Anchiano therapeutics

TARGETING GENETICALLY-DEFINED CANCERS

September 2019

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Targeted Therapies for Genetically-Defined Cancers

GENE THERAPY

First-in-class gene therapy targeting H19 in registrational development in early stage bladder cancer: **inodiftagene vixteplasmid**

Data from six clinical trials show activity in pancreatic, ovarian and bladder cancer, with complete and durable responses in NMIBC

First pivotal clinical trial is open to enrollment nationwide, interim data coming soon

SMALL MOLECULE TARGETED THERAPIES

Pipeline expanded in option to license agreement with ADT Pharmaceuticals to include preclinical small molecule inhibitors:

To target mutated and activated RAS, exhibiting pan-RAS activity in a broad spectrum of tumor types

And to target phosphodiesterase 10 (PDE10), inhibiting the β-catenin pathway mutated in most colon cancers and other tumor types

Targeted Therapies for Multiple Common Indications

Inodiftagene Uses H19 to Target Cancer Cells and Avoid Normal Cells

OPEN ACCESS Freely available online

PLoS one

The H19 Non-Coding RNA Is Essential for Human Tumor Growth

Imad J. Matouk[1], Nathan DeGroot[2], Shaul Mezan[1], Suhail Ayesh[1], Rasha Abu-lail[1], Abraham Hochberg[1], Eithan Galun[1]*

1 Department of Biological Chemistry, Institute of Life Sciences, Hebrew University, Jerusalem, Israel, 2 Goldyne Savad Institute of Gene Therapy, Hadassah Hebrew University Hospital, Jerusalem, Israel

SCIENTIFIC REPORTS

OPEN

Hypoxia induces H19 expression through direct and indirect Hif-1α activity, promoting oncogenic effects in glioblastoma

www.impactjournals.com/oncotarget/ Oncotarget, 2016, Vol. 7, (No. 50), pp: 83177-83186

Research Paper

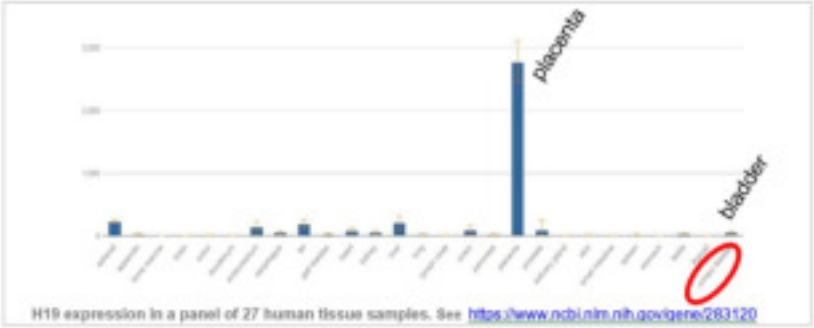
Prognostic and clinicopathological significance of long noncoding RNA H19 overexpression in human solid tumors: evidence from a meta-analysis

Fang-teng Liu[1], Hua Pan[1], Guang-feng Xia[1], Cheng Qiu[1], Zheng-ming Zhu[1]

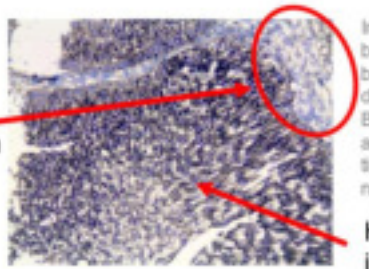
FEBS Journal

Upregulated H19 contributes to bladder cancer cell proliferation by regulating ID2 expression

Ming Luo[1], Zuowei Li[2], Wei Wang[2], Yigang Zeng[2], Zhihong Liu[2] and Jianxin Qiu[2]



H19 expression in a panel of 27 human tissue samples. See https://www.ncbi.nlm.nih.gov/gene/283120



