



A New Era in Oncology

Forward-Looking Statements

This presentation contains “forward-looking” statements within the meaning of the Private Securities Litigation Reform Act of 1995 that are based on the beliefs and assumptions and on information currently available to management of NuCana plc (the “Company”). All statements other than statements of historical fact contained in this presentation are forward-looking statements. Forward-looking statements include, but are not limited to, information concerning the Company’s planned and ongoing preclinical and clinical studies for the Company’s product candidates and the potential advantages of those product candidates, including NUC-7738 and NUC-3373; the initiation, enrollment, timing, progress, release of data from and results of the Company’s planned and ongoing clinical studies; the Company’s goals with respect to the development, regulatory pathway and potential use, if approved, of each of its product candidates; the utility of prior preclinical and clinical data in determining future clinical results; the timing or likelihood of regulatory filings and approvals for any of its product candidates; the Company’s intellectual property; the amount and sufficiency of the Company’s cash and cash equivalents to achieve its projected milestones and to fund its planned operations into 2029; and estimates regarding the Company’s expenses, future revenues and future capital requirements. In some cases, you can identify forward-looking statements by terminology such as “may,” “will,” “should,” “expects,” “plans,” “anticipates,” “believes,” “estimates,” “predicts,” “potential” or “continue” or the negative of these terms or other comparable terminology.

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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

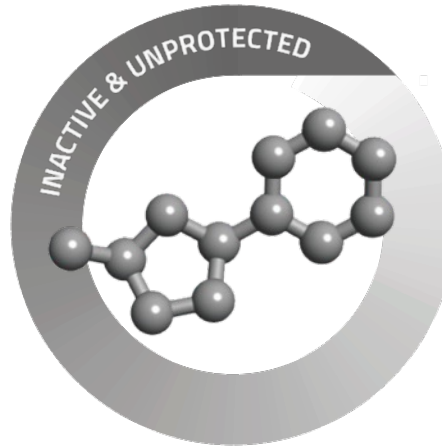
GEMZAR
gemcitabine

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

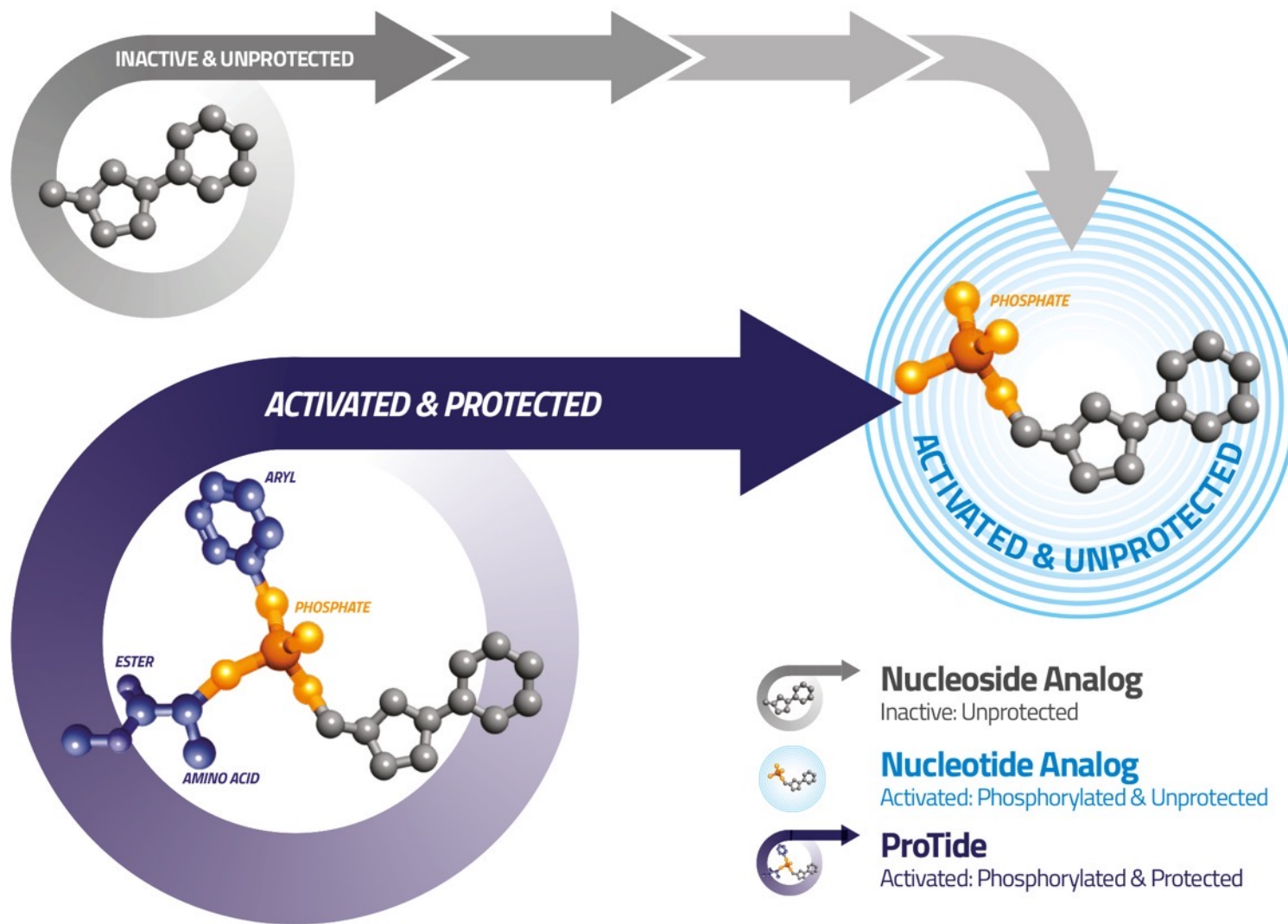
**Breakdown
& Toxic
Byproducts**
Off-target
toxicity

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**¹

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

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

¹ Sovaldi + Harvoni + Epclusa + Vosevi cumulative sales through December 31, 2025

² Genvoya + Descovy + Odefsey + Biktarvy + Symtuza + Vemlidy cumulative sales through December 31, 2025

³ Veklury cumulative sales through December 31, 2025

NUC-7738



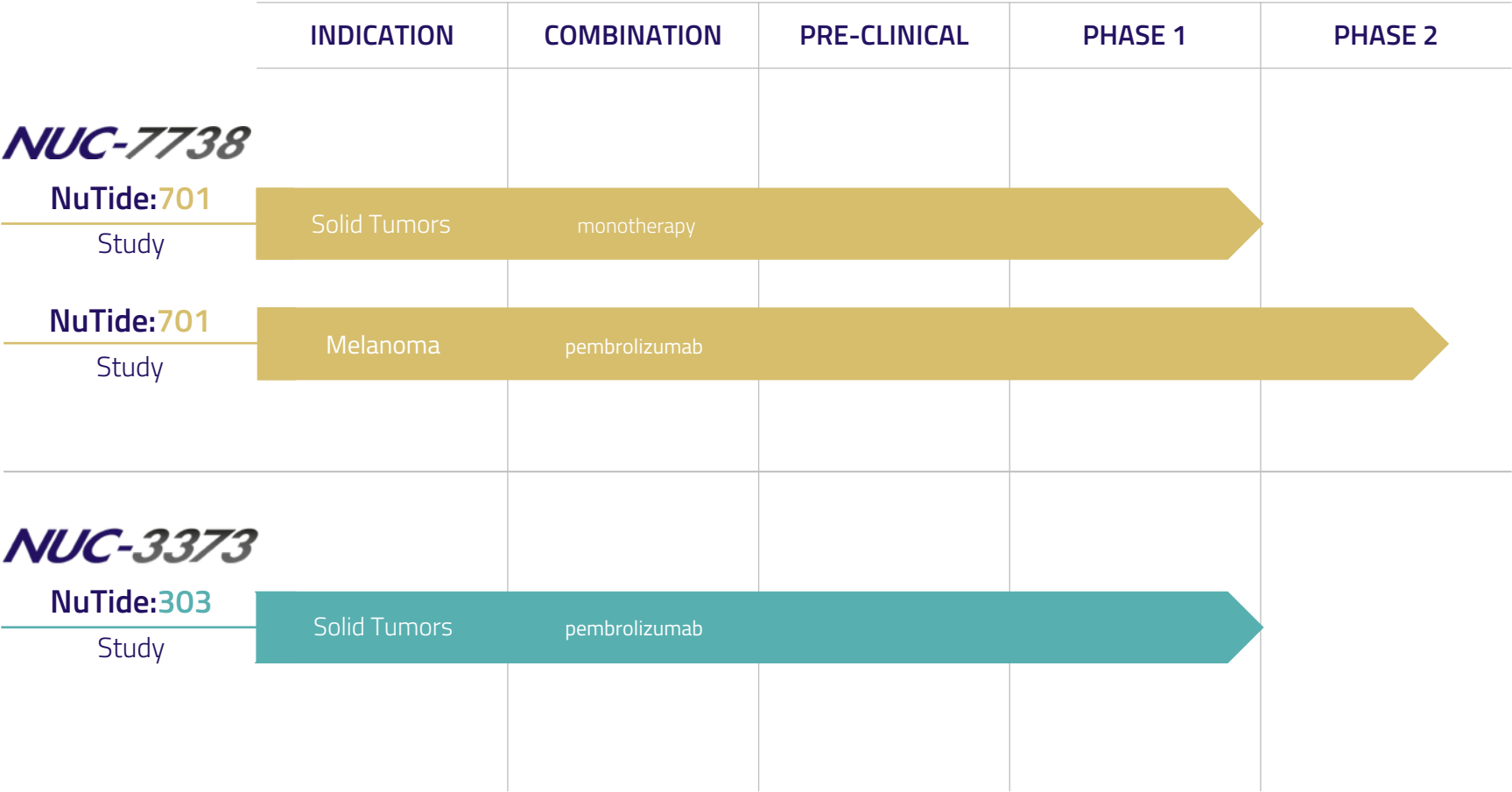
- Transformed novel nucleoside analog: 3'-dA
- Profoundly impacts gene expression in cancer cells
- Targets the tumor microenvironment

NUC-3373



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

Current Development Status



Multiple Inflection Points in 2026



Cash & Cash Equivalents
June 30, 2026
~\$25.9 million*



Cash Runway
into
2029



Important Data Readouts
in
2026

*Based on exchange rate of £1.00 to \$1.33 and reported cash of £19.5 million as of June 30, 2026

