

Anchiano

therapeutics

INODIFTAGENE

Gene Therapy for Bladder Cancer

March 2019



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Inodiftagene for Non-Muscle Invasive Bladder Cancer

INODIFTAGENE

First-in-class, DNA-based gene therapy moving into registrational development in early stage bladder cancer

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


Conducting 2 pivotal trials, each of which could lead to approval. The first is open to enrollment, the second planned for 2019

Non-Muscle Invasive Bladder Cancer (NMIBC)

A large and underserved population

More than \$1.5 billion commercial global opportunity

Current standard-of-care is a therapy introduced in the 1970s; patients who relapse go on to radical surgery or distant metastasis



Potential market of
\$1.5 billion

Non-Muscle Invasive Bladder Cancer: NMIBC

NMIBC is a common cancer in need of new therapies



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

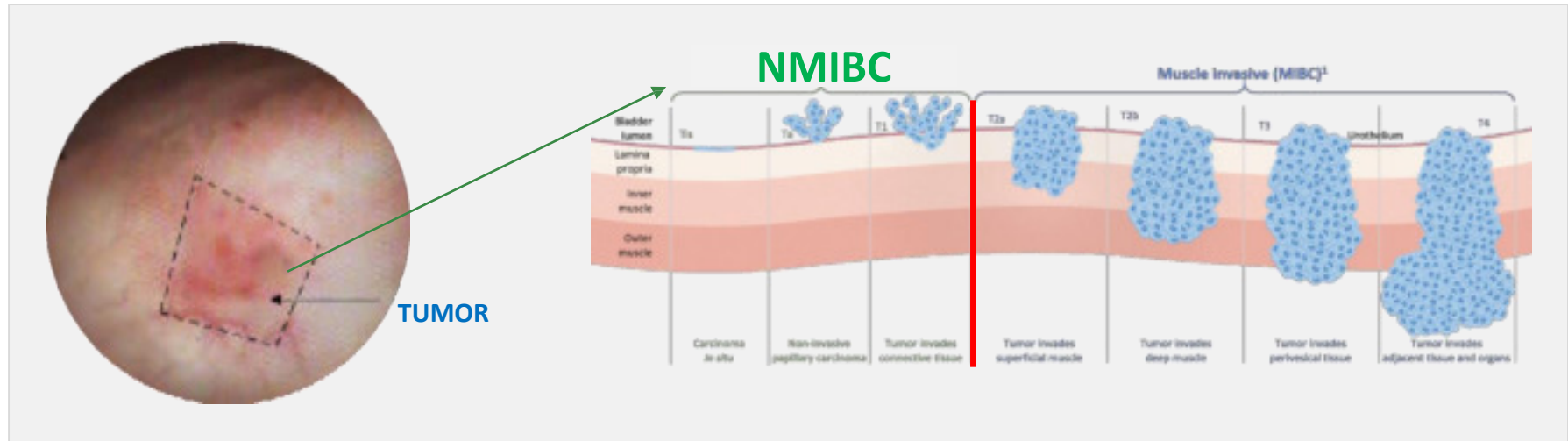
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Drugs approved by FDA since 1998 for NMIBC