No H19 expression in normal tissue

H19 expression in tumor

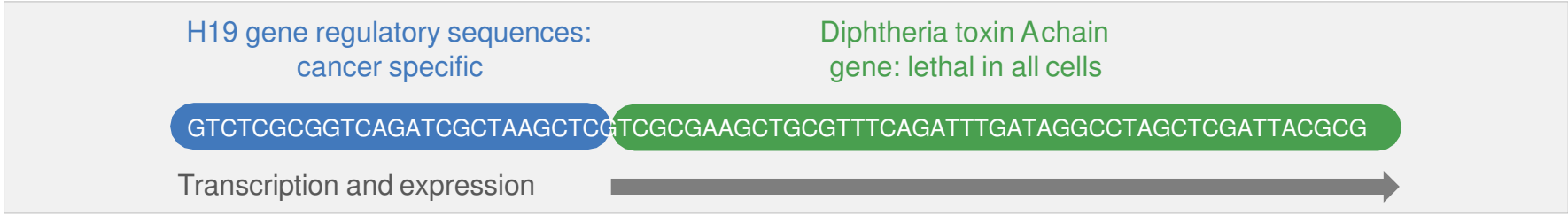
In situ hybridization (ISH) of H19 in bladder cancer. Histopathology of bladder cancer stained to demonstrate H19 expression. Black grains (arrow) demonstrate abnormal expression. Normal tissue (top right of section) does not stain for H19.

First-in-Class, First-of-its-Kind Treatment

Inodiftagene vixteplasmid gene therapy

Targeted gene therapy

Inodiftagene is a recombinant DNA molecule containing regulatory sequences from the H19 gene driving expression of diphtheria toxin A chain gene **only in malignant cells**



Diphtheria toxin gene: efficient delivery

Plasmid facilitates high transfection efficiency. In vitro uptake demonstrable in 85% of cells after a single exposure; in clinic detectable in bladder more than 48 hours after instillation, and administered weekly to every third week for up to 3 years

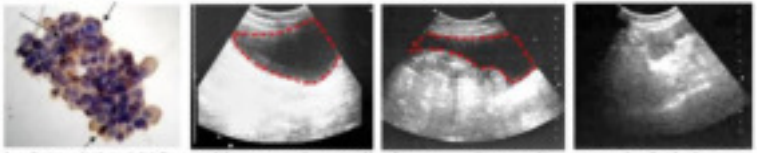
Well-understood and validated mechanism-of-action

Lethal inhibition of protein synthesis

Responses in Advanced Ovarian and Pancreatic Cancer

Inodiftagene activity in solid tumors validates mechanism of action

Complete resolution of ascites following instillation of inodiftagene



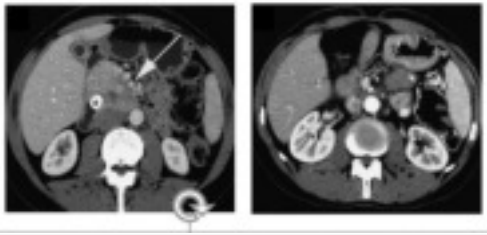
Left to right: H19-positive ovarian cells from ascites; ultrasound of abdomen at baseline, prior to 5th treatment, and after 10th treatment. Red border demarcates ascites, resolved at right

Advanced pancreatic cancer responses to monotherapy: 2 partial responses with inodiftagene alone

Table 5. Subject status at 3 months follow-up

Cohort #	Subject ID	End of study at 4 weeks	3 Months	Other treatments
1	201	PD	PD	None
1	202	PD	SD	Chemotherapy
1	602	SD	[illegible]	[illegible]
2	204	PD[a]	PR[a]	None
2	205	SD	[illegible]	[illegible]
2	301	PD	SD	Chemotherapy
2	501	SD	[illegible]	[illegible]
2	604	SD[b]	PR[b]	None
2	1102	SD	SD	[illegible] - Complete Resection at 3 months

Complete resection of advanced pancreatic cancer following inodiftagene, chemoradiation and surgery

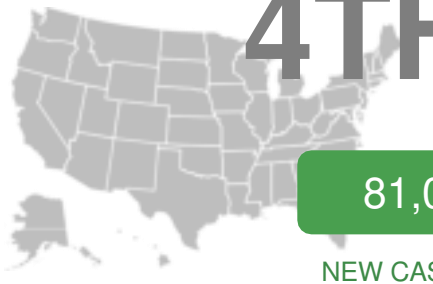


Left baseline tumor; right complete resection of tumor following inodiftagene and multimodality therapy

1. Mizrahi et al., J. Med. Case Reports 2:228, 2010 http://www.jmedicalcasereports.com/content/4/1/228; 2. Ohana et al., Cancer Gene Therapy 19:374, 2012.

