NUCANA

Corporate Presentation

January 2025

Disclaimer

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 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-3373 and NUC-7738; the initiation, enrollment, timing, progress, release of data from and results of the Company's planned and ongoing clinical studies; 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 Q2 2025; 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.

Forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause the Company's actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. These risks and uncertainties include, but are not limited to, the risks and uncertainties set forth in the "Risk Factors" section of our Annual Report on Form 20-F for the year ended December 31, 2023 filed with the Securities and Exchange Commission ("SEC") on March 20, 2024, and subsequent reports that the Company files with the SEC.

Forward-looking statements represent the Company's beliefs and assumptions only as of the date of this presentation. Although the Company believes that the expectations reflected in the forward-looking statements are reasonable, it cannot guarantee future results, levels of activity, performance or achievements. Except as required by law, the Company assumes no obligation to publicly update any forward-looking statements for any reason after the date of this presentation to conform any of the forward-looking statements to actual results or to changes in its expectations.

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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® Ribavirinum

RETROVIR® Zidovudin AZT®

EPIVIR® (lamivudine)

ZERIT® (stavudine)

ZIAGEN® (abacavir)

Limitations of Nucleoside Analogs

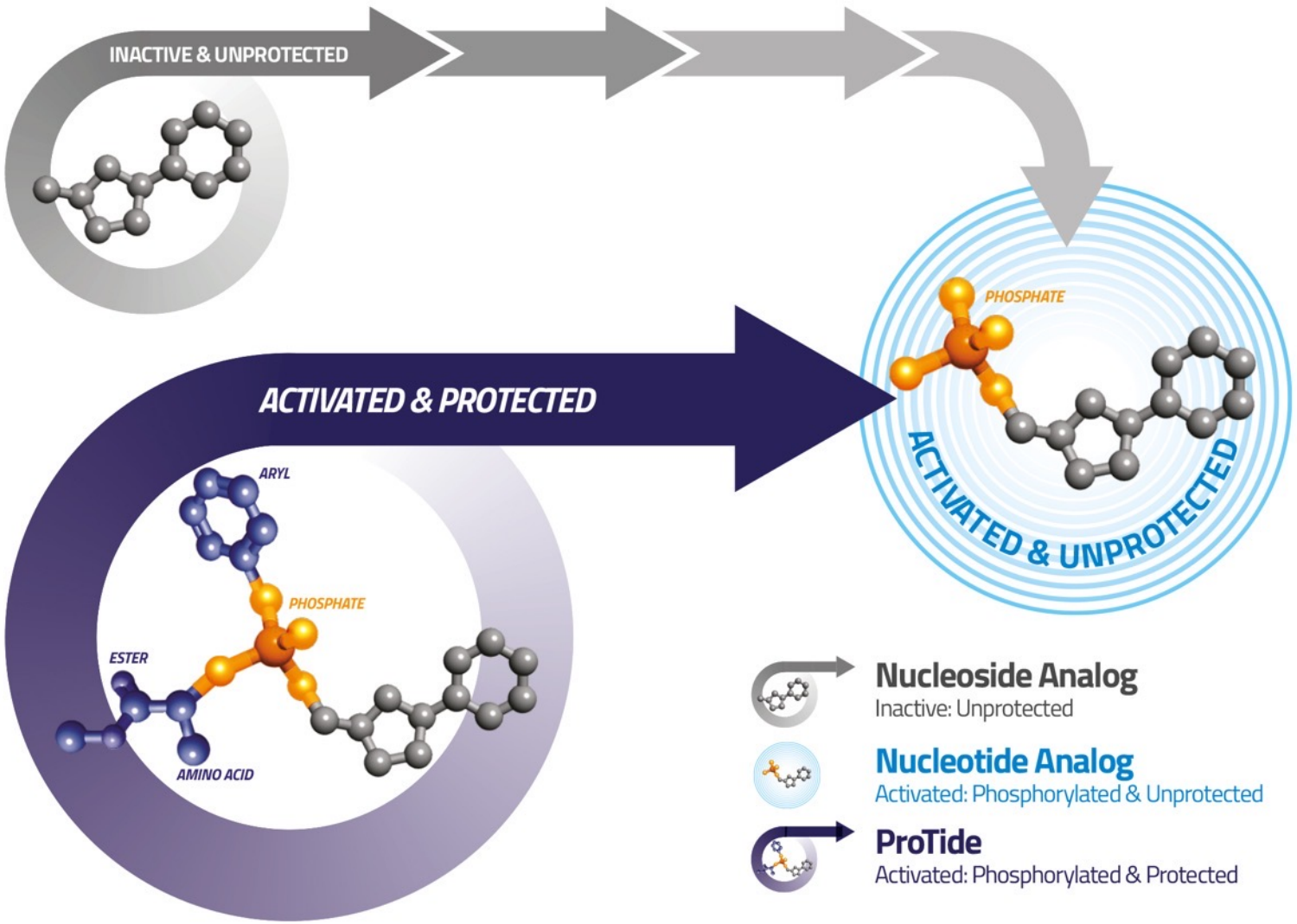
Breakdown & Toxic Byproducts
Off-target toxicity

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

SOVALDI® SOFOSBUVIR
Hepatitis C

- Transformed novel nucleoside analog
- Highly effective treatment for chronic Hepatitis C infection
- Sales: **$71 billion**[1]

TAF tenofovir alafenamide
HIV & Hepatitis B

- Transformed nucleoside analog: Viread® (tenofovir disoproxil fumarate)
- More effective & safer treatment for HIV & HBV than Viread®
- Sales: **$108 billion**[2]

Veklury® remdesivir
COVID-19

- Transformed novel nucleoside analog
- Treatment for COVID-19
- Sales: **$16 billion**[3]

[1] Sovaldi + Harvoni + Epclusa + Vosevi cumulative sales through September 30, 2024
[2] Genvoya + Descovy + Odefsey + Biktarvy + Symtuza + Vemlidy cumulative sales through September 30, 2024
[3] Veklury cumulative sales through September 30, 2024

ProTides: A New Era in Oncology

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

Key Expected Milestones: 2025

	INDICATION	COMBINATION	PHASE	MILESTONE
NUC-7738 NuTide:701 Study	Melanoma	pembrolizumab	Phase 2	Initiate Study Expansion Announce Expansion Data Obtain FDA Feedback on Registration Strategy Initiate Pivotal Study
NUC-3373 NuTide:303 Study	Solid Tumors	pembrolizumab	Phase 1b/2	Initiate Study Expansion Announce Expansion Data

Multiple Inflection Points in 2025

Nasdaq NCNA

Cash & Cash Equivalents
September 30, 2024
~$15 million[#]

Cash Runway
into
Q2 2025

Important Data Readouts
in
2025

[#]Based on exchange rate of £1.00 to $1.34 as of September 30, 2024

NUC-7738

Unlocking the Potential of Immunotherapy

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

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

Expression of immune checkpoint molecules

Secretion of cytokines to suppress immune cell function

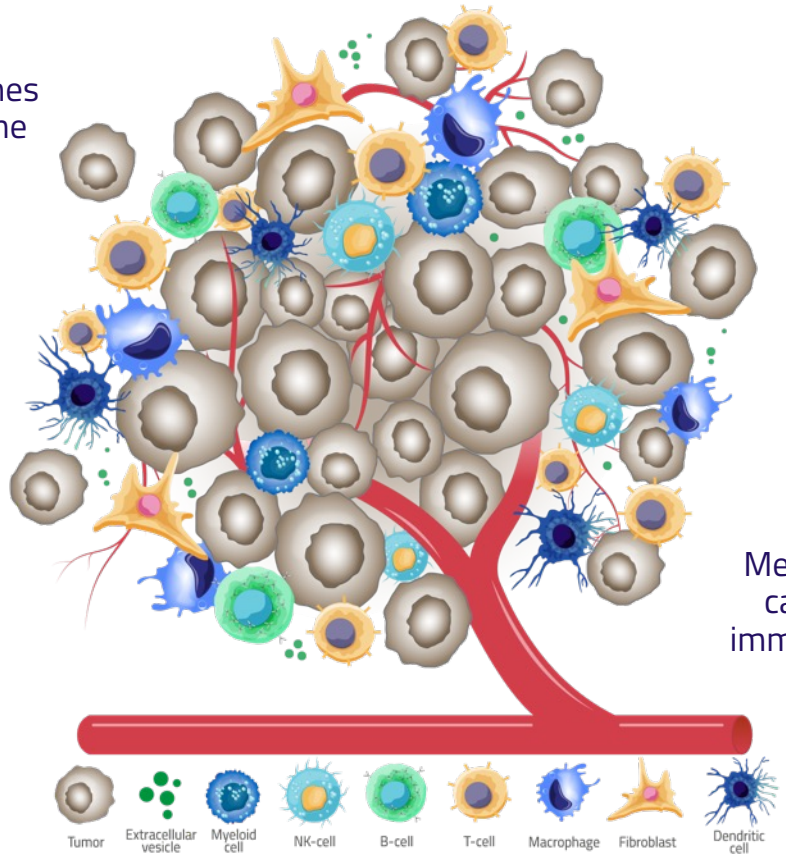
Reduced antigen presentation by cancer cells

