Safety and Activity of DCR-MYC, a First-in-Class Dicer-Substrate Small Interfering RNA (DsiRNA) Targeting MYC, in a Phase 1 Study in Patients with Advanced Solid Tumors

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PRESENTED AT: ASCO Annual '15 Meeting

Disclosures: past 5 years

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MYC: One of the First Discovered and Broadly Implicated Oncogenes, Often Considered an "Undruggable" Target

Deregulation of MYC has been described in several human cancers

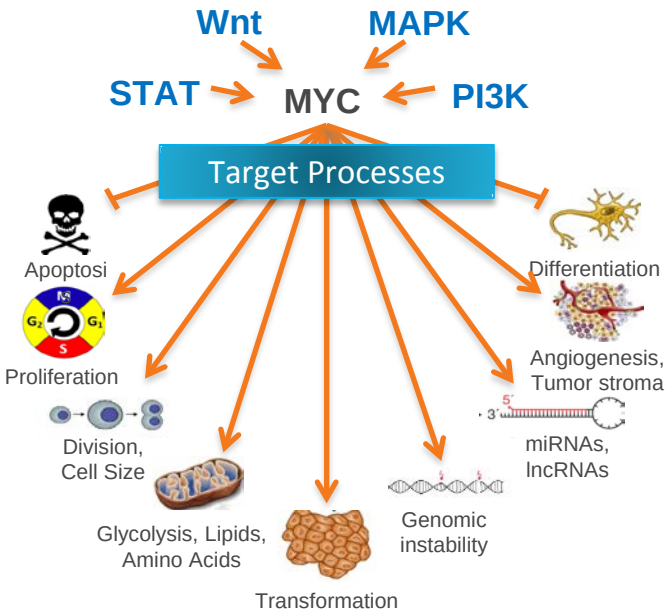
MYC Genomic Duplication or Higher Order Amplification Rate

- Hepatocellular 50%
- Breast 80%
- Colorectal 70%
- Gastric 51-77%
- Gynecological 90%
- Prostate 80-90%
- SCLC 18-30%

Human translocations and cancer-associated SNPs also occur for MYC

Genes and Cancer 1 (2010), pg. 532

MYC is a central regulator of several oncogenic processes: "Universal Amplifier"



Cell 151 (2012), pg. 68

Genetic models show the powerful antitumor effects of MYC inhibition

related to the amount of sensory fibers associated with the rudimentary gland.

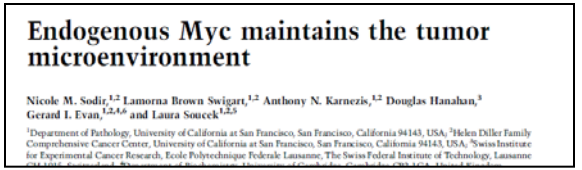
To determine whether the truncated form of TrkB expressed in the male mammary mesenchyme at E13 plays an essential role in the sexually dimorphic patterning of mammary gland innervation, we analyzed mammary gland innervation in *TrkB.T1* mutant mice in which the exon encoding the C-terminal residues unique to TrkB.T1 is missing (*20*). These mice do not express TrkB.T1, but they do express normal levels of full-length TrkB. Because TrkB.T1 is not expressed in DRG neurons at E13 (fig. S17), performing experiments using *TrkB.T1* mutant mice allowed us to address the role of TrkB.T1 without directly af-

Mice Lacking a *Myc* Enhancer That Includes Human SNP rs6983267 Are Resistant to Intestinal Tumors

Inderpreet Kaur Sur,[1,2] Outi Hallikas,[1] Anna Vähärautio,[1,2] Jian Yan,[1] Mikko Turunen,[1] Martin Enge,[1] Minna Taipale,[1,3] Auli Kaihu,[4] Lauri A. Aaltonen,[4] Jussi Taipale[1,3]*

Multiple cancer-associated single-nucleotide polymorphisms (SNPs) have been mapped to conserved sequences within a 500-kilobase region upstream of the *MYC* oncogene on human chromosome 8q24. These SNPs may affect cancer development through altered regulation of *MYC* expression, but this hypothesis has been difficult to confirm. We generated mice deficient in Myc-335, a putative *MYC*

