



A New Era in Oncology

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# Harnessing the Power of Phosphoramidate Chemistry



Transforming Nucleoside Analogs into ProTides

# Nucleoside Analogs: Cornerstones of Cancer & Viral Treatments

## 16 FDA Approved Anti-Cancer Nucleoside Analogs

Including:

**Vidaza®**  
Azacitidine

**5-FU**  
Fluorouracil

**Xeloda**  
capecitabine

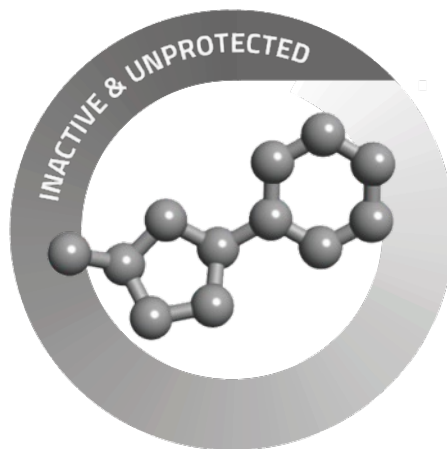
**GEMZAR®**  
gemcitabine

**DACOGEN®**  
decitabine

**FUDR**  
floxuridine

**Fludara®**  
FLUDARABINE

**Clolar®**  
clofarabine



## 22 FDA Approved Anti-Viral Nucleoside Analogs

Including:

**Zovirax**  
(Acyclovir)

**Viread**  
tenofovir disoproxil fumarate

**VALTREX**  
VALACYCLOVIR HCl

**Copegus®**  
Ribavirin

**RETROVIR®**  
Zidovudin AZT®

**EPIVIR**  
(lamivudine)

**ZERIT®**  
(stavudine)

**ZIAGEN**  
(abacavir)

## Limitations of Nucleoside Analogs

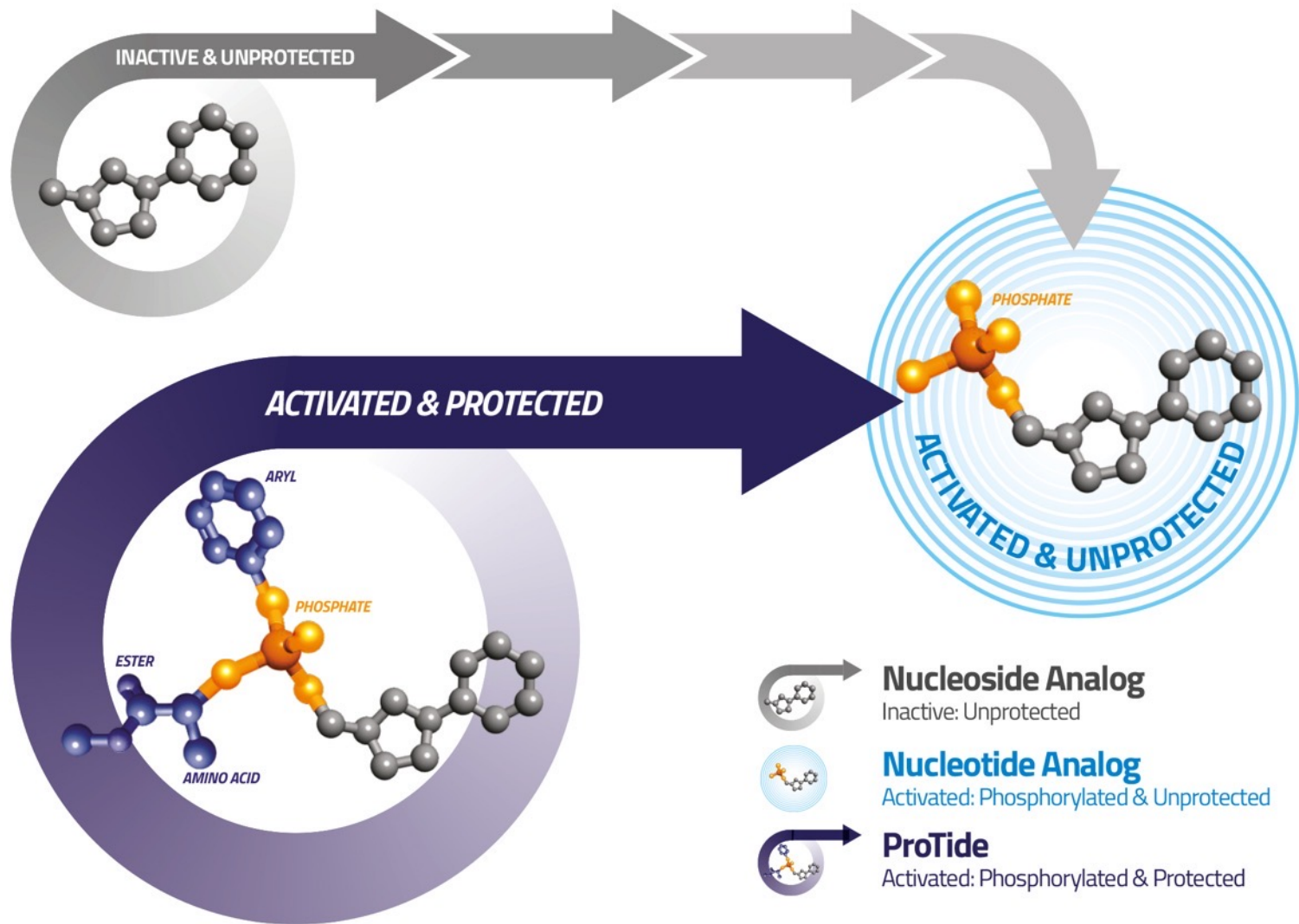
**Breakdown  
& Toxic  
Byproducts**  
Off-target  
toxicity

**Uptake**  
Dependent on  
transporters  
to enter  
cells

**Activation**  
Inefficient  
generation of  
active  
metabolites

**Administration  
Challenges**  
Poor PK leads to  
sub-optimal  
dosing

# Transforming Nucleoside Analogs into ProTides



# ProTides: A New Era In Anti-Virals



- Transformed novel nucleoside analog
- Highly effective treatment for chronic Hepatitis C infection
- Sales: **\$74 billion**<sup>1</sup>

- Transformed nucleoside analog: Viread® (tenofovir disoproxil fumarate)
- More effective & safer treatment for HIV & HBV than Viread®
- Sales: **\$135 billion**<sup>2</sup>

- Transformed novel nucleoside analog
- Treatment for COVID-19
- Sales: **\$17 billion**<sup>3</sup>

<sup>1</sup> Sovaldi + Harvoni + Epclusa + Vosevi cumulative sales through December 31, 2025

<sup>2</sup> Genvoya + Descovy + Odefsey + Biktarvy + Symtuza + Vemlidy cumulative sales through December 31, 2025

<sup>3</sup> Veklury cumulative sales through December 31, 2025

## ***NUC-7738***



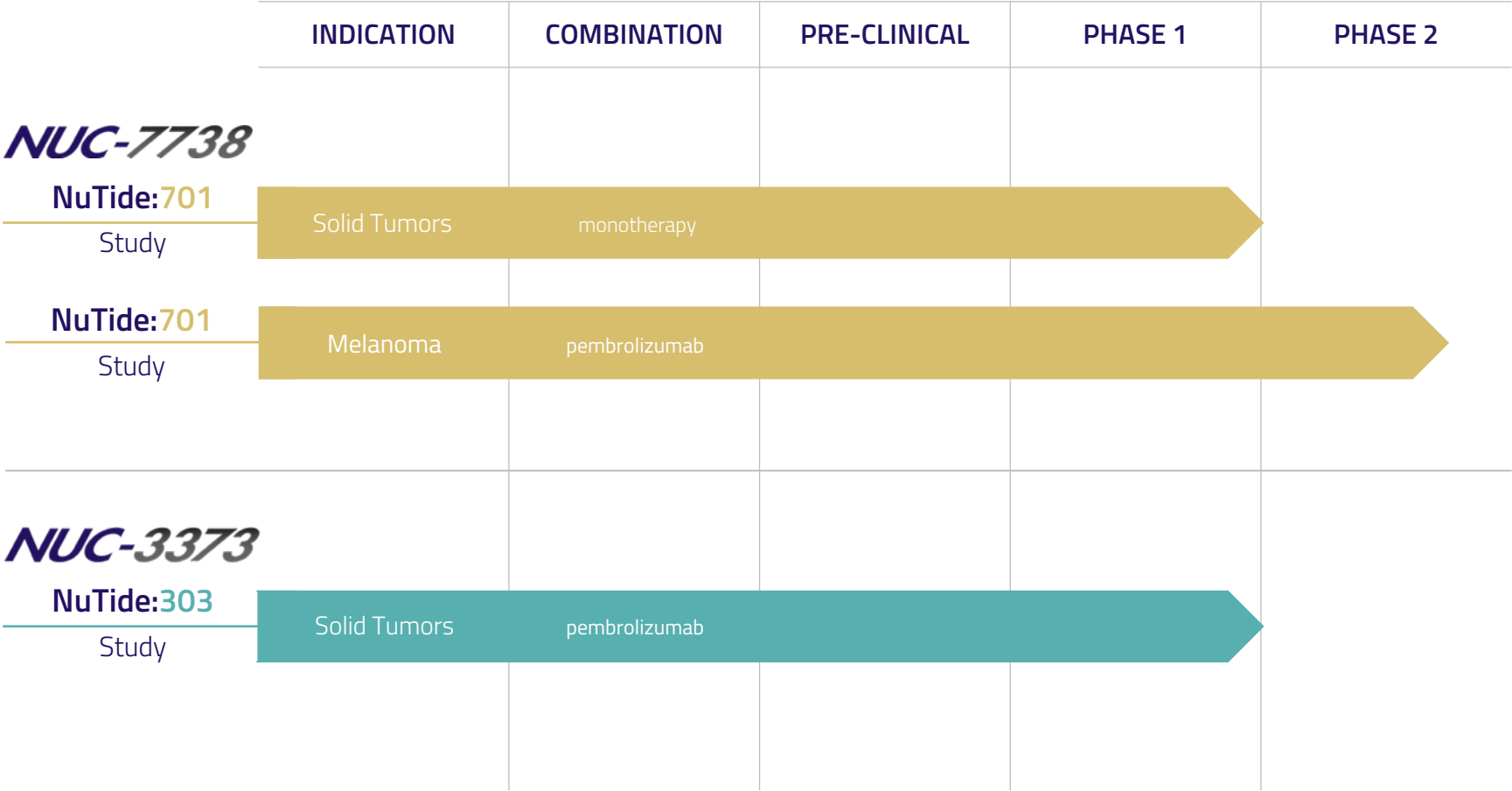
## ***NUC-3373***



- Transformed novel nucleoside analog: 3'-dA
- Profoundly impacts gene expression in cancer cells
- Targets the tumor microenvironment

- Transformed nucleoside analog: FUDR
- Targeted Thymidylate Synthase Inhibitor
- Induces DNA damage

# Current Development Status



# Multiple Inflection Points in 2026



**Cash & Cash Equivalents**  
December 31, 2025  
~\$32.6 million\*



**Cash Runway**  
*into*  
2029



**Important Data Readouts**  
*in*  
2026

\*Based on exchange rate of £1.00 to \$1.34 and reported cash of £24.3 million as of December 31, 2025

