

A new Era in Oncology



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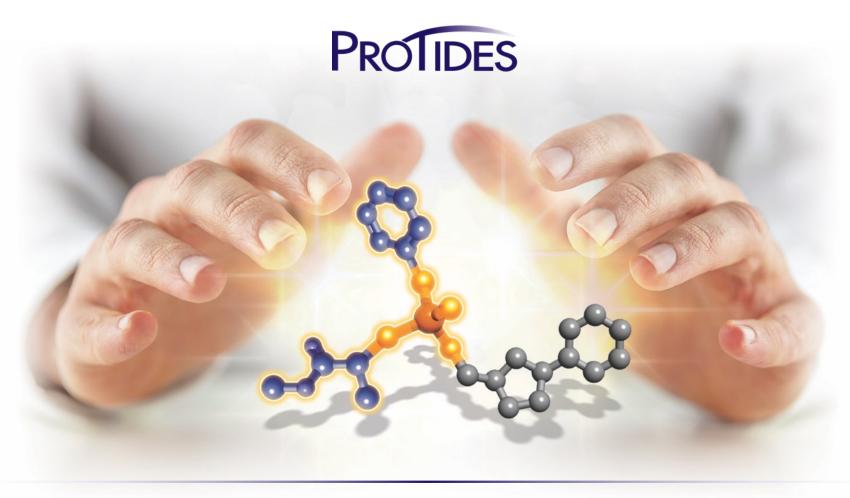
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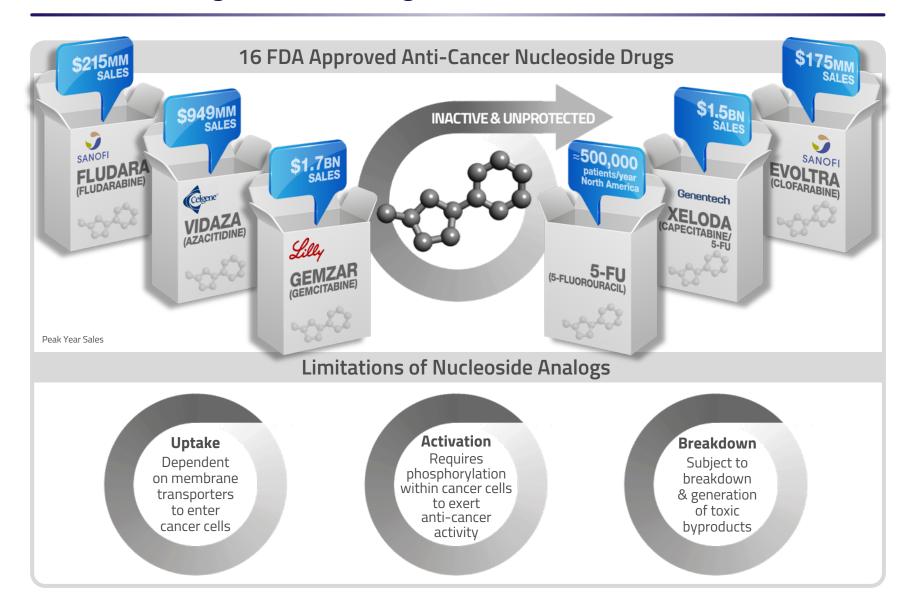
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Harnessing the Power of Phosphoramidate Chemistry

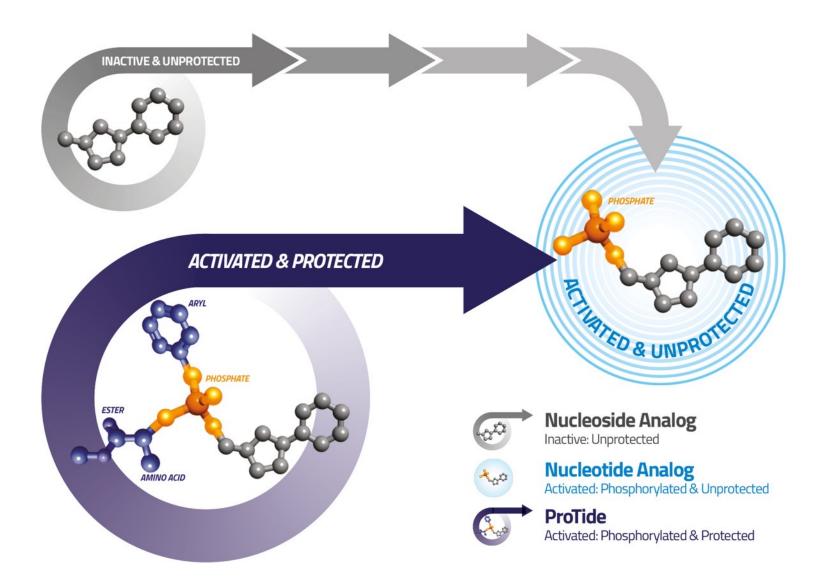


A New Era in Oncology

Nucleoside Analogs: Flawed ProDrugs



Transforming Nucleoside Analogs into ProTides



ProTides: A New Era In Anti-Virals

















Veklury® remdesivir



Transforms Therapeutic Index

Overcomes Viral Resistance Mechanisms

^{*} Sovaldi + Harvoni + Epclusa + Vosevi cumulative sales through 30 June 2021

^{**} Genvoya + Descovy + Odefsey + Biktarvy + Symtuza cumulative sales through 30 June 2021

ProTides: A New Era in Oncology















Transforms Therapeutic Index

Overcomes Cancer Resistance Mechanisms

¹ Efficacy evaluable patients with advanced biliary tract cancers (n=16) - McNamara et al. (2020) The Oncologist;25: 1-10

² Pre-clinical data - Ghazaly et al ESMO September 2017

³ Pre-clinical data – Symeonides *et al* ESMO September 2020

Development Status: Current

	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3
ACELARIN				
Biliary				
NUC-3373				
Solid Tumors				
Colorectal				
NUC-7738				
Solid Tumors				

Development Status: Planned End 2021

-ACELA?	///	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3
Biliary					
NUC-337	73				
Solid Tumors					
Colorectal					
NUC-773	38				
Solid Tumors					