Hypoxic & acidic environment

Recruitment of immunosuppressive cells

Promotion of angiogenic environment

Metabolic reprogramming causes the secretion of immunosuppressive factors



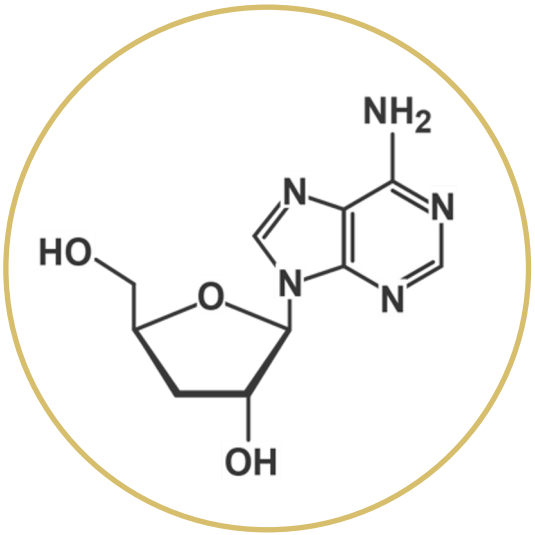
Novel Nucleoside Analog: 3'-deoxyadenosine (3'-dA)

Cordycepin

A Traditional Chinese Medicine found in the Himalayas

3'-dA

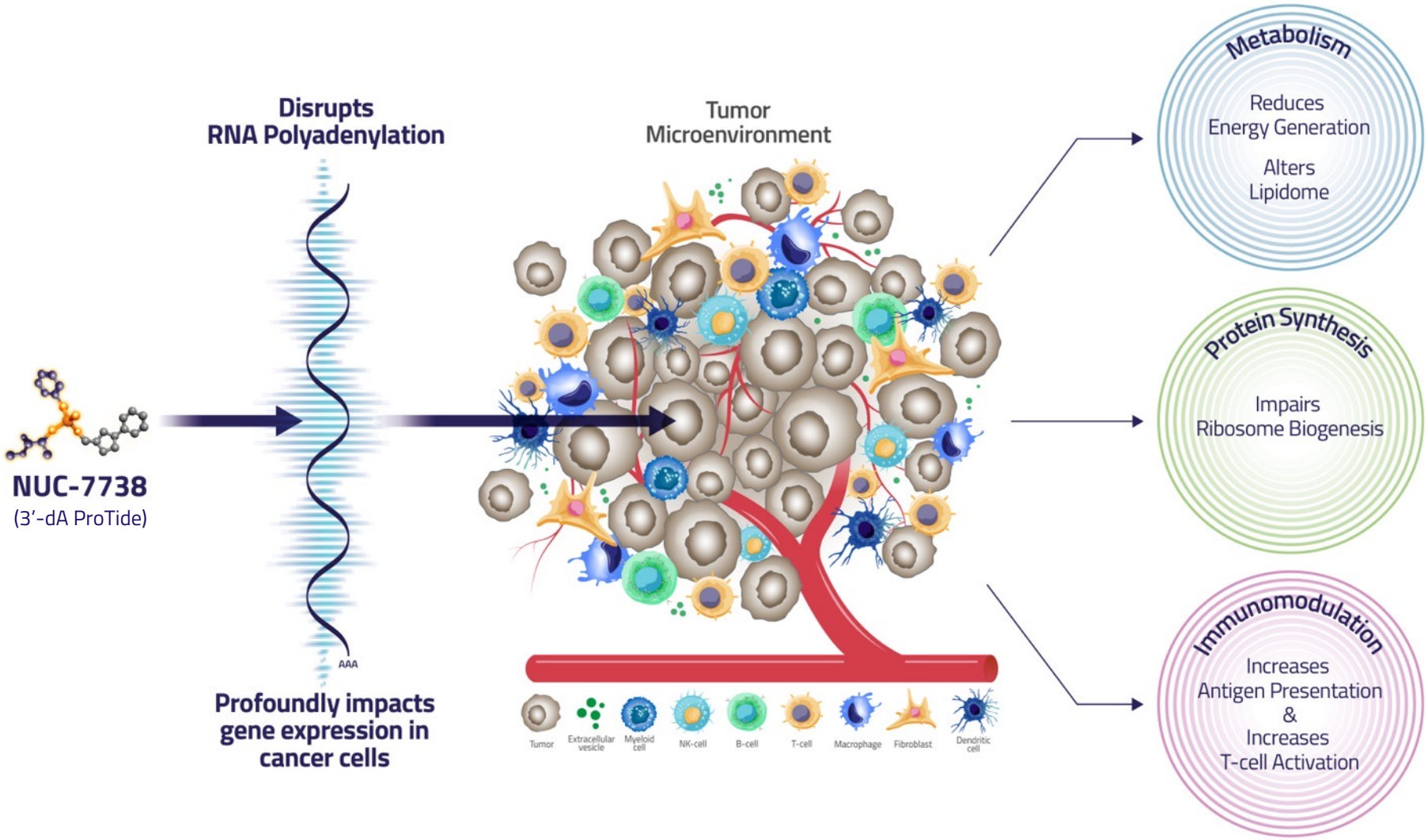
Originally isolated from *Cordyceps sinensis* in1950



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 : Phase 1/2 Study (ongoing)

NuTide:701 Study

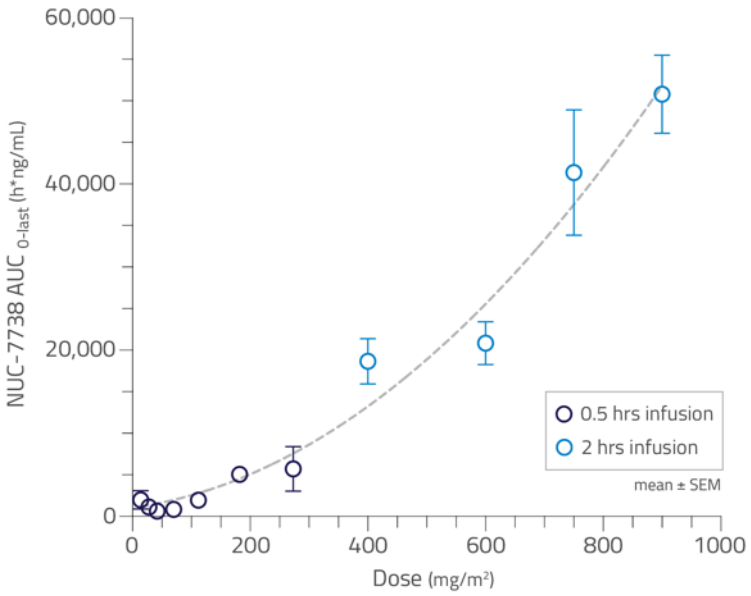
	Phase 1 Dose Escalation (monotherapy)	Phase 2 Dose Optimization (monotherapy)	Phase 2 Dose Confirmation (combination)
	NUC-7738 *completed*	**NUC-7738** *completed*	**NUC-7738** + **pembrolizumab** *ongoing*
Number of patients	**38**	**11**	**12**
Tumor Type	**Solid Tumors**	**Solid Tumors**	**Cutaneous Melanoma**
Patient Population	**Exhausted all treatment options**	**Exhausted all treatment options**	**PD-1 inhibitor resistant**