NUC-7738

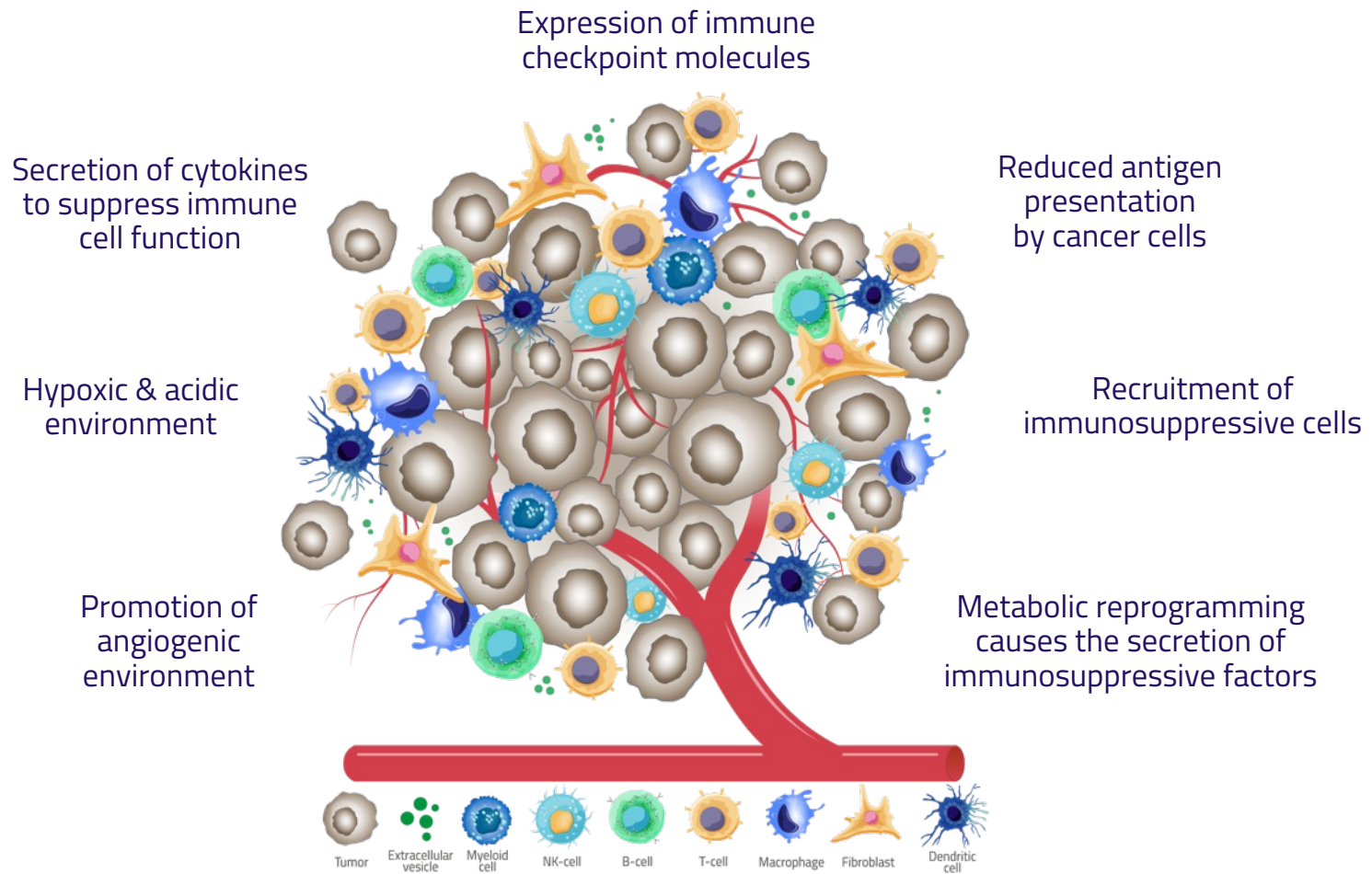


Unlocking the Potential of Immunotherapy

# The Immunotherapy Conundrum

Significant progress, however only 15-20% of patients achieve long-term remission

Numerous Tumor Microenvironment characteristics reduce the effectiveness of PD-(L)1 inhibitors



# Novel Nucleoside Analog: 3'-deoxyadenosine (3'-dA)

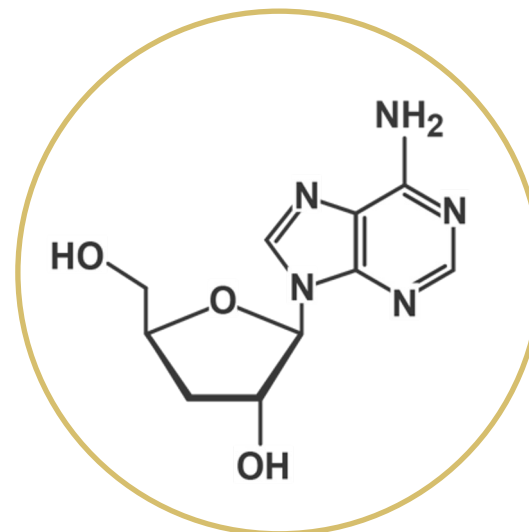
## Cordycepin

A Traditional Chinese Medicine found in the Himalayas



## 3'-dA

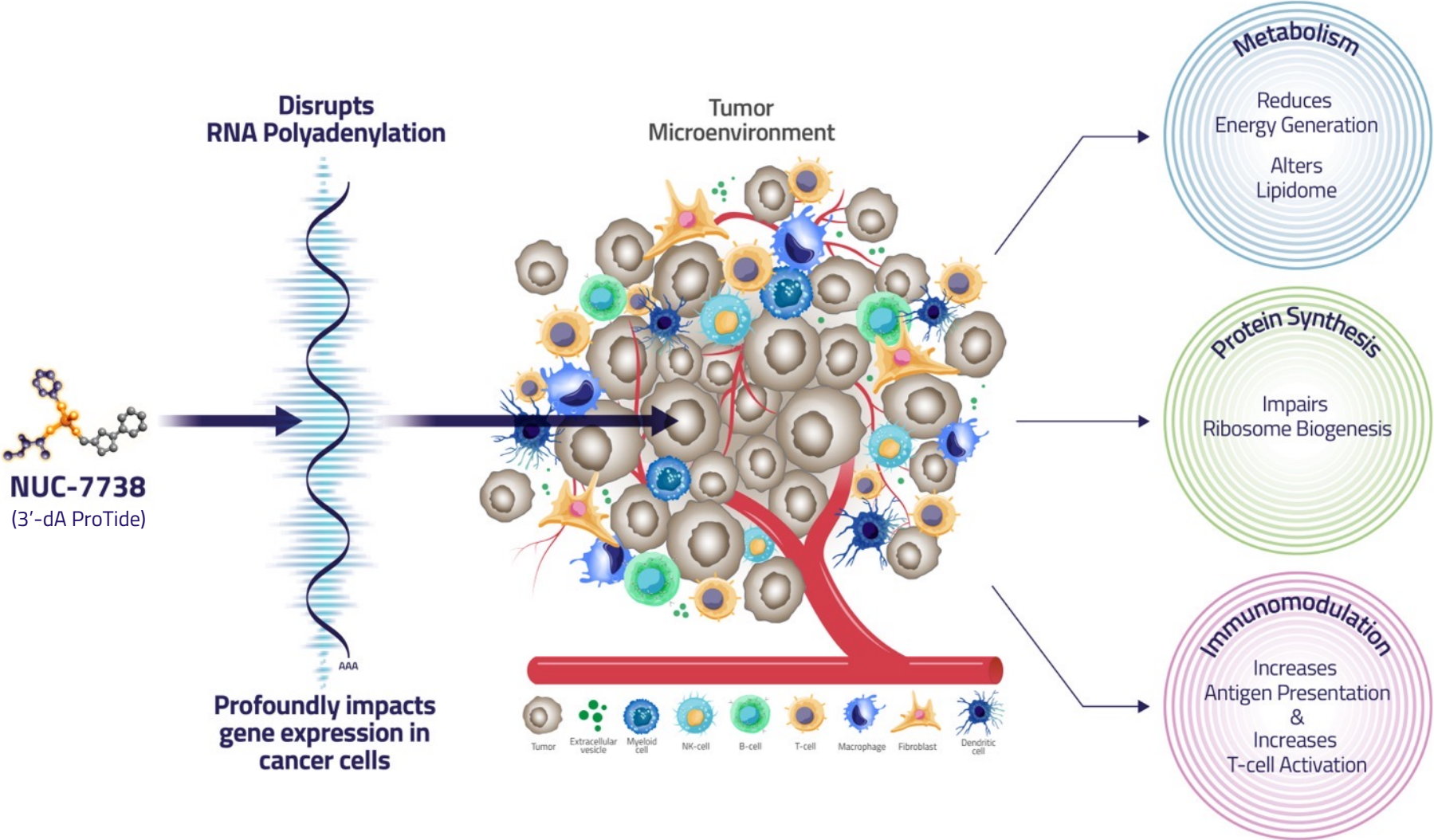
Originally isolated from *Cordyceps sinensis* in 1950



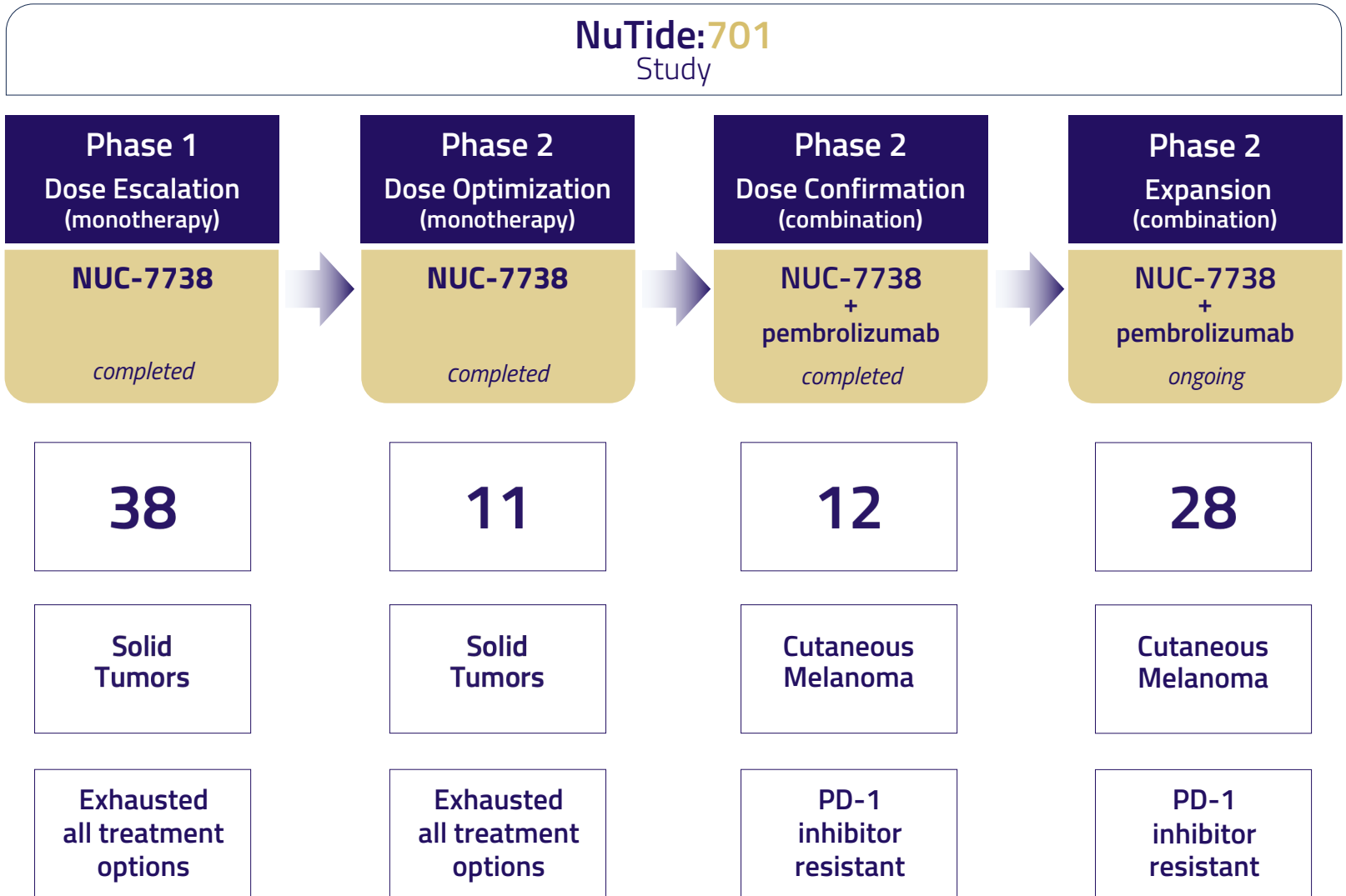
3'-dA has potent anti-cancer activity *in vitro* and can modulate components of the TME

Despite this, it has not been successfully developed due to rapid breakdown by adenosine deaminase

# NUC-7738 : Targets Multiple Aspects of the Tumor Microenvironment



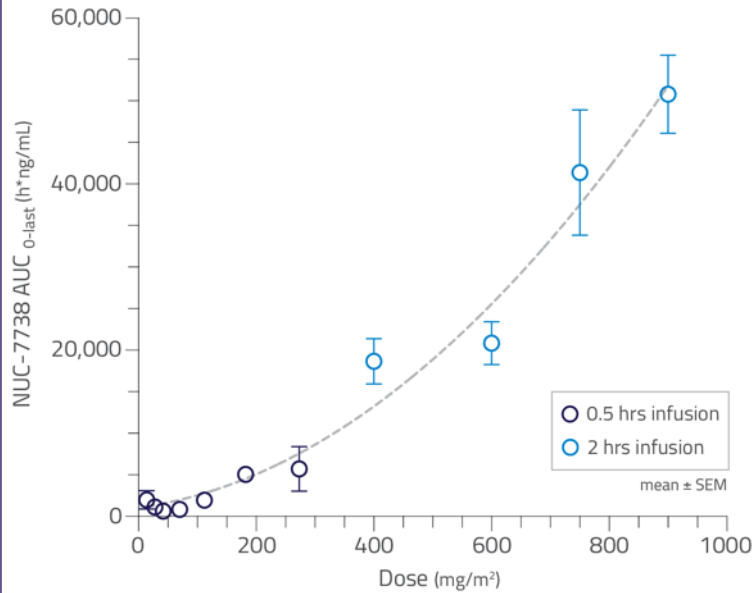
NUC-7738 transforms PD-1 resistant TME into a therapeutically responsive state