NMIBC Classification and Treatment

Recurrence leads to progression and metastasis



DIAGNOSIS

Patients are diagnosed and evaluated via cystoscope

LOCALIZATION

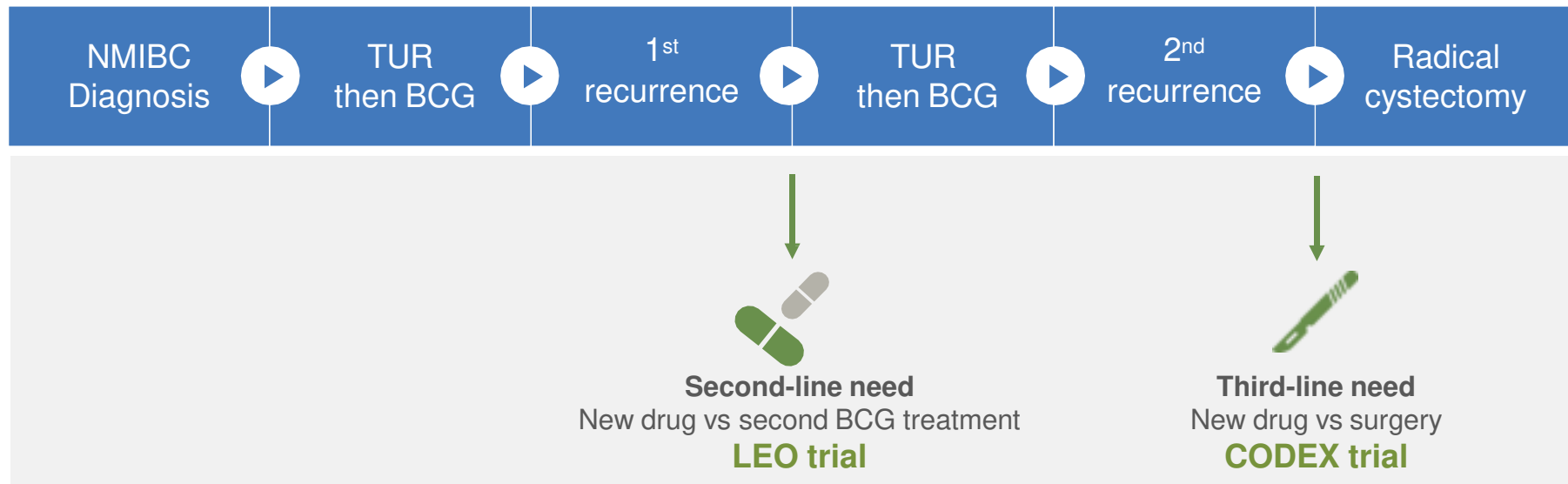
Tumors are identified on the inner surface of the bladder, resected and classified by depth

THERAPY

NMIBC patients initially receive Bacillus Calmette Guerin (BCG) and are the focus of indifitogene therapy

Two Unmet Needs in NMIBC Therapy

Inodiftagene addresses both



Patients whose tumors recur after one or two courses of BCG are those who are eligible for inodiftagene

Over 90,000 NMIBC Patients Are Eligible for Inodiftagene Annually

285,000 constitute NMIBC global incident and recurrent population



260,000

Number of incident bladder cancer cases in 2017 in US, EU, and Japan



195,000

Cases of bladder cancer that is NMIBC, about 70-80% of total



90,000

Annual number of NMIBC patients who suffer recurrence after treatment



285,000

Total number of incident and recurrent NMIBC cases who are eligible for treatment annually

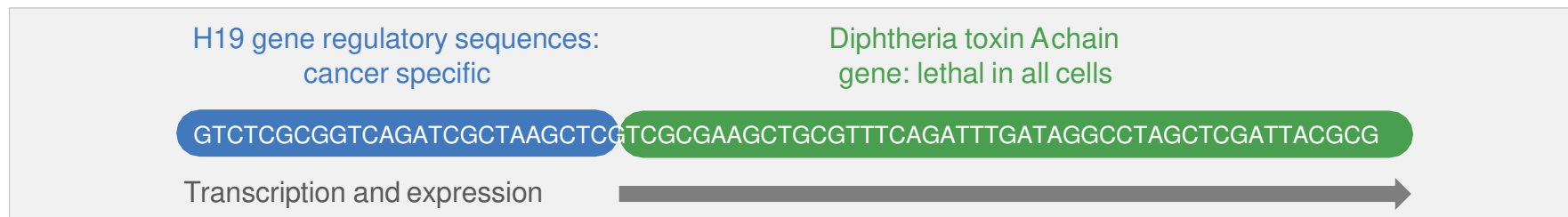
Of these, approximately **90,000** intermediate and high-risk patients whose first-line or second-line BCG therapy has failed are eligible for therapy with inodiftagene

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

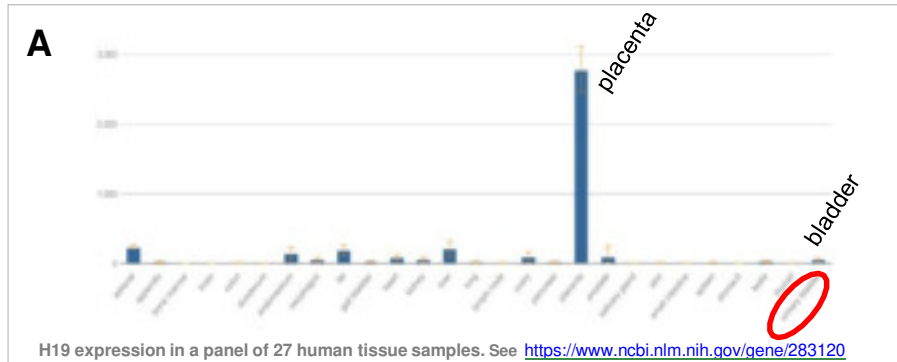
Plasmid facilitates high transfection efficiency. In vitro uptake demonstrable in 85% of cells after a single exposure; in clinic detectable in bladder more than 48 hours after instillation, and administered weekly to every third week for up to 3 years