Strong Balance Sheet & Multiple Inflection Points





Cash & Cash Equivalents at June 30, 2021 ~\$101 million* **Important Data Readouts**

throughout **2021 & 2022**

*Based on exchange rate of £1.00 to \$1.38 at 30 June 2021

Well Capitalized to Achieve Key Milestones



- Complete ongoing Phase 3 BTC study (NuTide:121)
- File NDA for BTC

NUC-3373

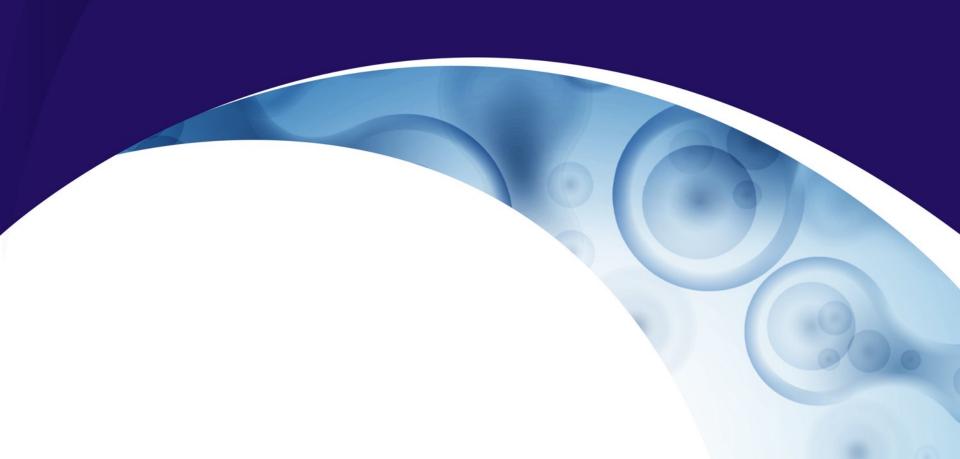
- Complete ongoing Phase 1 solid tumor study (NuTide:301)
- Complete ongoing Phase 1b/2 CRC study (NuTide:302)
- Initiate & complete Phase 3 CRC study (NuTide:323)
- Initiate & complete Phase 1b solid tumor basket study (NuTide:303)
- File NDA for CRC

NUC-7738

- Complete ongoing Phase 1 study (NuTide:701)
- Initiate & complete Phase 2 study



A transformation of gemcitabine



CELAPIN: Overview of Gemcitabine



- WHO list of essential medicines
- First approved for medical use in 1995
- Approved in pancreatic, ovarian, breast & lung
- Widely used in other cancers
- Peak annual sales of \$1.7 billion





Limitations of Gemcitabine



UptakeDependent on membrane transporters to enter cancer cells

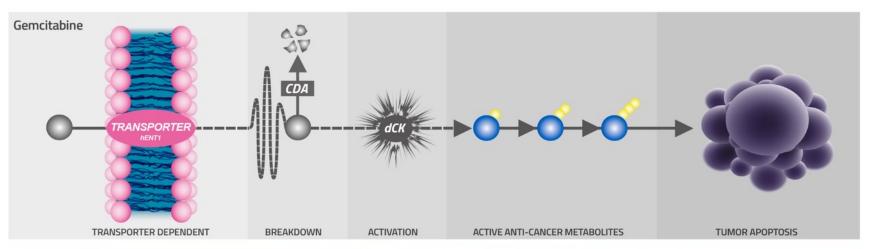


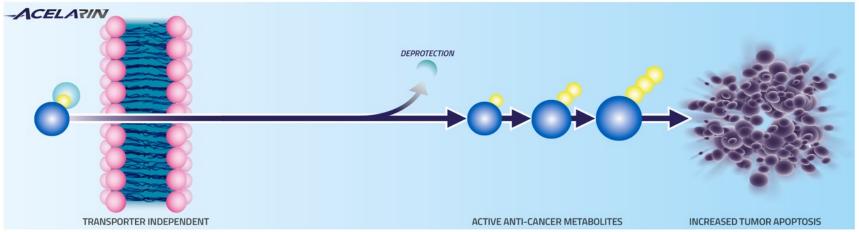
BreakdownSubject to breakdown and generation of toxic
byproducts



Activation
Requires phosphorylation within cancer cells to exert anti-cancer activity

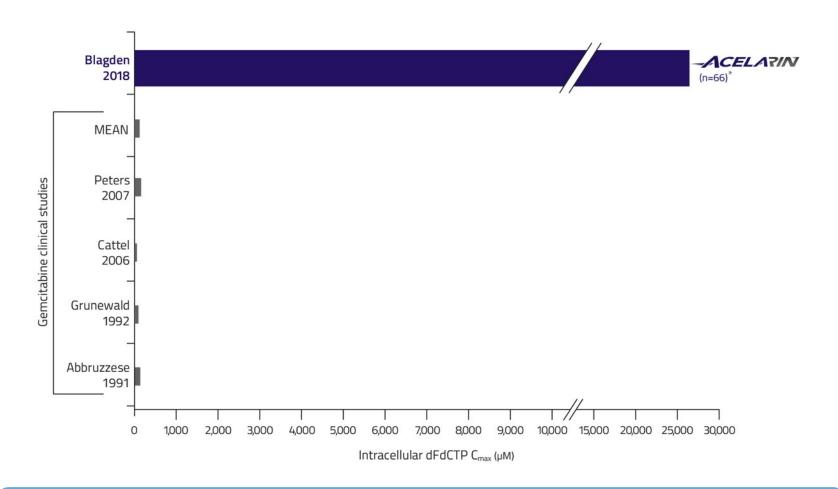
CELAPIN: Overcomes The Key Cancer Resistance Mechanisms







CELAPIN: Very High Intracellular dFdCTP (Cmax)

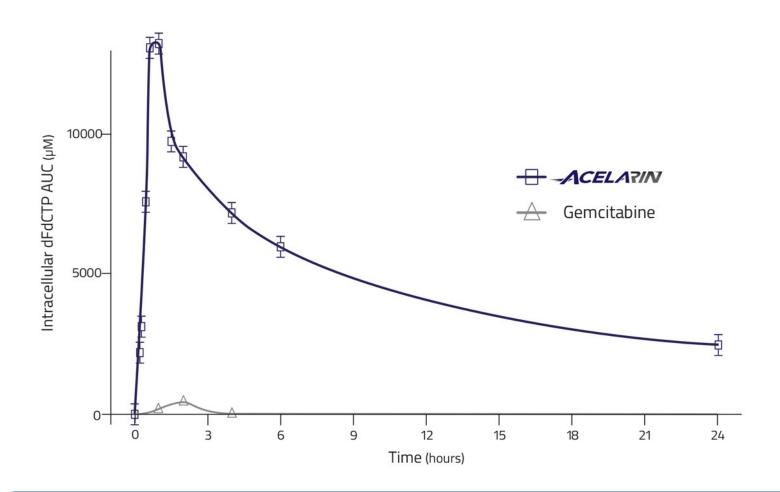


CELATIN achieved 217x higher intracellular levels of dFdCTP than gemcitabine

Equimolar dose comparison

^{*} Blagden et al (2018) Br J Cancer; 119:815-822

ACELATIN: Very High Intracellular dFdCTP (AUC)