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

NUC-7738 : Attractive Pharmacokinetic Profile (monotherapy)

Plasma

Dose proportional increase in C_{max} and AUC

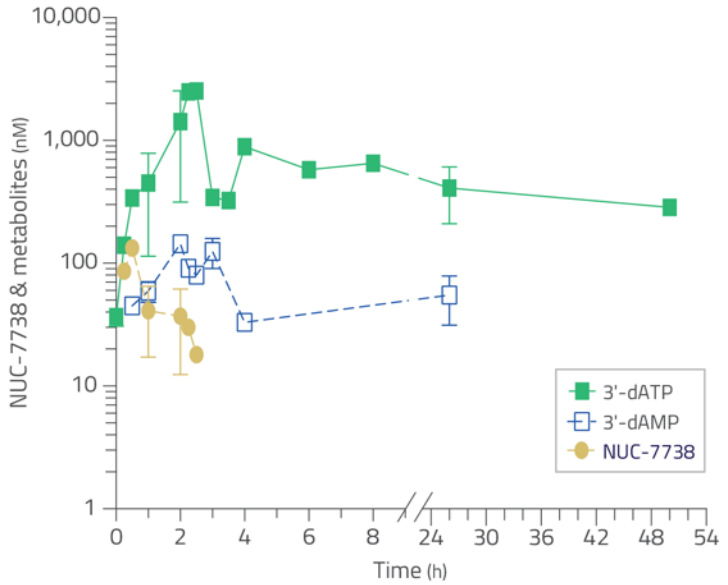


Patients (n=27) dosed at 14 – 900 mg/m²

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

Dose AE occurred (mg/m²)	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 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

NUC-7738 : Encouraging Signs of Efficacy (monotherapy)

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^2
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^2
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^2
Stable disease: 6 months
45% reduction in mandibular lesion
Complete disappearance of lip lesion
Bleeding from nasal lesion resolved

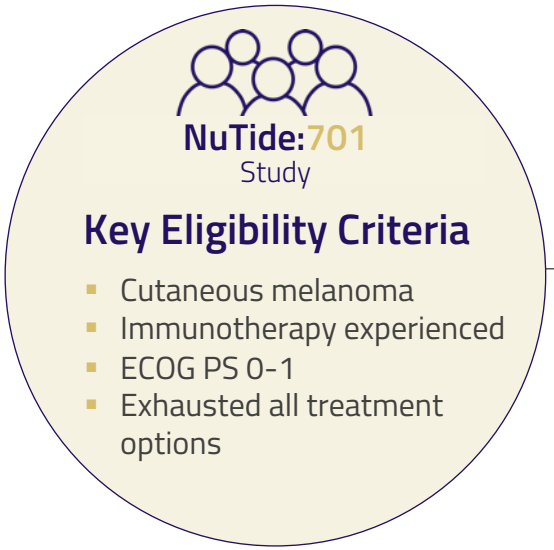
Metastatic Lung Adenocarcinoma

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^2
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

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

NUC-7738 : Phase 2 Study (combination)



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 : Favorable Safety Profile (combination)

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
Anemia	5 (42)	0	0
AST increased	4 (33)	1 (8)	1 (8)
ALP increased	2 (17)	0	0
Blood magnesium decreased	2 (17)	0	0
Blood sodium decreased	2 (17)	0	0
Decreased appetite	2 (17)	0	0
Fatigue	2 (17)	1 (8)	0
GGT increased	2 (17)	1 (8)	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); immune-mediated hepatitis (1 pt); adrenal insufficiency, hypercalcemia and hypotension (1 pt). No additional Grade 4 TRAEs

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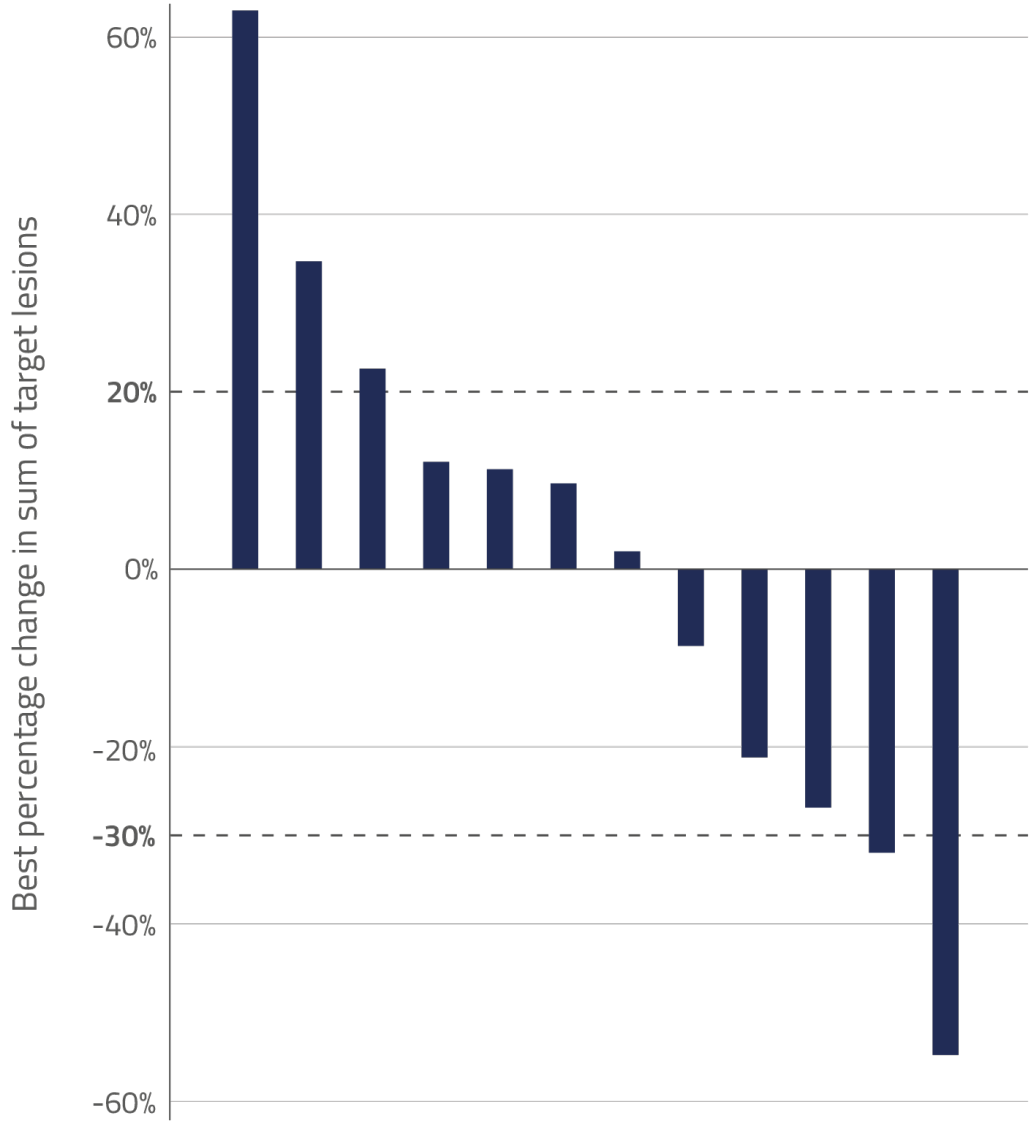
NUC-7738 : Tumor Volume Reductions in PD-1 Inhibitor Resistant Patients (combination)