Well-understood and validated mechanism-of-action

Lethal inhibition of protein synthesis

Uses H19 to Target Cancer Cells Avoiding Normal Cells

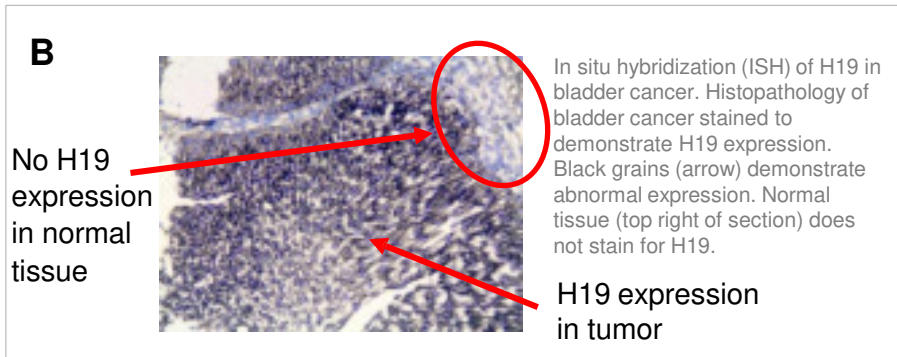
Inodiftagene mechanism of action



H19 is not normally expressed in adult tissues, but is expressed in a variety of human cancers

Figure A: Shows virtually **no H19 expression in normal human tissues** including in normal bladder (in red circle)

Figure B: H19 expression has been identified broadly in human cancers, including **especially bladder carcinoma**

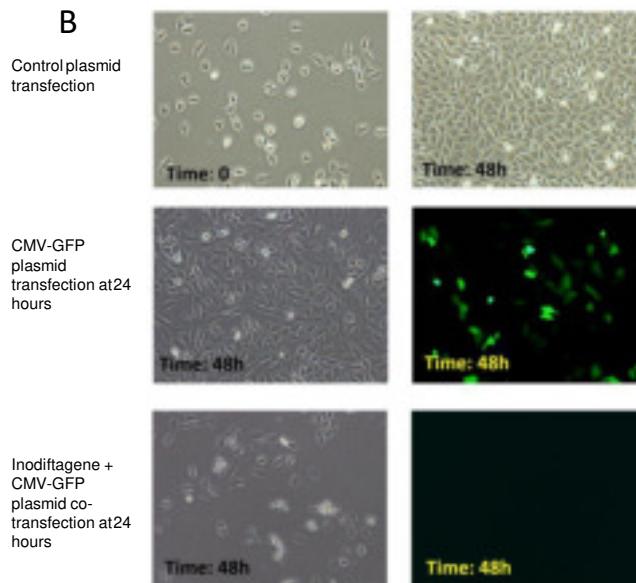
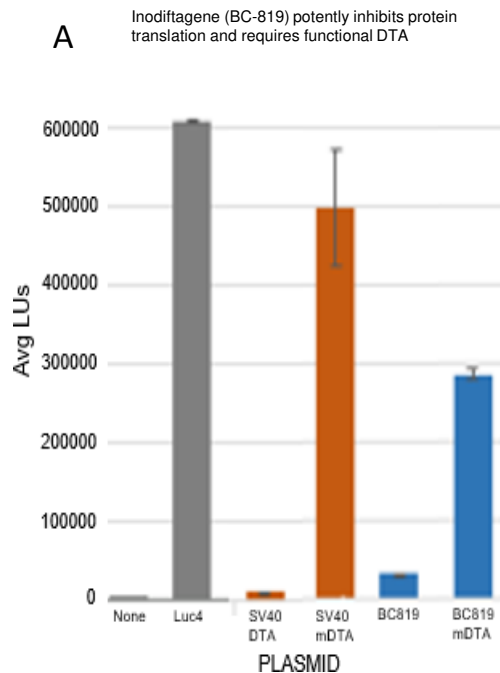


