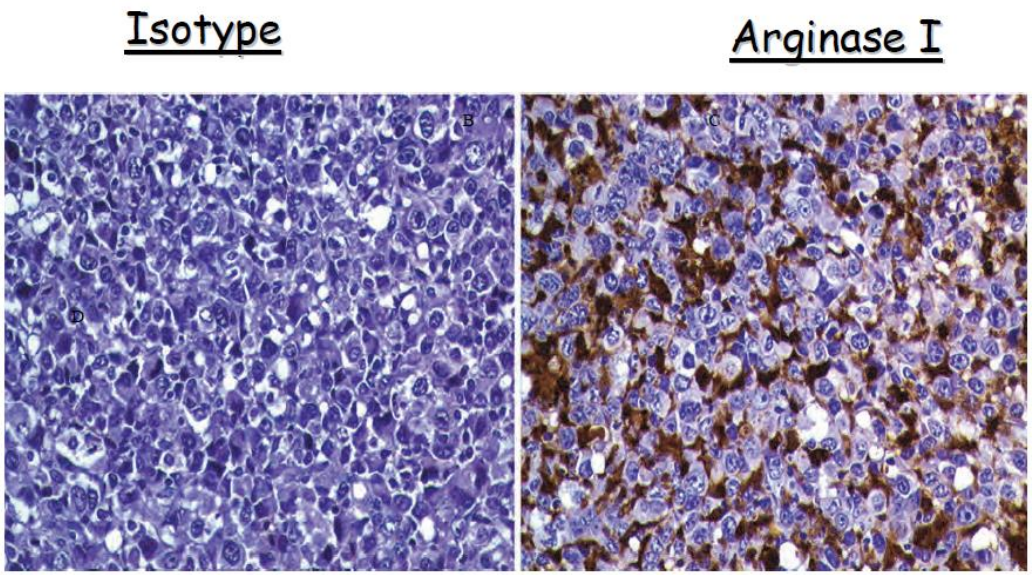


- Aberrations during normal myelopoiesis lead to the proliferation of cells, known as myeloid derived suppressor cells (MDSC) that have immunosuppressive activity in the bone marrow, secondary lymphoid organs and blood that impairs T-cell functions
- MDSCs express Arginase, this results in excessive consumption of arginine, which is shown to inhibit T-cell responses to antigen
- Arginine, an amino acid is essential for activation, proliferation and survival of CTLs. In the absence of arginine, antigen specific CTLs are unable to express a functional T cell receptor and as a result CTLs cannot be activated and fail to eliminate tumor cells.
- Myeloid cells extracted from a mouse lung carcinoma consumed l-arginine and as result inhibited re-expression of the ζ-chain of CD3 after TCR-signaling-induced internalization by antigen-stimulated T cells, thereby impairing the function of these cells