Non-Muscle Invasive Bladder Cancer: NMIBC

NMIBC is a common cancer in need of new therapies



4TH MOST COMMON CANCER IN MALES BEHIND ONLY LUNG, COLON, PROSTATE

In the United States[1]

81,000
NEW CASES IN 2018

708,000
PREVALENT CASES IN 2015

5TH MOST COMMON CANCER OVERALL IN EU

EU and Worldwide[2,3]

141,000
EU EXPECTED NEW CASES IN 2020

550,000
WORLDWIDE NEW CASES/YEAR

Quality of Life Issues

Repeated recurrence
Repeated cystoscopy, surgery and drug treatment cycles
Lifelong cystoscopy follow-up
Most expensive cancer to treat

No New Drugs in 20 Years

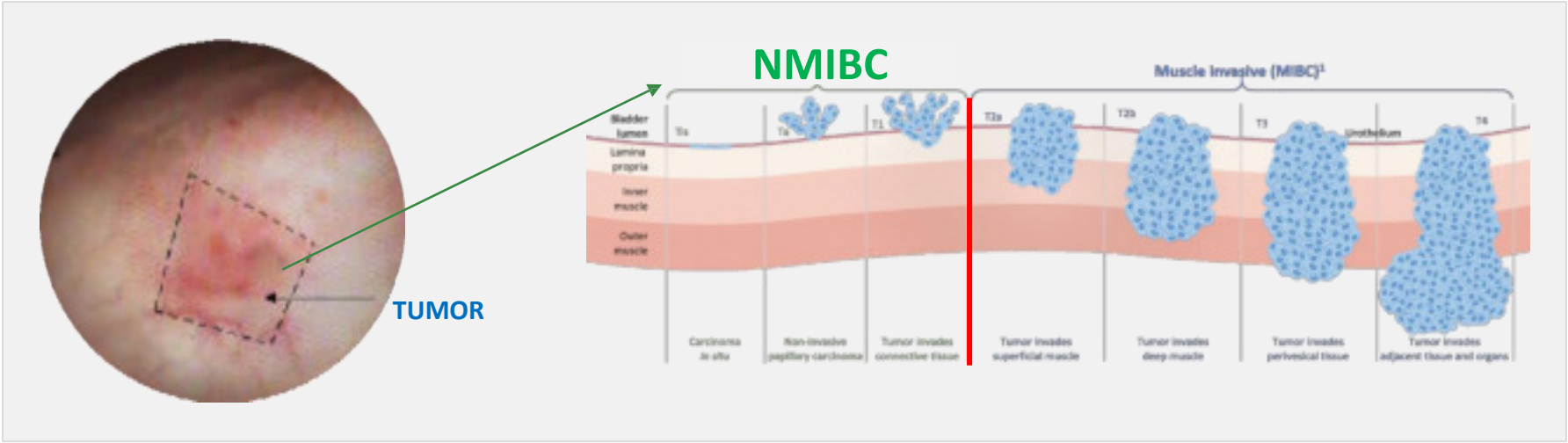
0

Drugs approved by FDA since 1998 for NMIBC

1. ACS Cancer Facts and Figures 2018, www.cancer.org; 2. https://ec.europa.eu/jrc/en/publication/epidemiology-bladder-cancer-Europe; 3.https://wcrf.org/dietandcancer/cancer-trends/bladder-cancer-statistics