Science *338* (2012), pg. 1360

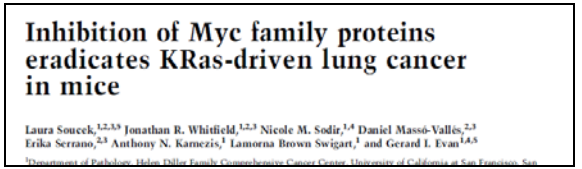


Endogenous Myc maintains the tumor microenvironment

Nicole M. Sodir,[1,2] Lamorna Brown Swigart,[1,2] Anthony N. Karnezis,[1,2] Douglas Hanahan,[3] Gerard I. Evan,[1,2,4,6] and Laura Soucek[1,2,5]

[1]Department of Pathology, University of California at San Francisco, San Francisco, California 94143, USA; [2]Helen Diller Family Comprehensive Cancer Center, University of California at San Francisco, San Francisco, California 94143, USA; [3]Swiss Institute for Experimental Cancer Research, Ecole Polytechnique Federale Lausanne, The Swiss Federal Institute of Technology, Lausanne

Genes Dev. *27* (2013), pg. 504



Inhibition of Myc family proteins eradicates KRas-driven lung cancer in mice

Laura Soucek,[1,2,3,5] Jonathan R. Whitfield,[1,2,3] Nicole M. Sodir,[1,4] Daniel Massó-Vallés,[2,3] Erika Serrano,[2,3] Anthony N. Karnezis,[1] Lamorna Brown Swigart,[1] and Gerard I. Evan[1,4,5]

[1]Department of Pathology, Helen Diller Family Comprehensive Cancer Center, University of California at San Francisco, San

Genes Dev. *25* (2011) pg. 907

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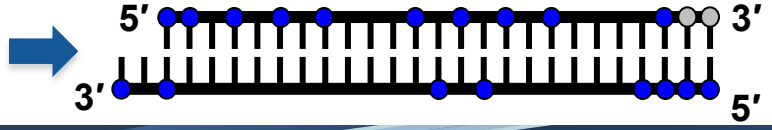
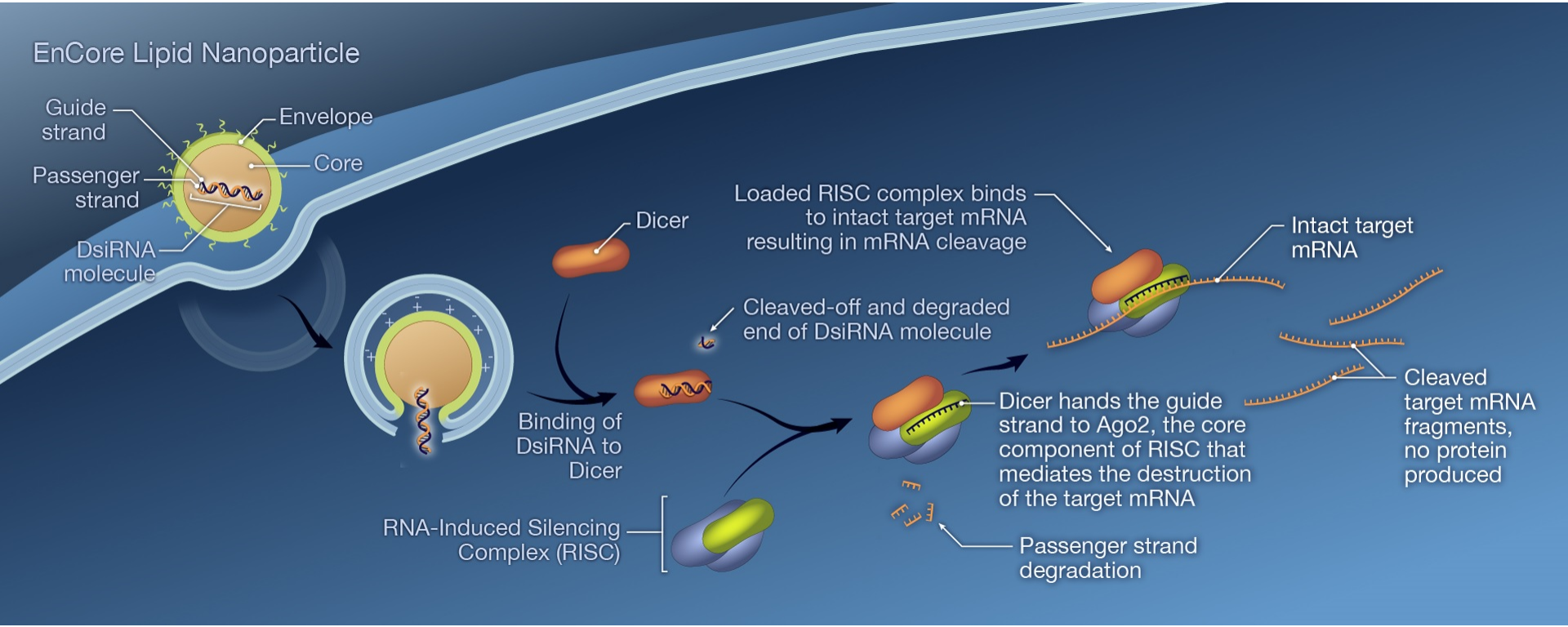
DCR-MYC Mechanism of Action