# NUC-7738 : Attractive Pharmacokinetic Profile (monotherapy)

## Plasma

Dose proportional increase in  $C_{max}$  and AUC

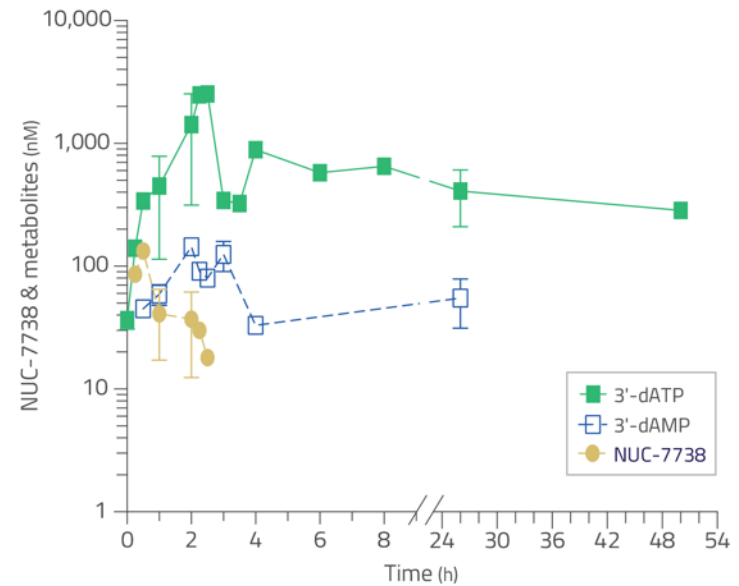


Patients (n=27) dosed at 14 – 900 mg/m<sup>2</sup>

## Intracellular

NUC-7738 efficiently generates active anti-cancer metabolite (3'-dATP)

Long half-life of 3'-dATP (42 hrs)



Patients (n=3) dosed at 900 mg/m<sup>2</sup>

Symeonides *et al* (2022) *Ann Oncol*: 33: S745-S746 Abstract ID: 455MO (ESMO September 2022). Data cut-off: July 7, 2022

# NUC-7738 : Favorable Safety Profile (monotherapy)

## NUC-7738 has been well tolerated

- No Grade 4 toxicities
- Low rates of Grade 3 toxicities

Dose AE occurred (mg/m <sup>2</sup> )	14 n=2	28 n=3	42 n=2	70 n=3	112 n=4	182 n=4	273 n=5	400 n=6	600 n=9	750 n=5	900 n=8	MTD		Total* n=38
												1350 n=11	2000 n=2	
<b>All Grade Treatment-Related Adverse Events (≥10%)</b>														
Nausea	0	1 (33%)	0	0	0	0	1 (20%)	0	3 (33%)	2 (40%)	3 (38%)	5 (45%)	1 (50%)	16 (42%)
Fatigue	0	1 (33%)	0	0	0	0	0	1 (17%)	3 (33%)	1 (20%)	3 (38%)	7 (64%)	2 (100%)	14 (37%)
Anemia	0	0	0	0	0	0	0	0	0	0	2 (25%)	4 (36%)	2 (100%)	7 (18%)
Diarrhea	0	0	0	0	0	0	1 (20%)	0	0	1 (20%)	1 (13%)	4 (36%)	0	6 (16%)
Vomiting	0	0	0	0	0	0	0	0	0	1 (20%)	1 (13%)	3 (27%)	1 (50%)	6 (16%)
Mucosal inflammation	0	0	0	0	0	0	0	0	1 (11%)	1 (20%)	0	1 (9%)	1 (50%)	4 (11%)
Decreased appetite	0	0	0	1 (33%)	0	1 (25%)	1 (20%)	0	0	0	1 (13%)	0	0	4 (11%)
<b>Grade 3 Treatment-Related Adverse Events (ALL)</b>														
Fatigue	0	0	0	0	0	0	0	0	0	0	0	3 (27%)	2 (100%)	4 (11%)
Anemia	0	0	0	0	0	0	0	0	0	0	1 (13%)	0	0	1 (3%)
Neutropenia	0	0	0	0	0	0	0	0	1 (11%)	0	0	0	0	1 (3%)
Vomiting	0	0	0	0	0	0	0	0	0	0	0	0	1 (50%)	1 (3%)

MTD: maximum tolerated dose

n= number of patients receiving each dose level at any time during the study

\*total number of patients who experienced TRAE

Symeonides *et al* (2022) *Ann Oncol*: 33: S745-S746 Abstract ID: 455MO (ESMO September 2022). Data cut-off: July 7, 2022

## Disease Control Rate: 41% (Efficacy Evaluable Patients)

### Metastatic Melanoma



62 years  
**2 prior lines**

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

**NUC-7738** starting dose 14 mg/m<sup>2</sup>  
**Stable Disease: 12 months**  
**14% reduction in tumor volume**  
**Treatment duration: 18 months**

- 8 dose escalations

### Metastatic Melanoma



65 years  
**1 prior line**

- 1) nivolumab + ipilimumab: discontinued within **1 month**

**NUC-7738** starting dose 400 mg/m<sup>2</sup>  
**Stable Disease: 9 months**  
**NUC-7738 treatment enabled complete resection**  
patient had diffuse disease that was inoperable  
**Treatment duration: 11 months**

- 1 dose escalation

### Metastatic Clival Chordoma



72 years  
**1 prior line**

- 1) imatinib: progressed at **19 months**

**NUC-7738** dose 1,350 mg/m<sup>2</sup>  
**Stable disease: 6 months**  
**45% reduction in mandibular lesion**  
**Complete disappearance of lip lesion**  
Bleeding from nasal lesion resolved

### Metastatic Lung Adenocarcinoma



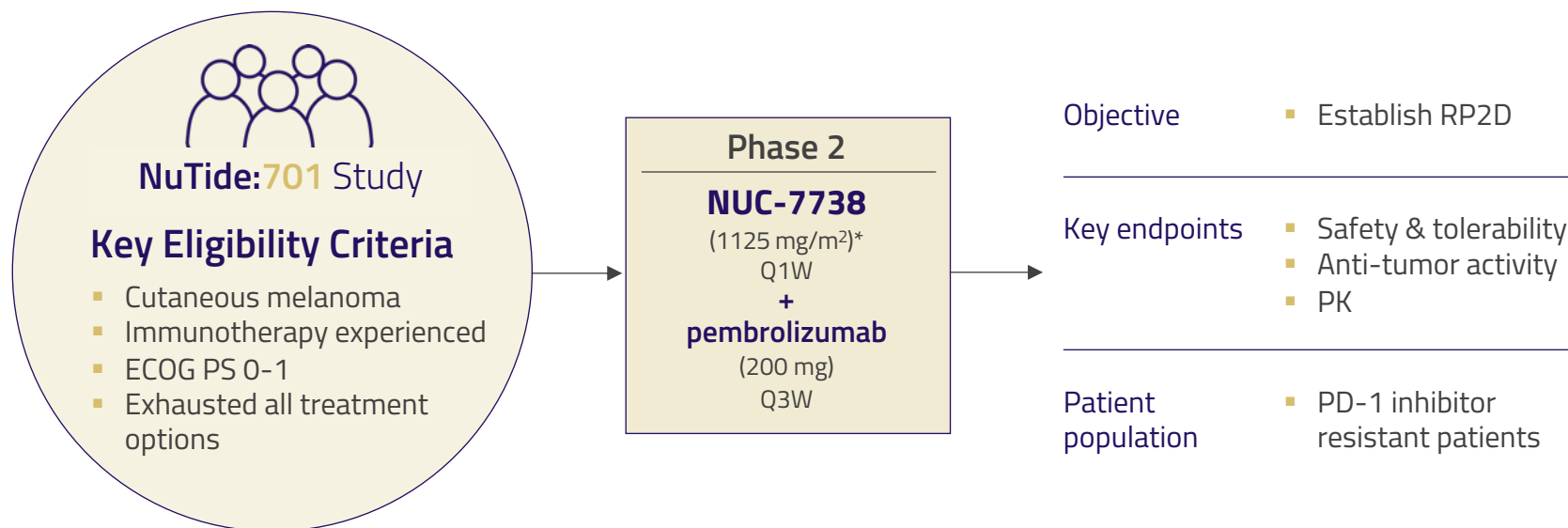
65 years  
**2 prior lines**

- 1) carboplatin + pemetrexed: progressed at **6 months**
- 2) docetaxel: progressed at **4 months**

**NUC-7738** starting dose 42 mg/m<sup>2</sup>  
**46% reduction in lung lesion 1**  
**Change in character in lung lesion 2** small dense core surrounded by a larger diffuse "ground-glass" periphery  
**Treatment duration: 6 months**

- 4 dose escalations

## Dose Confirmation Cohort (n=12)



Prior Therapy: median (range)	2 (1-3)
PD-1 inhibitor	12
PD-1 inhibitor (adjuvant)	8
PD-1 inhibitor (non-adjuvant)	8
CTLA-4 inhibitor	11
PD-1 + CTLA-4 inhibitor	9
BRAF + MEK inhibitor	1

\*Starting dose was 1125 mg/m<sup>2</sup> which was escalated to 1350 mg/m<sup>2</sup> if well tolerated

Blagden *et al* (2024) *Ann Oncol*: 35: S482-S535 Abstract ID: 666P (ESMO September 2024). Data cut-off: August 1, 2024

## NUC-7738 + pembrolizumab has been well tolerated (n=12)

- Low rates of Grade ≥3 toxicities
- 1 patient experienced Grade 4 transaminitis (ALT/AST increased)

### Treatment Related Adverse Events

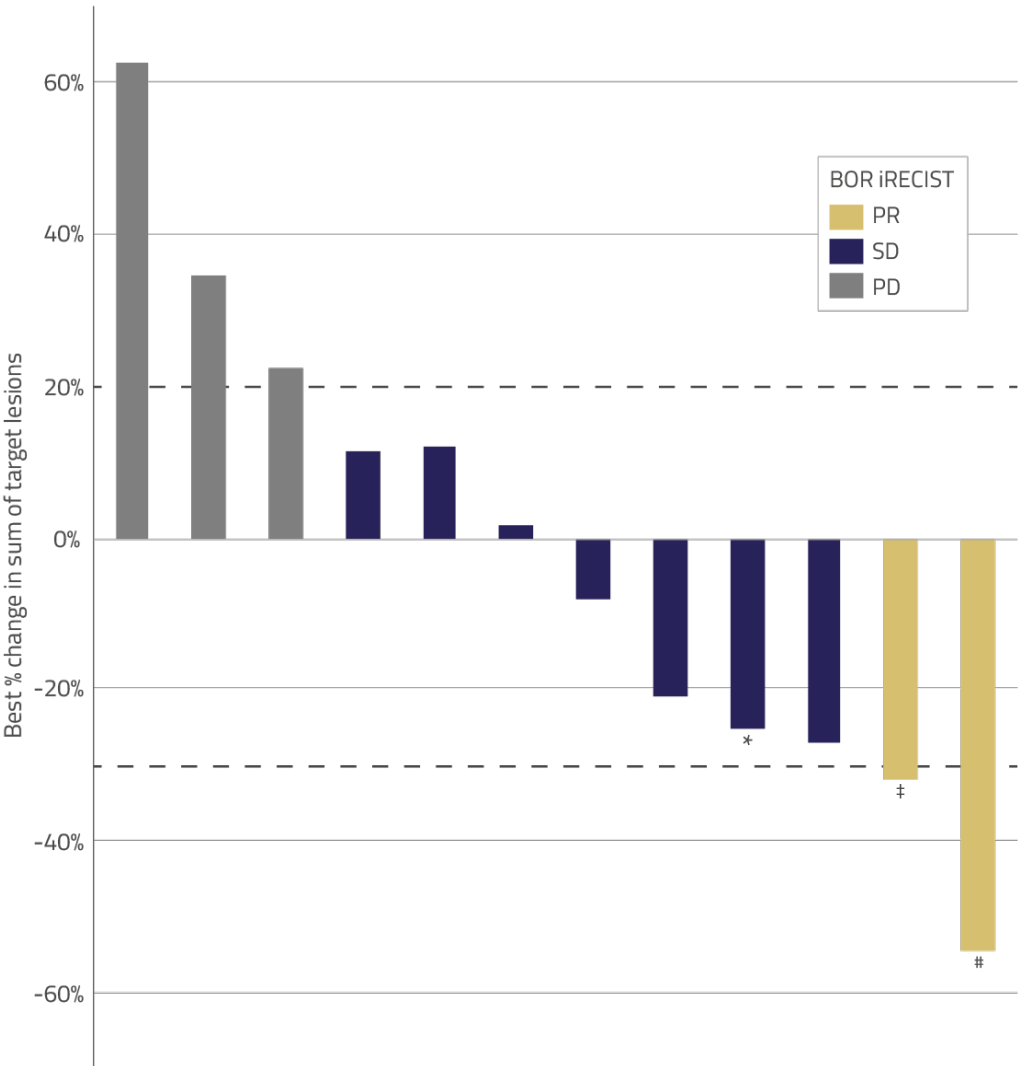
	All Grades n(%)	Grade 3 n(%)	Grade 4 n(%)
Nausea	9 (75)	0	0
ALT increased	6 (50)	1 (8)	1 (8)
Diarrhea	6 (50)	1 (8)	0
Vomiting	6 (50)	1 (8)	0
Fatigue	5 (42)	1 (8)	0
Anemia	5 (42)	0	0
AST increased	4 (33)	1 (8)	1 (8)
ALP increased	2 (17)	0	0
GGT increased	2 (17)	1 (8)	0
Blood magnesium decreased	2 (17)	0	0
Blood sodium decreased	2 (17)	0	0
Decreased appetite	2 (17)	0	0
Hypophosphatemia	2 (17)	0	0
Rash	2 (17)	0	0