NMIBC Classification and Treatment

Recurrence leads to progression and metastasis

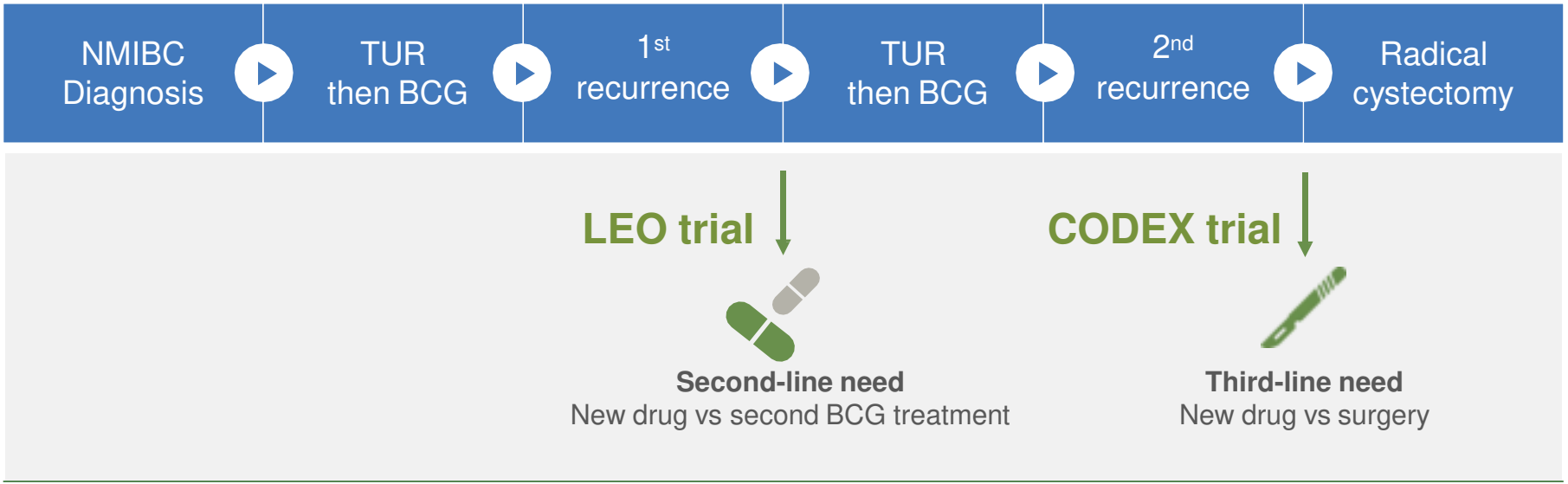


DIAGNOSIS	LOCALIZATION	THERAPY
Patients are diagnosed and evaluated via cystoscope	Tumors are identified on the inner surface of the bladder, resected and classified by depth	NMIBC patients initially receive Bacillus Calmette Guerin (BCG) and are the focus of inodiftagene therapy

Sources: Knowles MA and CD Hurst, 2015. *Nature Rev Cancer*, 15: 25-41, Link. : NCCN Bladder Cancer Guidelines, v. 1.2017.

Two Unmet Needs in NMIBC Therapy

Inodiftagene addresses both



90,000 patients whose tumors recur after one or two courses of BCG are eligible for inodiftagene annually in the US, EU and Japan

Three Studies Support Path to Potential Approvability

Inodiftagene Clinical Data in NMIBC in Three Clinical Trials

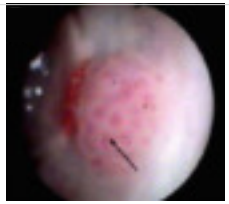
Inodiftagene results in 33% complete responses in marker papillary tumors, 86% (6/7) CRs in CIS alone and with BCG

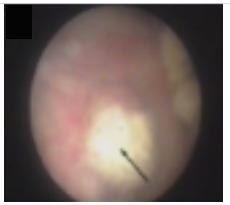
Safety observations: no DLT or MTD in phase 1 study, 23% related AEs in phase 2, 3/47 patients with SAEs

In phase 2 monotherapy trial, 32% 24-month DFS

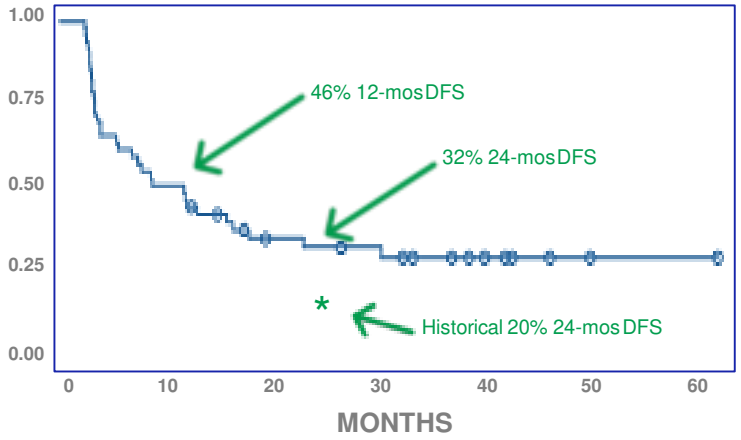
- FDA specified in CIS 30% recurrence-free rate at 18-24 months, excluding 20%, as being an approvable endpoint enpoint[1]
- Phase 2 papillary study demonstrates 18- and 24- month rates are >30% (right)