Source: Bronte et al., Nat. Rev. Imm., 2005

ARGINASE I IS SPECIFICALLY EXPRESSED IN 3LL LEWIS LUNG CARCINOMA CELLS

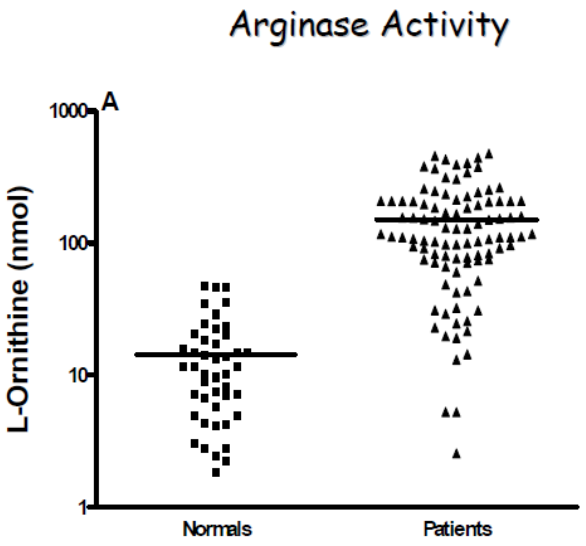


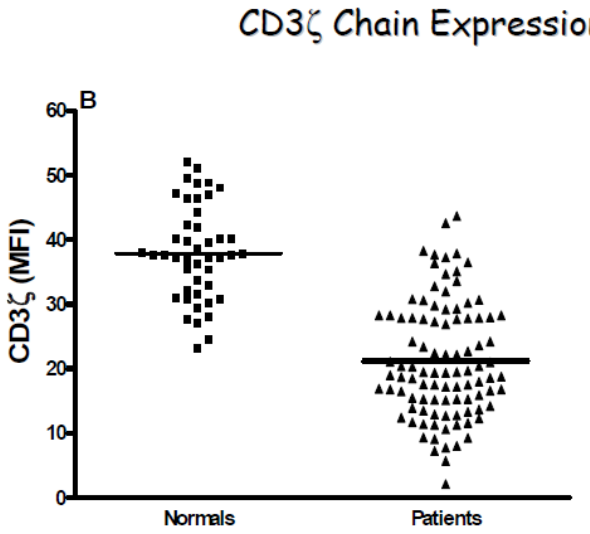


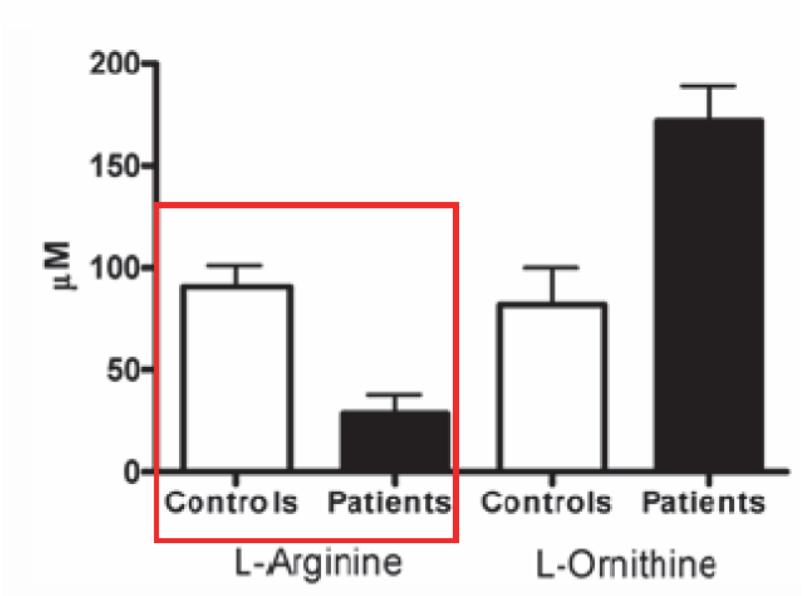
- Arginase I and II are both highly expressed in 3LL tumor cells; however, Arginase I expression is unique to tumor cells
- Arginase I is produced by mature myeloid cells in tumors

Source: Rodriguez et al., Cancer Research, 2004

ARGINASE ACTIVITY IS ELEVATED IN RCC PATIENTS



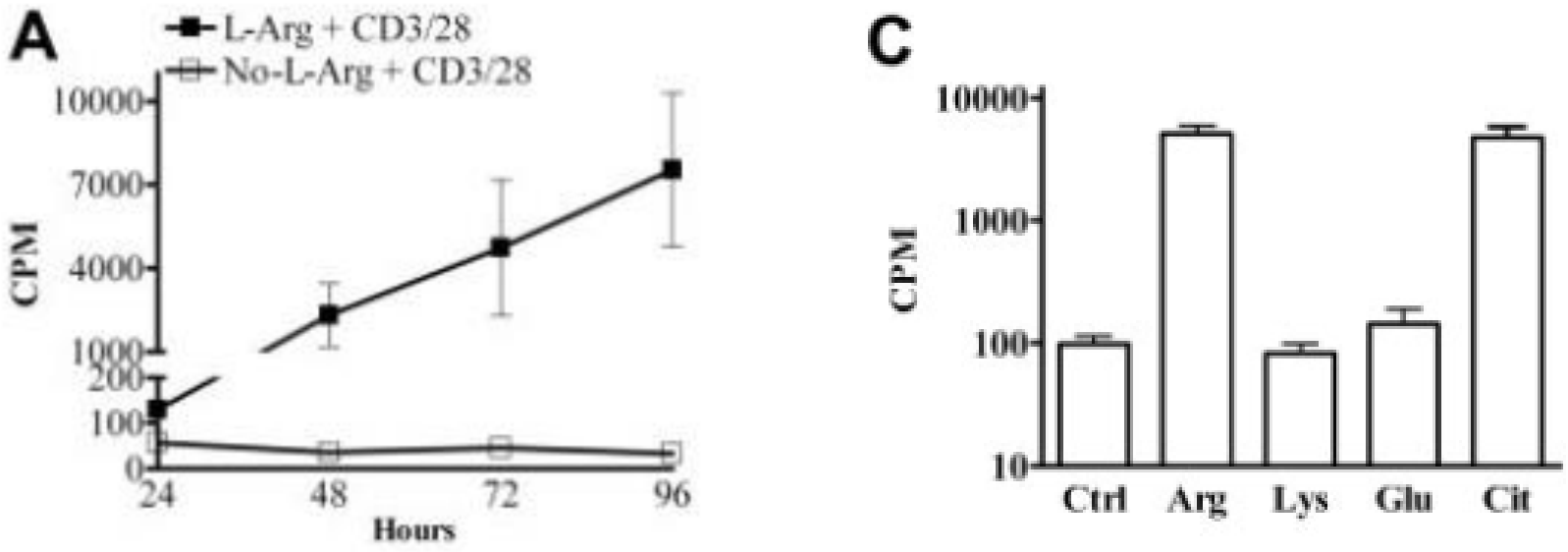




- Arginase activity is elevated in metastatic RCC patients compared to control group
- In addition, as would be expected, the levels of CD3ζ chain expression are significantly lower in the RCC patient population
- Arginase metabolizes arginine to ornithine; as a result tumor cells should express high levels of ornithine
- Arginine and ornithine levels were measured in plasma from 15 RCC patients and 7 control patients.
- RCC patients showed lower levels of arginine and high levels of ornithine