NUC-7738

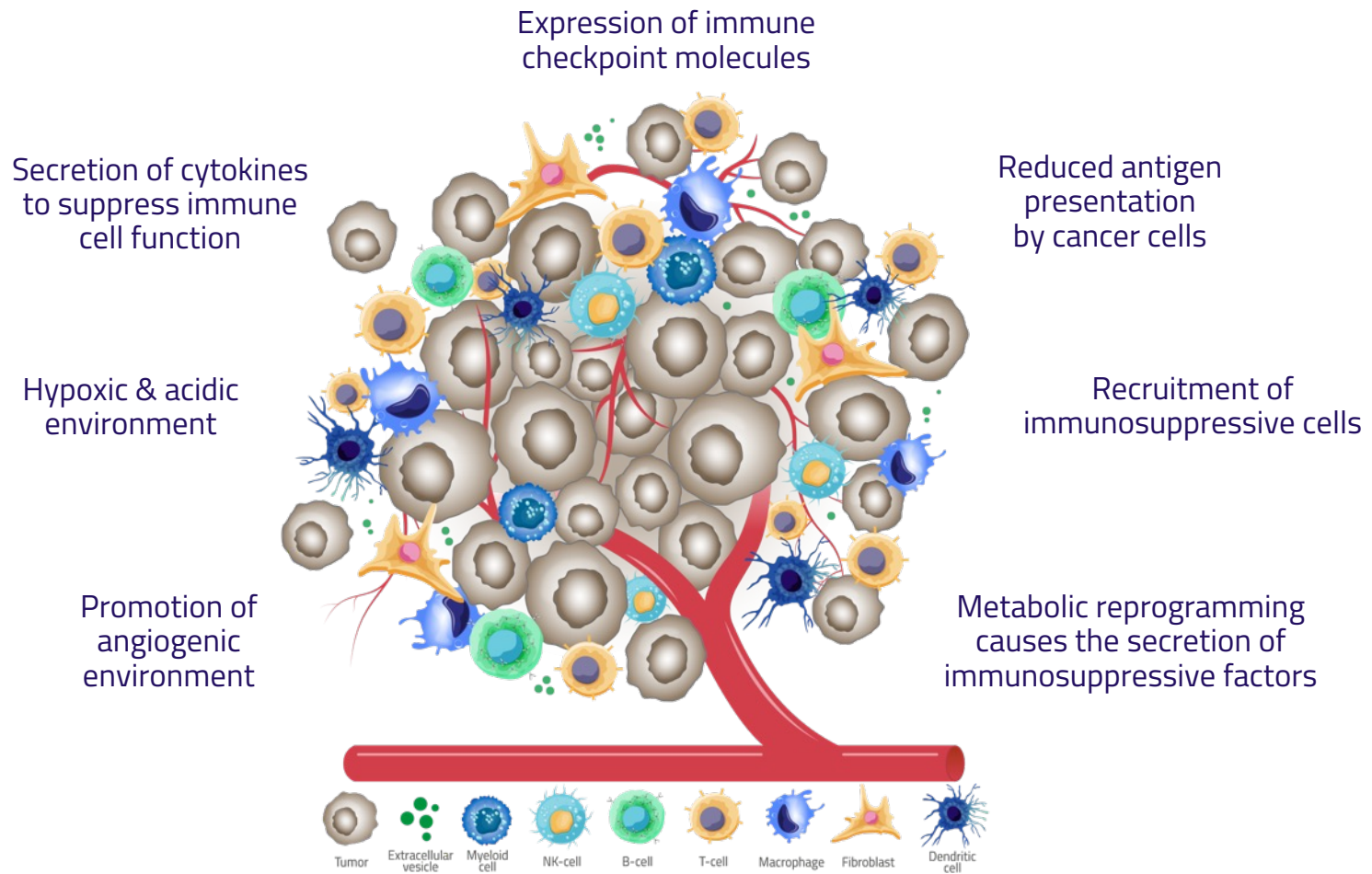


Unlocking the Potential of Immunotherapy

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)

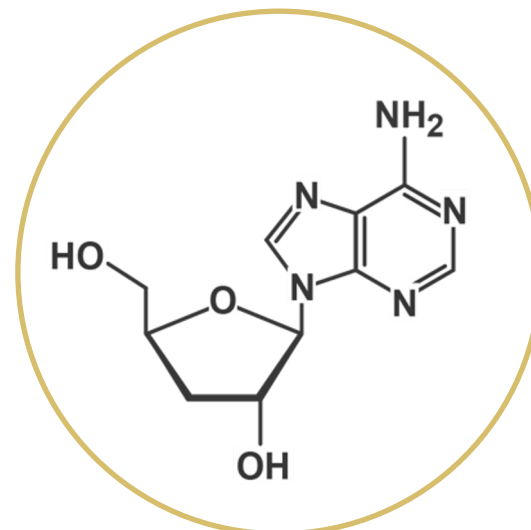
Cordycepin

A Traditional Chinese Medicine found in the Himalayas



3'-dA

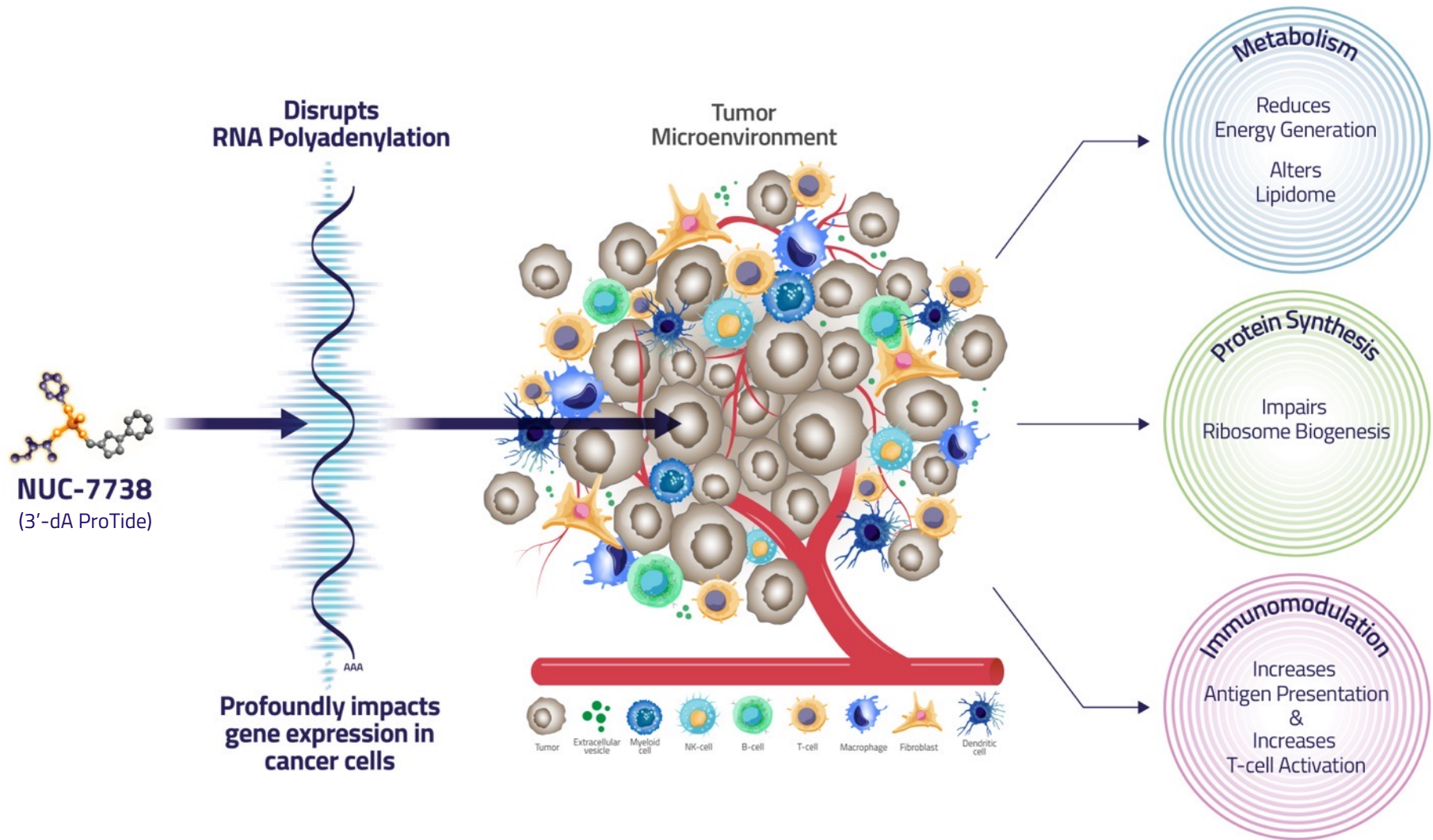
Originally isolated from *Cordyceps sinensis* in 1950



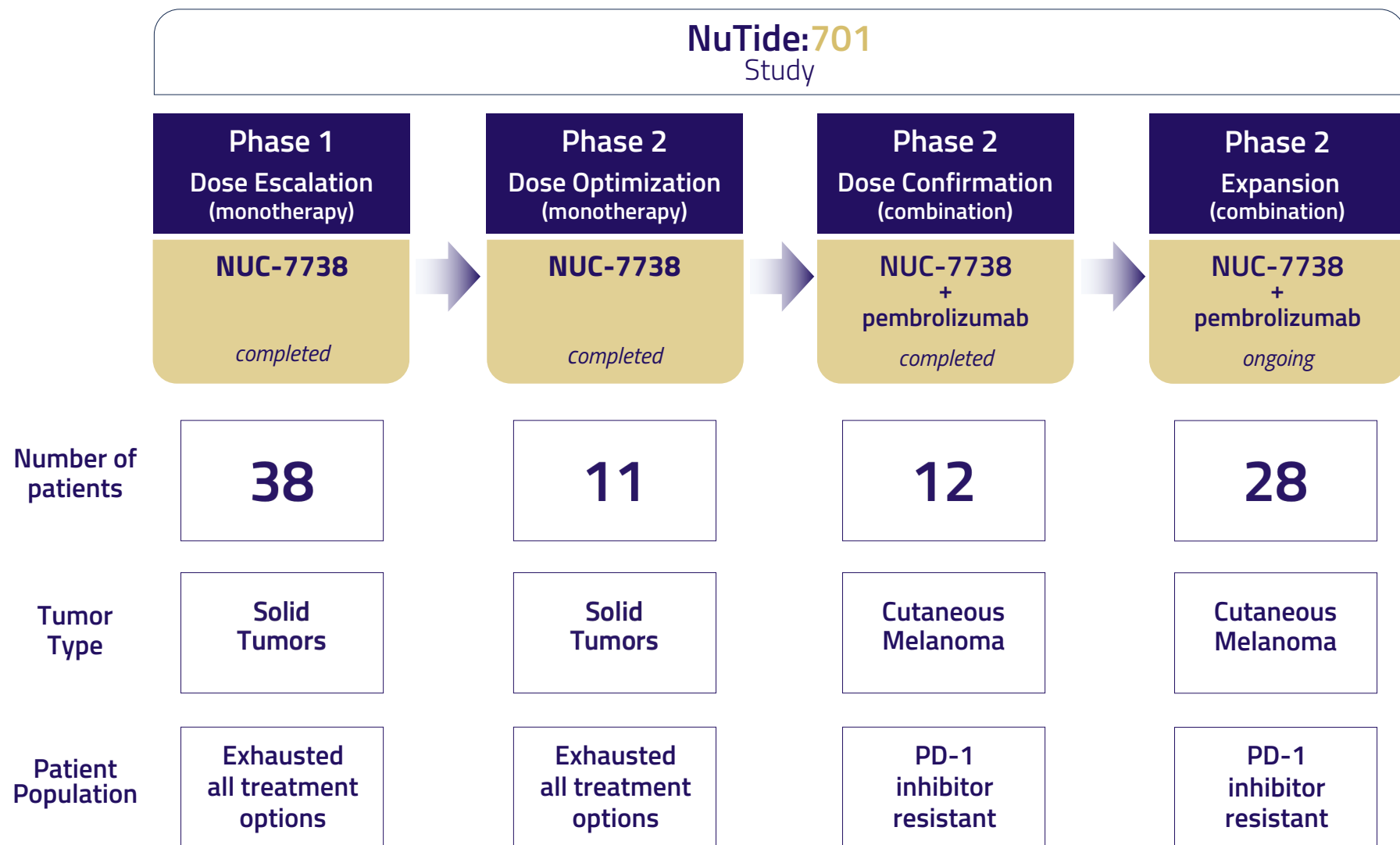
3'-dA has potent anti-cancer activity *in vitro* and can modulate components of the TME