CELATIN achieved **139x** greater intracellular AUC of dFdCTP than gemcitabine

Blagden *et al* (2015) *J Clin Oncol*; 33; Suppl Abstract ID: 2547 (ASCO poster May 2015) Cattel *et al* (2006) *Annals Onc* (supp); 17: v142-v147 Blagden *et al* (2018) *Br J Cancer*; 119:815-822

CELATIN: Solid Tumor Phase 1 Study (monotherapy)



- Phase 1 dose-escalation study in patients with advanced solid tumors
- All patients had metastatic spread
- Rapidly progressing disease
- Exhausted all other therapeutic options
- Objective: Recommended Phase 2 dose

PRO-001

Number of patients

68

Evaluable patients (≥2 cycles)

49

Primary cancer types

19

Age (median)

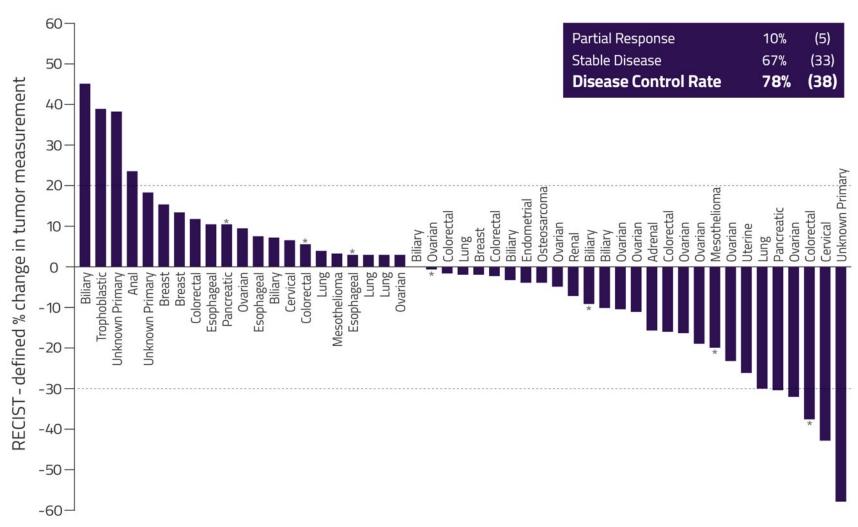
56 (range 20-83)

Prior chemotherapy regimens

(range 1-10)

Blagden et al (2018) Br J Cancer; 119:815-822

CELATIN: Solid Tumor Phase 1 Study Best Overall Response (monotherapy)



Evaluable patients (n=49) Blagden *et al* (2018) *Br J Cancer*; 119:815-822

PRO-001

CELAPINV: Ovarian Phase 1b Study (combination)



- Combination: Acelarin + carboplatin
- Dose escalation: 3 + 3
 - Acelarin: 500 mg/m² to 750 mg/m²
 - Carboplatin: AUC 4 to 5
- All patients had metastatic spread
- Rapidly progressing disease
- Objective: Recommended Phase 2 dose

PRO-002

Number of patients

25

Evaluable patients (≥1 cycle)

23

Age (median)

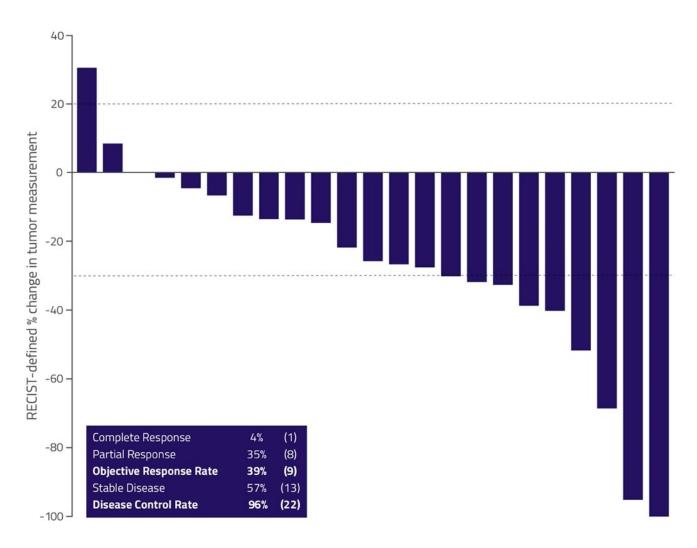
64(range 37-77)

Prior chemotherapy regimens

(range 2-8)

Blagden et al (2017) Ann Oncol; 28; Suppl 5 Abstract ID: 968P (ESMO poster September 2017)

ACELATIN: Ovarian Phase 1b Study Best Overall Response (combination)



Evaluable patients (n=23)
Blagden *et al* (2017) *Ann Oncol*; 28; Suppl 5 Abstract ID: 968P (ESMO poster September 2017)
Data as of September 2017

PRO-002

ACELATIN: Biliary Phase 1b Study (combination)



- First-line treatment
- Locally advanced or metastatic biliary tract cancer
- Objectives: Safety & dose selection
 - Cohort 1: Acelarin 625 mg/m² + cisplatin 25 mg/m² (n=8)
 - Cohort 2: Acelarin 725 mg/m² + cisplatin 25 mg/m² (n=6)
 - Cohort 3: Acelarin 625 mg/m² + cisplatin 25 mg/m² (n=7)

ABC-08

Number of patients

21

Evaluable patients*

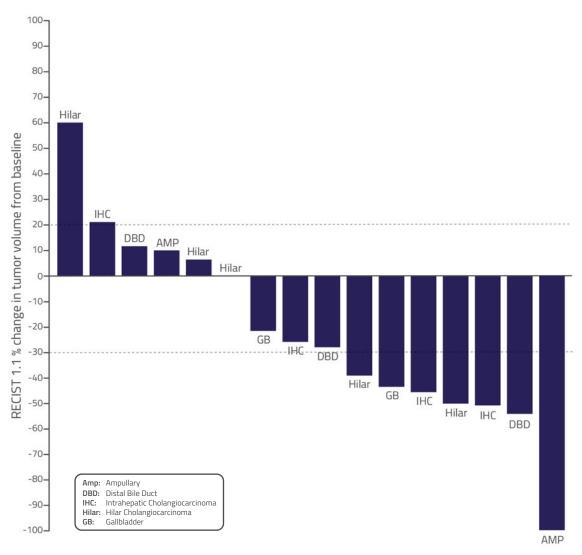
16

Age (median)

61 (range 47-78)

^{*} Efficacy evaluable patients: measurable disease at baseline; ≥1 cycle Acelarin; ≥1 follow-up radiographic assessment McNamara et al (2020) Oncologist; 26 (4):e699-e678

ACELATIN: Biliary Phase 1b Study Best Overall Response (combination)



McNamara *et al* (2020) *Oncologist*; 26 (4):e699-e678 Efficacy Evaluable Population