All Grade TRAEs with prevalence ≥10% patients related to NUC-7738, pembrolizumab or both

Additional Grade 3 TRAEs ≤10%: abdominal pain (1 pt); hypertension (1pt); immune-mediated hepatitis (1 pt); adrenal insufficiency, hypercalcemia and hypotension (1 pt). No additional Grade 4 TRAEs

Payne *et al* (2025) *Immuno-Oncology Technol* 28: Supplement. Abstract ID: 321TiP (ESMO IO December 2025). Data cut-off: October 30, 2025

# NUC-7738 : Tumor Volume Reductions in PD-1 Inhibitor Resistant Patients (combination)



Patient previously refractory to PD-1 inhibitor (nivolumab) + CTLA-4 inhibitor (ipilimumab) had 55% reduction<sup>#</sup>

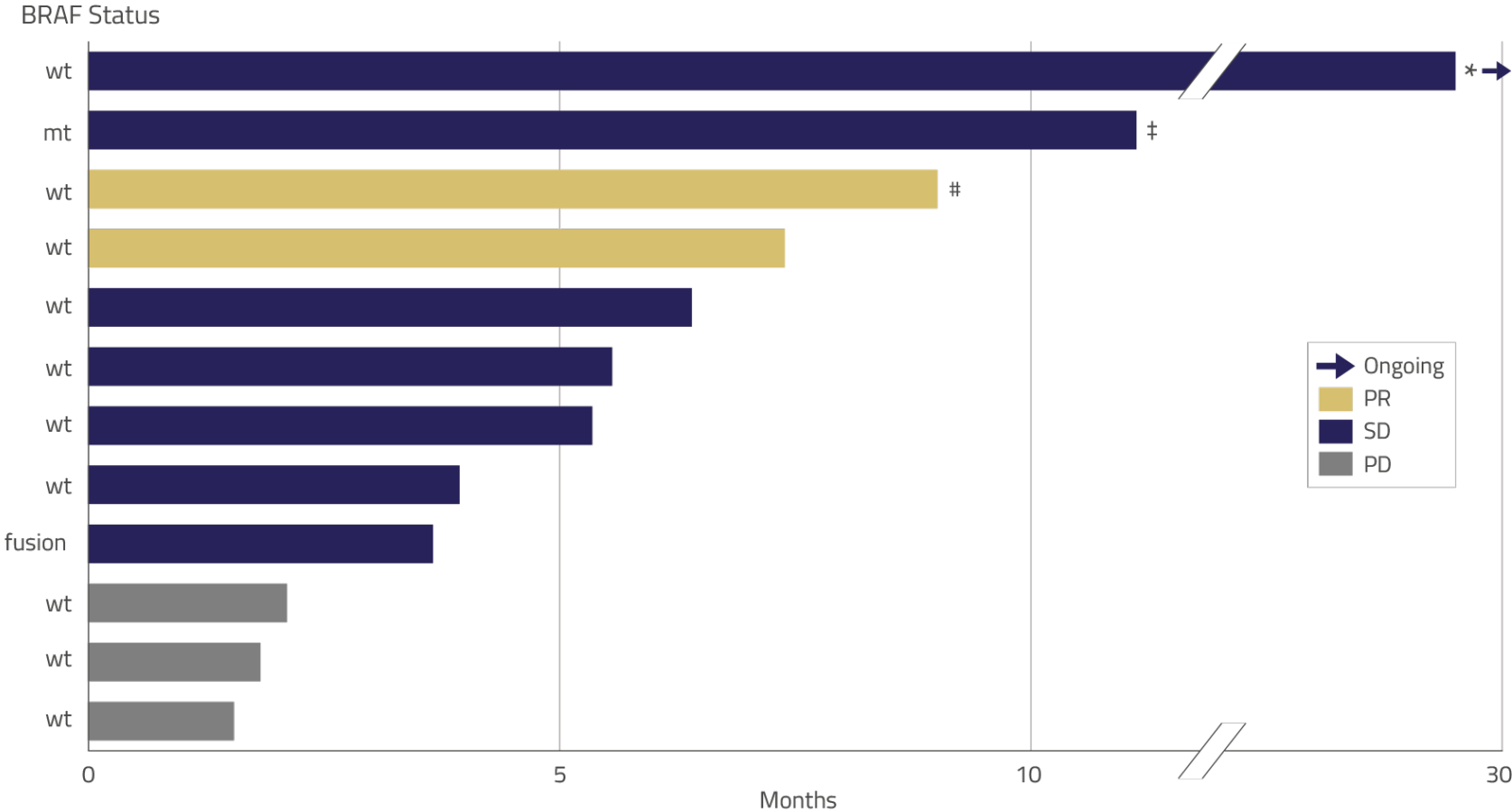
Patient with progression on three prior PD-1 therapies (nivolumab x1, pembrolizumab x2) achieved a 32% tumour reduction<sup>‡</sup>

Patient who progressed after PD-1 inhibitor (nivolumab) + CTLA-4 inhibitor (ipilimumab) has ongoing complete metabolic response<sup>\*</sup>

<sup>#</sup> Discontinued by patient choice; follow-up imaging showed progression of non-target lesion, target lesions remained stable (-55%)

Payne et al (2025) *Immuno-Oncology Technol* 28: Supplement. Abstract ID: 321TiP (ESMO IO December 2025). Data cut-off: October 30, 2025

**PD-1 inhibitor rechallenge typically results in patients progressing at their first scan (2-3 months)**



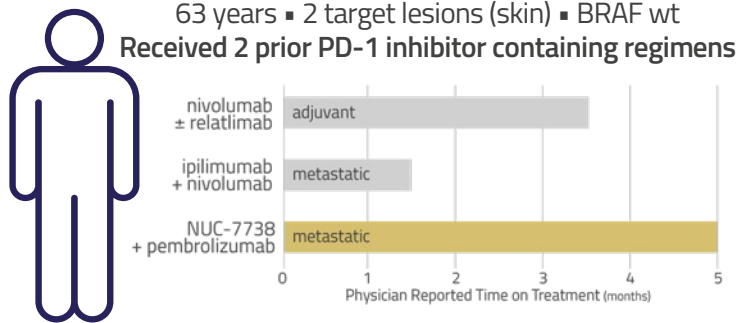
\* Patient achieved complete metabolic response on PET (no FDG uptake), while CT-based iRECIST assessment remained stable disease (BOR-25%)  
 ‡ Discontinued by patient choice; no follow-up, stable disease throughout treatment (BOR-2%)  
 # Discontinued by patient choice; follow-up imaging showed progression of non-target lesion, target lesions remained stable (~55%)

Payne et al (2025) *Immuno-Oncology Technol* 28: Supplement. Abstract ID: 321TiP (ESMO IO December 2025). Data cut-off: October 30, 2025

# NUC-7738 : Encouraging Efficacy in PD-1 Inhibitor Resistant Patients (combination)

## Case Study 1

Partial Response in patient with resistance to PD-1 inhibition



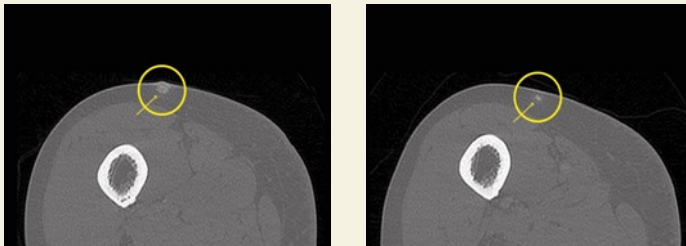
### NUC-7738 + pembrolizumab

Partial Response (confirmed): 55% reduction in sum of target lesions

- 42% reduction in target lesion 1
- 70% reduction in target lesion 2 (see scans)

### Time to progression 9 months

- 5 months treatment, discontinued due to unrelated SAE
- No further therapy, PR sustained for additional 4 months

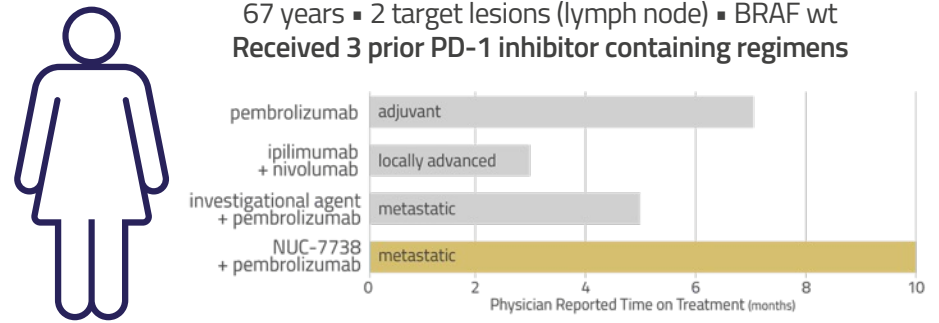


Baseline: 1.0 cm

Week 17: 0.3 cm

## Case Study 2

Evidence of anti-cancer immune response in TME



### NUC-7738 + pembrolizumab

Partial Response (unconfirmed): 32% reduction in sum of target lesions

- 22% reduction in target lesion 1
- 45% reduction in target lesion 2 (see scans)

### Time to progression 8 months

- Remains on treatment at 10 months due to clinical benefit (mixed response to oligometastatic disease; palliative radiotherapy to progressive lesions)

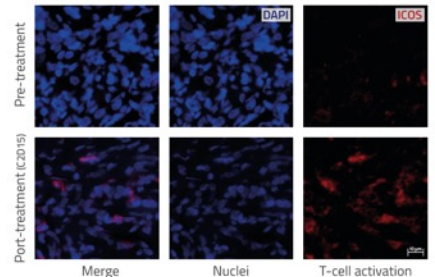


Baseline: 5.53 cm

Week 24: 3.04 cm

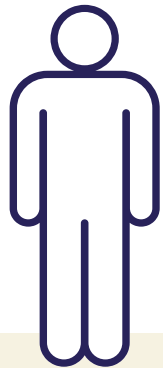
### T-cell activation post-treatment

Increased expression of ICOS (red) post-treatment indicates T-cell activation



## Case Study 3

Complete Metabolic Response (PET-based); PFS 29+ months



66 years ■ 2 target lesions (both liver) ■ BRAF wt

Received prior PD-1 inhibitor containing regimen



### NUC-7738 + pembrolizumab

Stable Disease converted to PET-based complete metabolic response

- 25% reduction in sum of target lesions
  - 18% reduction in target lesion 1
  - 21% reduction in target lesion 2

Time to progression 29+ months, ongoing

- Treatment discontinued at 25 months following sustained clinical benefit & no metabolically active disease on PET



Cancer Detectives:  
Finding the Cures

featured on UK Channel



## RNA Regulatory Disruption by 3'-dATP: A Novel Approach to Inhibit Ribosome Biogenesis in Cancer

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Abstract Number: 5650

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### Background

#### Ribosome Biogenesis & Cancer

- Ribosomes, a complex ensemble of RNA and proteins, play a key role in cell survival, growth, and proliferation
- Ribosome biogenesis (RB) is a complex function governed by precise checkpoints and surveillance mechanisms which may become dysregulated in cancer, leading to tumor growth and therapeutic resistance
- Regulation of RNA through polyadenylation is a key post-transcriptional mechanism that influences mRNA metabolism<sup>1</sup>
- Poly(A) tail length of mRNAs, particularly those encoding ribosomal subunits and components of the translational apparatus, is critical for efficient production of proteins
- These mRNAs are often categorized as 5' terminal oligopyrimidine tract (5'TOP) mRNAs
- Impairment of 5'TOP mRNA translation can directly impact ribosome biogenesis and function, which in turn can halt cellular proliferation; a hallmark of cancer progression<sup>2,3</sup>
- Targeting polyadenylation machinery to influence the poly(A) tail length of mRNAs encoding ribosomal subunits could be a promising strategy to disrupt the aberrant protein synthesis that supports cancer cell growth
- Ribosome-targeted therapy could provide a promising treatment for cancer

#### NUC-7738: ProTide formation of 3'-dA

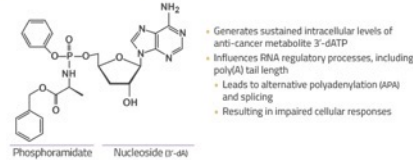


Figure 1. NUC-7738, 3'-deoxyadenosine (3'-dA) phosphoramidate and protected with a phosphoramidate moiety attached at the 5'-position

**Aim:** to investigate the impact of 3'-dATP on RNA regulation and RIBI utilizing a novel bioinformatic pipeline

### Methods

#### Cell Culture

- Melanoma (A375, MeWo, CH1, SK-MEL28) and renal cell carcinoma (7860 & 769F) cell lines were treated with 100 nM of NUC-7738. Cells were harvested 24 hours post-treatment for RNA-seq. For protein analysis whole cell lysates were extracted at 24, 48, 72 and 96 hours. All experiments were carried out on 3 biologically independent replicates.