Inodiftagene in combination with BCG shows 3-mo and 6-mo DFS of 95% and 74%





L: Baseline: papillary tumor
R: 3 weeks following 6th instillation of inodiftagene: necrosis

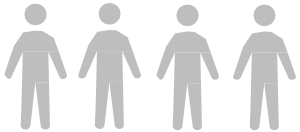


1. Jarow et al., J. Urology, 2014

Pathway to Registration in Two Discrete Indications

Inodiftagene registrational program

Codex



Codex phase 2 pivotal study
trial is a single-arm path with FDA concurrence designed for approval in **third line** patients

Monotherapy, 140 patients, single arm

Open label, interim analysis at 35 patients essentially allows repeat of phase 2 experience in US

Open to enrollment in US

Leo

Leo phase 3 pivotal study
trial is approved under SPA and will support indication in **second line** patients

Combination therapy, 500 patients, randomized

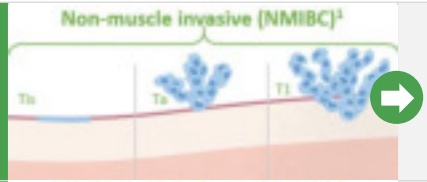
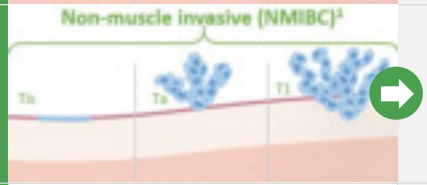
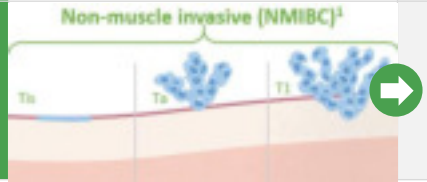
Trial has been granted an SPA by the FDA

This trial is complementary to the phase 2

These two trials provide independent routes to potential approval in two separate (but related) indications

Unique Strategy for Inodiftagene Approval in Two Indications

Inodiftagene clinical development strategy

Standard of care		**TUR BCG 1L**	→	**Recurrence TUR, BCG 2L**	→	**Recurrence Cystectomy**
Codex		TUR BCG	→	Recurrence TUR, BCG	→	Recurrence **Inodiftagene 3L**
Leo		TUR BCG	→	Recurrence TUR, BCG **Inodiftagene 2L**	→	Recurrence Cystectomy

Development plan in second-line patients, the Leo patient population, addresses the majority of the market potential of NMIBC therapy

Codex Milestones: Update

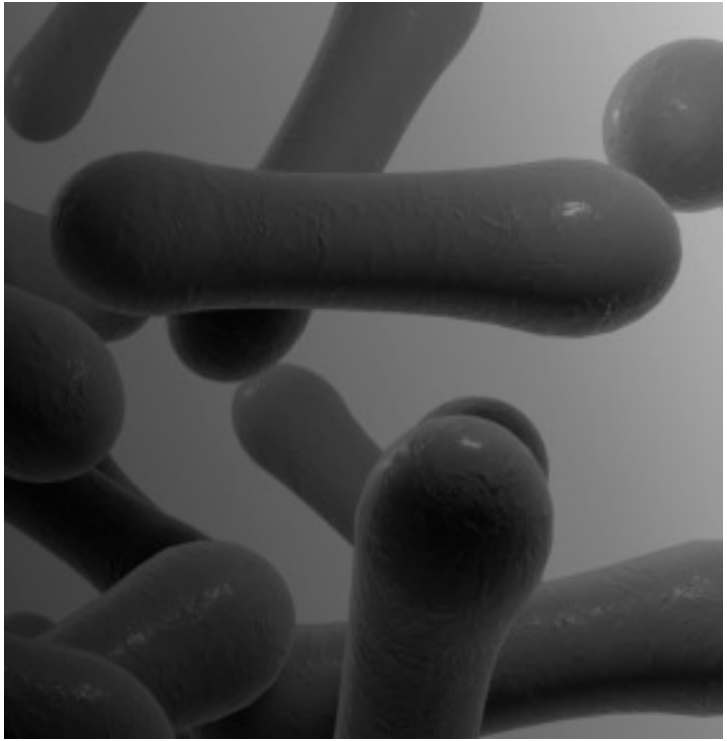
Clinical trial timelines

CURRENT STATUS:

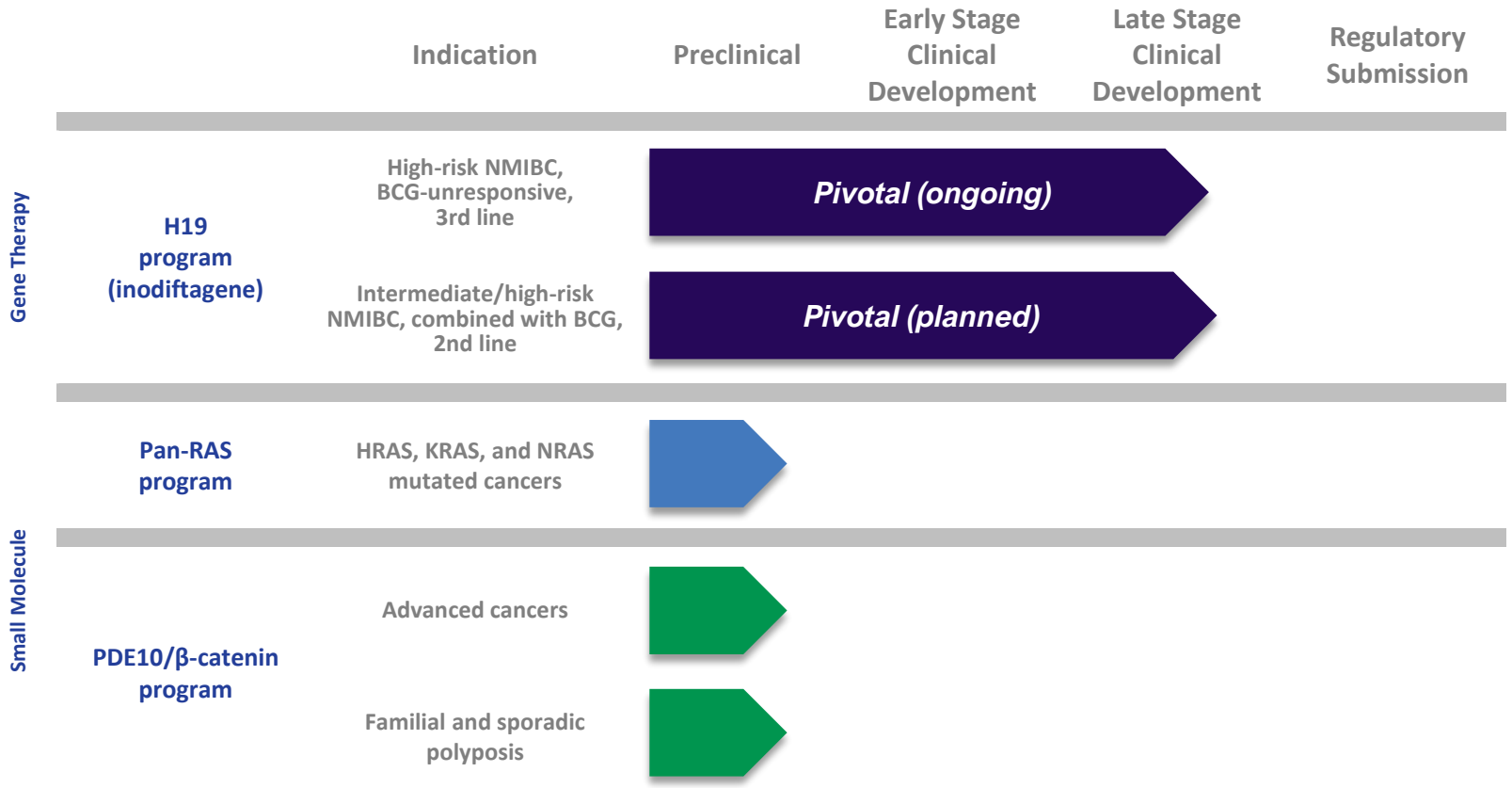
31 patients consented or enrolled, 23 patients dosed

Initial interim analysis will be performed tabulating 12-week CRs in first 35 CIS patients