ABC-08

ACELATIN: ABC-08 and ABC-02 Comparison

ABC-08 Study

(625 & 725 mg/m²) + cisplatin

Complete Response

6% (1/16)

Partial Response

38% (6/16)

Objective Response Rate

44% (7/16)

ABC-02 Study

Gemcitabine

 $(1000 \text{ mg/m}^2) + \text{cisplatin}$

Complete Response

0.6% (1/161)

Partial Response

25% (41/161)

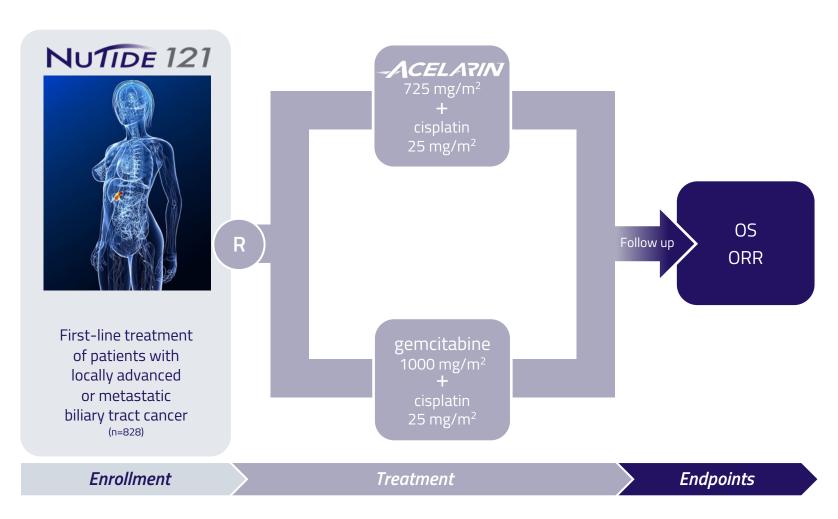
Objective Response Rate

26% (42/161)

McNamara *et al* (2020) *Oncologist*; 26 (4):e699-e678 Valle *et al* (2010). *N Eng J Med*; 362: 1273-1281 Efficacy Evaluable Population

ABC-08

CELAPIN: Ongoing Biliary Phase 3 Study





CELATIN: Ongoing Biliary Phase 3 Study (Statistical Plan)

NUTIDE 121 Primary Endpoints: OS; ORR

RECRUITMENT	FOLLO	OW UP	FINAL ANALYSIS		
	d Approval signed to support				
	Regular Approval Interim 2, 3 or 4 designed to support				
Interim1	Interim 2	Interim 3	Final		
ORR 418 evaluable patients DIP≥14% [#]	ORR 644 evaluable patients DIP≥9% [#]				
	OS ~425 events DIM ≥3.4m*	OS ~541 events DIM ≥2.6m*	Final OS ~637 events DIM ≥2.2m*		



[#] DIP = Difference in observed proportions (vs. an estimated 19.0%) for statistical significance. Measurable disease at baseline and ≥28 weeks follow-up.

^{*} DIM = Difference in observed medians (vs. an estimated 11.7 months) for statistical significance.

NUC-3373

A transformation of 5-FU

NUC-3373: Overview of Fluorouracil (5-FU)



- WHO list of essential medicines
- First approved for medical use in 1962
- ~500,000 patients receive 5-FU annually in North America
- Unpredictable PK profile
- 10-15% Overall Response Rate (colorectal cancer)





Limitations of Fluorouracil (5-FU)