#### Paired Biopsies

- Patient paired tumor biopsies were collected from 5 cutaneous melanoma patients treated with 1125 mg/m<sup>2</sup> NUC-7738 on days 1, 8 & 15 of a 21-day cycle in combination with 200mg pembrolizumab on day 1
- Biopsies were collected pre- (SCB) and post- (OTB) drug infusion (with post infusion) and preserved in Zymo RNA/DNA Shield (Zymo, Cat#R1100)

#### RNA Extraction

- RNA extracted from cell lines using RNeasy kits (Qiagen 74004)
- Paired patient biopsies, macroscopically assessed for viable tumor, were homogenized using ceramic beads and Precellys 24 homogenizer. RNA isolated using Quick-RNA-Mini kit.

#### Long-read RNA-Seq library preparation

- Sequencing libraries for PCR-cDNA sequencing were constructed utilizing SQK-PCS111.24 kit from Oxford Nanopore Technologies

#### RNA seq data processing and analysis

- Sequencing libraries were processed using R9.4.1 flow cells on PromethION P2 sequencer by Nanopore. The sequenced Fast5 files were basecalled using Guppy v6.0.6, employing the settings: -fast5\_out and -trim\_strategy none. Fast5 files were analyzed with the tailfind package in R to estimate poly A tail lengths for each read.
- For gene expression analysis, basecalled FastQ files were aligned to Gencode v4.1 transcriptome reference using minimap2 v2.17 aligner. Aligned FastQ files were processed through pychopper to identify and orient full-length reads based on their barcodes. Gene-level expression quantification was conducted using Salmon in long-read counting mode (-use). Differential gene expression was assessed with DESeq2 package in R.

#### Poly(A) tail analysis

Tail lengths extracted from tailfindr output together with unique read\_id and transcriptome aligned bam files. Jupyter Notebook environment with Python programming language was employed to process graphs and execute statistical analysis.

#### JESS capillary Western blots

- Whole cell protein lysates were probed with RPL11, RPS3, RPL6 and YAE1 specific antibodies and analyzed by automated JESS Western blot

#### Multiplexed IF

- Multiplexed immunofluorescence (IF) was carried out on biopsies using the in-house optimized automated methods and the Leica BOND RX autostainer. Each antibody concentration was optimized using a wide range tissue TMA and single staining and multiplexed staining prior to staining biopsies.

### Results

#### NUC-7738 causes a global reduction in poly(A) tail length in cell lines and biopsies

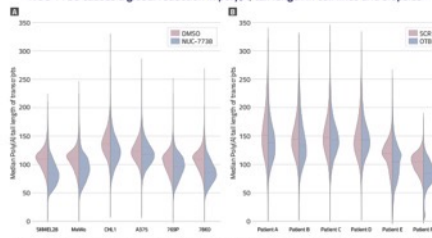


Figure 2. Poly(A) tail changes in cancer cell lines (A) treated with NUC-7738 and paired biopsies from patients (B) treated with NUC-7738 + pembrolizumab. Violin plots depicting the median poly(A) tail length of transcripts from melanoma and renal cell cancer cell lines and paired biopsies. Each plot represents a different cell line or patient paired biopsy with the median value denoted by a dashed red line. The width of each 'violin' indicates the density of data points at different lengths.

- NUC-7738 caused a shortening of poly(A) tails (blue vs red) in cell lines treated with NUC-7738 and patients' paired biopsies treated with NUC-7738 and pembrolizumab

#### NUC-7738 shortens poly(A) tails of 5'TOP mRNA and SNHG non-coding RNAs

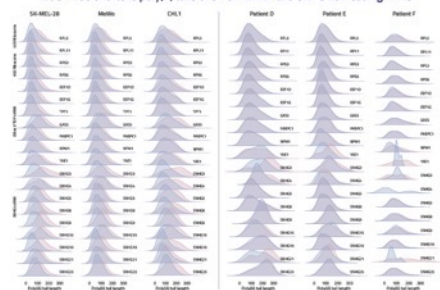


Figure 3. Ridge Plots of Poly(A) Tail Length of genes in cell lines and patients' paired biopsies. The genes are representative of 5'TOP mRNA genes and SNHG non-coding RNA. The x-axis quantifies the poly(A) tail length in nucleotides, while the y-axis represents the kernel density estimation of gene expression.

### Results (cont)

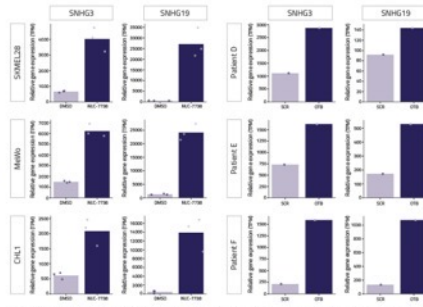


Figure 3B. Transcript levels of SNHG3 and SNHG19 across multiple cell lines and patient paired biopsies. The figure presents bar plots of transcript per million (TPM) measurements for SNHG3 and SNHG19 in a variety of human cell lines treated with NUC-7738 and paired patient biopsies.

- NUC-7738 reduces poly(A) tail length of all 5'TOP genes (median reduction of 15 adenosines)
- NUC-7738 reduces poly(A) tail length of SNHG non-coding RNAs (median reduction of 25 adenosines)
- NUC-7738 reduces poly(A) tail length of PAXT lncRNAs, SNHG3 and SNHG19, by ~50 adenosines, accompanied with an increase in transcript abundance

#### NUC-7738 reduces the protein levels of ribosomal subunits and YAE1

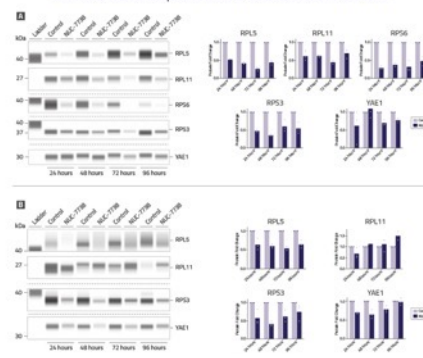


Figure 4. Ribosomal subunit proteins in melanoma cell lines. (A) MeWo and (B) SK-MEL-28 cell lines. Each data point represents an independent biological replicate (n=3)

- NUC-7738 reduces expression of ribosomal subunit proteins by up to 70% across all cell lines
- Expression of YAE1, a regulator of RIBI, also decreased, indicative of impaired RIBI
- These data suggest NUC-7738 targets ribosomal subunits proteins

#### NUC-7738 + pembrolizumab reduces RPS3 and YAE1 protein

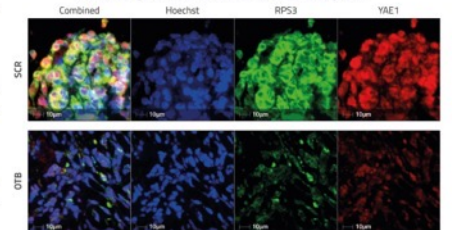


Figure 5. RPS3 and YAE1 protein expression in representative patient paired biopsy treated with NUC-7738 + pembrolizumab. Hoechst staining represents cell nuclei.

- NUC-7738 + pembrolizumab reduces the expression of ribosomal protein RPS3 and YAE1 confirming cell line data

### CONCLUSION

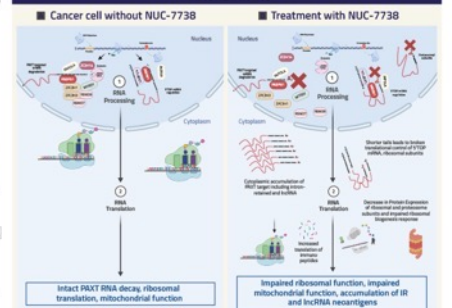


Figure 6. Proposed mechanisms of action of NUC-7738 contributing to impaired ribosome biogenesis. (A) In the absence of NUC-7738, RNA processing and translation proceed regularly, maintaining intact PAXT RNA decay and ribosomal subunits translation.

(B) NUC-7738 generates anticancer metabolite 3'-dATP incorporation of 3'-dATP by Poly(A) Polymerase results in the premature termination of poly(A) tail elongation. This inhibition disrupts the poly(A) tail enzyme targeting (PAXT), causing an accumulation of SNHG gene transcripts and intra-retained transcripts. Reduction of poly(A) tail length impairs the translational control of protein-coding ribosomal mRNAs. Consequently, there is a decrease in protein expression of ribosomal subunits, leading to inhibition of ribosomal biogenesis and protein translation, as well as impaired ribosomal function.

- NUC-7738 significantly modulates RNA stability, particularly affecting 5' TOP genes crucial for translational control
- Global poly(A) tail shortening, observed across cancer cell lines, as well as in paired biopsies, indicates broad and targeted mRNA stability impact
- Specific shortening of poly(A) tails within the 5'TOP gene set suggests interference with mRNA regulation, leading to decreased protein translation
- Preliminary data highlight NUC-7738's potential to influence gene regulation, especially in the translational machinery critical for cancer cell growth and survival

Elshani M, Zhang Y, Um IH, Plummer R, Blagden S, Symeonides S, Cook N, Evans TRJ, Harrison DJ, Dickson AL (2024) RNA Regulatory Disruption by 3'-dATP: A Novel Approach to Inhibit Ribosome Biogenesis in Cancer. AACR 2024 Meeting Abstracts, Abstract 5650. doi:10.1158/1538-7445.2024-5650

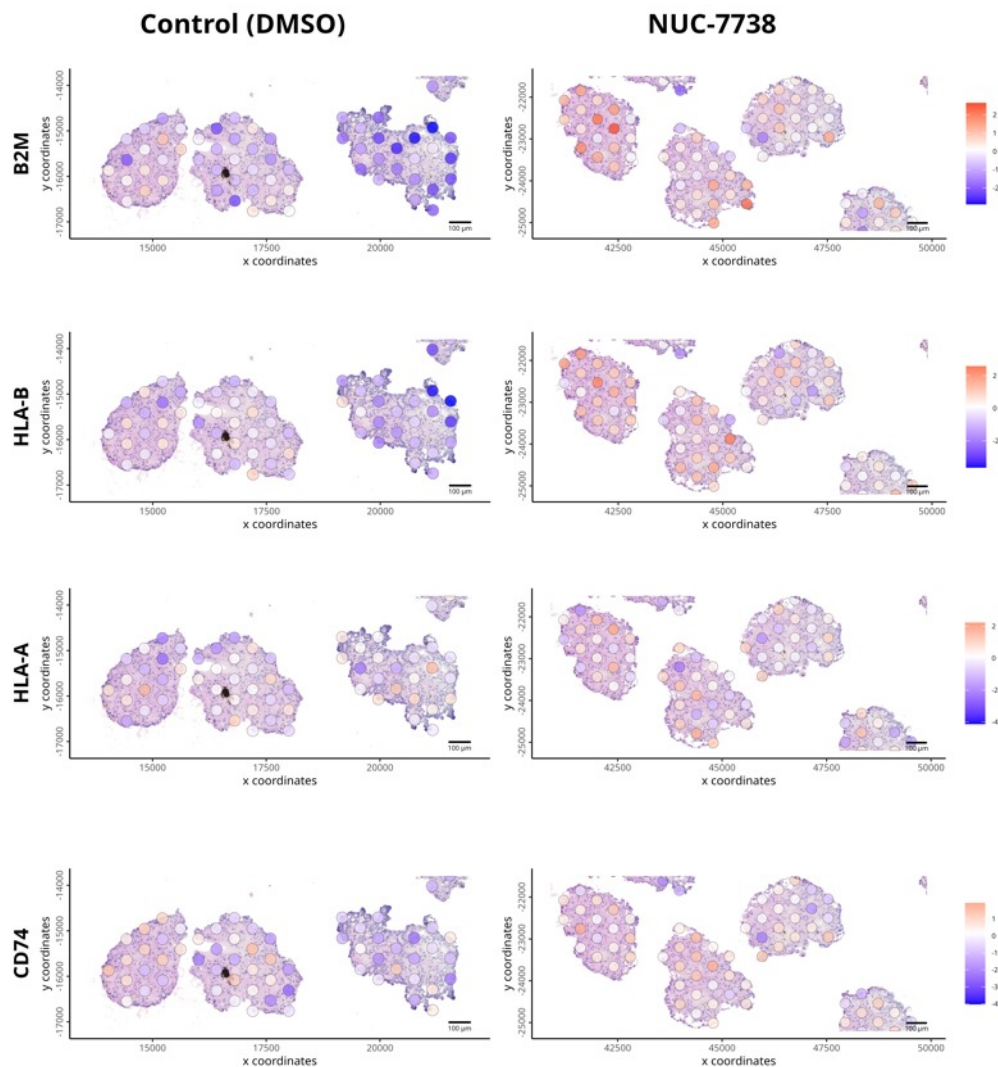


# NUC-7738 : Increases Abundance of RNA Transcripts Associated with Immune Presentation in Tumoroids (MHC I & II)

Primary kidney cancer tissue was dissociated & grown for 3 weeks *in vitro* before treatment. Spatial transcriptomic analysis was then performed on harvested tumoroids.