H19 is expressed in all subtypes of NMIBC, including carcinoma in situ (CIS)

In our phase 2 study of inodiftagene, 96% of screened patients expressed H19, and **all 47 entered patients demonstrated H19 expression.**

Inodiftagene Inhibits Protein Translation and Cell Proliferation

In vitro studies demonstrate mechanism of action



Inhibition of protein translation and proliferation by inodiftagene in tissue culture

Inodiftagene potently inhibits luciferase translation and is specific to the activity of functional DTA (A)

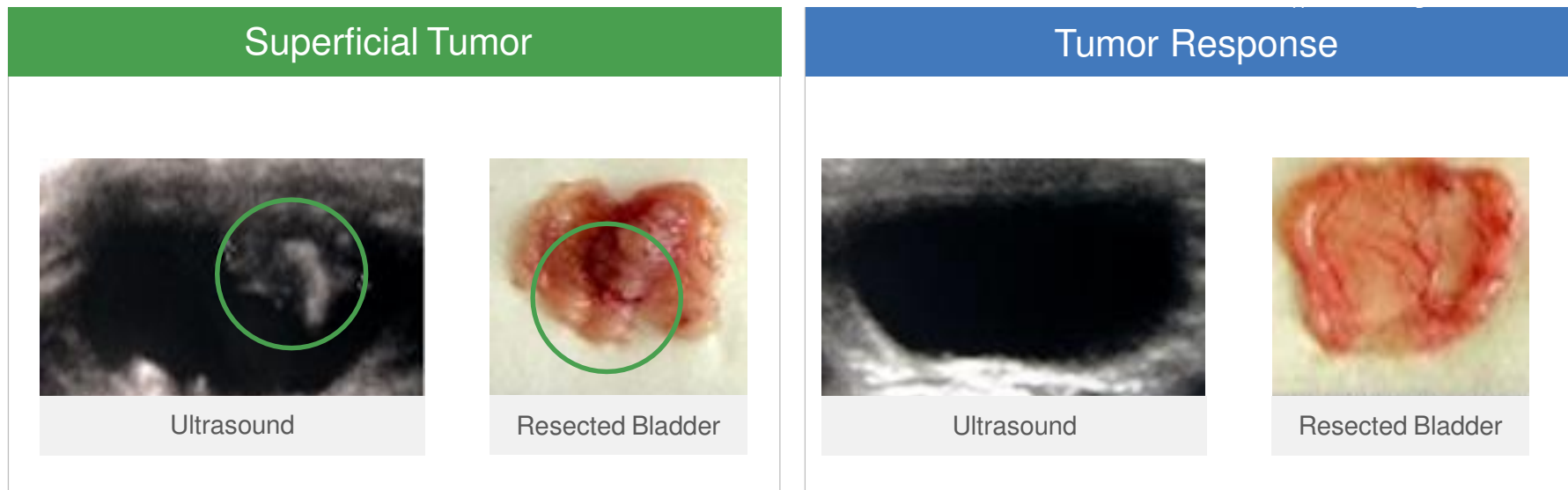
Inodiftagene inhibits translation and bladder cancer cell proliferation (B)

Inodiftagene activity was investigated in tissue culture. Bladder cancer cells were transfected with plasmid/PEI under various conditions. (A) Co-transfection of a luciferase reporter plasmid with inodiftagene (BC-819 in the figure) and control plasmids shows inhibition of luciferase activity by inodiftagene and DTA plasmid BC-821 but not by a variety of plasmids lacking DTA. (B) DTA expressed from an SV40 promoter or in inodiftagene (BC-819) potently inhibits luciferase. Constructs containing attenuated DTA carrying point mutations (mDTA) are less effective, demonstrating specificity of inhibition to active DTA. (C) Inodiftagene co-transfected with a green fluorescent protein (GFP)-producing plasmid into bladder cancer cells demonstrates inhibition of proliferation and abrogation of translation of GFP.

Effective in Eliminating Experimental Bladder Cancer

Inodiftagene in vivo

Animal model data demonstrate that intravesical instillation of inodiftagene eliminates rat bladder cancers. Analysis of inodiftagene-treated rat bladders by ultrasound and at necropsy shows progression of experimentally induced tumor when treated with control vector (left) but absence of tumor when treated with inodiftagene (right).