Source: Zea et al., Cancer Res., 2005

ARGININE REGULATES PROLIFERATION OF ACTIVATED T-CELLS

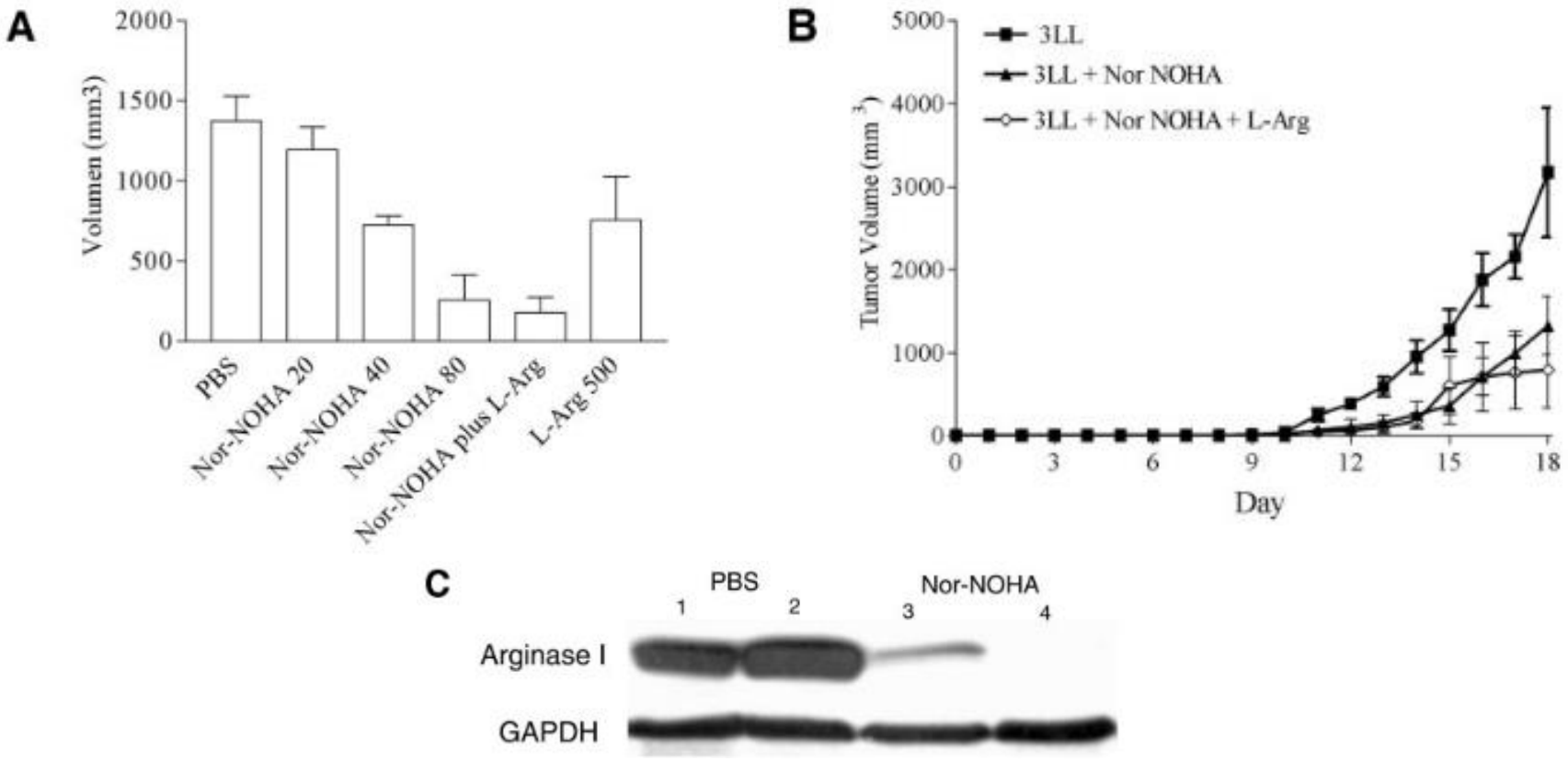


- T-cells from healthy patients were stimulated with CD28 in culture with and without L-Arginine (L-Arg)
- T-cells devoid of a L-Arg exhibited significant reduction in proliferation compared to the T-cells with access to L-Arg
- Furthermore, addition of only L-Arg or citrulline (Cit) and no other amino acid led to the normalization T cell proliferation upon stimulation

Abbreviations: CPM- counts per minute.

Source: Rodriguez et al., Immunobiology, 2007

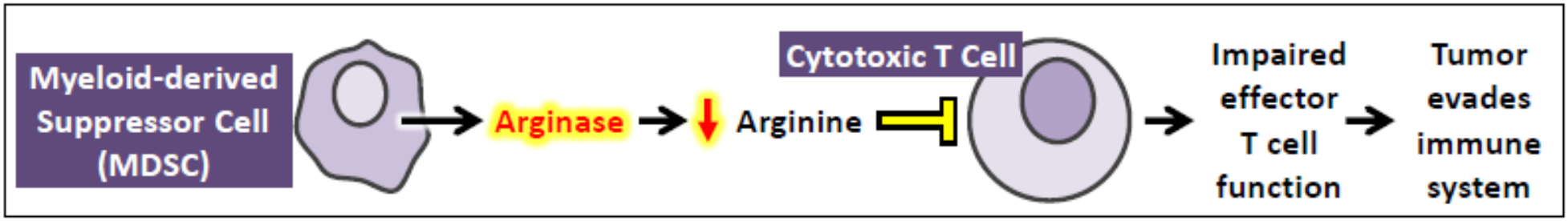
ARGINASE I INHIBITION REDUCES TUMOR GROWTH *IN VIVO*