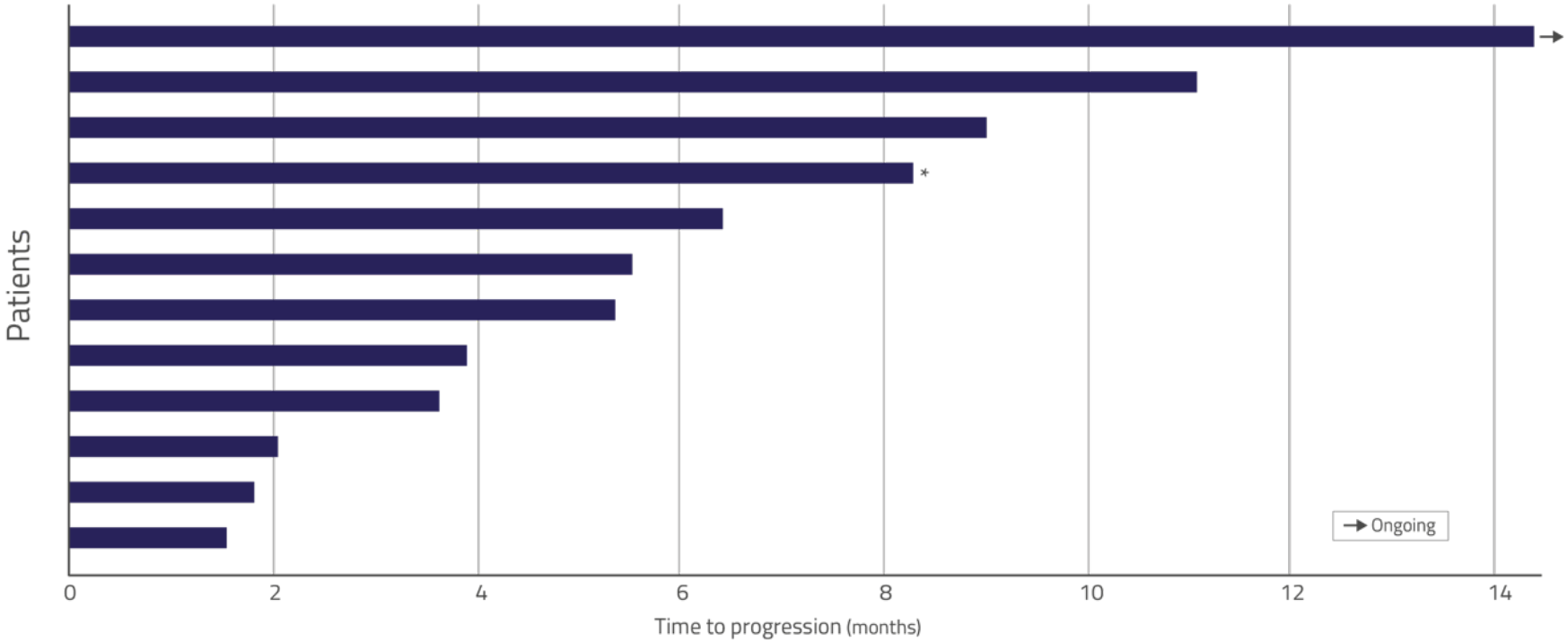
Patient previously refractory to PD-1 inhibitor (nivolumab) + CTLA-4 inhibitor (ipilimumab) had 55% reduction

Patient with resistance to PD-1 inhibition (pembrolizumab) had 32% reduction

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

NUC-7738 : Durable PFS in PD-1 Inhibitor Resistant Patients (combination)

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



*Patient had mixed response with almost all sub-cutaneous lesions resolved and just two lymph nodes that required RT with resection intended. Patient remains on therapy.

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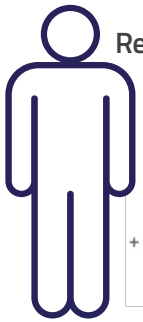
NUC-7738 : Encouraging Efficacy in PD-1 Inhibitor Resistant Patients (combination)

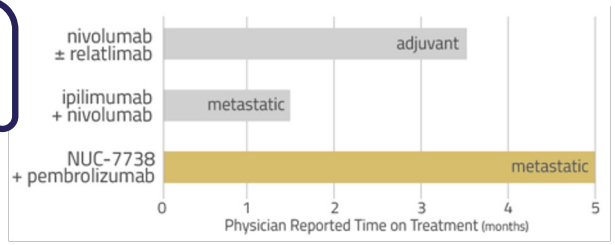
62 years
2 rior lines

Case Study 1

Partial Response in patient with resistance to PD-1 inhibition



63 years ▪ 2 target lesions (skin) ▪ BRAF wt
Received 2 prior PD-1 inhibitor containing regimens



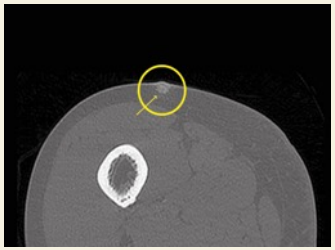
NUC-7738 + pembrolizumab

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

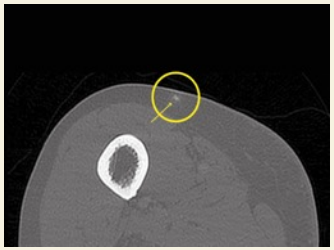
- 42% reduction in target lesion 1
- 70% reduction in target lesion 2 (see scans)

Time to progression 9 months

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



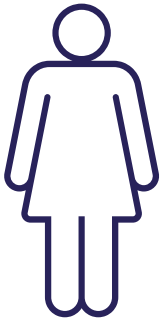
Baseline: 1.0 cm



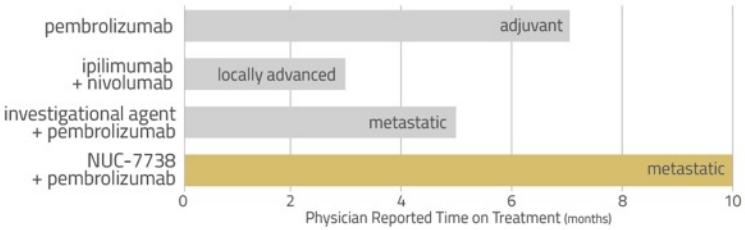
Week 17: 0.3 cm

Case Study 2

Evidence of anti-cancer immune response in TME



67 years ▪ 2 target lesions (lymph node) ▪ BRAF wt
Received 3 prior PD-1 inhibitor containing regimens



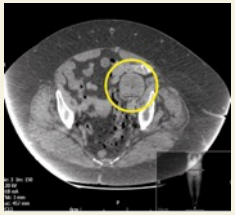
NUC-7738 + pembrolizumab

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

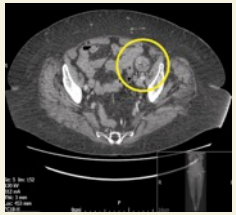
- 22% reduction in target lesion 1
- 45% reduction in target lesion 2 (see scans)

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)