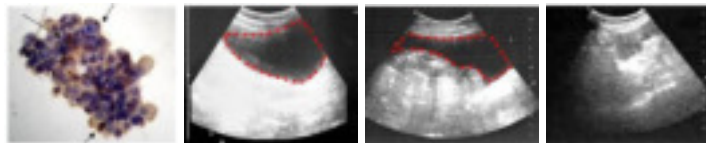


Wistar rats received N-butyl-N(4-hydroxybutyl) nitrosamine (BBN), a potent carcinogenic alkylating agent, in drinking water for 5-30 weeks. Tumors were evident by 10 weeks, with superficial invasion evident by 15 weeks and typically deep invasion by 20 weeks. At 19 weeks 100 ug of control luciferase vector (left) or inodiftagene (right) was instilled weekly for 5 weeks intravesically.

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

Complete resolution of refractory malignant ascites in ovarian cancer patient who received inodiftagene injected intra-abdominally as compassionate use¹

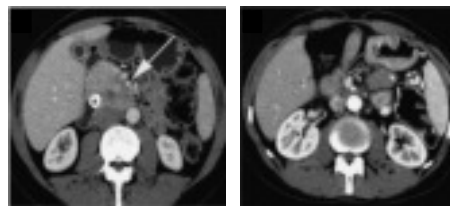
Advanced pancreatic cancer responses to monotherapy: 2 partial responses with inodiftagene alone

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	PR	Chemotherapy
2	204	PD ^a	PR ^b	None
2	205	SD	PR	Chemotherapy
2	301	PD	SD	Chemotherapy
2	501	SD	PR	Surgery
2	604	SD ^a	PR ^b	None
2	1102	SD	SD	Chemotherapy - Complete Resection at 3 months

Partial responses observed in 2/9 patients with advanced localized pancreatic cancer who received only inodiftagene intratumoral injection; third patient had complete control of tumor following chemo-radiation and resection (shown)². In additional trial with gemcitabine, 1/12 partial responses

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



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

Three Completed NMIBC Trials Support Pivotal Study Designs



Inodiftagene clinical strategy

CLINICAL PROGRAM	Trial	Status	Result
	Phase 1/2 Monotherapy	Complete; N = 18	Well tolerated, no DLT or MTD identified at doses tested; 22% complete responses in marker tumors
	Phase 2 Monotherapy	Complete; N = 47	33% complete responses in marker tumors; 46% durable response rate at 1 year
	Phase 2 Combination with BCG	Complete; N = 38	3 month DFS 95%; 6 month DFS 78%; median time to progression not yet reached

Trial Results Support Path to Approval Based on FDA Guidance

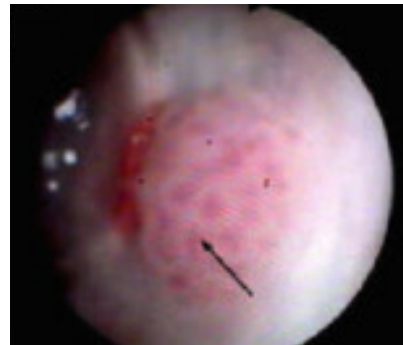
Complete Responses in all Three NMIBC Trials

Inodiftagene consistently showed clinically meaningful anti-cancer activity

Complete responses observed in 17/57 patients (30%) in two monotherapy trials demonstrating activity against unresected papillary cancer

In addition, **complete responses in 6/7 (86%) of CIS patients** (most in combination study) at 3 months

This is not standard of care: it is an investigative approach to demonstrating anti-tumor activity and is FDA-recommended