Structure of DsiRNA targeting MYC (25-27 mer synthetic RNA duplex)





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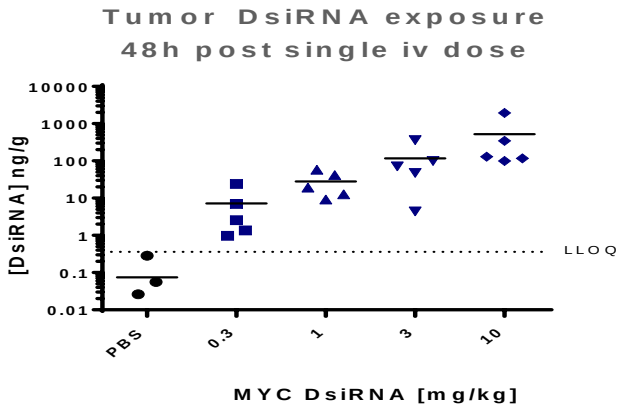
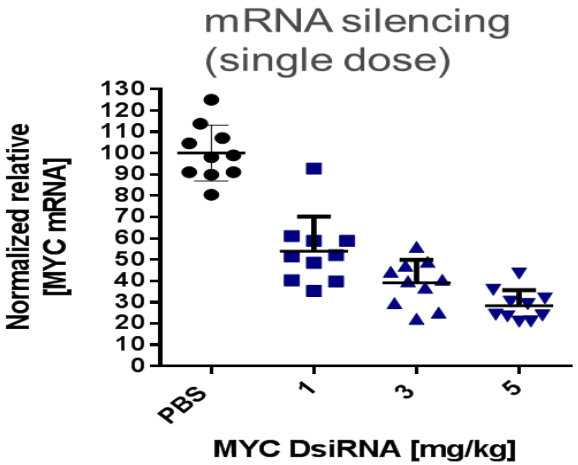
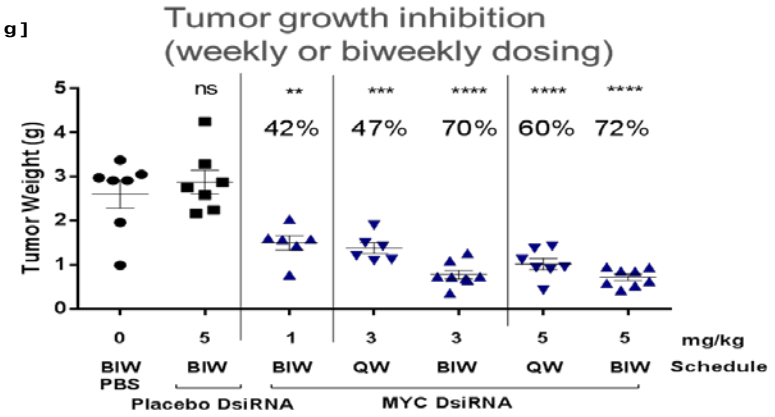
DCR-MYC Delivers DsiRNA to Hep3B HCC Orthotopic Liver Tumors and Yields Tumor Growth Inhibition