- Tumor growth in the lung cancer cell line on day 14 was significantly inhibited by N-hydroxy-nor-L–Arg (commercial arginase inhibitor) in a dose-dependent manner.
- C57BL/6 mice injected with 3LL tumor cells together with varying doses of the arginase inhibitor N-hydroxy-nor-L-Arg or N-hydroxy-nor-L-Arg plus L-Arg showed reduced tumor growth
- The expression of arginase I was markedly decreased in the tumor-associated myeloid cells infiltrating the tumors of mice receiving N-hydroxy-nor-L-Arg

Source: Rodriguez et al., Canc Res. 2004

SUMMARY OF THE TUMOR IMMUNOLOGY PROGRAM- ARGINASE INHIBITORS

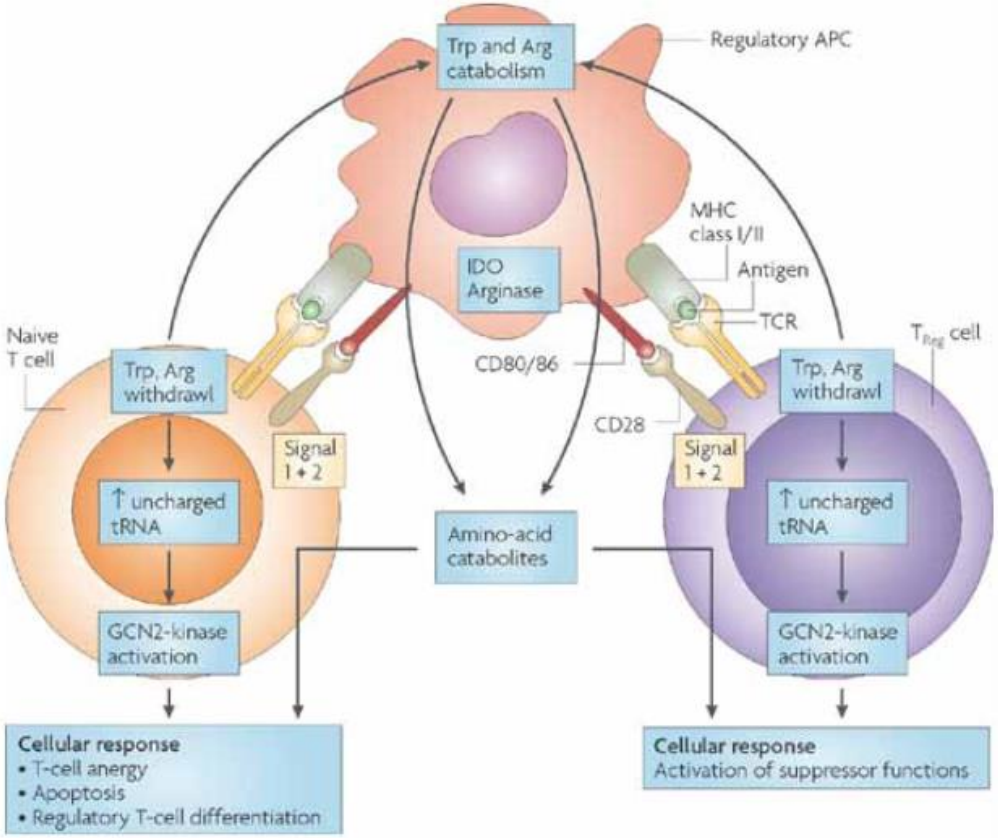


- Cancer cells can evade the immune system to avoid detection and elimination in a number of ways. One such mechanism is through the suppression of cytotoxic T cells (CTLs)
- Tumor cells and immature myeloid cells have been linked to the induction of T cell dysfunction in cancer via the depletion of arginine and tryptophan
- Arginine is an amino acid is essential for activation, proliferation and survival of CTLs. In the absence of arginine, antigen specific CTLs are unable to express a functional T cell receptor and as a result CTLs cannot be activated and fail to eliminate tumor cells.
- Arginase is an enzyme that depletes arginine (amino acid) essential for activation, growth and survival of CTLs.
- In many cancers such as AML, RCC, breast and pancreatic cancer, it is secreted by myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment in response to tumor secreted factors
- Calithera's second compound is an arginase inhibitor that prevents suppression of CTLs by blocking arginine depletion
- A similar rationale had been employed in the development of an inhibitor for Indoleamine 2,3-doxygenase (IDO), a tryptophan metabolizing enzyme that depletes tryptophan from the tumor microenvironment resulting in suppression of T cell function.
- Calithera plans to submit an IND for the arginase inhibitor in YE:15