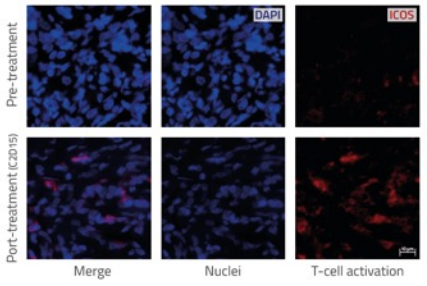
Baseline: 5.53 cm



Week 24: 3.04 cm

T-cell activation post-treatment

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



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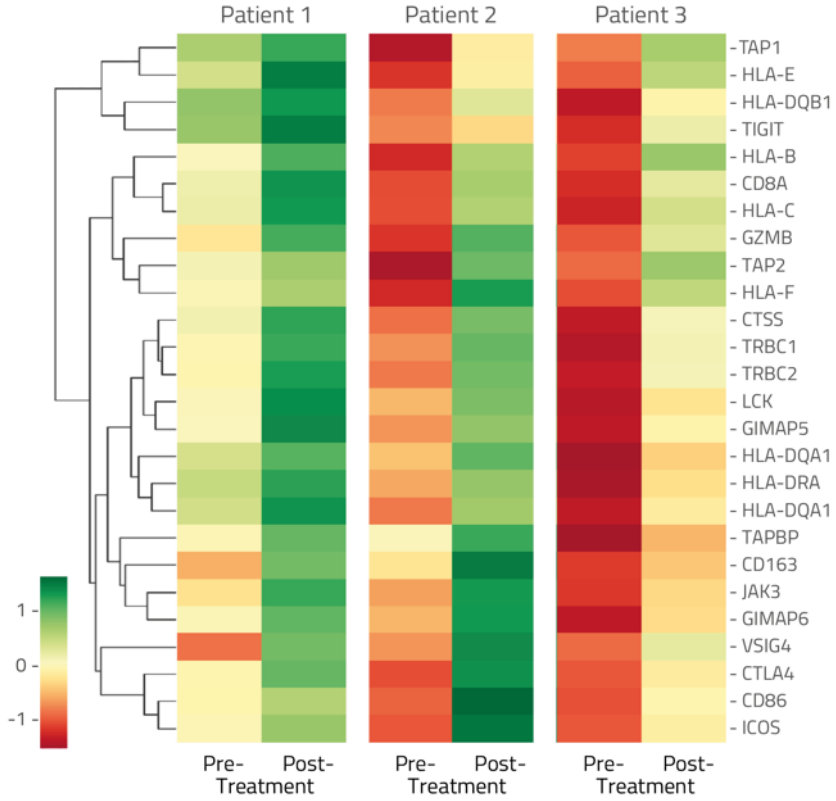
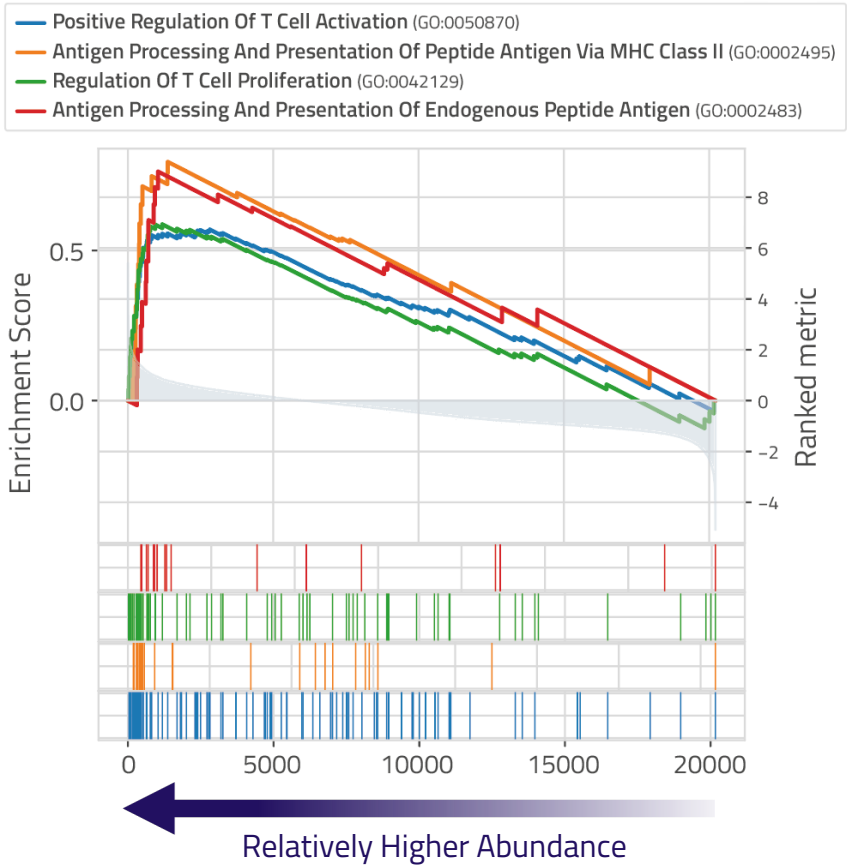
NUC-7738 : Increases Antigen Presentation & T-cell Activation in Patient Biopsies

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



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



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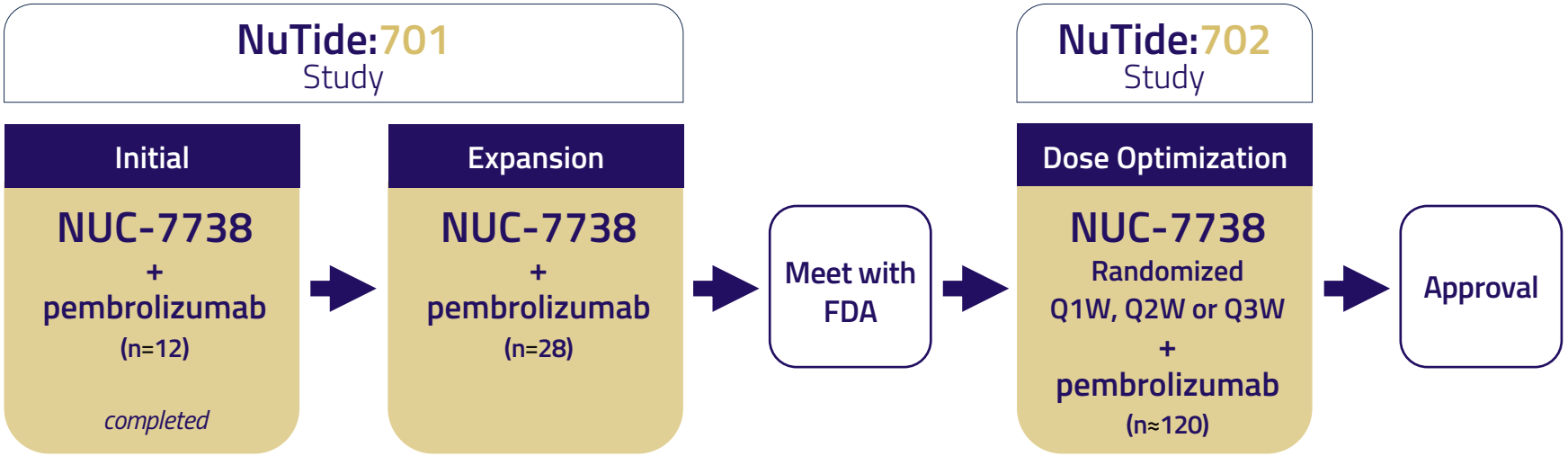
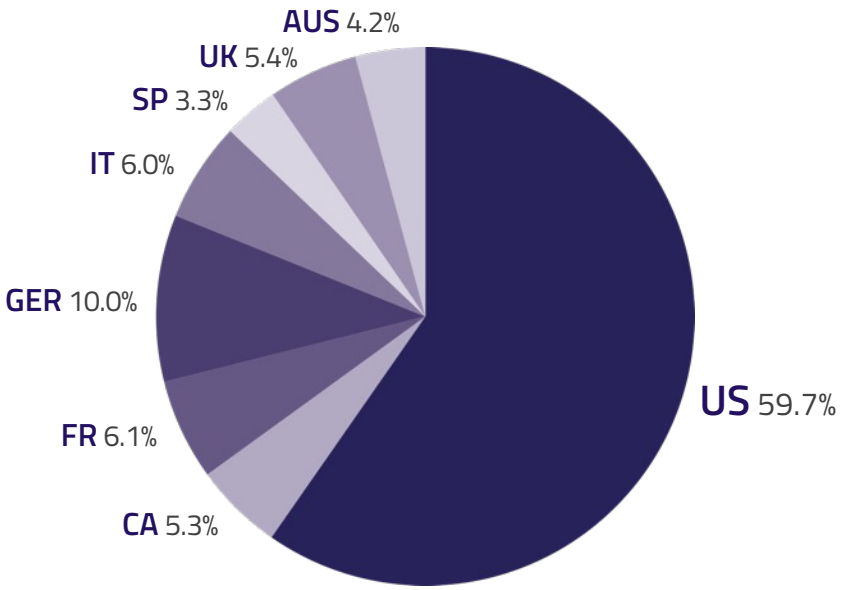
NUC-7738 : Melanoma Development Pathway



NUC-7738 : Melanoma Market Opportunity

$7.4B

Estimated sales in 8 major markets in 2029[2]