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

NUC-7738 : Targets Multiple Aspects of the Tumor Microenvironment



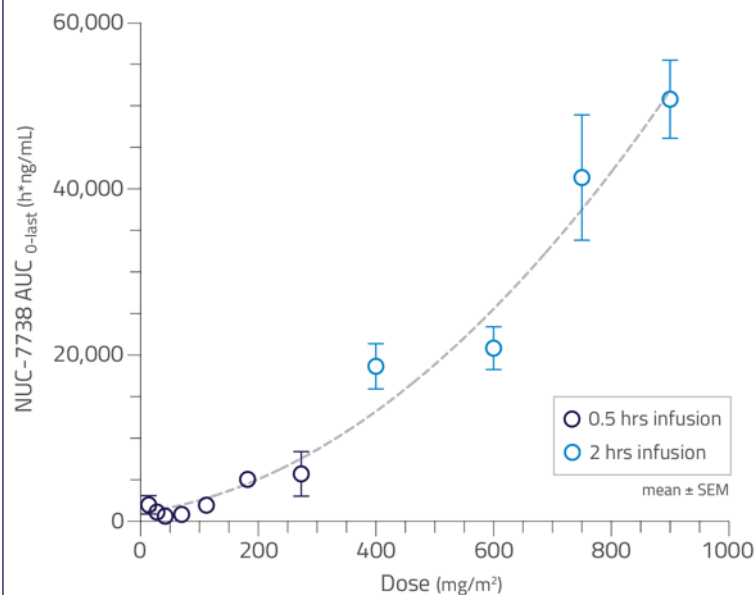
NUC-7738 transforms PD-1 resistant TME into a therapeutically responsive state



NUC-7738 : Attractive Pharmacokinetic Profile (monotherapy)

Plasma

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

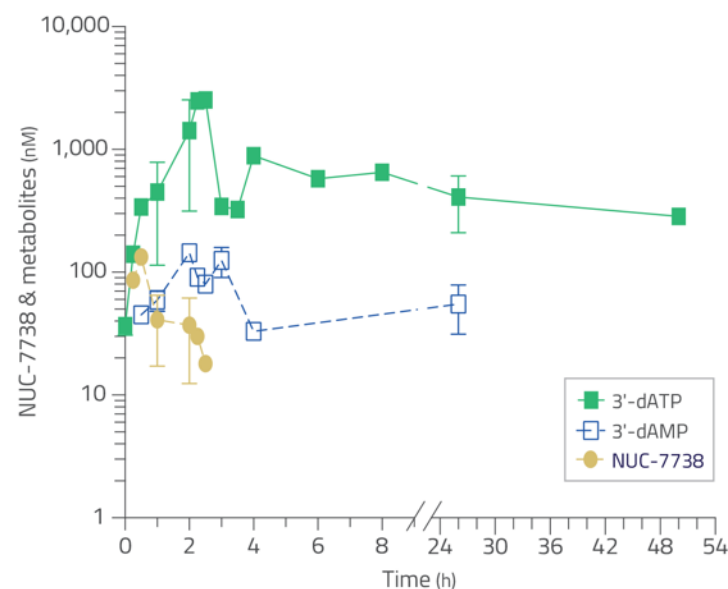


Patients (n=27) dosed at 14 – 900 mg/m²

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/m²

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

NUC-7738 has been well tolerated

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

												MTD		
Dose AE occurred (mg/m ²)	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	1350 n=11	2000 n=2	Total* n=38
All Grade Treatment-Related Adverse Events (≥10%)														
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%)
Grade 3 Treatment-Related Adverse Events (ALL)														
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/m²

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/m²

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/m²

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/m²

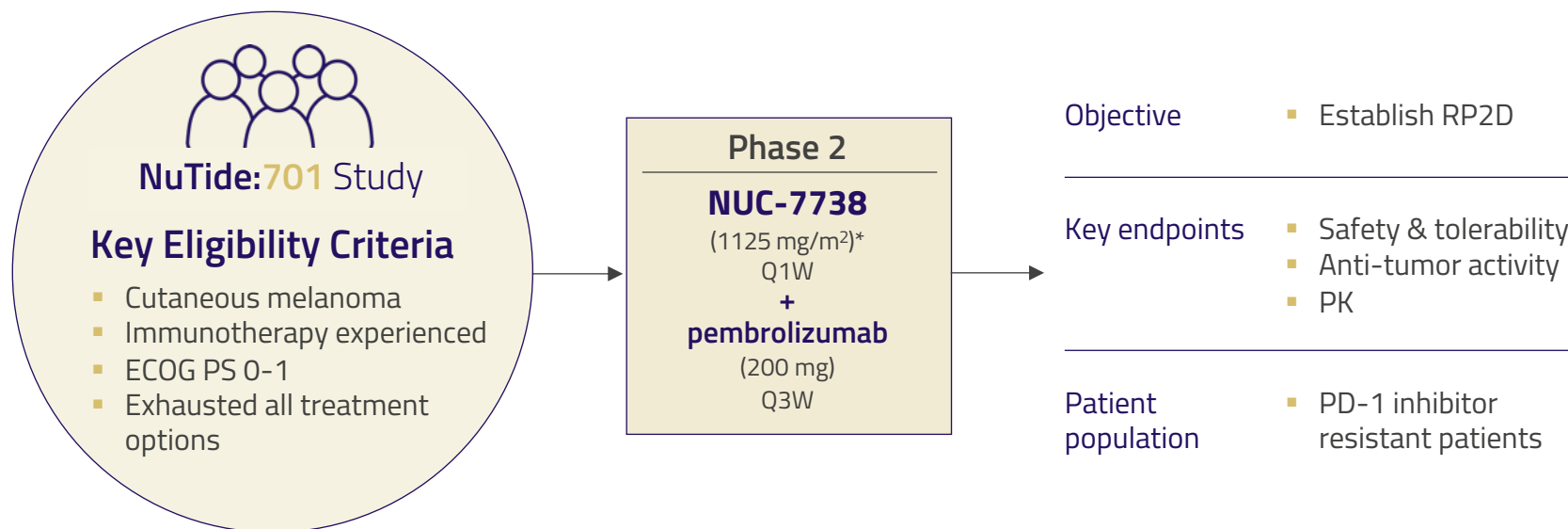
46% reduction in lung lesion 1

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/m² which was escalated to 1350 mg/m² 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

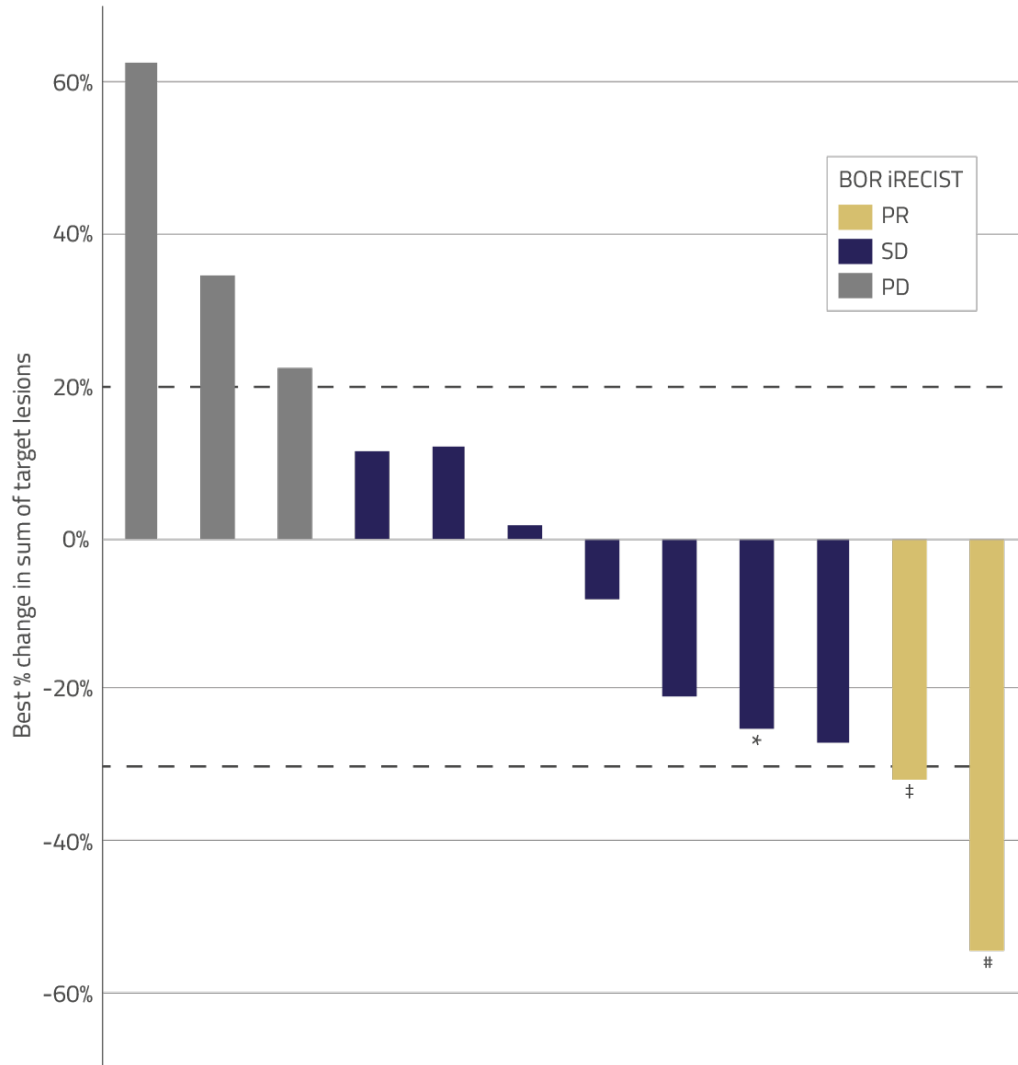
	All Grades n(%)	Grade 3 n(%)	Grade 4 n(%)
Nausea	9 (75)	0	0
ALT increased	6 (50)	1 (8)	1 (8)
Diarrhea	6 (50)	1 (8)	0
Vomiting	6 (50)	1 (8)	0
Fatigue	5 (42)	1 (8)	0
Anemia	5 (42)	0	0
AST increased	4 (33)	1 (8)	1 (8)
ALP increased	2 (17)	0	0
GGT increased	2 (17)	1 (8)	0
Blood magnesium decreased	2 (17)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