B2M is beta 2 microglobulin, and together with HLA-A and HLA-B form class 1 Major Histocompatibility Complex (MHC). Class I MHC is recognized by CD8+ T lymphocytes.

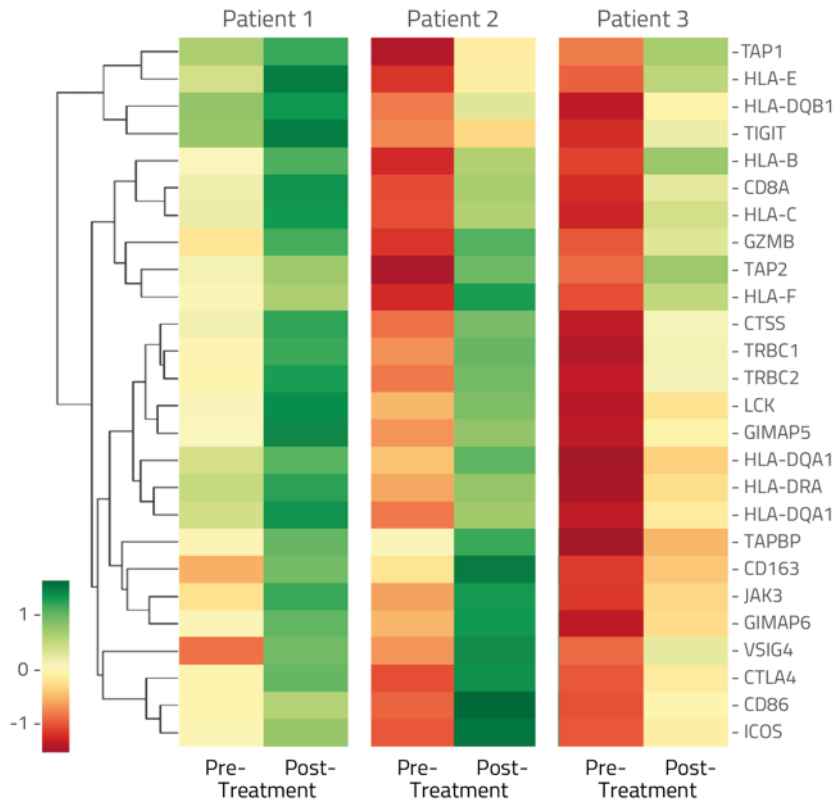
CD74 (also called HLA-DR antigens-associated invariant chain, part of Class II MHC) helps to transport peptide needed for T-cell activation. Class II MHC is recognized by CD4+ T lymphocytes.



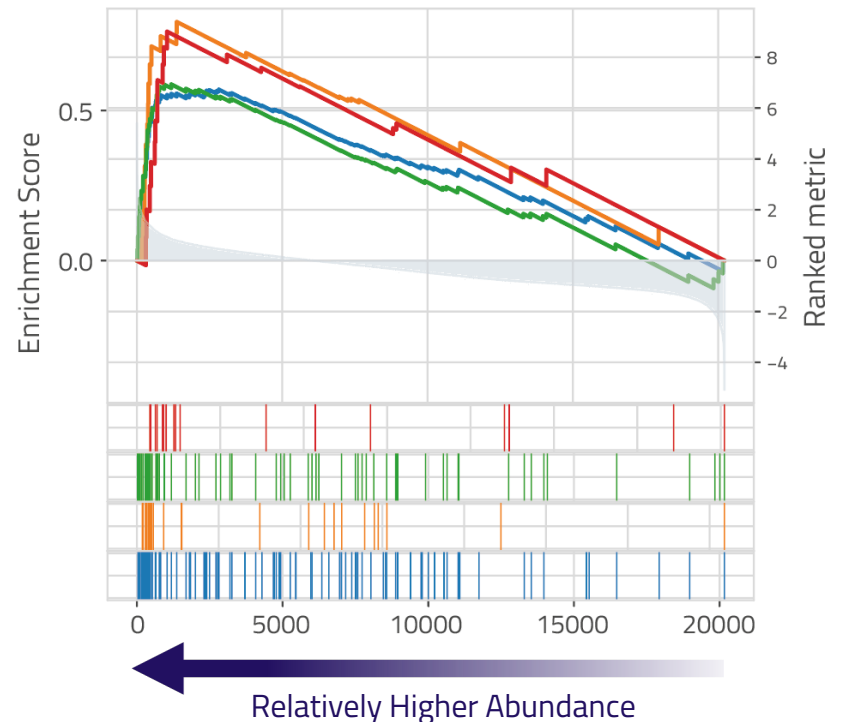
# NUC-7738 : Increases Antigen Presentation & T-cell Activation in Patient Biopsies

Heatmaps illustrating RNA expression reveal a relative increase in mRNA levels of genes associated with antigen transport & presentation and T-cell activation

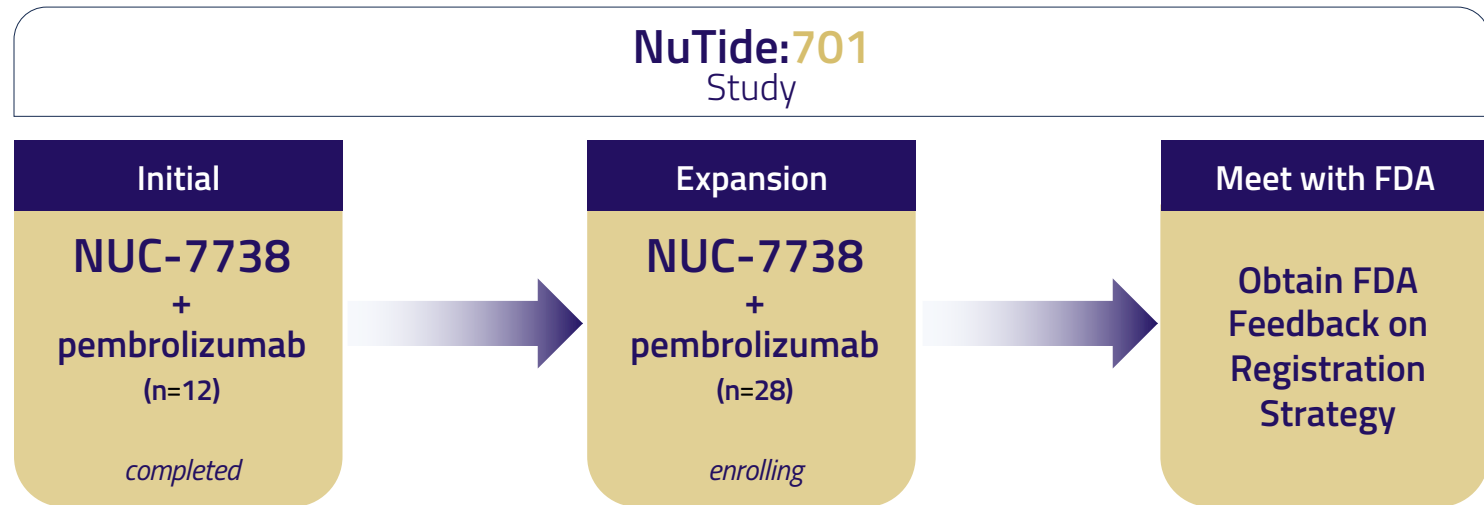
Comparative gene enrichment analysis from biopsies shows immune pathway activation related to antigen processing & presentation, T-cell activation & proliferation



- Positive Regulation Of T Cell Activation (GO:0050870)
- Antigen Processing And Presentation Of Peptide Antigen Via MHC Class II (GO:0002495)
- Regulation Of T Cell Proliferation (GO:0042129)
- Antigen Processing And Presentation Of Endogenous Peptide Antigen (GO:0002483)



Blagden *et al* (2024) *Ann Oncol*: 35: S482-S535 Abstract ID: 666P (ESMO September 2024). Data cut-off: August 1, 2024



# NUC-7738 : Melanoma Market Opportunity

## \$7.4B

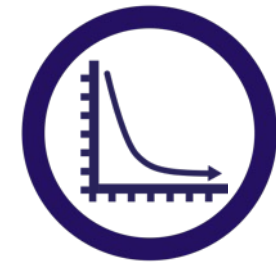
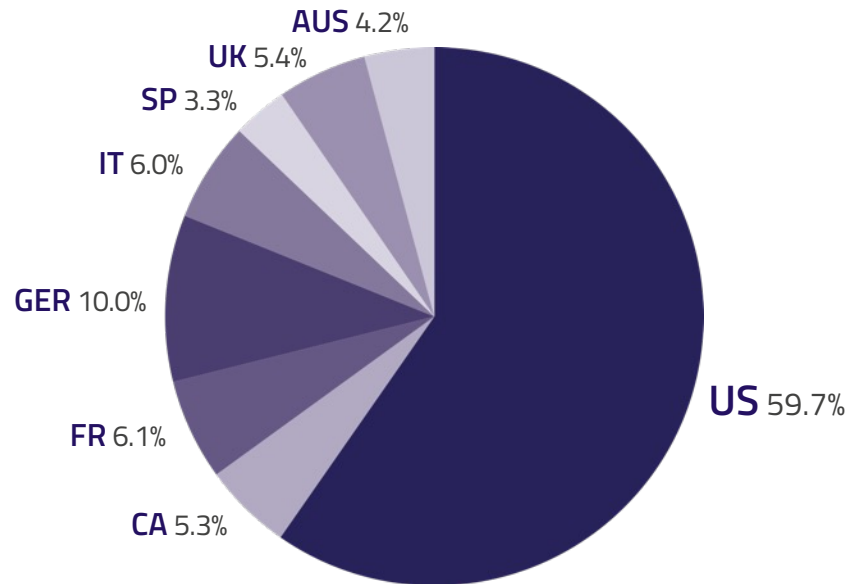
Estimated sales in 8 major markets in 2029<sup>2</sup>