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Study Objectives

- Primary Objective
  - Safety, tolerability, dose-limiting toxicities (DLT), and maximum tolerated dose (MTD)
- Correlative Studies
  - Pharmacokinetic (PK) profile
  - Pharmacodynamic (PD) markers including:
    - FDG-PET for evaluation of effects on tumor metabolism
    - Cytokines in peripheral blood to evaluate immunological effects of LNP
    - Pre- and Post-dosing tumor biopsies for measurement of:
      - MYC mRNA at baseline
      - 5'RACE assay for MYC degradation products post-dosing
  - Preliminary evaluation of anti-tumor activity (using RECIST 1.1)

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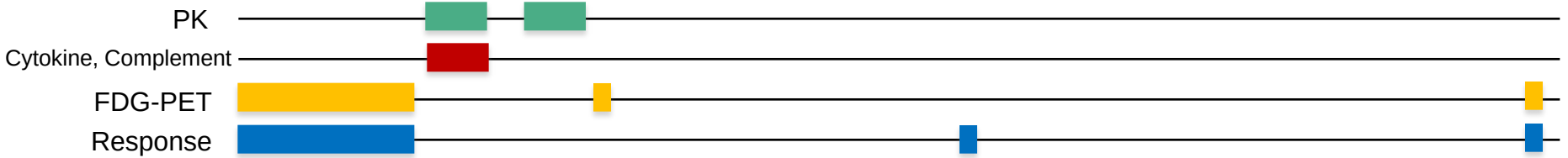
Study Design

- Two-center, dose-escalation study; standard (3 + 3) study design
- DCR-MYC administered as a 2-hour IV infusion once-weekly for 2 weeks, followed by a 1 week break (3 weeks = 1 cycle)
- All patients receive IV premedications (dexamethasone, diphenhydramine, H-2 blocker) administered 30-minues prior to dosing
  - Oral premedication with dexamethasone (12-hr & 6-hr prior to infusion) added at Cohort 4 onwards
- Starting dose 0.1 mg/kg; currently dosing at 0.68 mg/kg

Screening	Cycle 1			Cycle 2			Cycle 3			Cycle 4		
	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3
DCR-MYC	X	X		X	X		X	X		X	X	



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Demographics and Baseline Characteristics

Characteristic	Result
Number of subjects treated	26
Median age (range)	58 years (34 – 78 years)
Gender	10 males - 16 females
ECOG performance status	PS 0 – 10; PS 1 – 15; PS 2 – 1
Median number of prior regimens (range; N=22)	4 (1 – 13)
Tumor Types	Breast - 6 Neuroendocrine - 4 (3 pancreatic, 1 lung) Colorectal - 3 Ovarian, Appendix, Esophagus, Salivary, Leiomyosarcoma – 2 each Endometrial, Small cell lung, Cholangiocarcinoma – 1 each

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Cohort Summary (N=26 as of 12 May 2015)

Cohort	Dose (mg/kg)	Treated (N)	Completed Cycle 1	Cycle 1 DLT (N)	Cohort Status
1a*	0.1	1	1	1 (increased AST-g3)	Restarted 05/12/15
1b	0.1	5	5	0	Completed
2	0.125	4	3	0	Completed
3	0.156	3	3	0	Completed
4	0.2	3	3	0	Completed (1 pt ongoing C8)
5	0.3	3	3	0	Completed (1 pt ongoing C6)
6	0.45	3	3	0	Completed (1 pt ongoing C4)
7	0.68	4	1	1	Enrolling

*Schedule: 3wks on, 1wk off; all subsequent cohorts 2wks on, 1wk off

Preliminary Data as of 12 May 2015

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Summary of Treatment Related AEs (occurring in > 5% pts)

Adverse Event (N=21*)	Grade 1	Grade 2	Grade 3	Grade 4	Total (%)
fatigue	3	5	-	-	8 (38%)
nausea	5	1	-	-	6 (29%)
Infusion-related reaction	3	2	-	-	5 (24%)
vomiting	2	-	-	-	2 (9%)
hiccups	1	1	-	-	2 (9%)

*As of 01 May 2015; data unavailable for 5 of 26 patients treated (1 in Cohort 6, 4 in Cohort 7)

Single occurrences:

- Grade 3: allergic reaction, increased AST
- Grade 2: anemia, diarrhea
- Grade 1: anorexia, bruising, chest tightness, dehydration, dizziness, facial flushing, hand felt cold, oral dysesthesia

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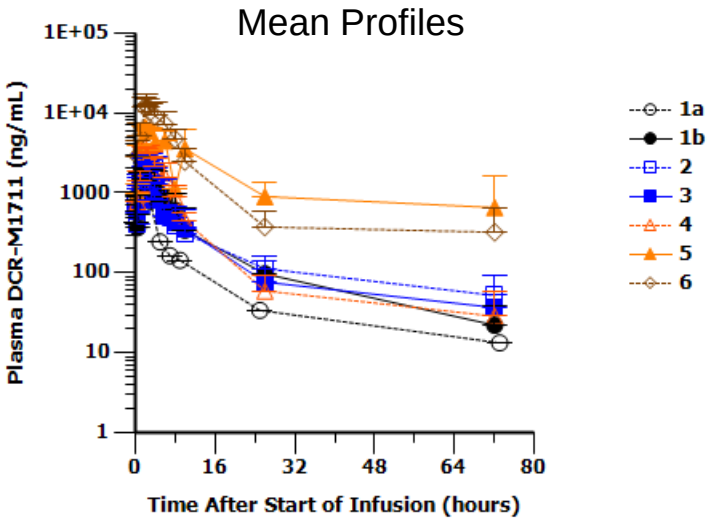
Pharmacokinetics



Cohort	Dose (mg/kg)	n	Mean Cmax (ng/mL)	Mean AUClast (hr*ng/mL)
1a	0.100	1	1,755	7,821
1b	0.100	5	1,780	15,096
2	0.125	4	2,570	19,674
3	0.156	3	2,110	14,792
4	0.200	3	3,751	22,179
5	0.300	3	6,813	108,052
6	0.450	3	12,860	106,135

- Plasma samples were analyzed using a validated capillary gel electrophoresis-hybridization method
- Greater than proportional increase in Cmax and AUClast seen at higher doses

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Clinical Anti-Tumor Activity

Total N	26
Patients evaluable for response*	18
Patients with clinical activity	
RECIST 1.1 response	
Partial Response	1 (5.5%)
Stable Disease	8 (44.4%)
FDG-PET response (PERCIST 1.0)	
Complete metabolic response	1 (5.5%)

*8 Patients not evaluable for response

Off study prior to completing C2 due to AE (IRR) (n=1) or PD (n=3)
Ongoing, have not reached end of C2 (n=4)

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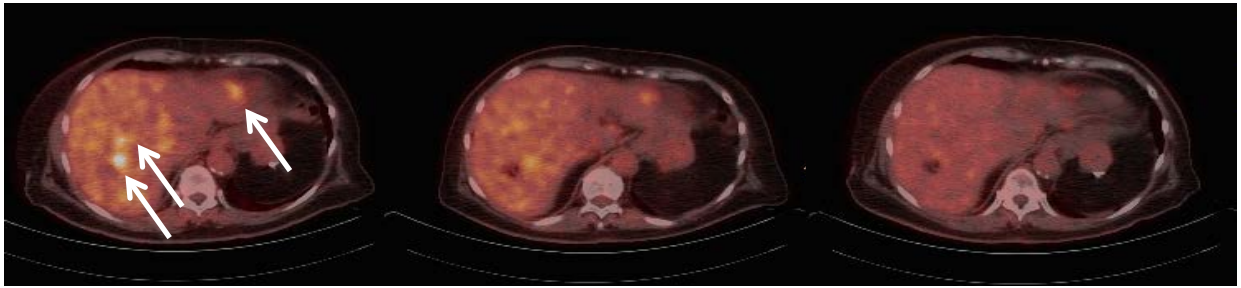
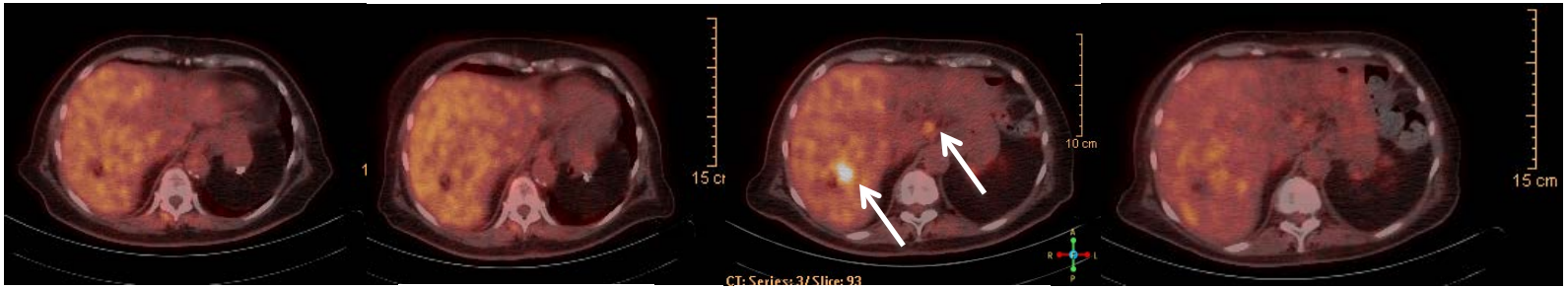
Pt# 01-001, Dose: 0.1 mg/kg (Cohort 1)