Source: Company Reports

Targeting Metabolic Regulation of Immune Response Has Generated High Interest

IDO AND ARGINASE INHIBIT T CELL ACTIVATION VIA A SIMILAR MECHANISM

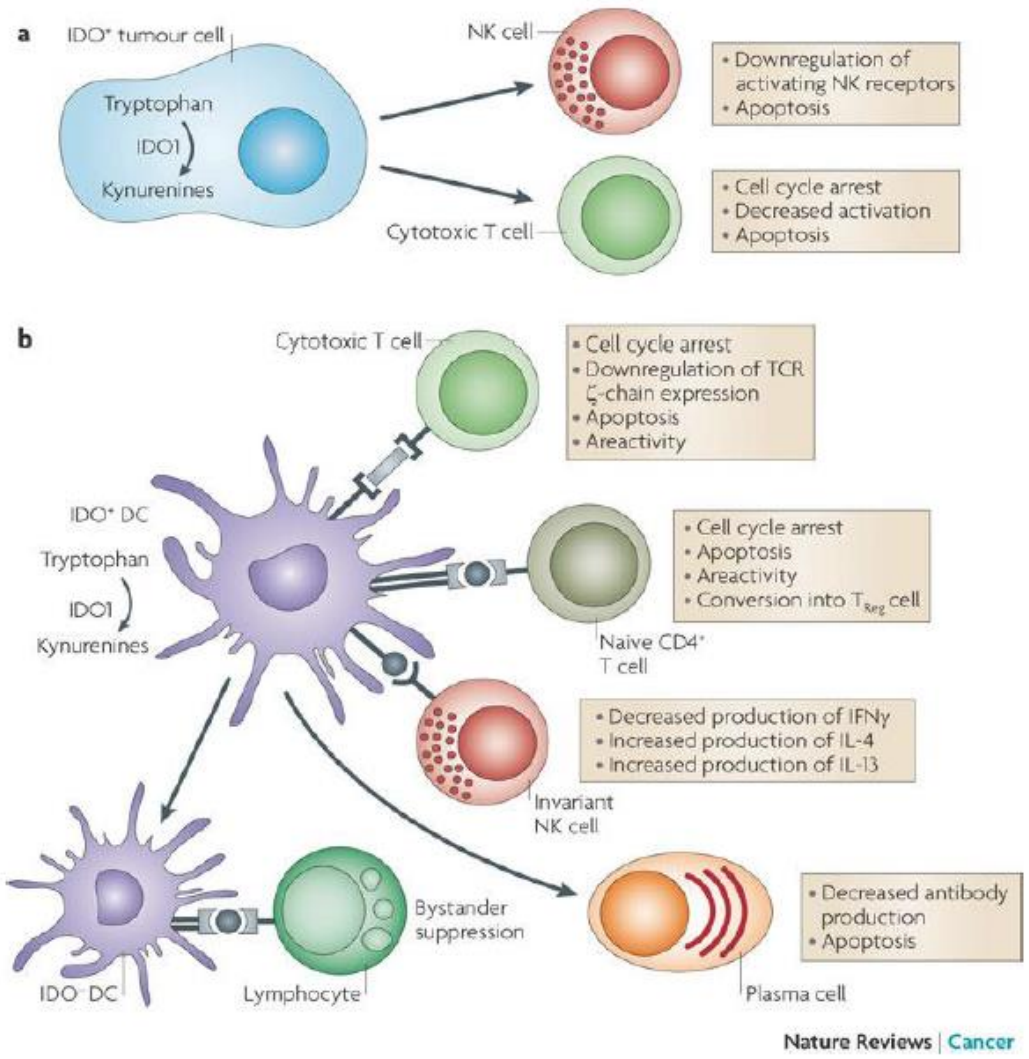


from Mellor & Munn, **Nature Reviews** | Immunology, 2008

- Tryptophan, like L-Arginine, is critical for activation T cells in response to tumor antigens
- Tryptophan is depleted by enzyme, idoleamine-2,3-dioxygenase (IDO) leads to T cell anergy and apoptosis
- Both tryptophan and L-arginine are depleted by enzymes expressed in tumor cells and tumor associated cells such as, MDSCs
- Given this, inhibiting these enzymes should potentially restore T cell activation upon antigen stimulation.
- Recent clinical data for IDO inhibitors and pre-clinical for arginase inhibitors appear to restore activity of cytotoxic T cells

Source: Company Reports

INDOLEAMINE 2,3- DIOXYGENASE (IDO) IS A METABOLIC ENZYME THAT AFFECTS T CELL ACTIVITY

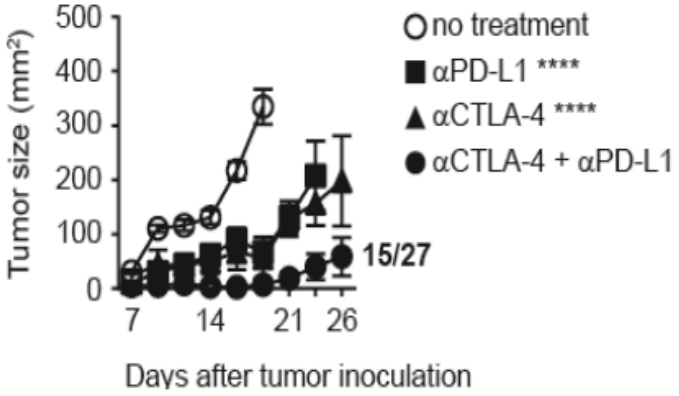


- IDO is a rate limiting immunomodulatory enzyme that metabolizes (depletes) tryptophan through the kynurenine pathway
- IDO1 activation in tumor cells induces the down regulation of activating natural killer (NK) cells and cytotoxic T cells by promotion of cell cycle arrest and apoptosis
- IDO expression can lead to acquired peripheral tolerance *de novo*
- IDO expression in tumor cells is induced on exposure to interferon-γ (IFNγ) and other inflammatory molecules that are produced by stimulated T cells