331,722 new cases
diagnosed annually[1]

58,667 deaths
annually[1]

13,000 patients
will fail PD-1 inhibitors in US[3]

5-year survival rate: 30%
Stage IV melanoma[4]

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)

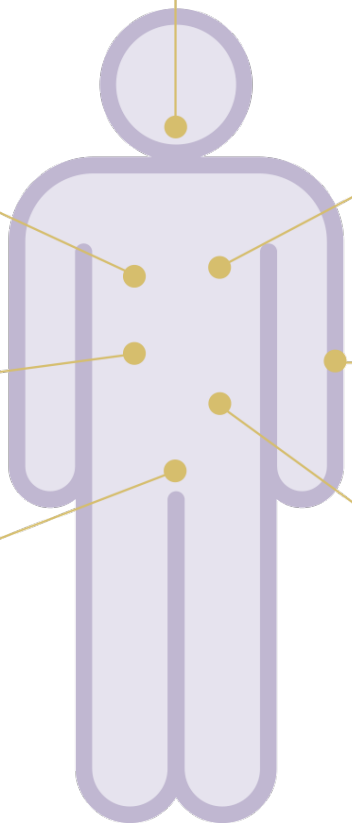
NUC-7738 : Multiple Development Opportunities

Head & Neck cancer
- PD-(L)1 resistant
- Chemo-ineligible

Non-Small Cell Lung cancer
- PD-(L)1 resistant
- Neoadjuvant setting
- Chemo-ineligible