Diagnosis: Pancreatic neuroendocrine tumor (PNET), liver metastasis

Prior Therapies: Regorafenib, AB0024, sunitinib, everolimus, AMG820, VX15/2503, OMP18R5, OPB-111077



Baseline: 4/14/14 → *Cycle 1* → Day 17: 5/1/14 → *DLT* → Off Treatment: 6/4/14



Off Tx 10/6/14 | Off Tx 12/10/14 | Recurrence 5/11/15 → 5/22/15

Re-treatment with DCR-MYC

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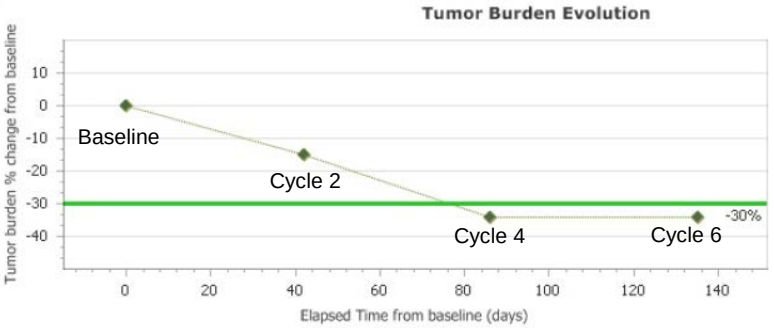
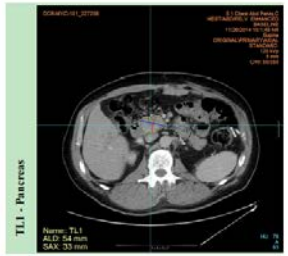
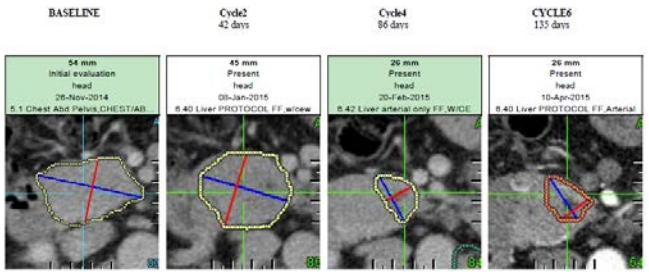
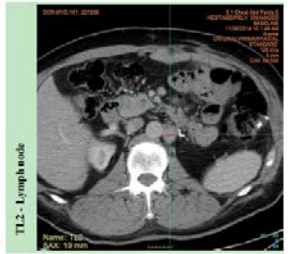
Pt# 01-016, Dose: 0.2 mg/kg (Cohort 4)