**331,722 new cases**  
diagnosed annually<sup>1</sup>



**13,000 patients**  
will fail PD-1 inhibitors in US<sup>3</sup>

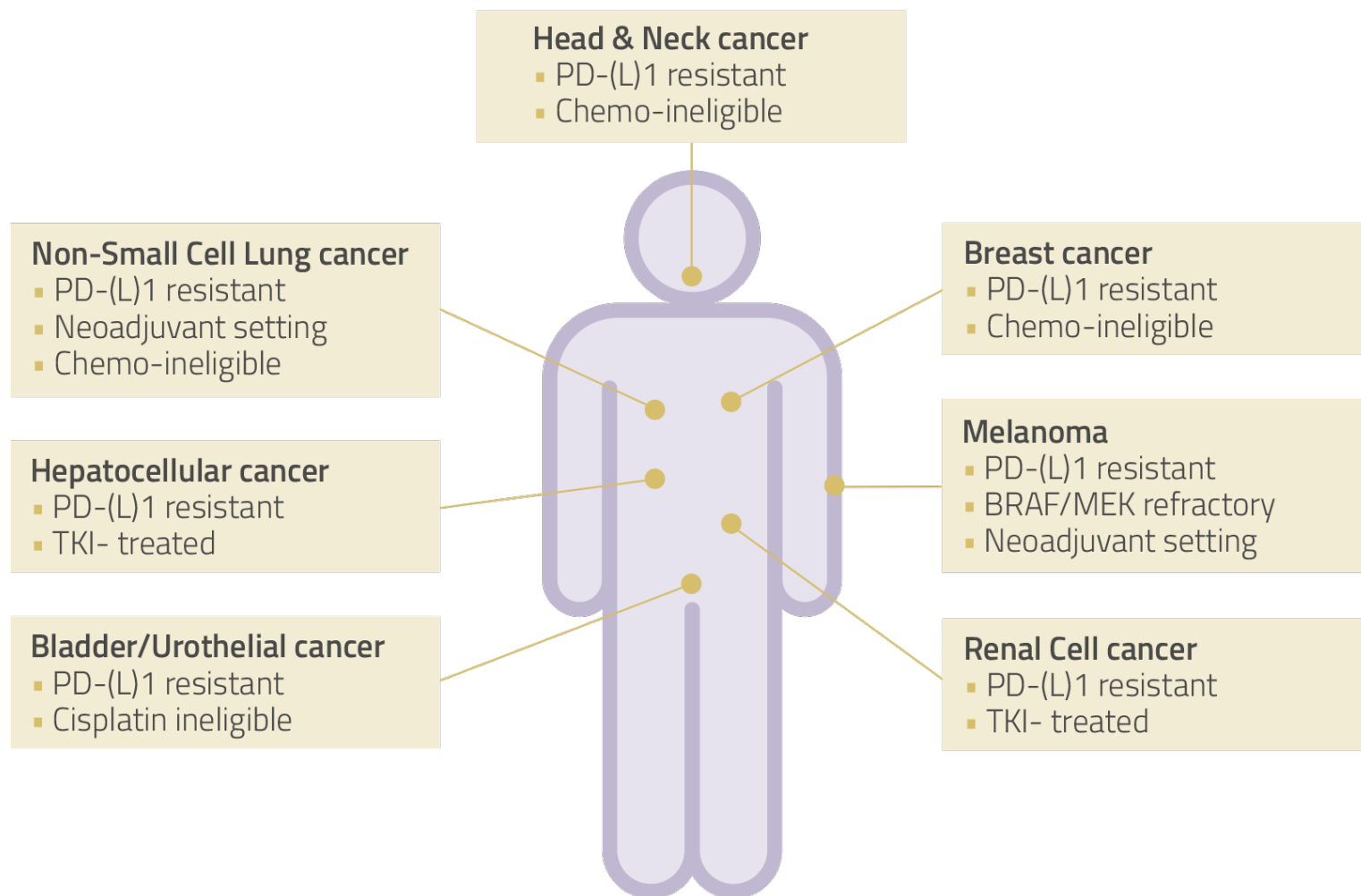


**5-year survival rate: 30%**  
Stage IV melanoma<sup>4</sup>



**58,667 deaths**  
annually<sup>1</sup>

1. GLOBOCAN 2022, Cancer Incidence and Mortality Worldwide  
2. Global Data Melanoma - Global Drug Forecast and Market Analysis to 2029  
3. 2030 estimate based on CancerMPact data and primary market research  
4. Melanoma Research Alliance (<https://www.curemelanoma.org>)



NUC-3373



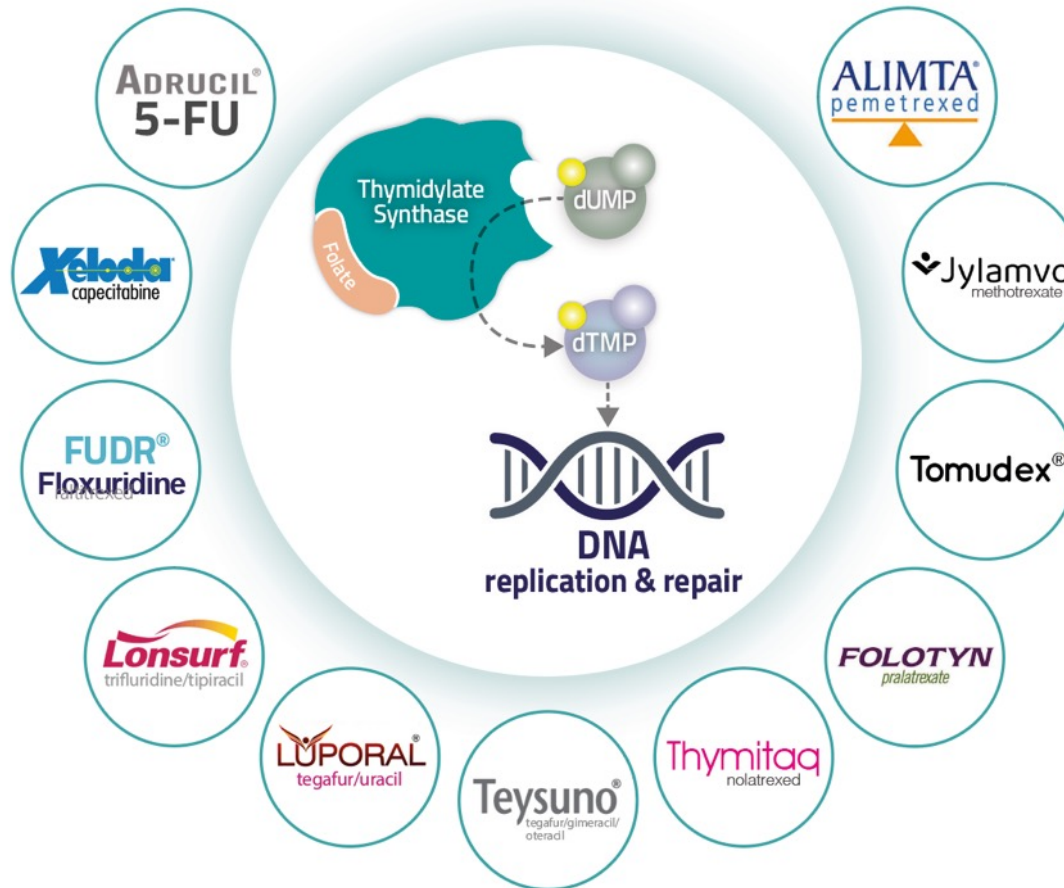
Targeted Thymidylate Synthase Inhibitor

# Thymidylate Synthase: An Important Target for Anti-Cancer Therapies

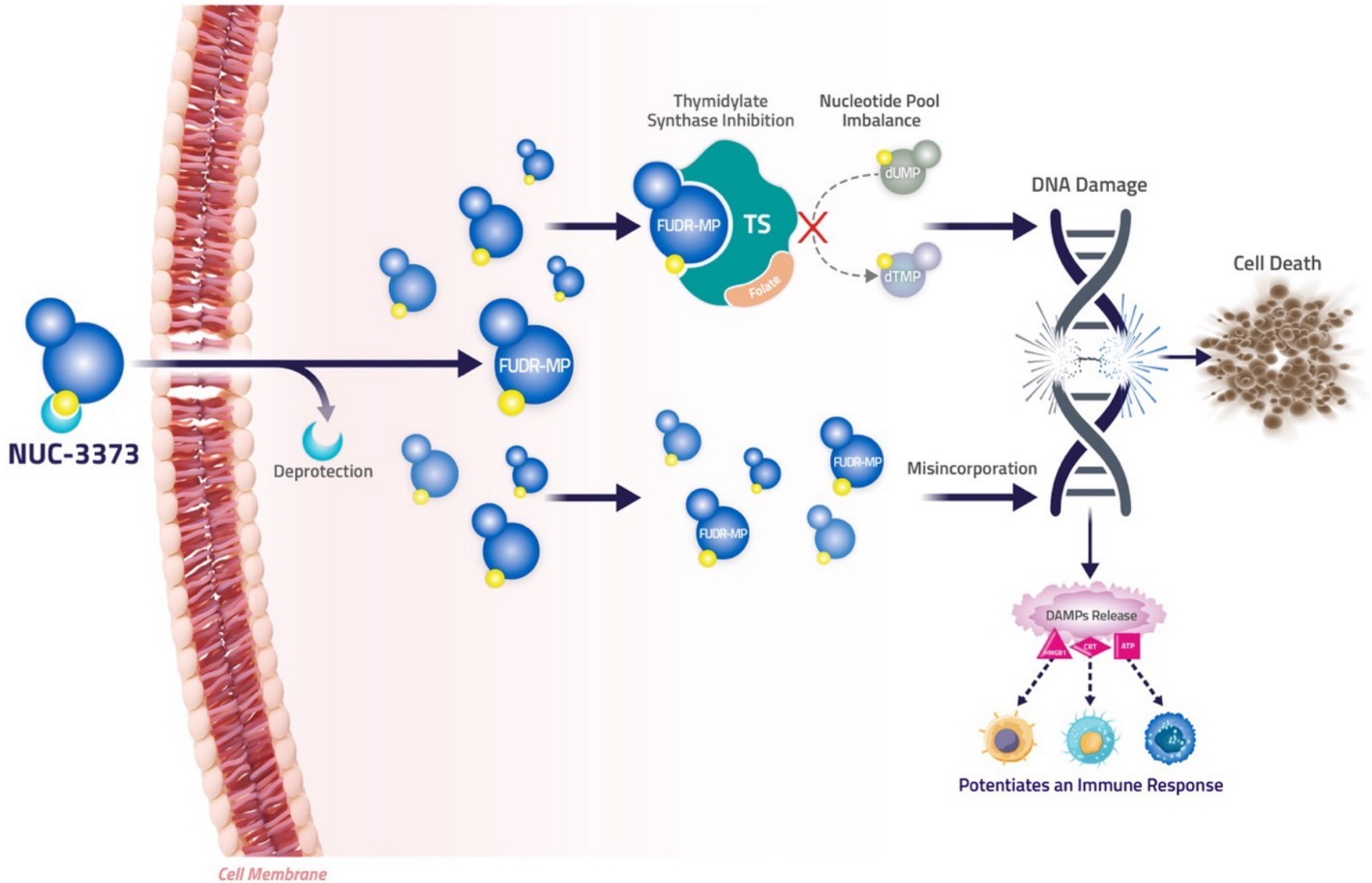
Thymidylate Synthase (TS) is a critical enzyme for nucleotide synthesis

- Converts uridine (dUMP) to thymidine (dTMP)
- Essential for DNA replication and cell proliferation
- Often upregulated in cancer cells

TS inhibitors are widely used despite their insufficient inhibition of the target enzyme



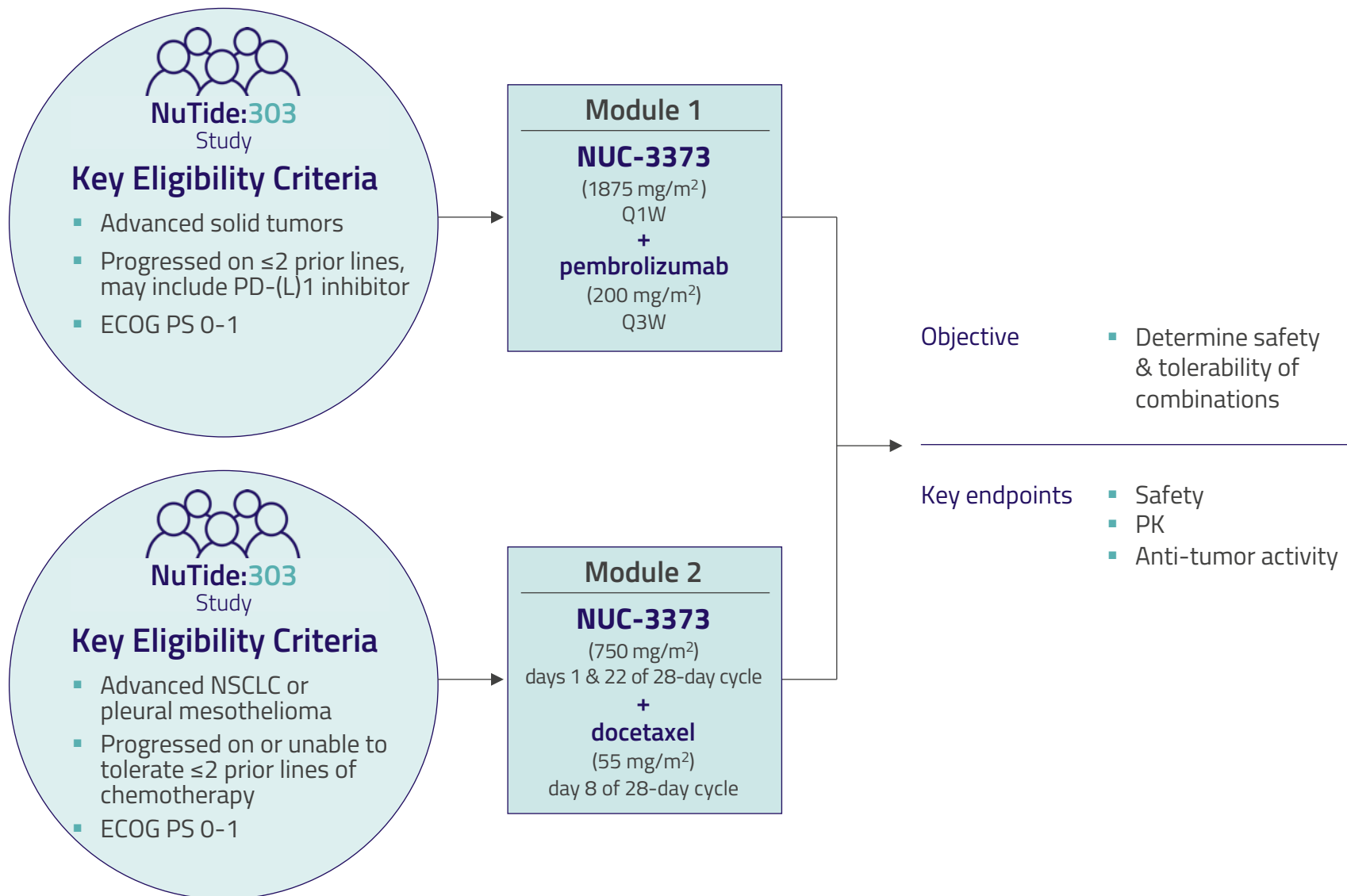
# NUC-3373 : Induces DNA Damage & Potentiates an Immune Response