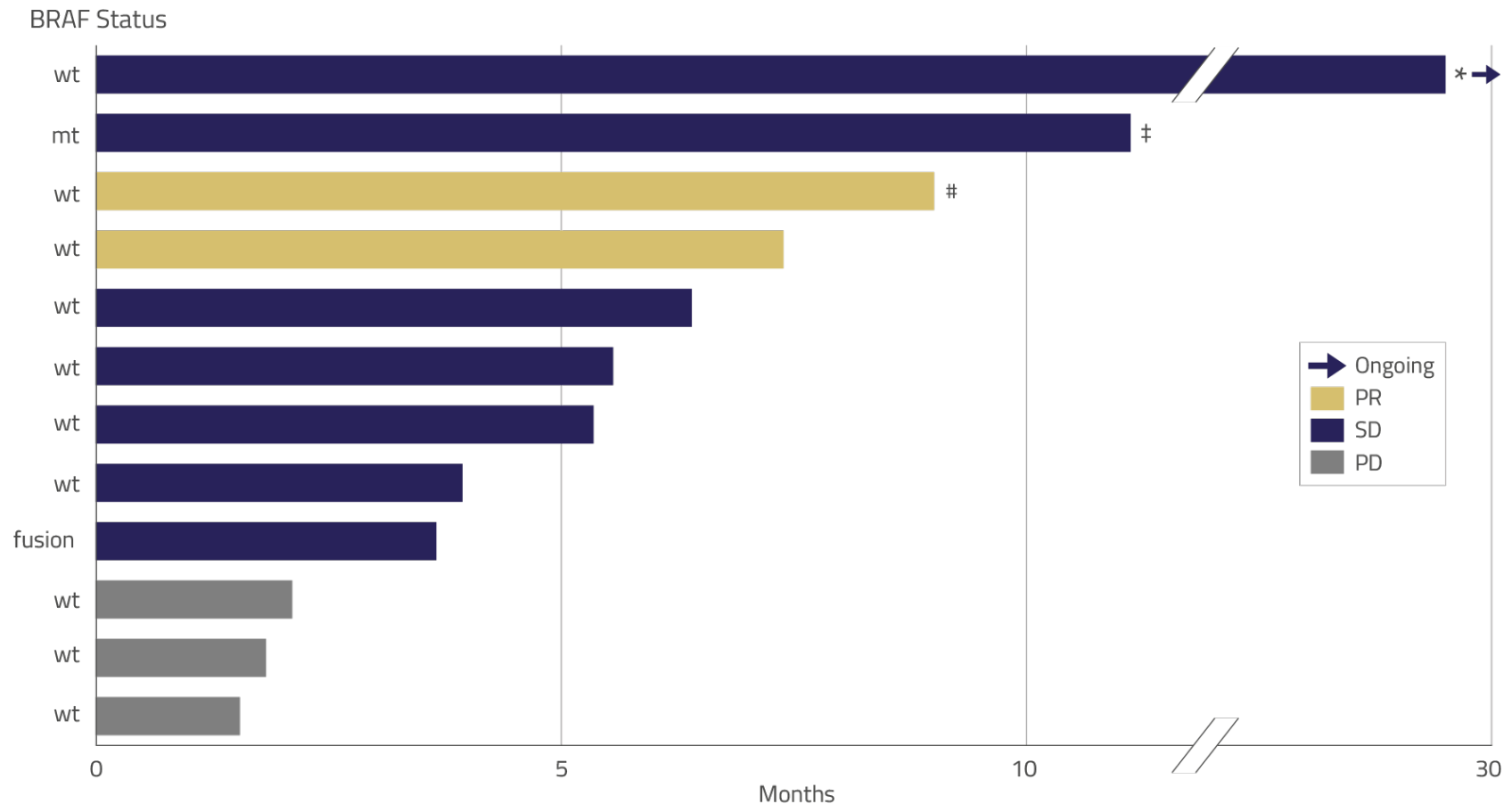
Patient with progression on three prior PD-1 therapies (nivolumab x1, pembrolizumab x2) achieved a 32% tumour reduction[‡]

Patient who progressed after PD-1 inhibitor (nivolumab) + CTLA-4 inhibitor (ipilimumab) has ongoing complete metabolic response^{*}

[#] 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%)

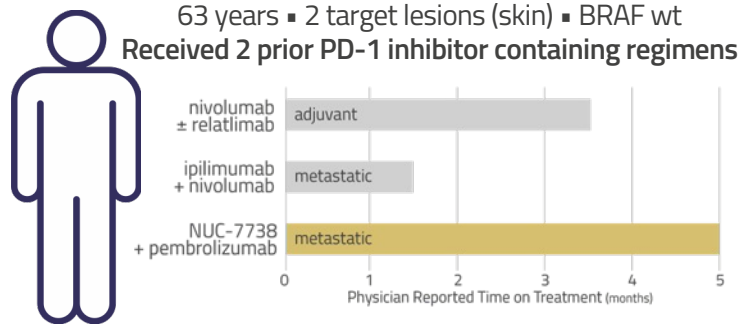
Discontinued by patient choice; follow-up imaging showed progression of non-target lesion, target lesions remained stable (~55%)

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



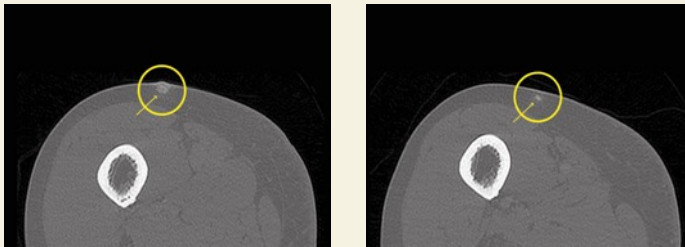
NUC-7738 + pembrolizumab

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

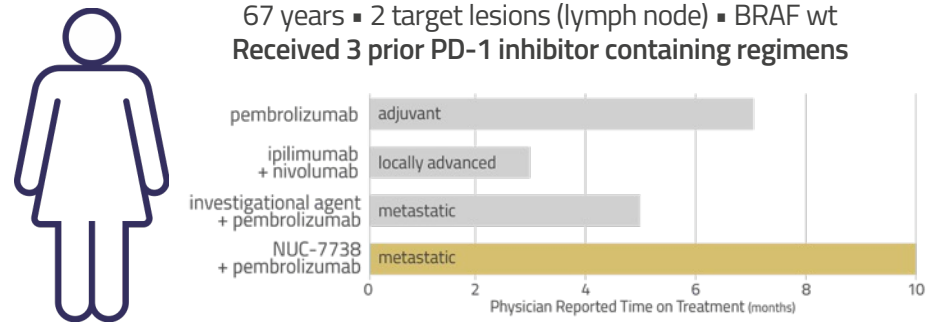


Baseline: 1.0 cm

Week 17: 0.3 cm

Case Study 2

Evidence of anti-cancer immune response in TME



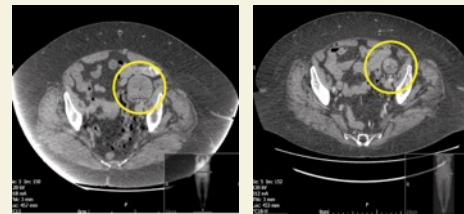
NUC-7738 + pembrolizumab

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)

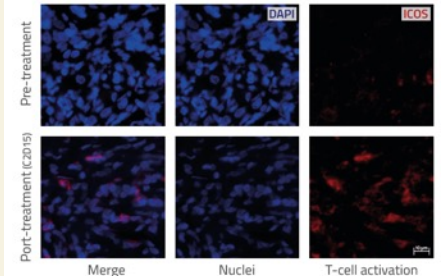


Baseline: 5.53 cm

Week 24: 3.04 cm

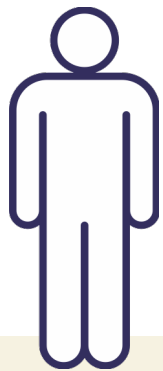
T-cell activation post-treatment

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

Mustafa Elshani^{1,2}, Ying Zhang³, In Hwa Um⁴, Ruth Plummer⁵, Sarah P. Blagden⁶, Stefan N. Symeonides⁷, Natalie Cook⁸, T.R. Jeffrey Evans⁹, Alison L. Dickson^{1,2} & David J. Harrison^{1,2}

¹University of St Andrews, St Andrews, UK; ²St. James's Hospital, Dublin, Ireland; ³University of Edinburgh, Edinburgh, UK; ⁴University of Edinburgh, Edinburgh, UK; ⁵University of Edinburgh, Edinburgh, UK; ⁶University of Edinburgh, Edinburgh, UK; ⁷University of Edinburgh, Edinburgh, UK; ⁸University of Edinburgh, Edinburgh, UK; ⁹University of Edinburgh, Edinburgh, UK

Abstract Number: 5650

Email: mustafa@stjames.ac.uk



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 metabolism¹
- 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^{2,3}
- 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 transformation of 3'-dA

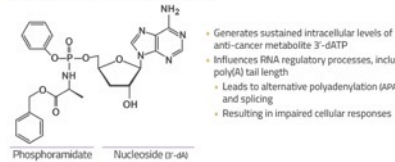


Figure 1: NUC-7738, 3'-deoxyadenosine (3'-dA) phosphoramidate and protected with a phosphoramidate moiety attached at the 3' position

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

Methods

Cell Culture

Melanoma (A375, MeWo, CHL1, SK-MEL28) and renal cell carcinoma (7860 & 769P) cell lines were treated with Ica levels of NUC-7738. Cells were harvested 24 hours post-treatment for RNA-sequencing. 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/m² NUC-7738 on days 1, 8 & 15 of a 21-day cycle in combination with 200mg pembrolizumab on day 1

Biopsies were collected pre- (SCR) and post- (OTB) drug infusion (with post infusion) and preserved in Zymo RNA/DNA Shield (Zymo, C4801100)

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 v2.17.1 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 Salmon⁴ in long-read counting mode (i.e., differential gene expression was assessed with DESeq2 package in R).

Poly(A) tail analysis

Tail lengths extracted from tailfind 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, RPS11, RPS16 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

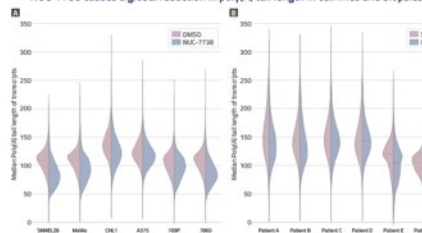


Figure 2: Poly(A) tail changes in cancer cell lines (A) treated with NUC-7738 and paired biopsies from patients (B) treated with NUC-7738 + pembrolizumab. Violin plots depicting the median poly(A) tail length of transcripts from melanoma and renal cell cancer cell lines and paired biopsies. Each plot 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 causes 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

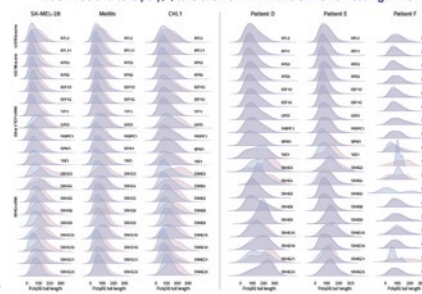


Figure 3: Ridge Plots of Poly(A) Tail Length of genes in cell lines and patients' paired biopsies. The genes are representative of 5'TOP mRNA genes and SNHG non-coding RNA. The x-axis quantifies the poly(A) tail length in nucleotides, while the y-axis represents the kernel density estimation of gene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

Results (cont)

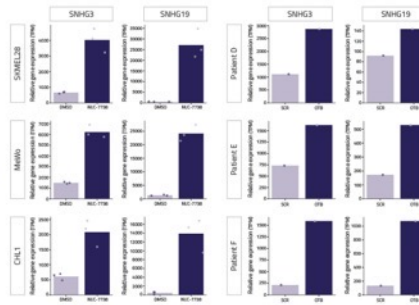


Figure 3B: Transcript levels of SNHG3 and SNHG19 across multiple cell lines and patient paired biopsies. The figure presents bar plots of transcript per million (TPM) measurements for SNHG3 and SNHG19 in a variety of human cell lines treated with NUC-7738 and paired patient biopsies.