We anticipate interim 12-week data from 35 patients will be available in 1Q2020

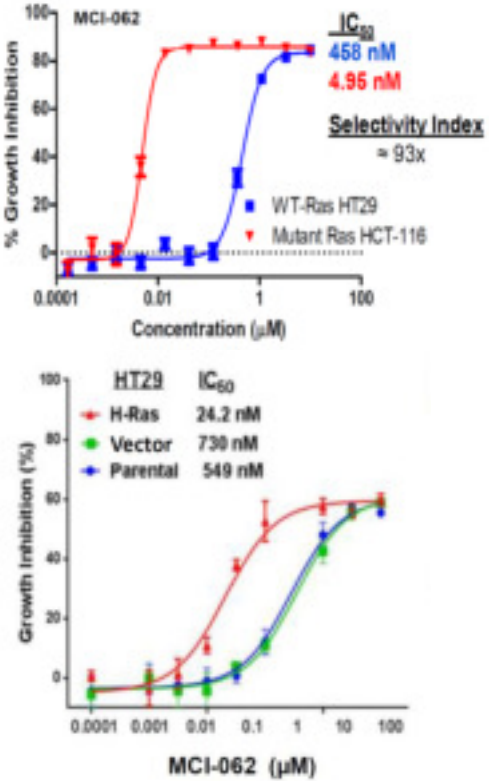


Anchiano Pipeline



RAS Inhibition by ADT Compounds

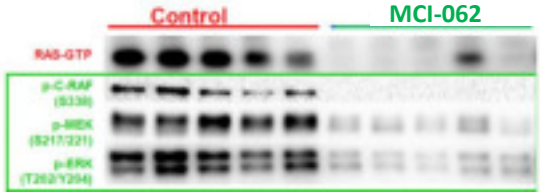
Cell Line	Tumor Origin	Mutation	Sensitivity (IC_{50} nM)
Hs578	Breast	HRAS G12D	3.9
MDA-MB-231	Breast	KRAS G13D	3.6
HCT116	Colon	KRAS G13D	4.7
HT29	Colon	WT RAS / mut. RAF	512
SW480	Colon	KRAS G12V	6.5
A548	Lung	KRAS G12S	6.8
H1975	Lung	WT RAS / mut. EGRF	3.9
H1299	Lung	NRAS Q61K	2.4
H3322	Lung	WT RAS	9600
NHAEC	Normal Lung	WT RAS	19100
SK-MEL-2	Melanoma	NRAS Q61K	2.1
SK-MEL-28	Melanoma	WT RAS	>25000
B16	Melanoma	WT RAS / mut. PDGFR	5.8
OV90	Ovarian	WT RAS	350
SKOV3	Ovarian	WT RAS / mut. NF1	6.7
BxPC3	Pancreatic	WT RAS / mut. RAF	~2500
CFPAC-1	Pancreatic	KRAS G12V	5.8
Mia PaCa-2	Pancreatic	KRAS G12C	2.1
PANC-1	Pancreatic	KRAS G12D	2.4
SW-1990	Pancreatic	KRAS G12D	6.3

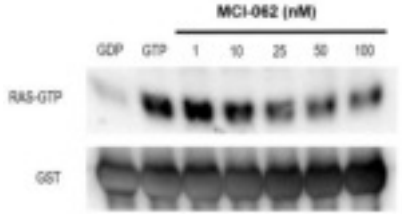


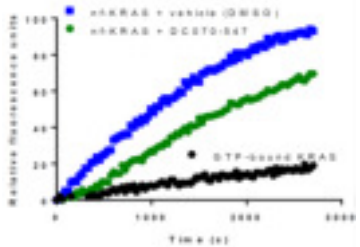
- RAS inhibition has recently been clinically validated with inhibitors of KRAS G12C mutants, a subset of RAS mutations that overall occur in 30% of cancer patients
- Opportunity exists for more broadly active agents
- Our compounds identified in extensive cell screen, are specific for mutant and active RAS, not specific isoform or mutation
- <10 nM cellular potency, >100 fold selectivity; sensitivity is conferred with transfection of mutant RAS

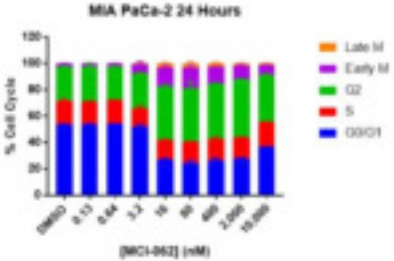
Source: Keeton et al., Mattox et al. AACR 2019