Baseline
papillary tumor



3 weeks following 6th instillation of inodiftagene
complete resolution

Durability of Response Demonstrated in Phase 2 Monotherapy Trial

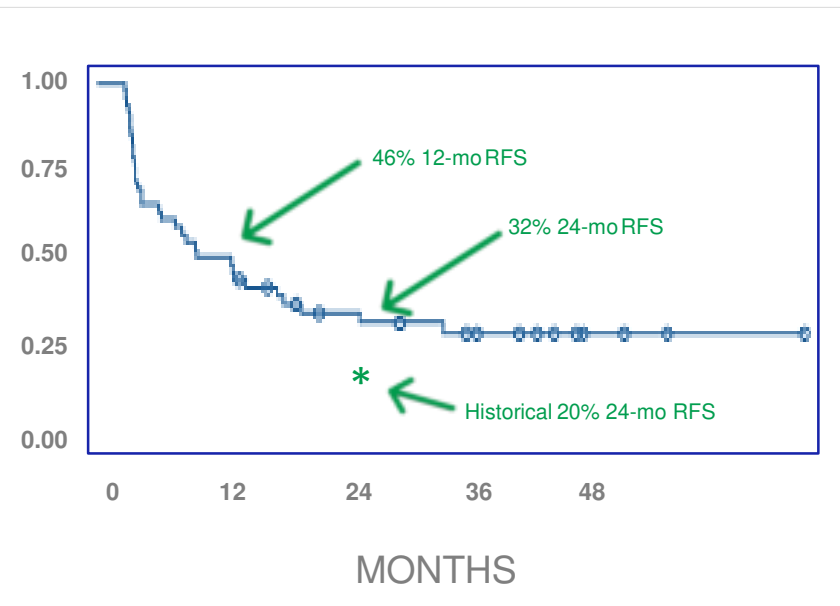
Inodiftagene phase 2 monotherapy results

33% CR rate in marker lesions

46% 12-month RFS rate

23% of patients has adverse events (AE) thought related to treatment; overall **3/47** serious adverse events (SAEs)

18- and 24-month RFS rates are ~**32%**. FDA guidance suggests >30% RFS rate at 18-24 months as being approvable in CIS in adequate population.¹



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

Codex Study (204 Trial): Initial Registrational Trial Design

Inodiftagene phase 2 trial in third-line patients

SINGLE ARM TRIAL

For approval

OPEN TO ENROLLMENT

Actively recruiting

OPEN LABEL

interim analysis of CR rate at or before
35 CIS patients beginning at 3 months

FDA AGREEMENT

stated single-arm study could lead to
approval. EU and Canadian regulators also
support study conduct

Third-line patients: high-risk BCG-unresponsive NMIBC
after two failed courses of BCG

N = approximately 140 patients



Inodiftagene administered QW x 10 weeks
then Q3W

Leo Study (301 Trial): Second Registrational Trial Design

Inodiftagene phase 3 trial in second-line patients

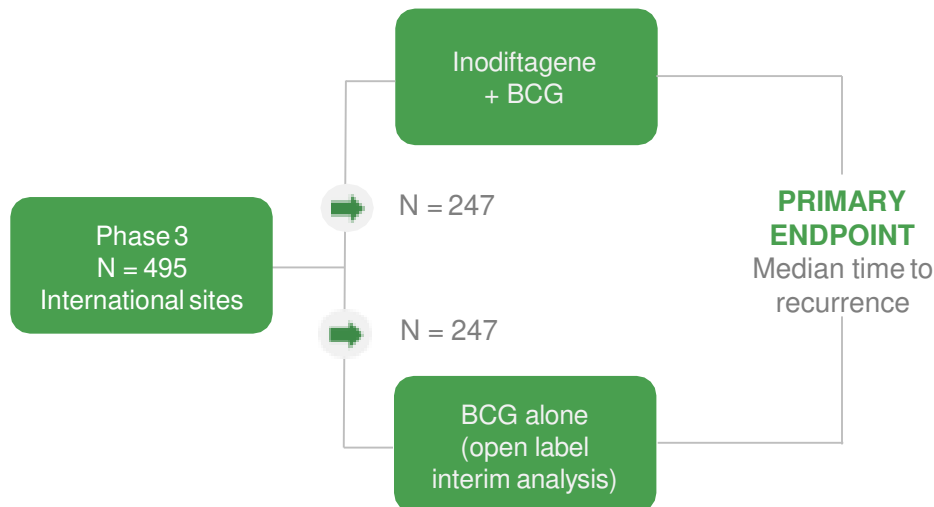
RANDOMIZED TRIAL

For approval

FDA REVIEWED, GRANTED SPA,
certifying it could meet condition for full approval¹

SPANISH, GERMAN, CANADIAN, UK
AND FRENCH REGULATORS
support study conduct as well