- 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, SNHG19, by ~50 adenosines, accompanied with an increase in transcript abundance

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

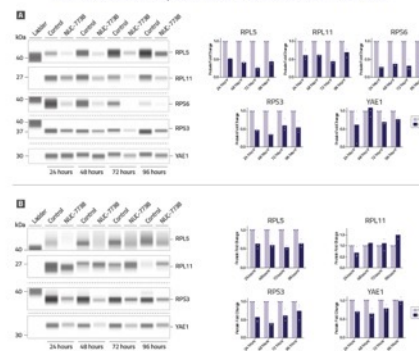


Figure 4: Ribosomal subunit proteins in melanoma cell lines. (A) MeWo and (B) SK-MEL-28 cell lines. Each data point represents an independent biological replicate (n=3)

- 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 subunit proteins

NUC-7738 + pembrolizumab reduces RPS3 and YAE1 protein

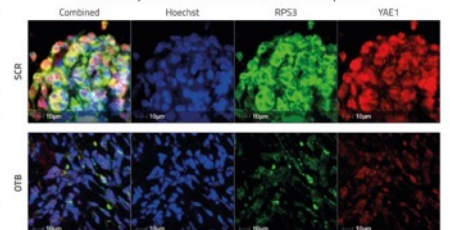


Figure 5: RPS3 and YAE1 protein expression in representative patient paired biopsies treated with NUC-7738 + pembrolizumab. Hoechst staining represents cell nuclei.

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

CONCLUSION

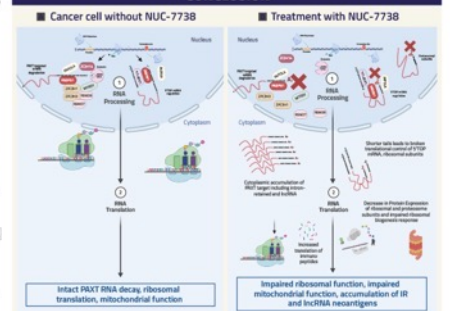


Figure 6: Proposed mechanisms of action of NUC-7738 contributing to impaired ribosome biogenesis. (A) In the absence of NUC-7738, RNA processing and translation proceed regularly, maintaining intact PAXT RNA decay and ribosomal subunit translation.

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

NUC-7738 is a novel 3'-dATP prodrug that targets ribosome biogenesis and is currently in phase I clinical trial. It is a novel 3'-dATP prodrug that targets ribosome biogenesis and is currently in phase I clinical trial. It is a novel 3'-dATP prodrug that targets ribosome biogenesis and is currently in phase I clinical trial.

NUC-7738 is a novel 3'-dATP prodrug that targets ribosome biogenesis and is currently in phase I clinical trial. It is a novel 3'-dATP prodrug that targets ribosome biogenesis and is currently in phase I clinical trial.

Exposing the Heterogeneity of the Lipidome in the TME of Cutaneous Melanoma Following Treatment with NUC-7738 in Combination with anti-PD-1 Therapy

Alison L. Dickson^{1,2}, Greice M. Zickuhr¹, In Hwa Um¹, Ying Zhang¹, Ruth Plummer³, Sarah P. Blagden⁴, Stefan N. Symeonides⁵, Natalie Cook⁶, T.R. Jeffrey Evans⁷, Mustafa Elshani^{1,2} & David J. Harrison^{1,2}

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Abstract Number: 6222

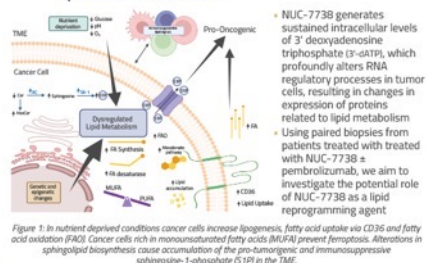
Email: alison.dickson@nu.ac.uk



Introduction

- Cancer cells adapt to hypoxic and nutrient deprived environments by reprogramming lipid biosynthesis to accelerate malignant behaviour¹
- Lipids are not only structural components of cell membranes but also serve as signaling molecules within the tumor microenvironment (TME) to modulate immune cells²
- Cancer cells transitioning to a malignant phenotype demonstrate marked changes in lipid metabolism including:
 - Changes in the ratio of monounsaturated fatty acids (MUFAs) to polyunsaturated fatty acids (PUFAs)
 - Dysregulation of sphingolipids, crucial for tumor progression and survival
- Reprogramming lipid metabolism within the TME is a recognised strategy for boosting the effects of immunotherapy³

Lipid Metabolism in the TME



Methods

- Snap frozen and FFPE biopsies were collected from 6 patients (1 x mucosal melanoma and 5 x cutaneous melanoma) treated with NUC-7738 + pembrolizumab. Biopsies were collected pre- and post- drug infusion (six post infusion).
- TIC normalised data was exported into MetaboAnalyst 5.0 for statistical analysis (SAM, PCA, fold-changes). LIPID MAPS[®] Structure Database was used to tentatively assign lipid species.

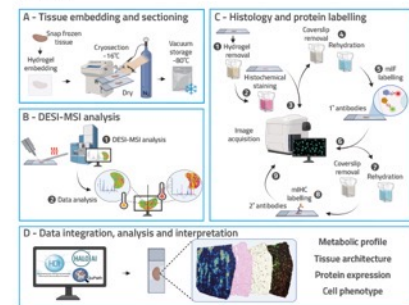


Figure 2: Multi-Modal Imaging Workflow for 10µm single-section tissue analysis

Lipid Profiles of Melanoma Cells Change Following Treatment

- The emergence of two distinct classes of lipids suggests NUC-7738 + pembrolizumab changes the lipidome in the melanoma TME

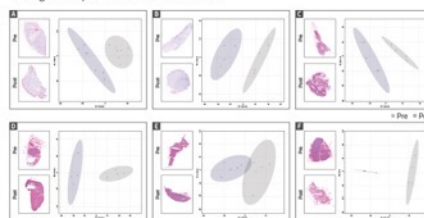


Figure 3: PCA 2D scores plots of lipids in tumor regions from biopsies pre- and post-treatment (JL mucosal and B-F cutaneous melanoma). ROI were selected by high-magnification analysis of visible tumor regions of H&E-stained sections following DESI-MSI.

Heterogeneity of Lipids and Immune Cells in the TME

- Dimension reduction analysis (UMAP) of data (>1000 lipids) reveals distinct regions within each biopsy

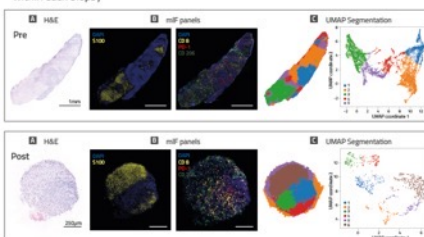


Figure 4: A) Post DESI-MSI H&E section, B) multiplex immunofluorescence (mIF) of DAPI co-localised with >100 positive cells (indicative of malignant melanoma), CD8 positive cells (T cells), CD206 positive cells (macrophages) and PD-1 positive cells. C) UMAP segmentation of single 10µm section based on UMAP cluster data.

Spatial Co-registration for Quantitative Image Analysis

- Quantification of individual cell types within distinct metabolic regions of the tissue show which cell types may be driving changes in lipid signatures

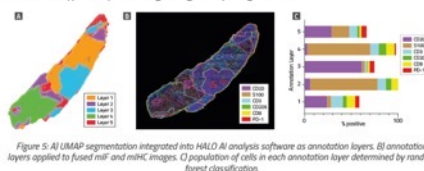


Figure 5: A) UMAP Segmentation integrated into HALO AI analysis software as annotation layers. B) annotation layers applied to fused mIF and mIMC images. C) population of cells in each annotation layer determined by random forest classification.

Fatty Acid Reprogramming

- NUC-7738 + pembrolizumab changes the balance of fatty acids in favor of PUFAs, indicative of a shift towards a less aggressive oncogenic phenotype
- MUFAs have been linked to malignant behaviour and resistance to chemotherapy whilst PUFAs have been associated with susceptibility to reactive oxygen species and ferroptosis⁴

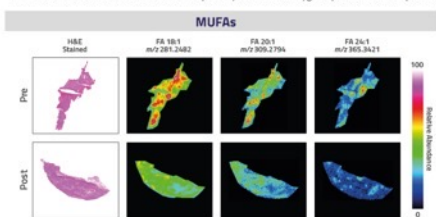


Figure 6: DESI-MSI ion heatmaps show spatial distribution and a decrease in the relative abundance of three MUFAs species and increase in three PUFA species in visible tumor regions following NUC-7738 + pembrolizumab treatment

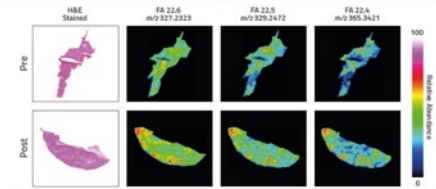


Figure 7: DESI-MSI ion heatmaps show spatial distribution and a significant decrease (p < .5) in the relative abundance of three HexCer species in visible tumor regions following NUC-7738 + pembrolizumab treatment

Multi-Modal Imaging Confirms Lipidomic Reprogramming

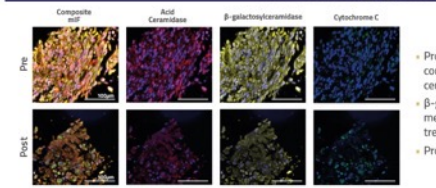


Figure 8: mIF of 3µm FFPE section show a decrease in the protein expression of key lipid metabolizing enzymes and an increase in the apoptotic marker cyt c following NUC-7738 treatment

Changes in Apoptotic Related Lipids

- NUC-7738 + pembrolizumab causes a reduction in levels of HexCer species in tumor area
- HexCer, a subclass of sphingolipids are anti-apoptotic and associated with chemoresistance in melanoma patients⁵

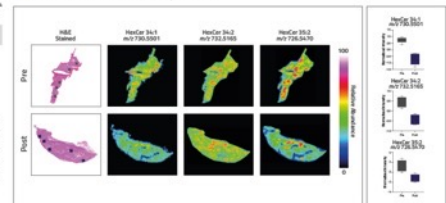


Figure 9: DESI-MSI ion heatmaps show spatial distribution and a significant increase (p < .5) in the relative abundance of three Cer species in visible tumor regions following NUC-7738 treatment

- Pro-apoptotic ceramide (Cer) species increase following treatment

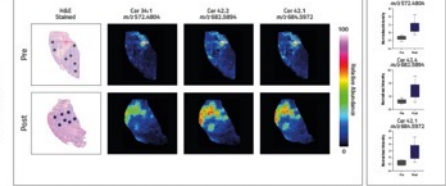


Figure 10: DESI-MSI ion heatmaps show spatial distribution and a significant increase (p < .5) in the relative abundance of three Cer species in visible tumor regions following NUC-7738 treatment