Breakdown>85% breakdown by DPD,
generating toxic
byproducts



TransportRequires
active
transport

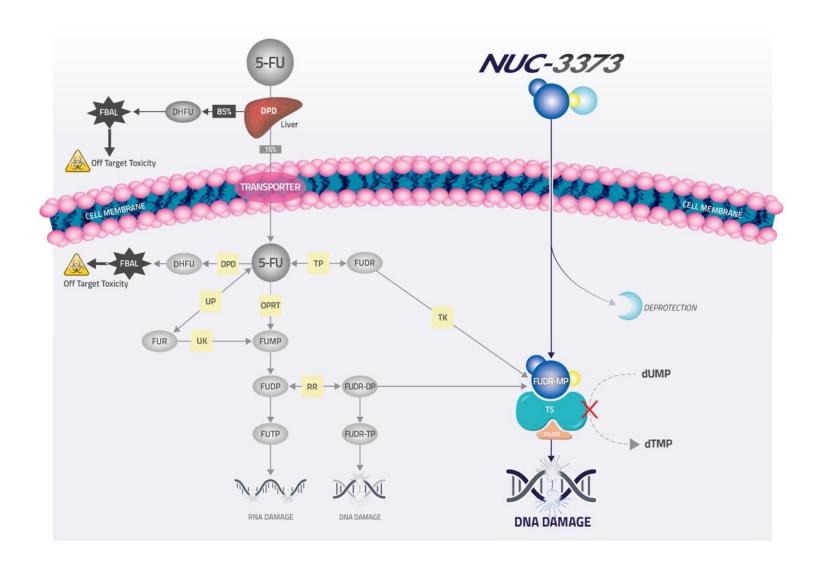


ActivationMulti-step
phosphorylation
process

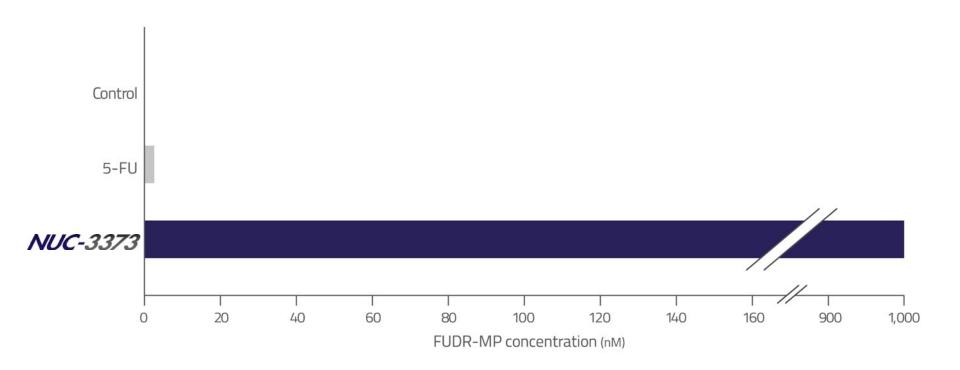


Dosing 46-hour continuous infusion

NUC-3373: 5-FU Metabolism and Mechanism of Action Comparison



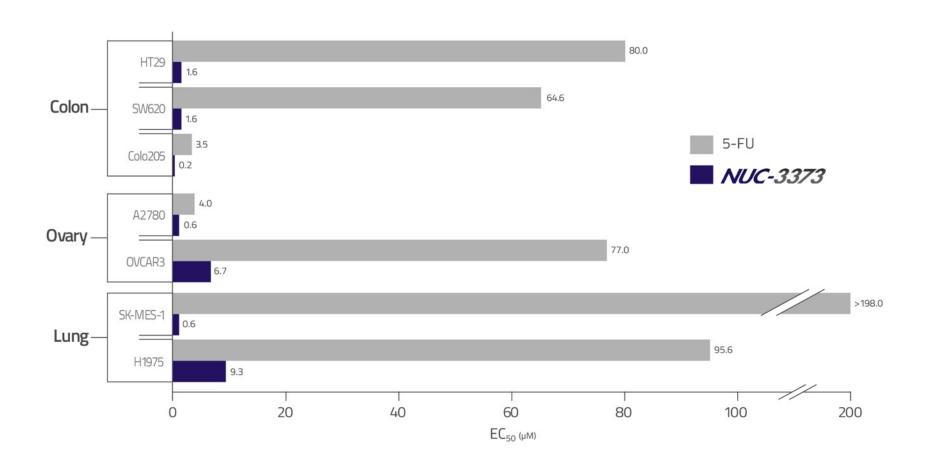
NUC-3373: Very high Intracellular FUDR-MP (pre-clinical)



NUC-3373 generated **366x** higher levels of active anti-cancer metabolite FUDR-MP than 5-FU

Equimolar dose comparison Ghazaly *et al* (2017) *Ann Oncol*; 25: Suppl 5 Abstract ID:385P (ESMO poster September 2017)

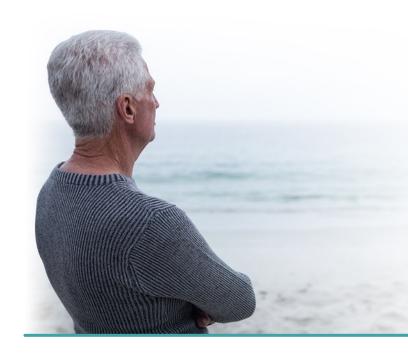
NUC-3373: Greater Anti-Cancer Activity than 5-FU (pre-clinical)



NUC-3373 had up to **330x** greater anti-cancer activity than 5-FU

Ghazaly et al (2017) Ann Oncol; 25: Suppl 5 Abstract ID:385P (ESMO poster September 2017)

NUC-3373: Solid Tumor Phase 1 Study (monotherapy)



- Phase 1 dose-escalation study in patients with advanced solid tumors
- All patients have metastatic spread
- Rapidly progressing disease
- Exhausted all other therapeutic options
- Objective: Recommended Phase 2 dose + schedule



Number of patients

59*
Part 1 (n= 43) Part 2 (n=16)

Age (median)

59 (range 20-77)

Prior chemotherapy regimens

(range 0-11)

Spiliopoulou *et al* (2021) *Ann Oncol*; 32: Suppl 5 Abstract ID 549P (ESMO poster September 2021) Data as of August 2021

^{*}Safety evaluable population; patients who received ≥1 dose of NUC-3373

NUC-3373: Solid Tumor Phase 1 Study (monotherapy)

Favorable safety profile

- NUC-3373 is well-tolerated
- No NUC-3373 related deaths
- 10 pts Grade 3 treatment-related AEs
- No Grade 4 treatment-related AEs
- RP2D for NUC-3373 monotherapy is 2500 mg/m² Q1W

Metastatic Colorectal Cancer

70 years, male **6 prior lines**

1) 5-FU:

based chemoradiotherapy (adjuvant)

2) FOLFIRI:

for metastatic disease

3) CAPOX:

progressed within 2 months

4) FOLFIRI:

progressed within 8 months

5) LONSURF:

progressed within 3 months

6) Irinotecan:

treatment for 1 month

NUC-3373 1,500 mg/m² q1w

Stable Disease: 9 months

Metastatic Basal Cell Carcinoma

55 years, male **2 prior lines**

1) Vismodegib:

for 11 months

2) Paclitaxel + carboplatin: for **3 months**

NUC-3373 1,500 mg/m² q2w

Stable Disease: 10 months

Metastatic Cholangiocarcinoma

60 years, female 1 prior line

1) Gemcitabine + cisplatin: progressed within **6 months**

NUC-3373 1,125 mg/m² q1w

Stable Disease: 11 months



Spiliopoulou *et al* (2021) *Ann Oncol;* 32: Suppl 5 Abstract ID 549P (ESMO poster September 2021) Data as of August 2021

NUC-3373: Ongoing Colorectal Phase 1b/2 Study (combination)



Patients with advanced colorectal cancer

- Phase 1b
 - Received ≥2 prior lines of fluoropyrimidine-based regimens
 - Exhausted all other therapeutic options
- Phase 2
 - Received 1 or 2 prior lines of fluoropyrimidine-based regimens



Number of patients (enrolled to date)

38

Age (median)

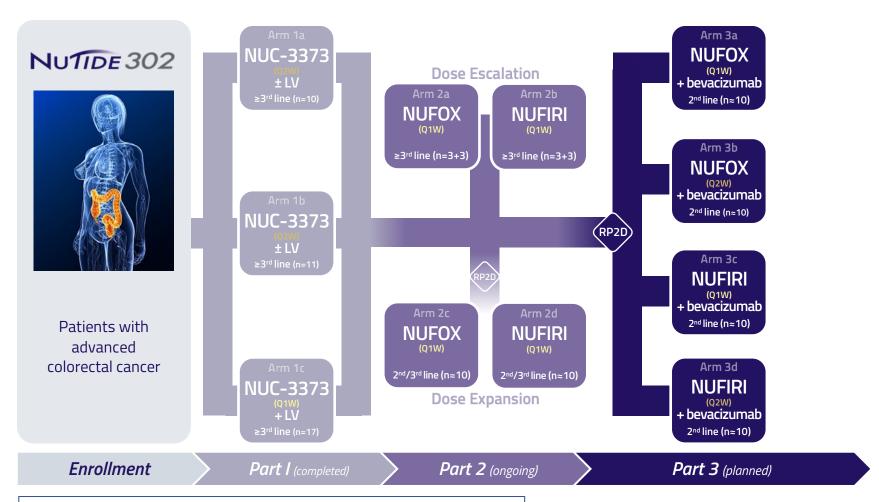
58 (range 33-75)

Prior chemotherapy regimens

(range 2-13)

Berlin et al (2021) Ann Oncol; 32: Suppl 5 Abstract ID 745P (ESMO poster September 2021) Data as of April 2021

NUC-3373: Ongoing Colorectal Phase 1b/2 Study (combination)



 $\begin{aligned} &\text{NUFOX (Q1W)} = \text{NUC-3373} + \text{LV Q1W} + \text{oxaliplatin Q2W} \\ &\text{NUFOX (Q2W)} = \text{NUC-3373} + \text{LV Q2W} + \text{oxaliplatin Q2W} \end{aligned}$

NUFIRI (Q1w) = NUC-3373 + LV Q1w + irinotecan Q2w NUFIRI (Q2w) = NUC-3373 + LV Q2w + irinotecan Q2w

Additional cohorts may be opened.