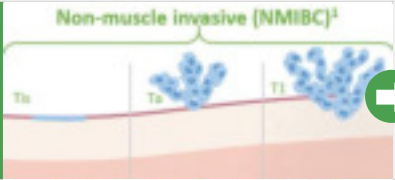
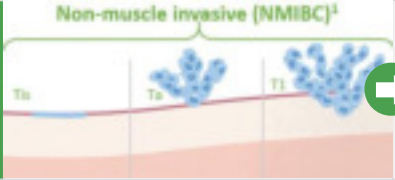
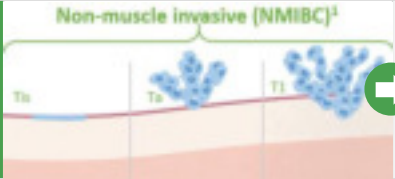
Second-line patients: intermediate or high risk NMIBC
after one failed course of BCG
N = approximately 495 patients



1. Granting of an SPA does not guarantee approval even if trial is positive

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

Experienced Management Team

US-based clinical development team with record of US approvals with FDA



Frank G. Haluska, MD, PhD
President and
Chief Executive Officer

Former Harvard Medical faculty,
ARIAD CMO, led global research team
and two oncology drug approvals



Jonathan Burgin, MBA, CPA
Chief Financial Officer and
Chief Operating Officer

Former Anchiano CEO, CFO of
TASE and Nasdaq companies



David Kerstein, MD
Chief Medical Officer

Former Takeda Lung Cancer Clinical
Portfolio Strategy Lead



Ron Knickerbocker, PhD
Senior Vice President of
Clinical Development and Data Sciences

Designed and analyzed clinical trials
for two successful NDAs



Sean Daly
Vice President of
Clinical Operations

Successfully conducted clinical trials
supporting two approvals



Michal Gilon, PhD
Vice President of Research and
Development

Extensive research experience in the
fields of molecular and developmental
biology



Funding Plans and Upcoming Milestones

Clinical trial timelines

4Q 2018: Codex trial initiated for registration of inodiftagene

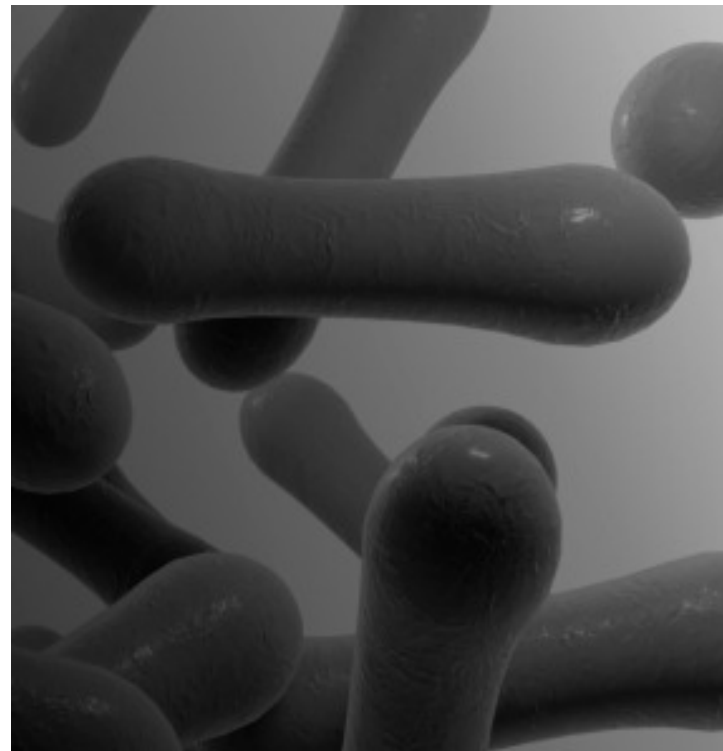
1Q 2019: \$30.5M IPO on Nasdaq (ANCN)

2Q 2019: Open label Codex data will begin to become available

3Q 2019: Complete 35 patient enrollment for interim analysis

4Q 2019: Final Codex interim analysis

4Q 2019- 1H2020: Initiation and first patient enrolled in Leo



Key Takeaways



Inodiftagene vixteplasmid is a first-of-its-kind gene therapy in non-muscle invasive bladder cancer (NMIBC)



Over \$1.5 billion commercial potential serving large global population in need of new therapy and addressing second line treatment



Preliminary data from development program and FDA agreement form foundation for path to approval with either of two trials



Strong balance sheet: \$30.5M US IPO (Nasdaq: ANCN) closed in February



Two registrational studies provide independent routes to approval in two separate, but related, indications. The first is open to enrollment



Experienced management team with history of successful drug development and newly expanding global organization