- Pro-apoptotic ceramide (Cer) species increase following treatment with NUC-7738 corresponding with a decrease in protein expression of acid ceramidase (AC) which hydrolyses ceramides into sphingosine and is associated with tumor progression⁶
- β-galactosylceramidase, a key enzyme in sphingolipid metabolism often upregulated in melanoma progression and associated with poor prognosis⁷ decreases following NUC-7738 treatment
- Protein expression of Cytochrome C, a marker of apoptosis increases following treatment

CONCLUSION

- Novel methodology developed to analyse the spatial relationship between the lipidome and TME of patient biopsies within a single-tissue section
- Preliminary results suggest that NUC-7738 + pembrolizumab reprograms cancer cell lipid metabolism in the TME
- This platform provides a powerful investigative tool to simultaneously explore the myriad of factors in the TME that contribute to tumorigenesis and therapeutic response

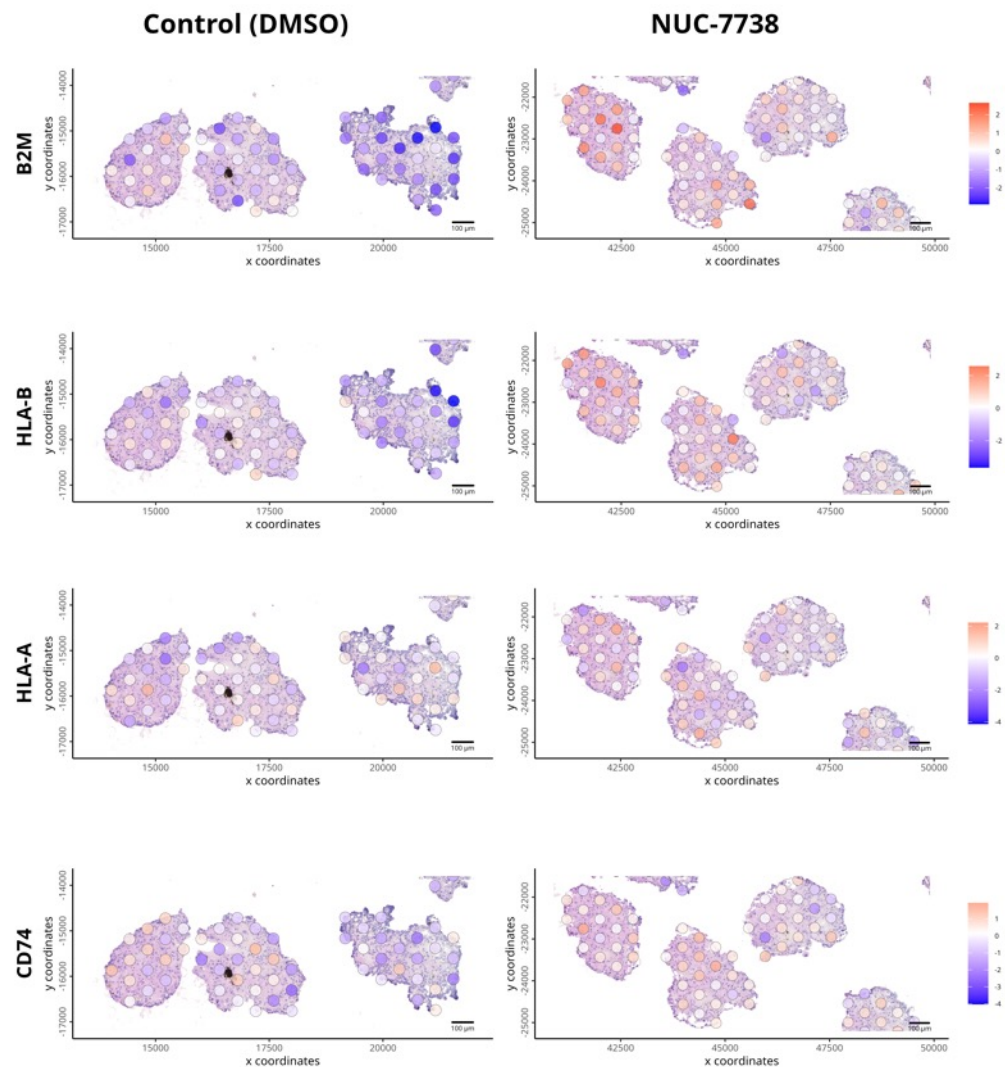
NUC-7738 is a novel, orally active, small molecule inhibitor of the sphingosine kinase 1 (SPK1) pathway. It is currently in phase I clinical trial for the treatment of advanced solid tumors. NUC-7738 is a novel, orally active, small molecule inhibitor of the sphingosine kinase 1 (SPK1) pathway. It is currently in phase I clinical trial for the treatment of advanced solid tumors.

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.

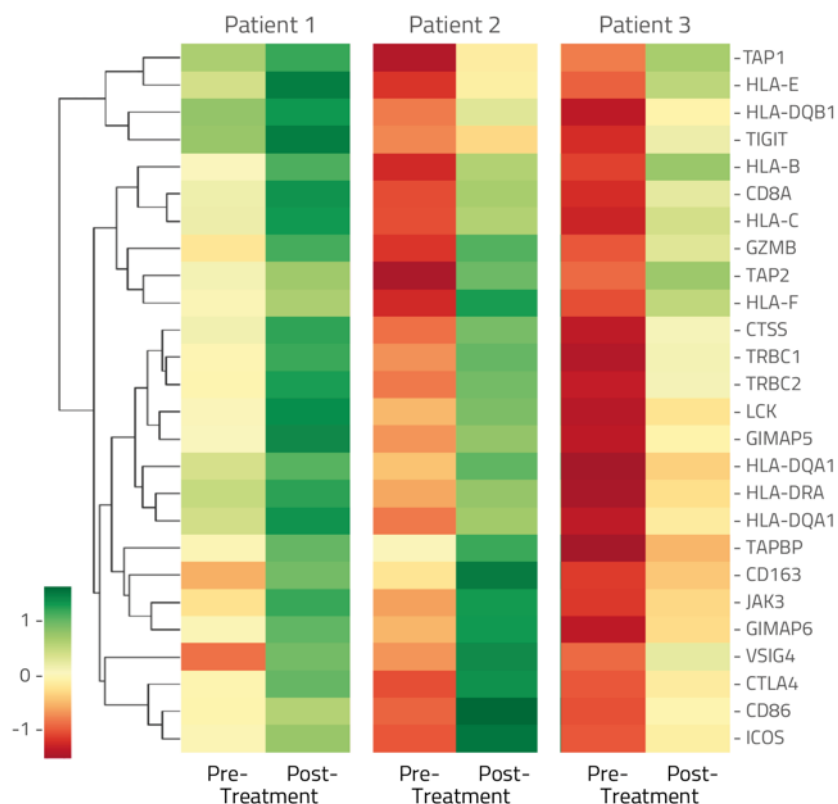
B2M is beta 2 microglobulin, and together with HLA-A and HLA-B form class 1 Major Histocompatibility Complex (MHC). Class I MHC is recognized by CD8+ T lymphocytes.

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.

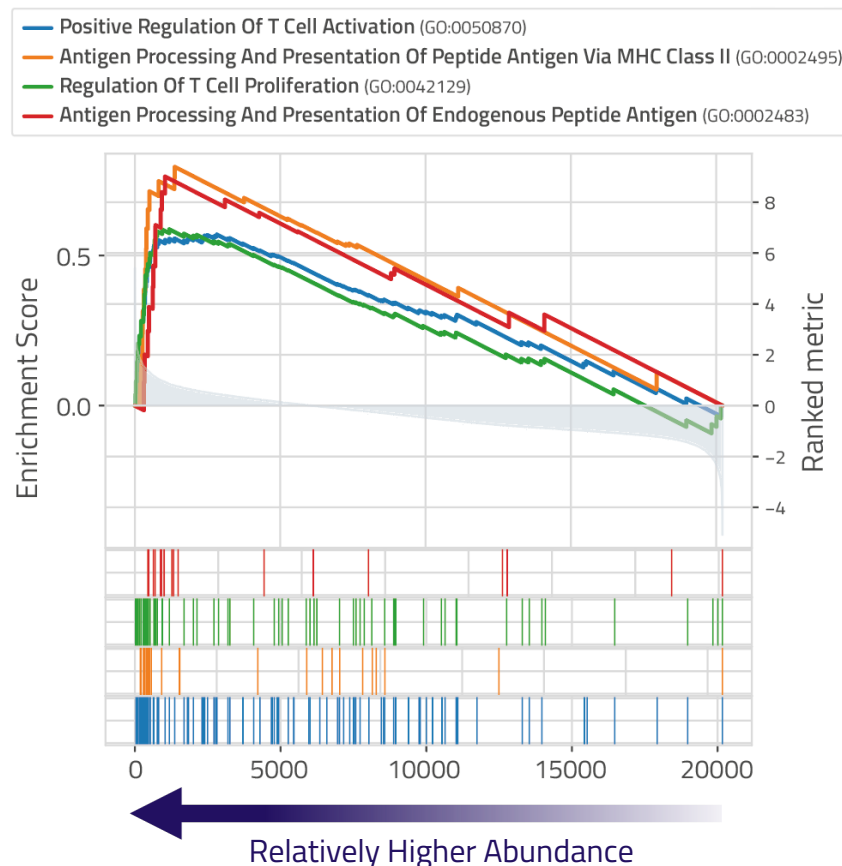


NUC-7738 : Increases Antigen Presentation & T-cell Activation in Patient Biopsies

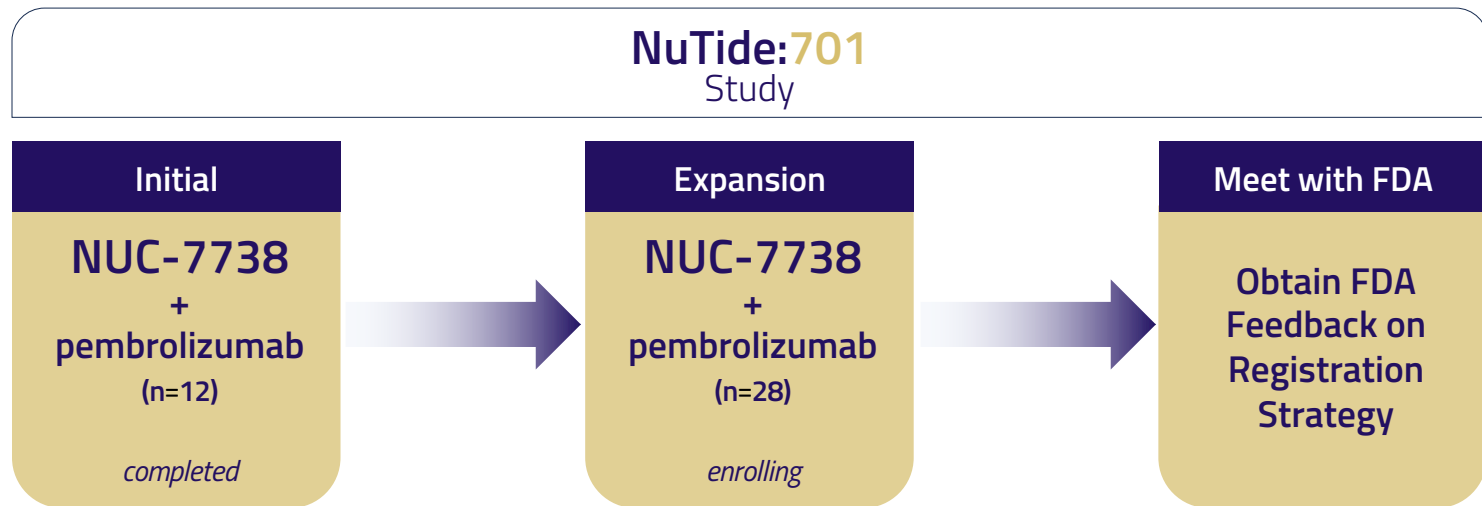
Heatmaps illustrating RNA expression reveal a relative increase in mRNA levels of genes associated with antigen transport & presentation and T-cell activation