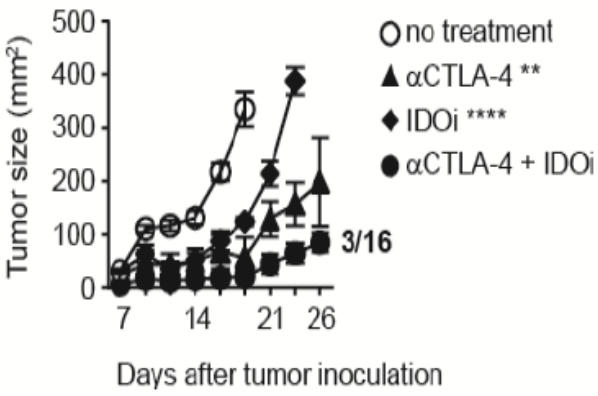
Source: Company Reports

COMBINATORIAL TARGETING OF CTLA4, PD-L1, and IDO IMPROVES TUMOR CONTROL IN MOUSE MODELS

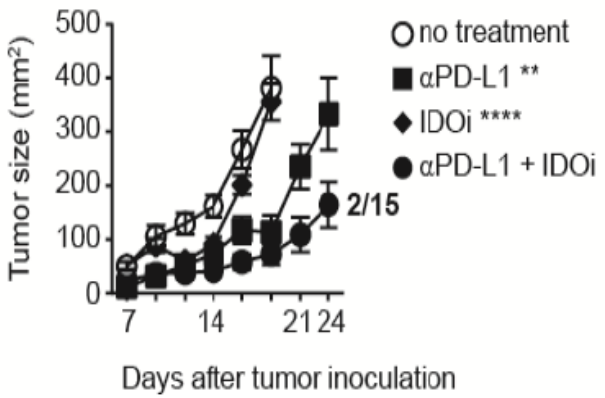
CTLA4 + PDL1



CTLA4 + IDOi



PDL1 + IDOi

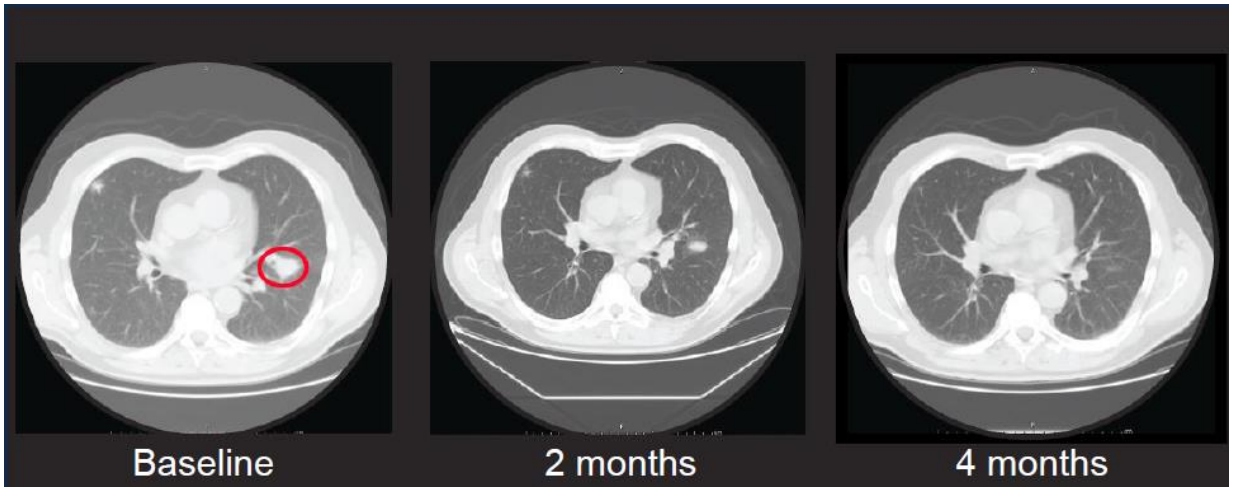


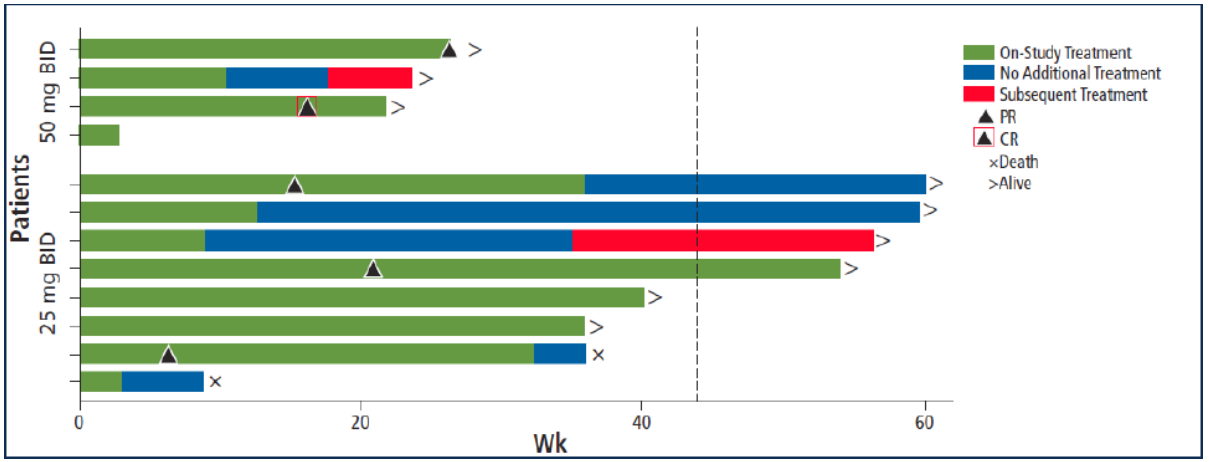
- Pre-clinically, single agent treatment outcomes were compared to the respective double treatment of CTLA-4 and PD-L1 C, CTLA-4 and IDOi and PD-L1 and IDOi

- Combination therapy was shown to be more effective to single agent, suggesting that combining checkpoint inhibitors with inhibitors of T cell suppressing enzymes could improve the overall response rate

Source: Spranger et al., JITC 2013

INITIAL CLINICAL DATA FROM INCY'S IDO INHIBITOR APPEARS PROMISING





- One patient with pulmonary metastases treated with INCY's (OP) IDO inhibitor INCB024360 at 50mg BID experienced a complete response (CR)
- Majority of the immunotherapy naïve patients are either continuing on the study or have not had the need for subsequent therapy

Source: Company Reports

THE DIFFERENT TUMOR IMMUNOLOGY TARGETS IN DEVELOPMENT

Company	Compound	Mechanism	Indication	Stage of development
INCY	INCB24360	IDO (Indoleamine 2,3-dioxygenase)	Ovarian cancer, melanoma, NSCLC	Phase I/II
NLNK	Indoximod	IDO (Indoleamine 2,3-dioxygenase)	Breast, pancreatic, brain and prostate cancer, melanoma and other solid tumors	Phase I/II

Source: Company Reports and Biomedtracker

Ongoing Clinical trials

CALA ONGOING TRIALS

Drug	Mechanism/ Class	Trial name/ ID	Status	Setting	Trial Design	n	Primary Endpoint	Trial initiation	Enrollment completed	Region	Primary completion date/ Interim Data
CB-839	Glutaminase Inhibitor	NCT02071862 CX-839-001	Phase I	TNBC, NSCLC, RCC and Mesothelioma	CB-839 (TID) in 21-day cycles	100	Safety	Feb. 2014	no	US	Dec. 2015