Brè et al (2023) *Cancer Chemother Pharmacol* 91(5): 401-412; Read et al (2025) *PLoS One*: 16; 20(9): e0331567

Over 300 patients have received NUC-3373 across the clinical program

STUDY	COMBINATION	POPULATION	PATIENTS
<b>NuTide:301</b> Phase 1	monotherapy	Solid Tumors (end-stage)	59
<b>NuTide:302</b> Phase 1b	leucovorin (LV)	CRC (end-stage)	38
<b>NuTide:302</b> Phase 1b	LV + irinotecan	CRC (end-stage)	32
<b>NuTide:302</b> Phase 1b	LV + oxaliplatin	CRC (end-stage)	23
<b>NuTide:302</b> Phase 2	LV + irinotecan + bevacizumab	CRC (end-stage)	8
<b>NuTide:302</b> Phase 2	LV + oxaliplatin + bevacizumab	CRC (end-stage)	6
<b>NuTide:323</b> Phase 2 (randomized)	LV + irinotecan + bevacizumab vs. FOLFIRI + bevacizumab	CRC (second-line)	120 (NUC-3373) 57 (5-FU)
<b>NuTide:303</b> Phase 1b/2	pembrolizumab	Solid Tumors (second/third-line)	13
<b>NuTide:303</b> Phase 1b/2	docetaxel	Lung Cancer (second/third-line)	4



## NUC-3373 + pembrolizumab has been well tolerated (n=13)

- No Grade 4 toxicities

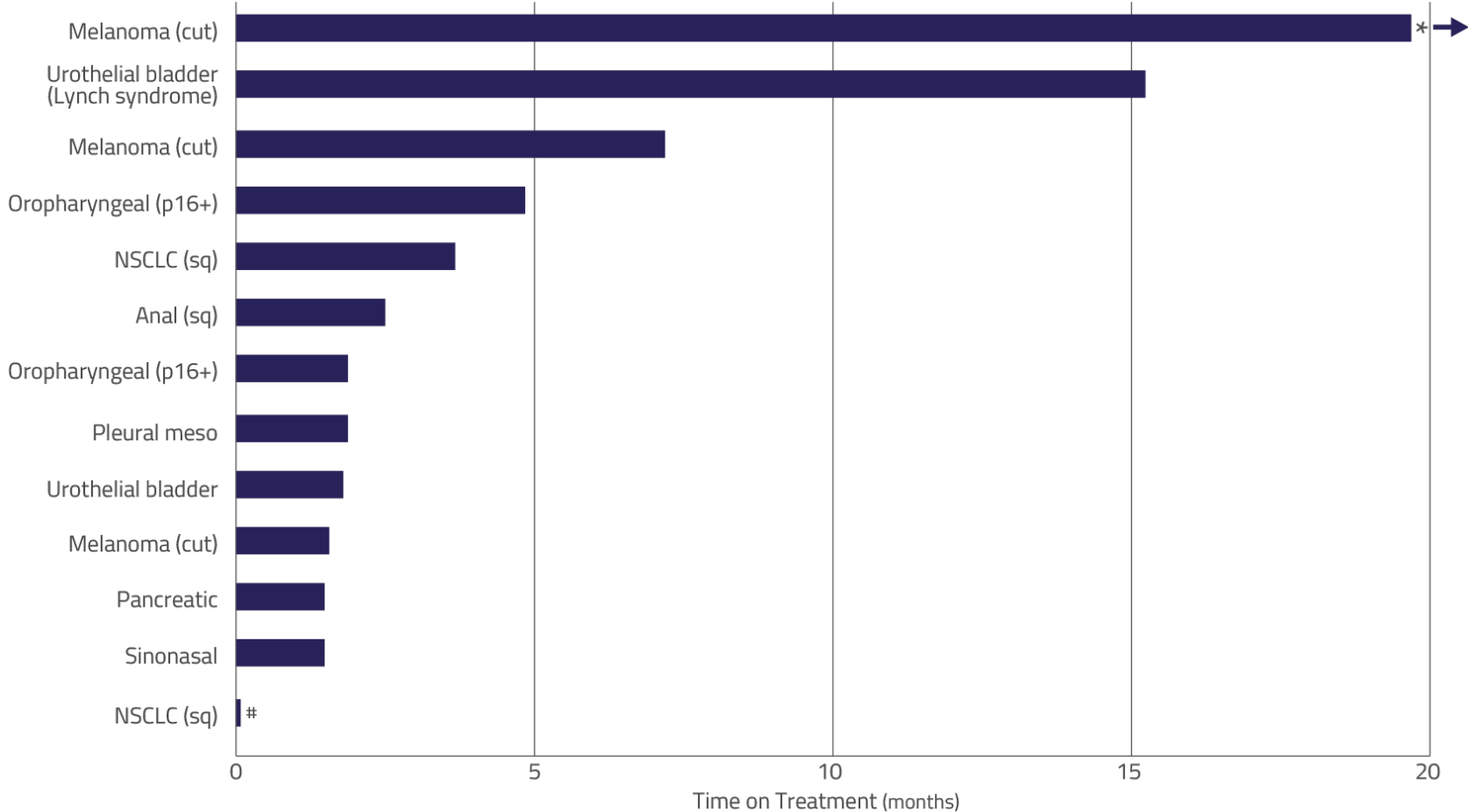
### Treatment Related Adverse Events

	All Grades n(%)	Grade 3 n(%)	Grade 4 n(%)
Vomiting	10 (77)	0	0
Nausea	9 (69)	0	0
Diarrhea	6 (46)	0	0
Fatigue	6 (46)	0	0
Infusion related reaction	4 (31)	0	0
ALT increased	4 (31)	0	0
AST increased	4 (31)	0	0
Anemia	4 (31)	1 (8)	0
Constipation	3 (23)	0	0
Abdominal pain	2 (15)	0	0
GGT increased	2 (15)	0	0
Dizziness	2 (15)	0	0
Headache	2 (15)	0	0
Flushing	2 (15)	0	0
Rash	2 (15)	0	0

All Grade TRAEs with prevalence  $\geq 20\%$  patients related to NUC-3373, pembrolizumab or both  
 Additional Grade 3 TRAE  $\leq 10\%$ : hyponatremia (1 pt)

Middleton et al (2025) medRxiv doi: 10.1101/2024.11.07.24316829. Data cut-off: May 30, 2025

## Encouraging duration of clinical benefit in PD-(L)1 experienced patients



\* Data presented as per end of study cut-off date (30 May 2025). This patient was progression-free as of 31 August 2025 (22 months ongoing) & continued to receive treatment after study ended

# Patient only received 1 dose of study treatment and was not DLT-evaluable

Middleton *et al* (2025) *medRxiv* doi: 10.1101/2024.11.07.24316829. Data cut-off: May 30, 2025

## Cutaneous Melanoma



75 years ▪ BRAF mt  
**2 prior lines**

- 1) pembrolizumab:  
progressive disease within **5 months**
- 2) trametinib + dabrafenib:  
trametinib discontinued after **1 month** (toxicity)  
dabrafenib for 7 years (progressive disease)

**NUC-3373** 1875 mg/m<sup>2</sup> + **pembrolizumab** 200 mg

- 1 target lesion (bilateral lymph node)

**Partial Response (confirmed): 81% reduction** in tumor volume

**Treatment duration: 19+ months (ongoing)**

- No dose reductions

## Bladder Cancer



72 years ▪ Lynch Syndrome  
**2 prior lines**

- 1) gemcitabine + cisplatin (adjuvant):  
discontinued due to myelosuppression **2 months**
- 2) atezolizumab (metastatic):  
best response SD, discontinued after **23 months**

**NUC-3373** 1875 mg/m<sup>2</sup> + **pembrolizumab** 200 mg

- 1 target lesion (lung)

**100% reduction in sum of target lesions**

**Partial Response (confirmed)** due to presence of non-target lesions

**Treatment duration: 15 months**

- No dose reductions

## Pleural Mesothelioma



60 years  
3 prior lines

- 1) cisplatin + pemetrexed:  
progressive disease within **4 months**
- 2) nivolumab:  
progressive disease within **4 months**
- 3) carboplatin + pemetrexed:  
progressive disease within **1 month**

**NUC-3373 750 mg/m<sup>2</sup> + docetaxel 55 mg/m<sup>2</sup>**

- 4 target lesions (2x lymph node, 2x mediastinum)

**Stable Disease: 13+ months (ongoing)**

**Treatment duration: 8.5 months (discontinued due to fatigue)**

- NUC-3373 + docetaxel (4 cycles), followed by NUC-3373 (5 cycles)

## NSCLC (squamous)



77 years  
2 prior lines

- 1) carboplatin + paclitaxel + pembrolizumab:  
stable disease for **2 months**
- 2) pembrolizumab (maintenance):  
progressive disease within **21 months**

**NUC-3373 750 mg/m<sup>2</sup> + docetaxel 55 mg/m<sup>2</sup>**

- 1 target lesion (lung)








**Stable Disease: 7 months**

**Treatment duration: 7 months**

- NUC-3373 + docetaxel (6 cycles), followed by NUC-3373 (2 cycles)

# Strong Intellectual Property Position

Worldwide exclusive rights for all programs: **284 granted patents** and **61 pending applications\***

KEY PATENTS	STATUS	EXPIRATION+ (excluding any extensions)	TERRITORIES
<b><i>NUC-7738</i></b>	100 granted, 42 pending, including:		
Composition of matter	Granted (US, EP, CN, JP)	2035	 + others
Formulation	Pending	2036	 + others
Manufacturing process	Pending	2038	 + others
Use	Pending	2043	 + others
<b><i>NUC-3373</i></b>	149 granted, 26 pending, including:		
Composition of matter	Granted (US, EP, CN, JP)	2032	 + others
Formulation	Granted (JP, US), Pending (EP, CN)	2036	 + others
Manufacturing process	Pending	2043	 + others

\*As of February 24, 2026

\*Expiration for pending patents if granted

# Key Expected Milestones: 2026

	INDICATION	COMBINATION	PHASE	MILESTONE
<b><i>NUC-7738</i></b> NuTide:701 Study	Melanoma	pembrolizumab	Phase 2	Complete Recruitment Announce Expansion Data Obtain FDA Feedback on Registration Strategy
<b><i>NUC-3373</i></b> NuTide:303 Study	Solid Tumors	pembrolizumab	Phase 1b/2	Announce Development Plan

# Investment Highlights

## ***NUC-7738***

### **Transforms Tumor Microenvironment**

Differentiated mode of action: RNA polyadenylation  
Encouraging signs of efficacy  
Favorable safety profile  
Potentiates PD-1 inhibition

## ***NUC-3373***

### **Targeted TS inhibitor**

Induces DNA damage  
Encouraging signs of efficacy as monotherapy  
& in combination with PD-1 inhibitor  
Favorable safety profile

### **Experienced Team**

Accomplished management  
team backed by leading  
biotech investors

**Nasdaq: NCNA**

### **Improving Survival Outcomes**

Synergy in combination  
with immune checkpoint  
inhibitor therapy

### **Strong IP Protection**

Worldwide  
exclusive rights

### **Significant Milestones**

Numerous value inflection  
points throughout 2026



**NUCANA**  
*Nasdaq: NCNA*  
nucana.com