NUC-3373: Favorable Safety Profile (interim data)

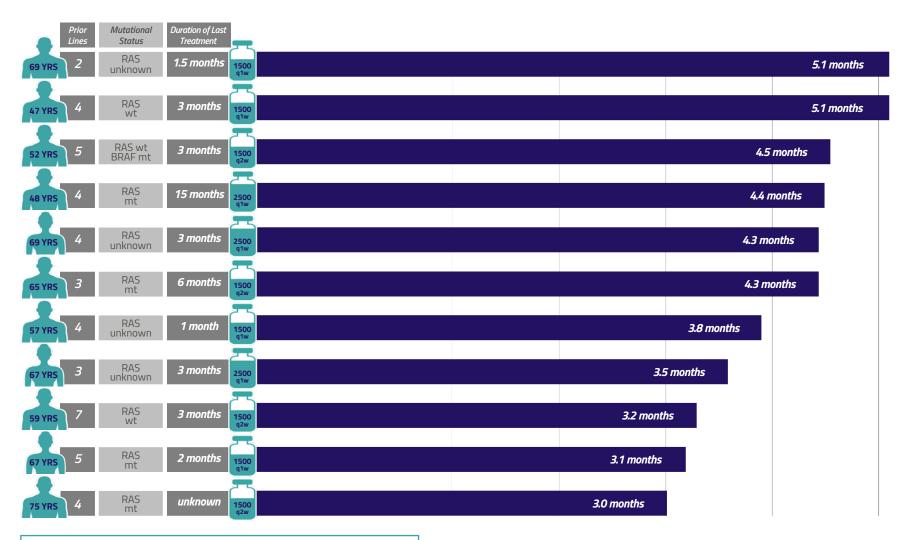
	NUC-3373 (n=38)*		5-FU IV (n=143)		5-FU Bolus (n=593)		Capecitabine (n=596)	
Category	All Grades (%)		All Grades (%)		All Grades (%)		All Grades (%)	
Neutropenia	0	0	48	13	46	21	13	3
Anemia	18	5	91	2	79	2	80	3
Diarrhea	32	0	45	6	61	12	55	15
Nausea	45	5	55	4	51	4	43	4
Vomiting	42	0	32	3	30	5	27	5
Mucositis/Stomatitis	11	0	29	3	62	15	25	3
Hand-foot syndrome	0	0	13	1	6	1	54	17
Dermatitis	11	0	20	0	26	1	27	1
Fatigue/asthenia	47	5	48	4	46	4	42	4
Elevated bilirubin	11	5	36	11	17	6	48	23
	Heavily pre-treated patients NUC-3373 ± LV Q1W or Q2W		First-line patients 5-FU/LV infusional days 1&2, Q2W		First-line patients 5-FU/LV bolus days 1-5, Q4W		First-line patients Capecitabine BID, 2wks on, 1wk off	

- Grade 4 treatment-related AE (1x bilirubin)
- Grade 3 treatment-related AEs (2x ALT, 2x ALP, 2x nausea, 2x anemia, 1x AST, 1x hyponatremia, 1x fever, 1x fatigue)
- FUTP, the primary cause of 5-FU toxicity and a dose-limiting factor, has not been detected in NUC-3373 treated patients



^{*} NUC-3373 All-cause adverse events, selected relevant to comparator data Berlin et al (2021) Ann Oncol; 32: Suppl 5 Abstract ID 745P (ESMO poster September 2021) Data as of Anril 2021

NUC-3373: Colorectal Cancer Patient Case Studies (interim data)



Disease Control Rate: 62% (efficacy evaluable population n=26)

Berlin et al (2021) Ann Oncol; 32: Suppl 5 Abstract ID 745P (ESMO poster September 2021) Data as of April 2021



NUC-3373: Ongoing Colorectal Phase 1b/2 Study (interim data)

Colorectal Cancer

67 years, female 3 prior lines

1) CAPOX (adjuvant):
for **3 months**relapsed 9 months post-adjuvant therapy

2) FOLFIRI: progressed within **3 months**

3) Lonsurf: progressed within **3 months**

RAS unknown
Target lesions: 1 (peritoneum)

NUC-3373 2,500 mg/m² q1w

40% reduction in target lesion

Partial Response: 3.5 months

Colorectal Cancer

69 years, male **2 prior lines**

Diagnosed with metastatic disease

1) CAPOX:

progressed within 2 months tumor increase of 35%

2) FOLFIRI:

progressed within 1.5 months

RAS unknown Target lesions: 2 (liver)

NUC-3373 1,500 mg/m² q1w

28% reduction in tumor volume

Stable Disease: **5.1 months***

* patient missed 6 consecutive doses due to COVID-19 and progressed, but continued on study for a total of 8 months due to clinical benefit

Colorectal Cancer

52 years, male **5 prior lines**

1) FOLFOX (adjuvant):

for 4 months

relapsed 4 months post-adjuvant therapy

2) FOLFIRI:

progressed within 6 months

3) Irinotecan + panitumumab: progressed within **6 months**

4) Irinotecan + panitumumab + telaglenastat: progressed within **6 months**

5) Nivolumab + enadenotucirev: progressed within **3 months**

RAS wildtype; BRAF mutant Target lesions: 3 (2 lung; 1 liver)

> NUC-3373 1,500 mg/m² q2w

15% reduction in tumor volume

Stable Disease: 4.5 months



Graham et al (2020) Ann Oncol 31: Suppl 4 Abstract ID: 464P (ESMO poster September 2020)
Coveler et al (2021) J Clin Oncol 39: Suppl 3 Abstract ID: 93 (ASCO GI poster January 2021)



NUC-3373: Ongoing Colorectal Phase 1b/2 Study (interim data)

Colorectal Cancer

47 years, male 4 prior lines

- FOLFOX (adjuvant):
 for **5 months** relapsed 8 months post-adjuvant therapy
- 2) FOLFIRI: + bevacizumab progressed within 18 months
- 3) FOLFIRI + cetuximab: progressed within **8 months**
- 4) Lonsurf: toxicity within **3 months**

RAS wildtype
Target lesions: 5 (2 lymph nodes;
2 peritoneum; 1 liver)