CB-839	Glutaminase Inhibitor	NCT02071927 CX-839-002	Phase I	AML, ALL	CB-839 (TID) in 21-day cycles	50	Safety	Feb. 2014	no	US	Dec. 2015
CB-840	Glutaminase Inhibitor	NCT02071888 CX-839-002	Phase I	NHL, DLBCL, MM, T-cell NHL	CB-839 (TID) in 21-day cycles	65	Safety	Feb. 2014	no	US	Dec. 2015

Source: Company Reports, clinicaltrials.gov and Leerink Partners

Financials

KEY FINANCIALS

- Cash and cash equivalents as of 7/30/14 – $40.8M
- IPO gross proceeds ~$80M
- Pro forma cash ~$110M
- Current cash is projected to support operations through 2017

. Source: Company reports and Leerink Partners Research

Intellectual Property and Patents

INTELLECTUAL PROPERTY AND PATENTS

- Strong matter of composition patent for CB-839 until **2032 (not including potential Hatch-Waxman extension)**. In addition, 6 US patents and 17 international patents are pending relating to matter of composition of CB-839 and related compounds, and methodologies related to their use.

- Method of treatment patent for heterocyclic inhibitors of glutaminase in the US was issued on Jul. 10th, 2014.

- US patent for the use of biomarkers to identify patient populations most likely to respond to treatment. Additionally, 23 similar patents are pending in Argentina, Australia, Brazil, Canada, Europe, India, Israel, Japan, Mexico, New Zealand, Singapore, South Africa, South Korea and Taiwan

Source: Company Reports

Management

MANAGEMENT

- **Susan M. Molineaux** – President and Chief Executive Officer

Former founder and Chief Executive Officer of Proteolix, Inc. that was responsible for the discovery and development of carfilzomib (marketed as Kyprolis), a proteasome inhibitor that was granted accelerated approval in 2012 for the treatment of refractory multiple myeloma. Proteolix was sold to Onyx Pharmaceuticals, Inc. in 2009. Previously, Dr. Molineaux held various senior scientific and management positions at Rigel Pharmaceuticals, and Merck & Co.