Hepatocellular cancer
- PD-(L)1 resistant
- TKI- treated

Bladder/Urothelial cancer
- PD-(L)1 resistant
- Cisplatin ineligible

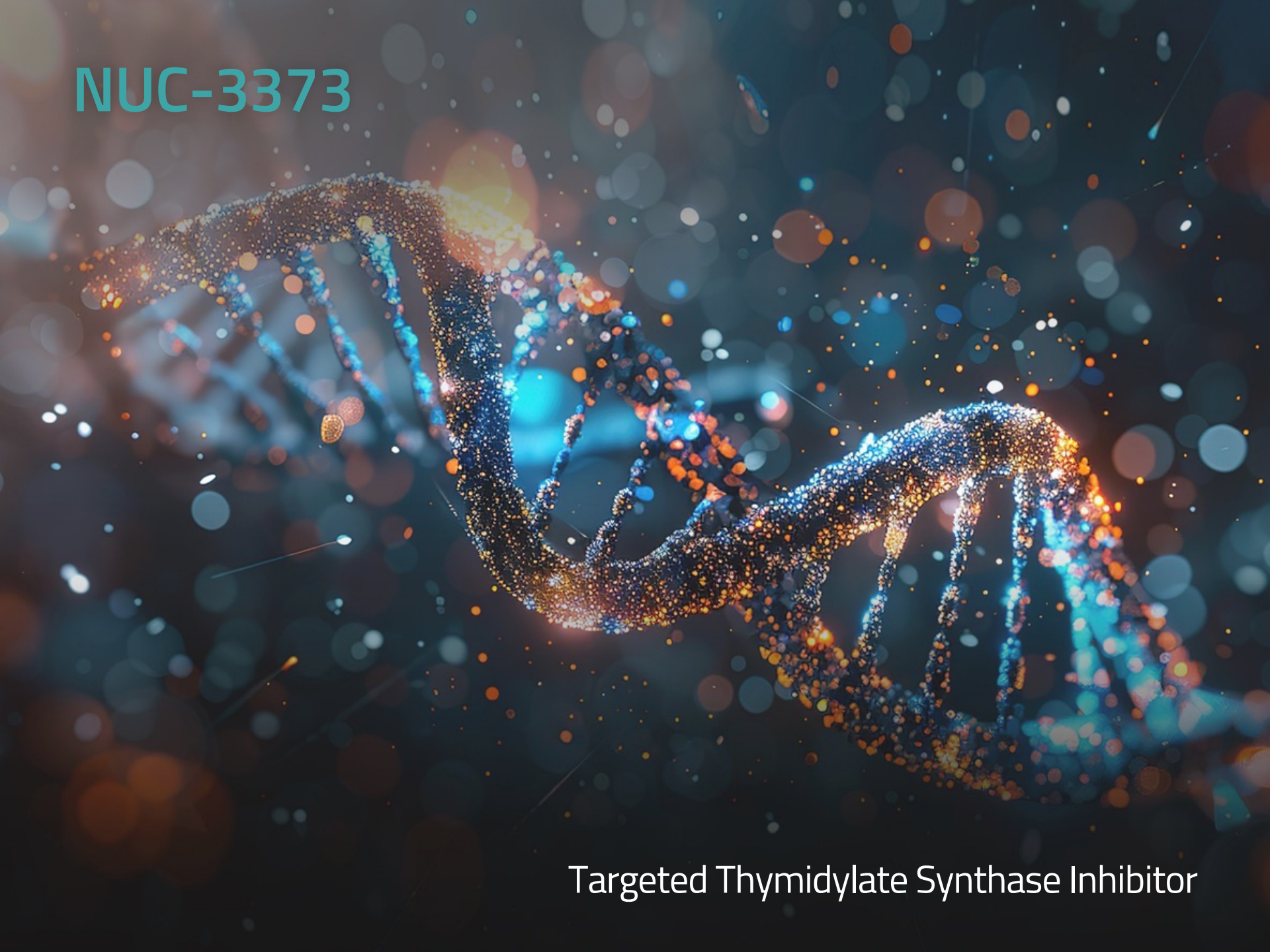


Breast cancer
- PD-(L)1 resistant
- Chemo-ineligible

Melanoma
- PD-(L)1 resistant
- BRAF/MEK refractory
- Neoadjuvant setting

Renal Cell cancer
- PD-(L)1 resistant
- TKI- treated

NUC-3373



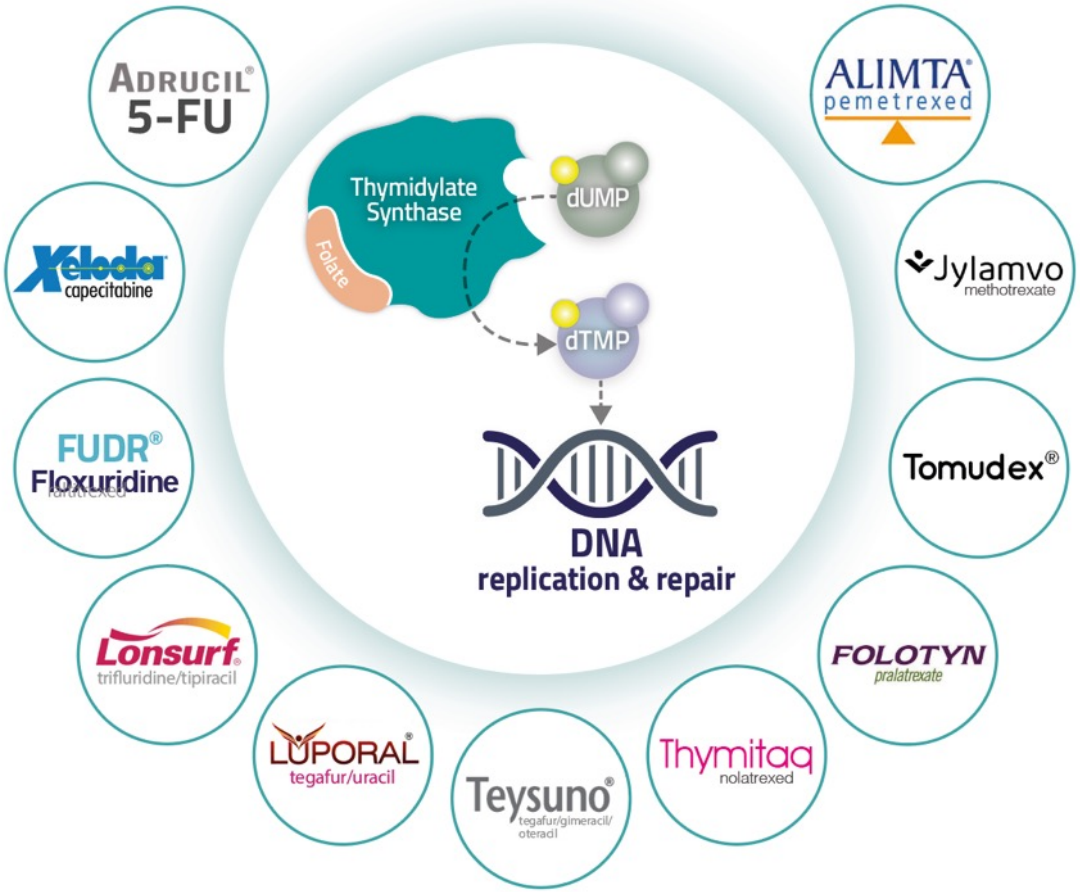
Targeted Thymidylate Synthase Inhibitor

Thymidylate Synthase: An Important Target for Anti-Cancer Therapies

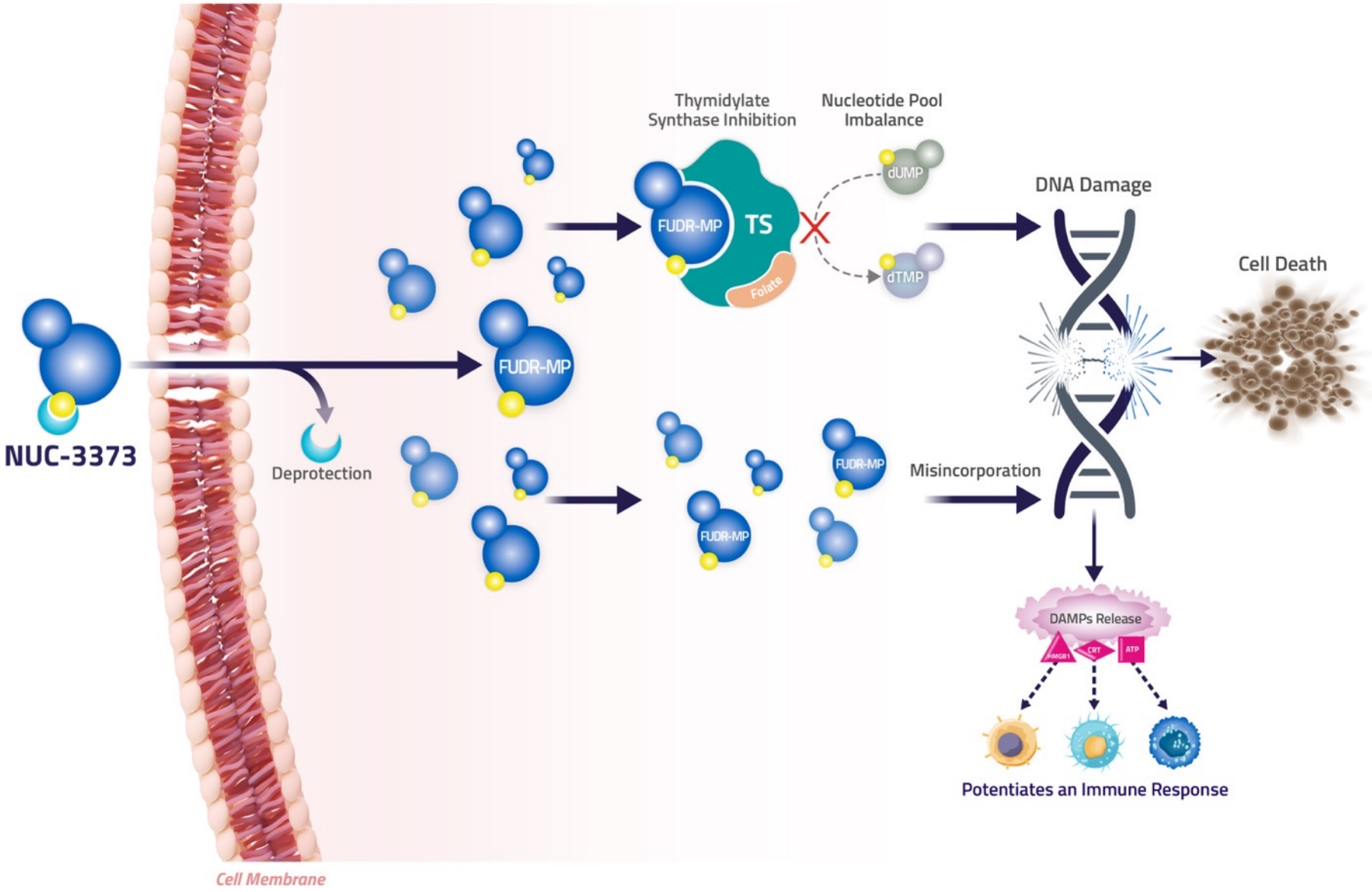
Thymidylate Synthase (TS) is a critical enzyme for nucleotide synthesis

- 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



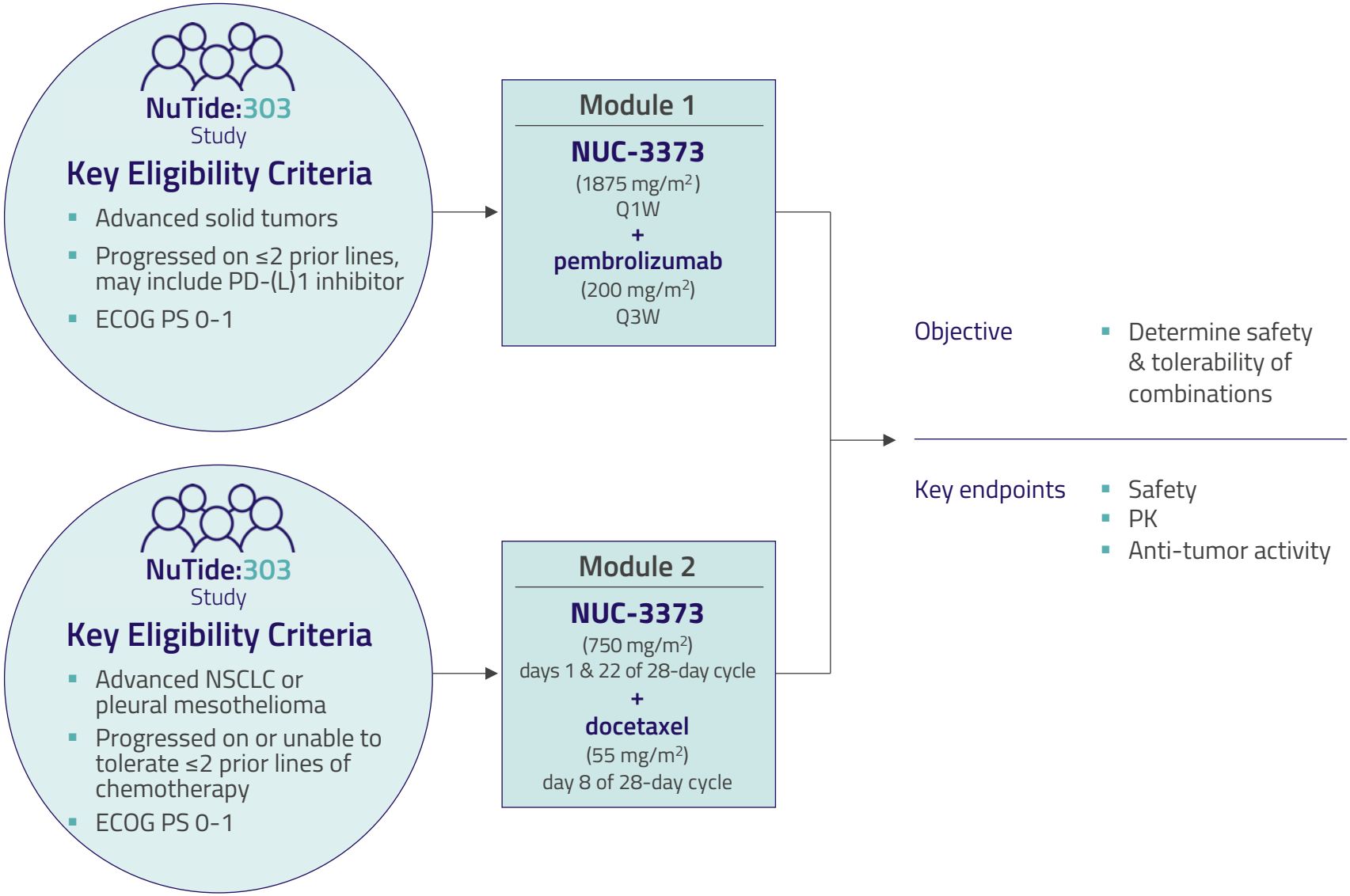
NUC-3373 : Induces DNA Damage & Potentiates an Immune Response