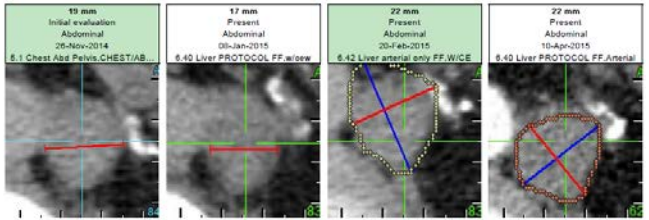
- **Diagnosis:** Pancreatic neuroendocrine tumor (PNET), lymph node and renal metastasis
- **Prior Therapies:** Everolimus, OPB111077 (STAT/metabolic inhibitor), Trametinib + GSK2141795 (MEK + Akt inhibitors)
- **Tumor Response:** 34% shrinkage after Cycle 4, confirmed after Cycle 6
  - Partial Response (PR) by RECIST 1.1 criteria











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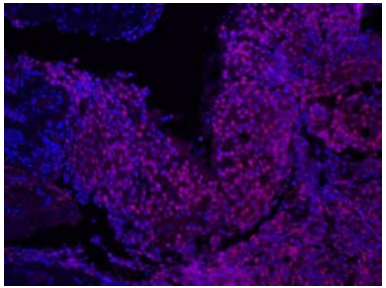
CONFIDENTIAL INFORMATION

MYC Amplification & Expression Data

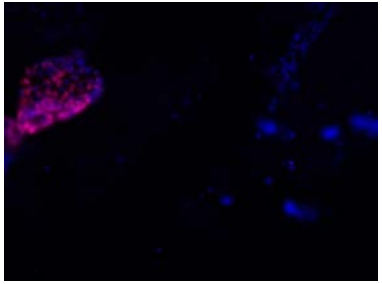
Pt#	Primary tumor	Myc amplification (copy #)	Nucleus Cy5 Weighting Mean	SD
01-001	PNET	Negative	15.45	6.98
01-004	Ovarian	Positive (2.5)	54.73	34.07
01-006	Breast	Positive (3)	9.48	9.29
01-010	Breast	Positive (3)	227.95	138.11
01-012	NET (lung)	Negative	19.19	4.77
01-013	Breast	Positive (3.21)	100.76	81.82
01-015	Breast	Positive (2.6)	40.61	21.00
01-016	PNET	Negative	40.46	4.10
01-017	Esophageal	Positive (3.75)	134.50	71.42
01-024	H&N (parotid)	Positive	224.17	87.90
02-014	CRC	N/A	149.81	61.97
02-018	H&N (mucoepidermoid)	N/A	13.84	2.11

MYC High Expression

Pt 01-024

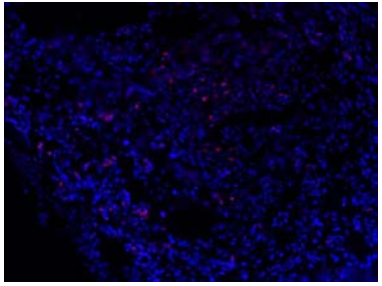


Pt 01-010

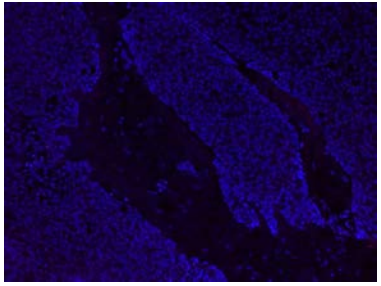


MYC Low Expression

Pt 01-006



Pt 02-018



Photos courtesy: Dr. M. Feldman, Univ. Pennsylvania

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Conclusions

DCR-MYC has been well-tolerated so far

- Dose escalation is ongoing (current dose is 0.68 mg/kg)

Clinical anti-tumor activity has been observed in 2 patients – both with advanced, treatment refractory PNET

- 1 PR (RECIST 1.1)
- 1 Complete Metabolic Response (FDG-PET, PERCIST 1.0)

FDG-PET pharmacodynamic responses have been observed in patients across several dose levels

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Next Steps

Dose escalation will continue until MTD is established

- Extrapolated clinically relevant dose is >0.5 mg/kg (preclinical data)

Pre- & Post-dose tumor biopsies will be obtained from patients enrolled MTD

Expansion cohort has been added to enroll patients with PNET at the MTD dose level

- Objective: To evaluate safety and preliminary anti-tumor activity in patients with low- or intermediate grade-PNET who have progressed following standard therapies

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Acknowledgements

Patients and their families

The DCR MYC Team including the site staff at START and University of Chicago, Dicerna, and our referral physicians

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