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



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



\$7.4B

Estimated sales in 8 major markets in 2029²



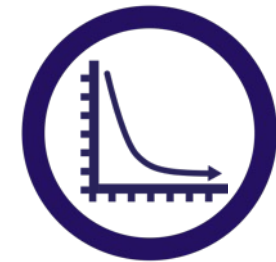
331,722 new cases
diagnosed annually¹



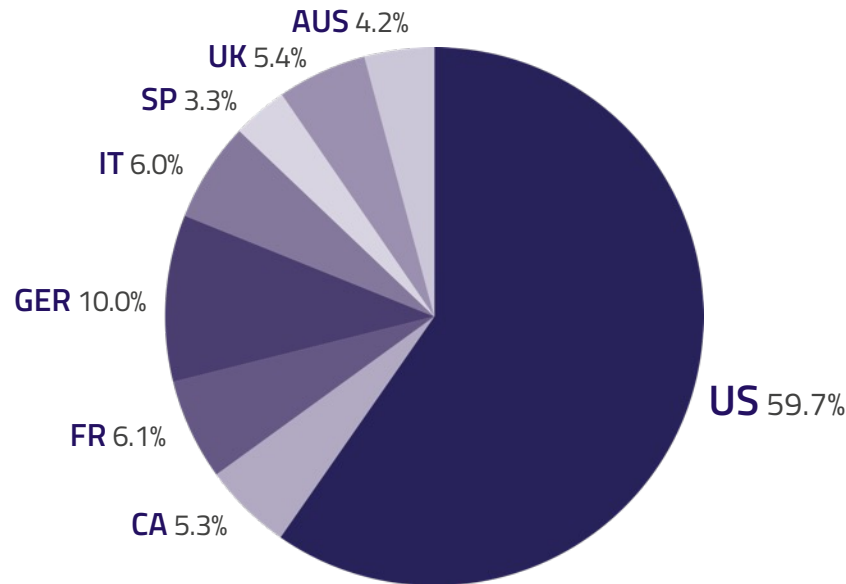
13,000 patients
will fail PD-1 inhibitors in US³