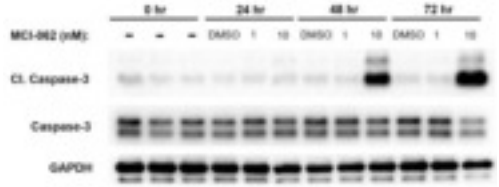
Characterization of RAS Inhibitors

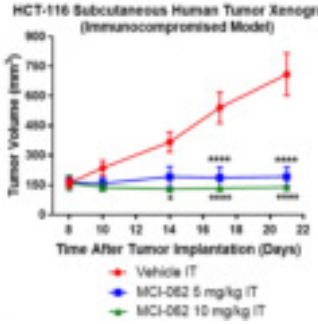










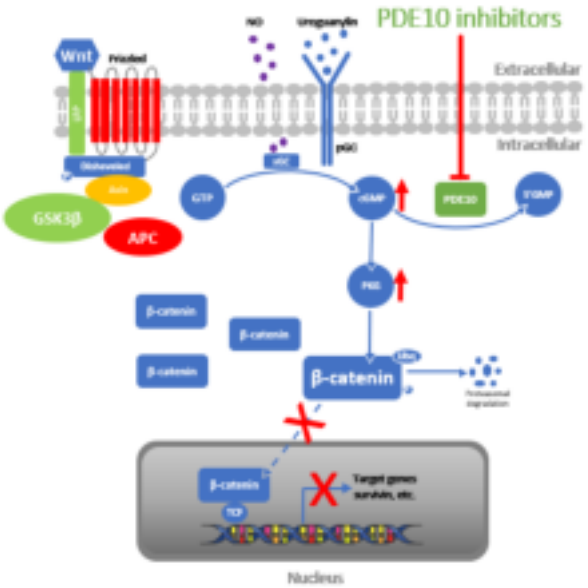


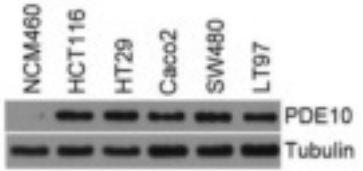
CT26 CRC line
D17 control (L), 062 (R)

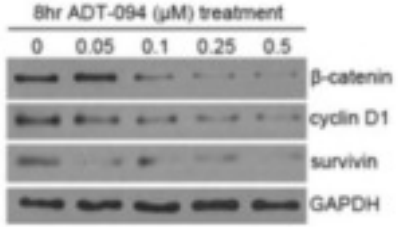
- Compound inhibits downstream signaling through RAF and PI3K pathways; in nucleotide-free RAS system decreases RAS-GTP in activated RBD pulldown; displaces binding of GTP from nf-RAS in GEF experiments
- Initiates cell-cycle arrest and induces apoptosis
- Reduces PD-L1 expression in tumor cells in vitro and in vivo, reduces PD-1 in TILs (not shown)
- Active in vivo
- In short, compounds have many of the characteristics of KRAS G12C inhibiting molecules, but with broad activity

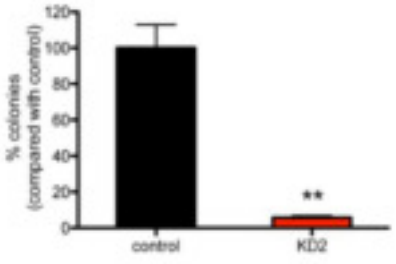
Source: Keeton et al., Mattox et al. AACR 2019

PDE10 Inhibition to Inhibit β–catenin









- The WntAPC/β-catenin pathway is altered in the great majority of colon cancers, as well as other types. The final common pathway is impaired degradation of β-catenin activity and potentiation of its activity in the nucleus
- PDE10 is overexpressed in colon adenoma and cancer, and its expression in lung cancer confers worse prognosis
- Inhibition of PDE10 decreases β-catenin mRNA and protein levels, and is a potent suppressor of tumor cell growth
- Our agents have potential for development in FAP, colon cancer, HCC, lung and other cancers

Source: Li et al., 2015; Lee et al., 2015

Key Takeaways

Inodiftagene vixteplasmid is a first-of-its-kind gene therapy for NMIBC

Preliminary data from development program and FDA SPA path to potential approval

Codex pivotal trial underway, with data coming soon

Expanded pipeline, with intake of pan-RAS inhibitor compounds, offers the potential to treat a broad spectrum of tumor types and patient populations

Strong balance sheet: $27M cash end Q2

Experienced management team with history of successful commercialization and expanding global organization