- **William D. Waddill** – Senior Vice President and Chief Finance Officer

Previously was the Senior Vice-President and CFO at OncoMed and Ilypsa .

- **Chris Molineaux, Ph.D**. – Senior Vice President of Development

Previously served as Vice President of Development at Proteolix and has worked Fibrogen, J&J, Praecis, Merck and Mt. Sinai Medical School

- **Mark Bennett, Ph.D** – Senior Vice President of Research

Previously Vice President of Research at Proteolix, Rigel and an assistant professor at UC Berkeley .

- **Eric Sjogren, Ph.D**. – Senior Vice President of Drug Discovery

Most recently he served as the vice president of Medicinal Chemistry at Roche and Syntex.

Source: Company Reports

Calithera
(In '000s, except per share items)

	2012	2013	1QE*	2QE*	3QE	4QE	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
REVENUE:															
CB-839(POS adjusted sales)	-	-	-	-	-	-		-	-	-	-	-	11,409	68,094	132,770
Milestone payments															
Other, net															
Total Revenue													**11,409**	**68,094**	**132,770**
OPERATING EXPENSES:															
Cost of product Sales											-	-	1,141	6,809	13,277
Research and Development	6,558	9,900	3,751	3,751	3,788	3,826	15,115	15,612	23,417	35,126	38,639	54,094	59,503	65,454	71,999
General and Adminstrative	1,417	2,478	1,071	1,071	1,081	1,103	4,325	4,590	4,682	5,618	6,180	20,000	60,000	90,000	108,000
Royalties	-														
Amortization of Acquired Intangible Assets															
Operating Loss/ Income	**(7,975)**	**(12,378)**	**(4,821)**	**(4,821)**	**(4,869)**	**(4,929)**	**(19,440)**	**(20,202)**	**(28,099)**	**(40,744)**	**(44,818)**	**(74,094)**	**(109,235)**	**(94,169)**	**(60,506)**
Investment, Interest and Other Income, Net		1	1	1			2								
Gain on extinguishment of convertible preferred stock	2889														
Change in fair value of convertible preferred stock warrant liability															
Net Income before Taxes	(7,975)	(12,377)	(4,820)	(4,820)	(4,869)	(4,929)	(19,438)	(20,202)	(28,099)	(40,744)	(44,818)	(74,094)	(109,235)	(94,169)	(60,506)
Income tax rate%														35%	35%
Income Tax														32,959	21,177
Net Loss	**(5,086)**	**(12,377)**	**(4,820)**	**(4,820)**	**(4,869)**	**(4,929)**	**(19,438)**	**(20,202)**	**(28,099)**	**(40,744)**	**(44,818)**	**(74,094)**	**(109,235)**	**(61,210)**	**(39,329)**
Basic and Diluted Net Loss per Common Share			(0.60)	(0.60)	(0.49)	(0.28)	(1.78)	(1.10)	(1.52)	(2.18)	(1.55)	(2.54)	(2.01)	(1.09)	(0.70)
Shares Used in Calculating Basic and Diluted Net Loss per Share(pro forma)			7,979	7,979	9,882	17,882	10,931	18,334	18,517	18,702	28,889	29,178	54,470	55,014	55,565
Dilutive shares			9,000	9,000	10,903	18,903	11,952	19,355	19,538	19,723	29,910	30,199	55,491	56,035	56,586
Cash and cash equivalents					111,281	106,352	106,352	86,151	58,051	17,307	102,489	28,395	244,160	182,950	143,621
Milestone payments															
Capital raise										130,000		325,000			
Shares issued										10,000		25,000			
Price per share										$ 13.00		$ 13.00			
Net Cash	-			27,750	111,281	106,352	106,352	86,151	58,051	147,307	102,489	353,395	244,160	182,950	143,621
Stock Options															
Restricted stock															
Total															
Stock price															
Market Cap															
EV															
Balance sheet data															
Working Capital															
Total assets															
Convertible preferred stock warrant liability															
Convertible preferred stock															
Total stockholder's (deficit) equity															

* 1H:14 results available but 1Q and 2Q were not broken out separately.
Source: Company reports and Leerink Partners

Disclosures Appendix

Analyst Certification

I, Howard Liang, Ph.D., certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.

Distribution of Ratings/Investment Banking Services (IB) as of 09/30/14				
			IB Serv./Past 12 Mos.	
Rating	Count	Percent	Count	Percent
BUY [OP]	138	69.30	51	37.00
HOLD [MP]	61	30.70	2	3.30
SELL [UP]	0	0.00	0	0.00

Explanation of Ratings

Outperform (Buy): We expect this stock to outperform its benchmark over the next 12 months.

Market Perform (Hold/Neutral): We expect this stock to perform in line with its benchmark over the next 12 months.

Underperform (Sell): We expect this stock to underperform its benchmark over the next 12 months.The degree of outperformance or underperformance required to warrant an Outperform or an Underperform rating should be commensurate with the risk profile of the company.

For the purposes of these definitions the relevant benchmark will be the S&P 600® Health Care Index for issuers with a market capitalization of less than $2 billion and the S&P 500® Health Care Index for issuers with a market capitalization over $2 billion.

Important Disclosures

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