58,667 deaths
annually¹



5-year survival rate: 30%
Stage IV melanoma⁴

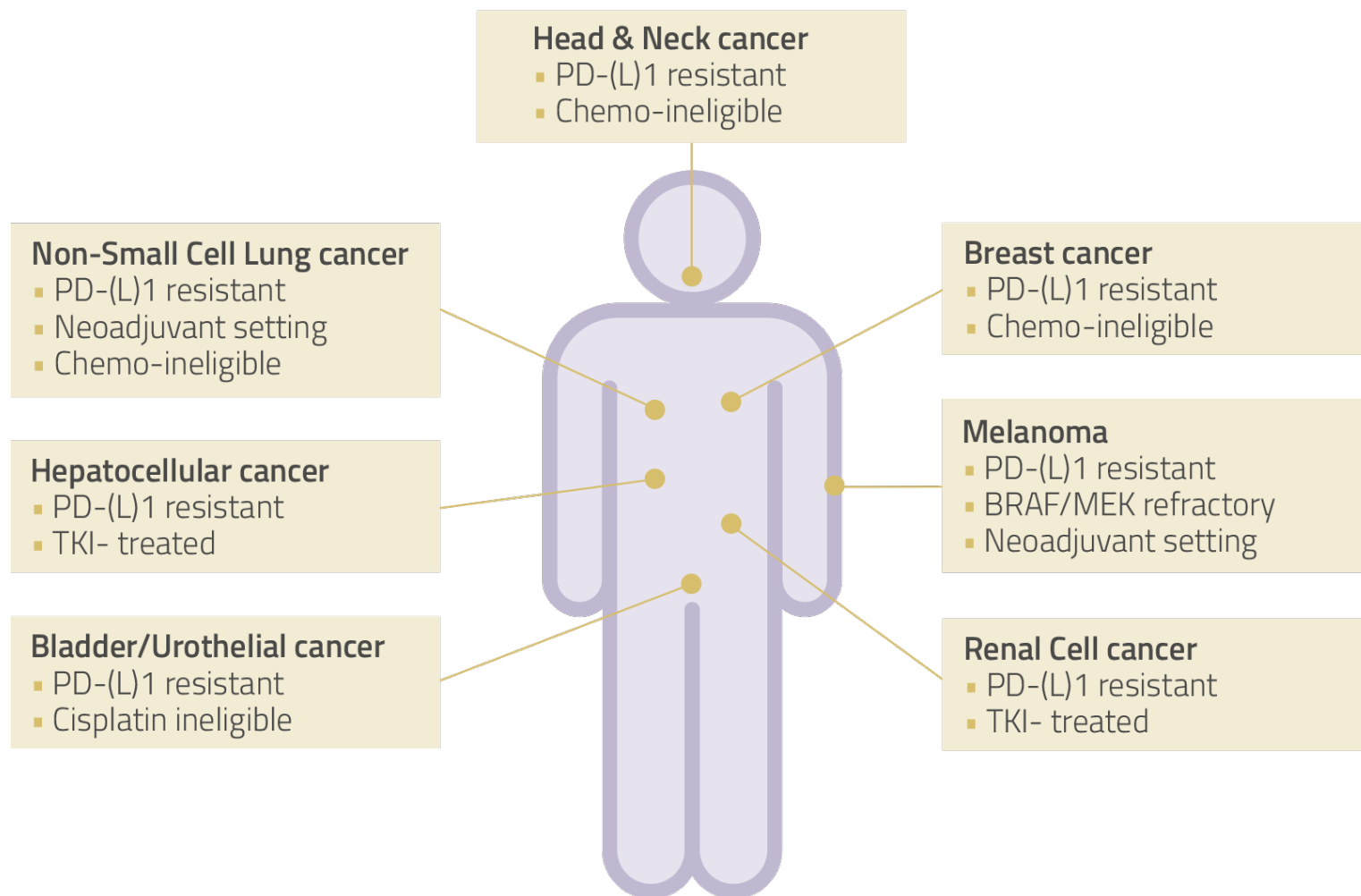


1. GLOBOCAN 2022, Cancer Incidence and Mortality Worldwide

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



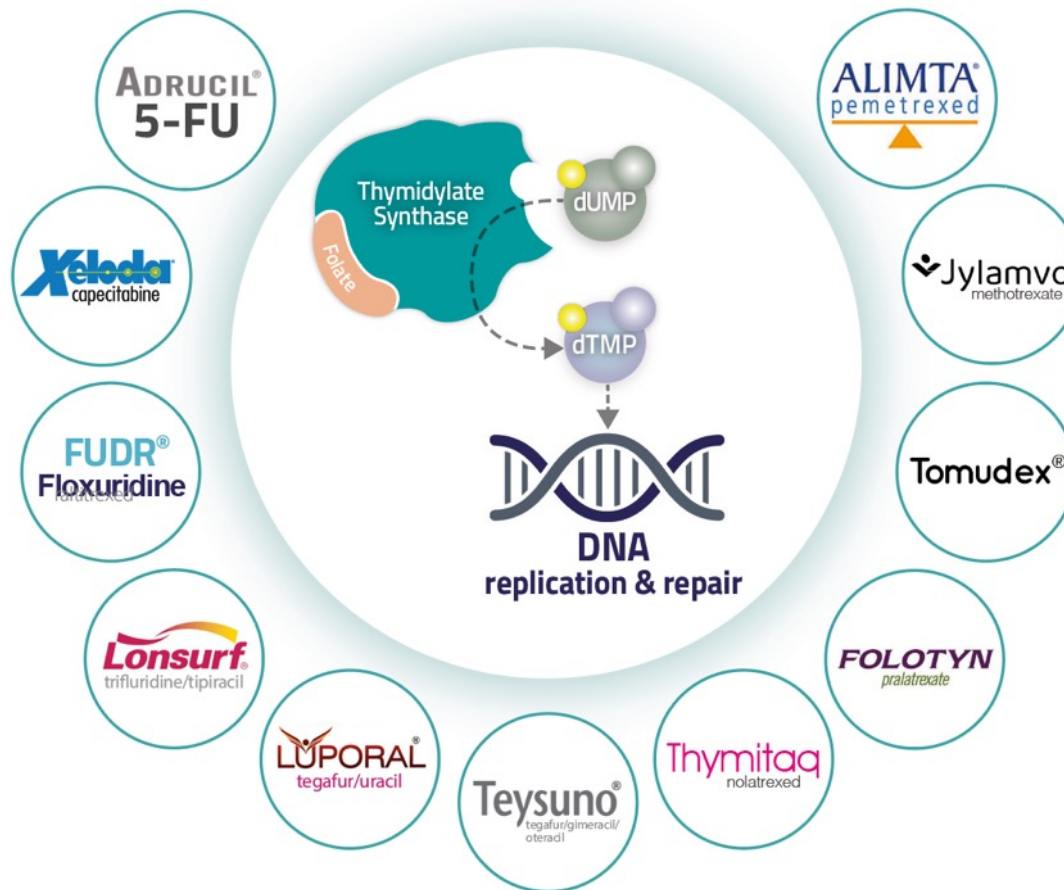
Targeted Thymidylate Synthase Inhibitor

Thymidylate Synthase: An Important Target for Anti-Cancer Therapies

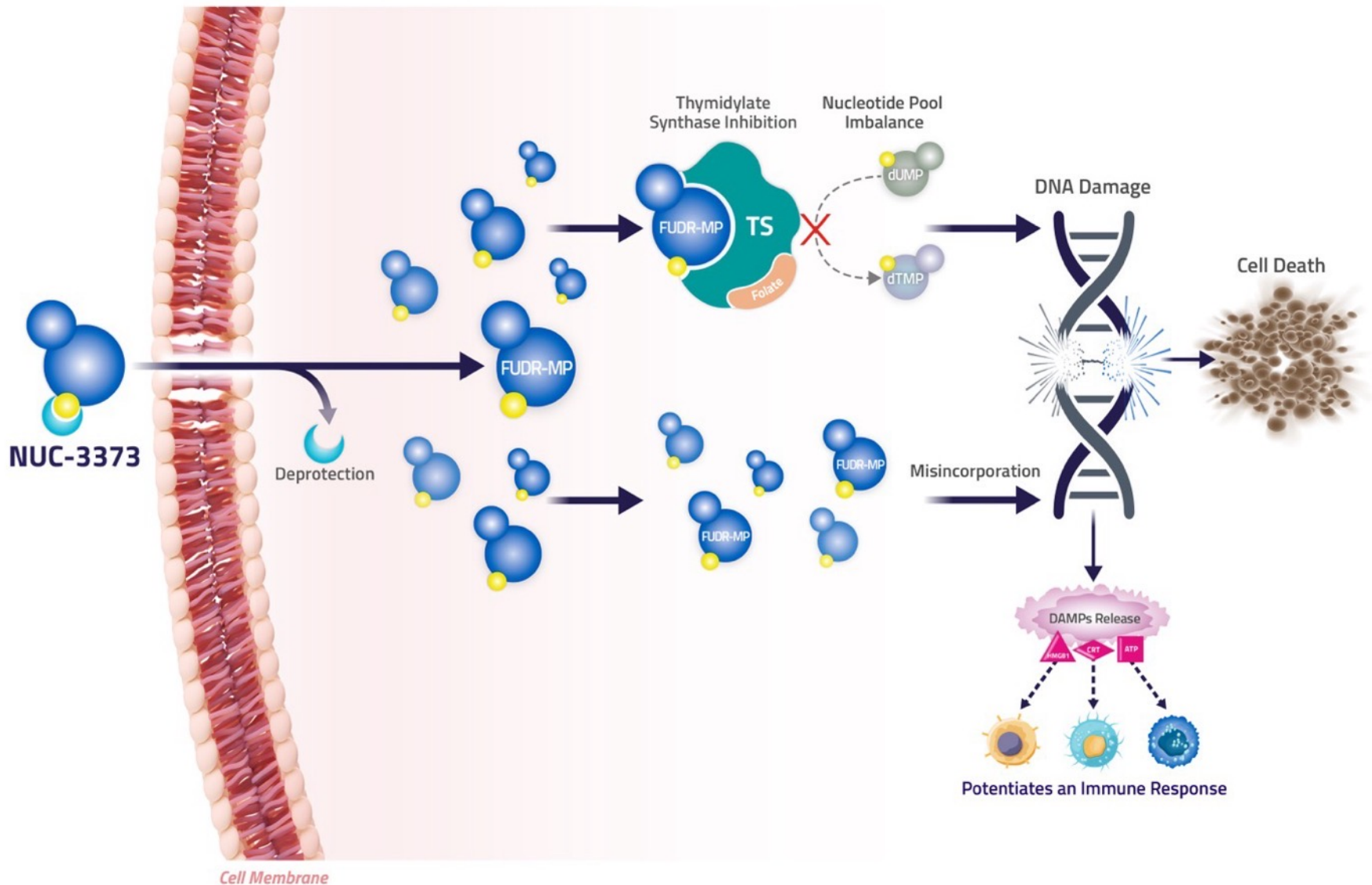
Thymidylate Synthase (TS) is a critical enzyme for nucleotide synthesis

- 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



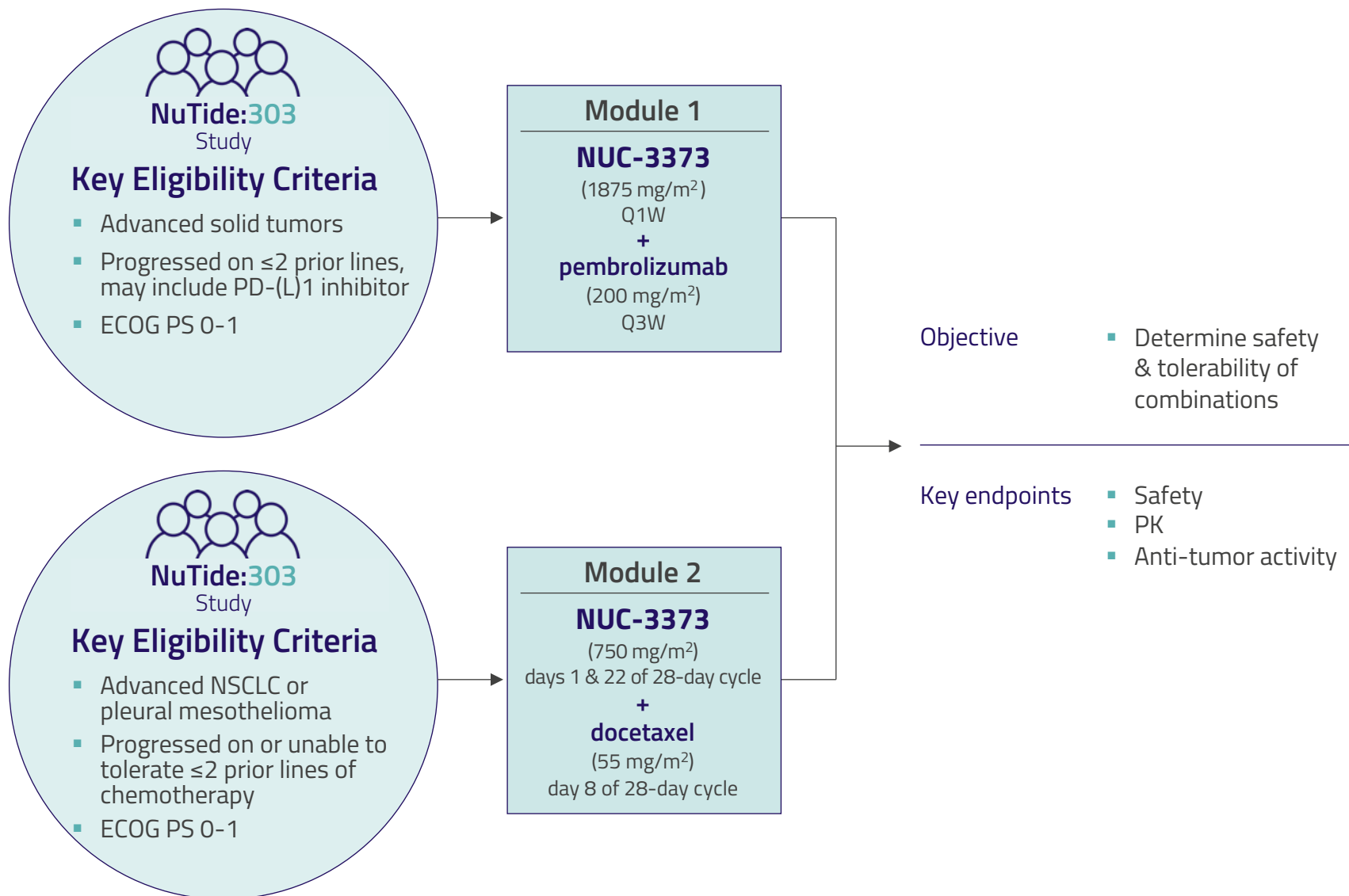
NUC-3373 : Induces DNA Damage & Potentiates an Immune Response



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



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

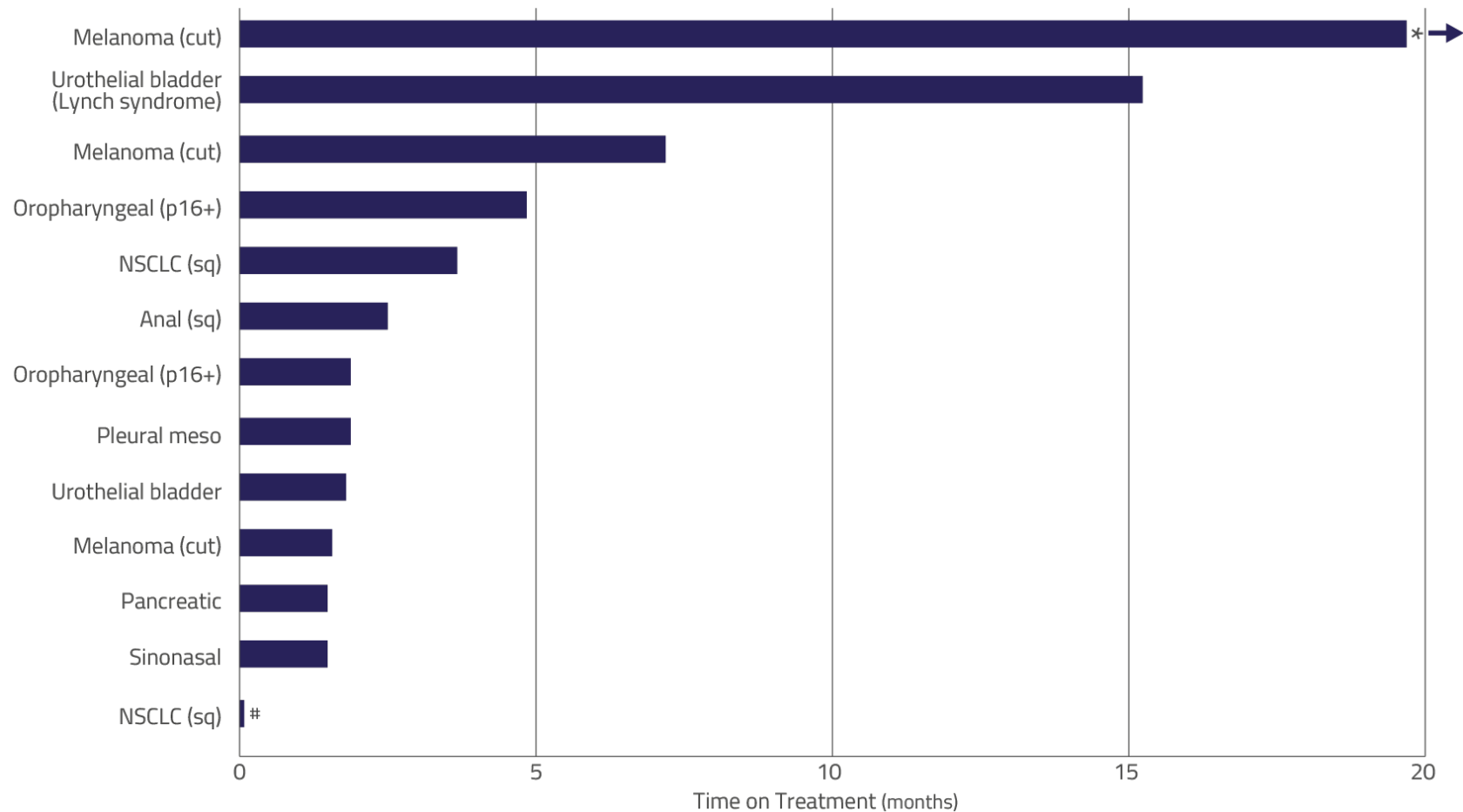
- No Grade 4 toxicities

	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 ≥20% patients related to NUC-3373, pembrolizumab or both
Additional Grade 3 TRAE ≤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/m² + 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/m² + 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/m² + docetaxel 55 mg/m²

- 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/m² + docetaxel 55 mg/m²

- 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
<i>NUC-7738</i>	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
<i>NUC-3373</i>	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
NUC-7738 NuTide:701 Study	Melanoma	pembrolizumab	Phase 2	Complete Recruitment
				Announce Expansion Data
				Obtain FDA Feedback on Registration Strategy
NUC-3373 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