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

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

NUC-3373 : Phase 1b Study (ongoing)



NUC-3373 : Favorable Safety Profile (combination with pembrolizumab)

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

- One Grade 3 TRAE: hyponatremia
- No Grade 4 toxicities

Treatment Related Adverse Events

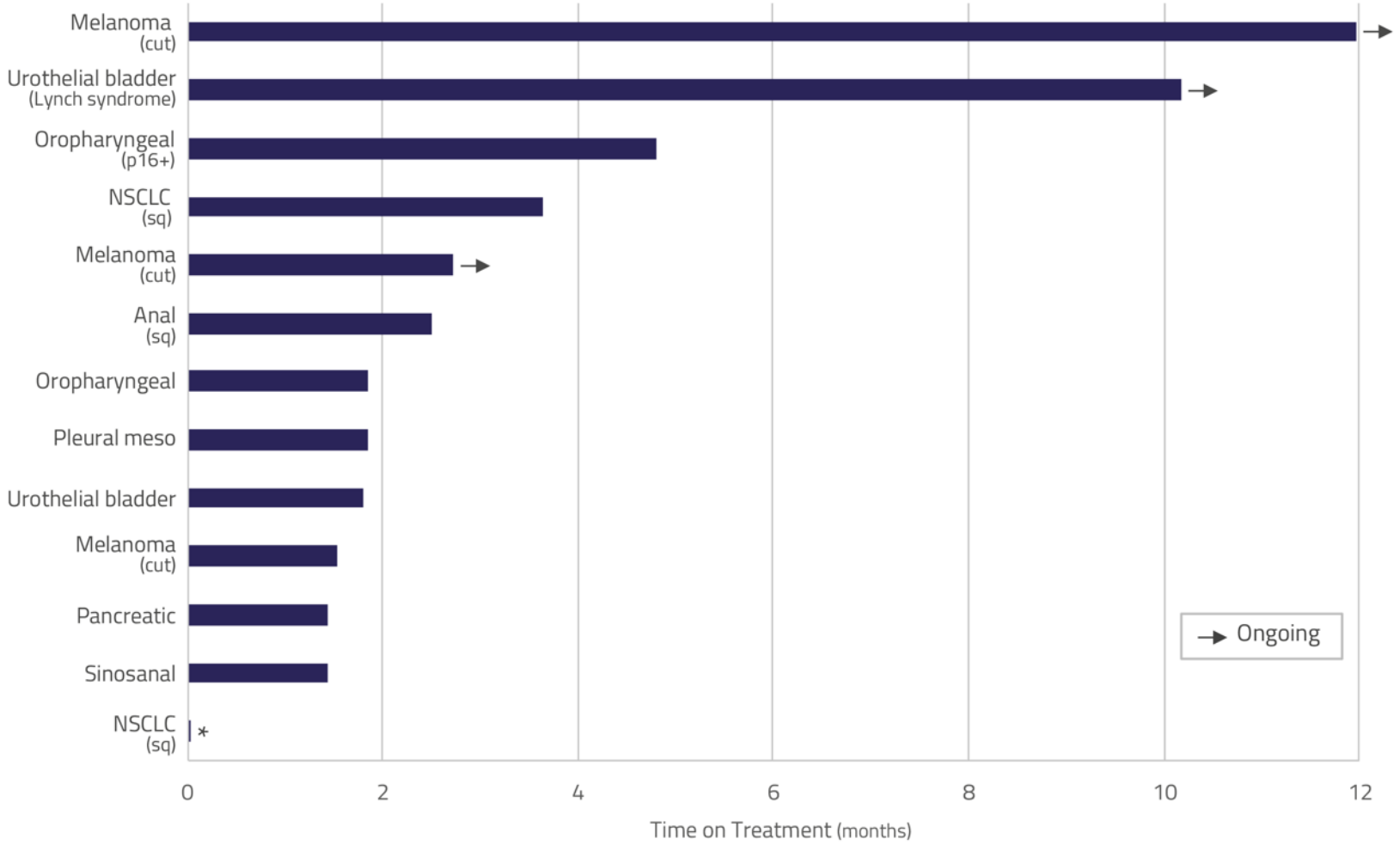
	All Grades n(%)	Grade 3 n(%)	Grade 4 n(%)
Nausea	9 (69)	0	0
Vomiting	9 (69)	0	0
Diarrhea	6 (46)	0	0
Fatigue	5 (38)	0	0
AST increased	4 (31)	0	0
Infusion related reaction	4 (31)	0	0
Anemia	3 (23)	0	0
Constipation	3 (23)	0	0
ALT increased	3 (23)	0	0
Hot flush	3 (23)	0	0
Abdominal pain	2 (15)	0	0
Flushing	2 (15)	0	0

All Grade TRAEs with prevalence ≥15% patients related to NUC-3373, pembrolizumab or both

Middleton *et al* (2024) *medRxiv* doi: 10.1101/2024.11.07.24316829. Data cut-off: October 8, 2024

NUC-3373 : Prolonged Time on Treatment (combination with pembrolizumab)

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



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

Middleton *et al* (2024) *medRxiv* doi: 10.1101/2024.11.07.24316829. Data cut-off: October 8, 2024

NUC-3373 : Encouraging Signs of Efficacy (combination with pembrolizumab)

Cutaneous Melanoma

75 years ▪ BRAF mt
2 prior lines

1) pembrolizumab:
progressive disease within **5 months**

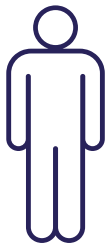
2) trametinib + dabrafenib:
trametinib discontinued after **1 month** (toxicity)
dabrafenib for 7 years (progressive disease)

NUC-3373 1875 mg/m^2 **+ pembrolizumab** 200 mg
- 1 target lesion (bilateral lymph node)

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

Treatment duration: 12+ 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^2 **+ 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: 10+ months (ongoing)
- No dose reductions

Middleton *et al* (2024) *medRxiv* doi: 10.1101/2024.11.07.24316829. Data cut-off: October 8, 2024

Strong Intellectual Property Position

Worldwide exclusive rights for all programs: **587 granted patents** and **114 pending applications***

KEY PATENTS	STATUS	EXPIRATION+ (excluding any extensions)	TERRITORIES
NUC-7738	**81 granted, 8 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
NUC-3373	**102 granted, 3 pending, including:**		
Composition of matter	Granted (US, EP, CN, JP)	2032	 + others
Formulation	Granted (JP), Pending (US, EP, CN)	2036	 + others
Manufacturing process	Pending	2043	 + others
Use	Pending	2037 / 2038	 + others

*As of February 22, 2024
+Expiration for pending patents if granted

Key Expected Milestones: 2025

	INDICATION	COMBINATION	PHASE	MILESTONE
NUC-7738 NuTide:701 Study	Melanoma	pembrolizumab	Phase 2	Initiate Study Expansion Announce Expansion Data Obtain FDA Feedback on Registration Strategy Initiate Pivotal Study
NUC-3373 NuTide:303 Study	Solid Tumors	pembrolizumab	Phase 1b/2	Initiate Study Expansion Announce Expansion Data

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

Improving Survival Outcomes

Synergy in combination with immune checkpoint inhibitor therapy

Strong IP Protection

Worldwide exclusive rights

Significant Milestones

Numerous value inflection points throughout 2025

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