NUC-3373 1,500 mg/m² q1w

Stable Disease: 5.1 months

Colorectal Cancer

57 years, male 4 prior lines

- 1) CAPOX (neoadjuvant/adjuvant):
 for **6 months**relapsed 2 months post-adjuvant therapy
- 2) FOLFIRI: progressed within **3 months**
- 3) Lonsurf: progressed within **2 months**
- 4) RXC004 (Wnt inhibitor): progressed within **1 month**

RAS unknown
Target lesions: 3 (lung)

NUC-3373 1,500 mg/m² q1w

Stable Disease: 3.8 months

Colorectal Cancer

67 years, female **5 prior lines**

- 1) FOLFOX (adjuvant):
 for **5 months**relapsed 2 years post-adjuvant therapy
- 2) FOLFIRI: for **5 months**
- 3) Irinotecan + Lonsurf + bevacizumab for **33 months**
- 4) CAPOX: progressed within **1 month**
- 5) Regorafenib: progressed within 2 months

RAS mutant Target lesions: 2 (1 liver; 1 abdomen)

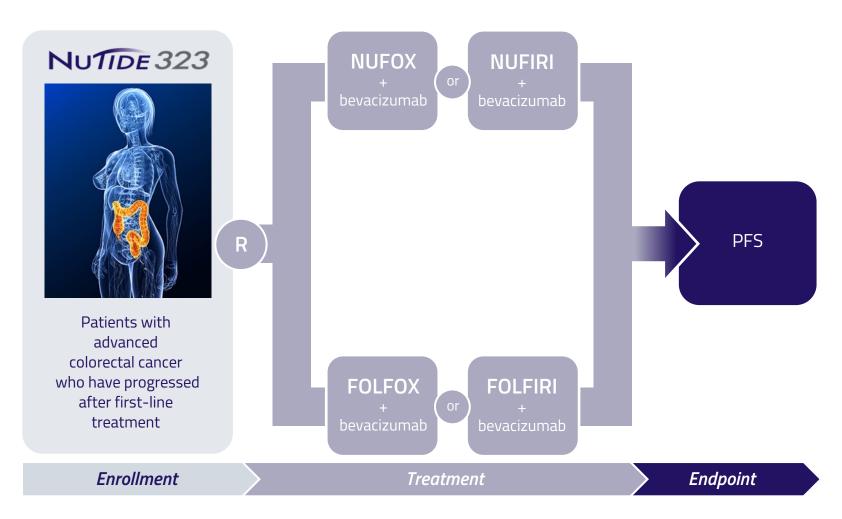
> NUC-3373 1,500 mg/m² q1w

Stable Disease: 3.1 months



Graham et al (2020) Ann Oncol 31: Suppl 4 Abstract ID: 464P (ESMO poster September 2020)
Coveler et al (2021) J Clin Oncol 39: Suppl 3 Abstract ID: 93 (ASCO GI poster January 2021)

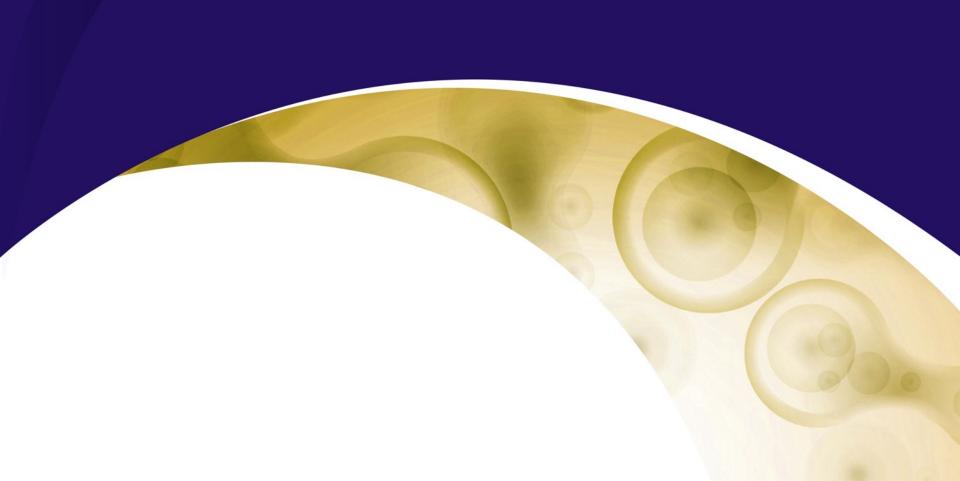
NUC-3373: Potential Colorectal Phase 3 Study





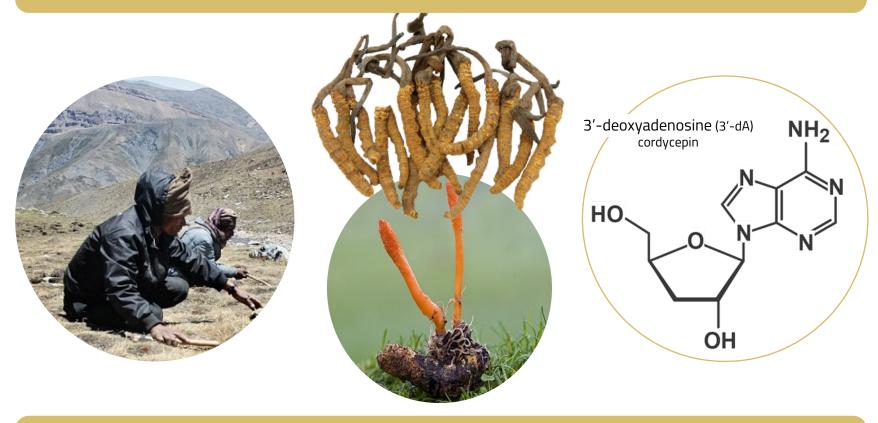
NUC-7738

A transformation of 3'-deoxyadenosine



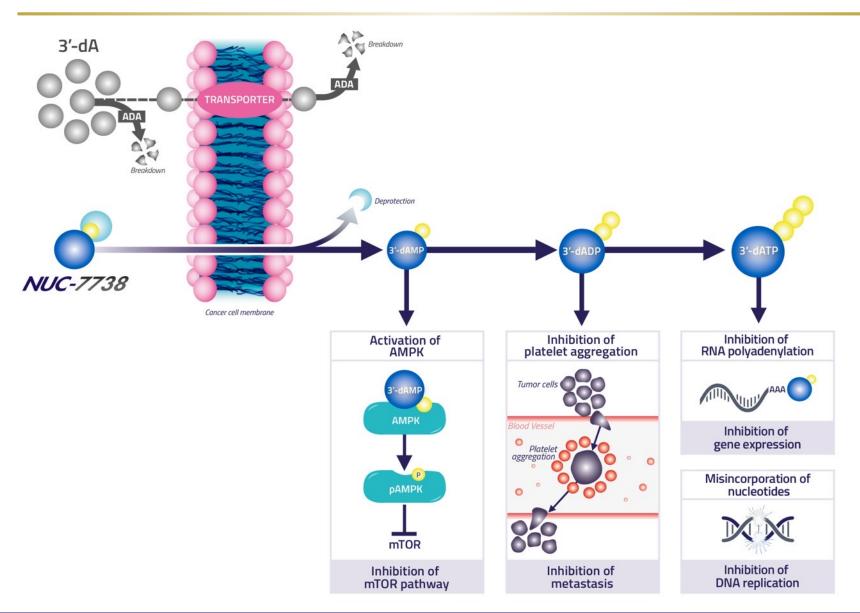
NUC-7738: Origin of 3'-deoxyadenosine

Cordycepin: A Traditional Chinese Medicine



1950: **3'-dA** isolated from *Cordyceps sinensis*

NUC-7738: Multiple Anti-Cancer Modes of Action



NUC-7738: Ongoing Solid Tumor Phase 1 Study



- Phase 1 dose-escalation study in patients with advanced solid tumors
- All patients have metastatic spread
- Rapidly progressing disease
- Exhausted all other therapeutic options
- Objective: Recommended Phase 2 dose + schedule



Number of patients (enrolled to date)

29

Age (median)

63(range 39-77)

Prior chemotherapy regimens

2.5 (range 1-7)

Blagden et al (2021) Ann Oncol: 32: Suppl 5 Abstract ID 566TiP (ESMO poster September 2021) Data as of July 2021

NUC-7738: Ongoing Solid Tumor Phase 1 Study (interim data)

Favorable safety profile

- No Grade 3 or 4 treatment-related AEs
- No DLTs

Attractive PK profile

- Efficient conversion of NUC-7738 to 3'-dATP
- Prolonged intracellular half-life of 3'-dATP (>50 hours)

Metastatic Melanoma

62 years, female **2 prior lines**

- 1) Nivolumab + ipilimumab: discontinued within **1 month**
- 2) CK7 inhibitor: progressed within **1 month**

Target lesion: 1 (pelvic side wall)

NUC-7738

Starting dose 14 mg/m² q1w (8 dose escalations)

14% reduction in tumor volume

Ongoing pleural effusion resolved: no further drainage required and lung function normalized

Treatment Duration: 18 months

(Stable disease for 12 months)*

Metastatic Melanoma

65 years, female 1 prior line

1) Nivolumab + ipilimumab: discontinued within **1 month**

Target lesion: 1 (lung)

NUC-7738

Starting dose 400 mg/m² q1w (1 dose escalation)

7% reduction in tumor volume

NUC-7738 treatment enabled complete resection (R0)

Treatment Duration: 11 months

(Stable disease for 9 months)*

Metastatic Lung Adenocarcinoma

65 years, male **2 prior lines**

- 1) Carboplatin + pemetrexed: progressed at **6 months**
- 2) Docetaxel: progressed at **4 months**

Target lesions: 2 (lung)

NUC-7738

Starting dose 42 mg/m² q1w (4 dose escalations)

46% reduction in target lesion 1

Target lesion 2 changed in character; small dense core surrounded by larger diffuse "ground-glass" periphery

Treatment Duration: 6 months

* Treatment beyond PD allowed per protocol for patients still receiving benefit



Blagden et al (2021) Ann Oncol: 32: Suppl 5 Abstract ID 566TiP (ESMO poster September 2021) Data as of July 2021

NUC-7738: Ongoing Solid Tumor Phase 1 Study (interim data)

Metastatic Lung Adenocarcinoma

65 years, male - 2 prior lines

Target Lesion 1:

Encouraging signs of anti-tumor activity with a **46% reduction** in lesion between week 8 -16 (41mm to 22mm)

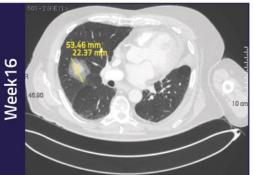




Target Lesion 2:

Positive change in character (week 8 -16), with a smaller dense core surrounded by a larger diffuse "ground-glass" periphery







Symeonides et al (2020) Ann Oncol: 31: S501 Abstract ID: 600TiP (ESMO poster September 2020)

Strong Intellectual Property Position

Worldwide exclusive rights for all programs: **697 granted patents** and **348 pending applications***

Key Patents	Status	Expiration ⁺ (excluding any extensions)		
-ACELATIN	463 granted, 168 pending, including:			
Composition of matter	Granted (EP, US), Pending (JP)	2033 / 2035	+ others	
Formulation	Granted (EP, US, JP)	2035	+ others	
Manufacturing process	Granted (US, JP), Pending (EP)	2035 / 2036	+ others	
Use	Granted (EP, US, JP)	2035 / 2038	+ others	
NUC-3373	66 granted, 104 pending, including:			
Composition of matter	Granted (US, EP, JP)	2032	+ others	
Formulation	Pending	2036	+ others	
Manufacturing process	Pending	2038	+ others	
Use	Pending	2037 / 2038	+ others	
NUC-7738	53 granted, 48 pending, including:			
Composition of matter	Granted (EP, US, JP)	2035	+ others	
Formulation	Pending	2036	+ others	
Manufacturing process	Pending	2038	+ others	
Use	Pending	2042	+ others	

^{*}Expiration for pending patents if granted

^{*}As of 16 August 2021

Key Milestones: 2H 2021 / 1H 2022

-ACELATIN	PHASE	EVENT	2021 2H	2022 1H
Biliary (NuTide:121)	Phase 3	First Interim Analysis	X Recruitment	X Readout
NUC-3373				
Solid Tumors (NuTide:301)	Phase 1	Data	X	
Colorectal (NuTide:302)	Phase 1b	Data	X	
	Phase 2	Initiate study / Data	X	Х
Colorectal (NuTide:323)	Phase 3	Initiate study	X	
Solid Tumors (NuTide:303)	Phase 1b	Initiate study		X
NUC-7738				
Solid Tumors (NuTide:701)	Phase 1	Data	X	Х
	Phase 2	Initiate study / Data	X	X

Investment Highlights

Improving Survival Outcomes

Focused on significantly improving survival outcomes for patients with cancer by applying our phosphoramidate chemistry technology

Broad IP Protection

Strong IP position for all product candidates and worldwide exclusive rights

Significant Milestones

Numerous value inflection points throughout 2021 and 2022

First-In-Class

Acelarin has achieved impressive response rates and has the opportunity for accelerated approval in front-line biliary tract cancer

Standard of Care

NUC-3373 has the potential to replace 5-FU in colorectal cancer and other solid tumors

Novel ProTide

NUC-7738 is a transformation of a novel nucleoside analog and has multiple anti-cancer modes of action

Experienced Team

Nasdaq : NCNA

Accomplished management team, backed by leading biotech investors



NUCANA

Nasdaq: NCNA

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