# Phase 2 expansion study of NUC-7738 in combination with pembrolizumab in patients with PD-1 inhibitor-resistant cutaneous melanoma (NuTide:701)

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Email: miranda.payne@ouh.nhs.uk

**Miranda J Payne[1], Magdalena Kielak[1,2], Natalie Cook[3,4], Rebecca Lee[3,4], Mark Stares[5], Heather M Shaw[6,7], James Larkin[8,9], Ruth Board[10], Pippa G Corrie[11], Pavlina Spiliopoulou[12,13], Michelle Myers[14], Jeffrey D Bloss[14], Stefan N Symeonides[5,15], Ruth Plummer[16], TR Jeffry Evans[12,13], Sarah P Blagden[1,2]**

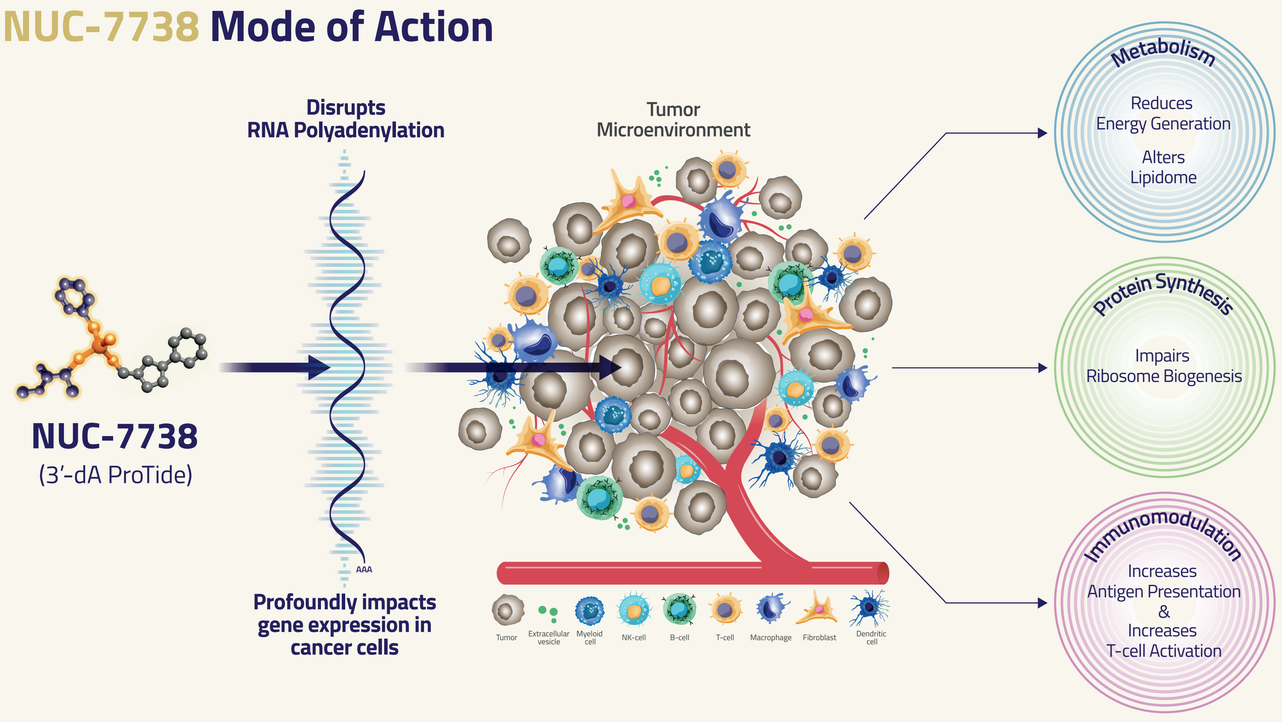
1) Department of Oncology, University of Oxford, UK 2) Oxford University NHS Foundation Trust, Early Phase Clinical Trials Unit, UK 3) Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK 4) University of Manchester, UK 5) Edinburgh Cancer Centre, NHS Lothian, UK 6) Department of Medical Oncology, University College London NHS Foundation Trust, UK 7) Department of Medical Oncology, Mount Vernon Cancer Centre, Northwood, UK 8) Renal Cancer and Melanoma Team, Institute of Cancer Research, London, UK 9) Renal and Skin Units, The Royal Marsden NHS Foundation Trust, London, UK 10) Department of Oncology, Lancashire Teaching Hospitals NHS Trust, Preston, UK 11) Department of Oncology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, UK 12) Beatson West of Scotland Cancer Centre, UK 13) School of Cancer Sciences, University of Glasgow, UK 14) NuCana plc, Edinburgh, UK 15) Edinburgh ECMC, Institute of Genetics and Cancer, University of Edinburgh, UK 16) Newcastle ECMC, Northern Centre for Cancer Care, Freeman Hospital, UK

## Background

### High Unmet Need in Metastatic Melanoma[1-4]

- Despite advances with immune checkpoint inhibitors, most patients experience disease progression following anti–PD-1 therapy
- PD-1 inhibitor resistance remains a key challenge with limited treatment options after PD-1 failure
- New therapeutic approaches urgently needed to improve survival outcomes

### NUC-7738 Mode of Action



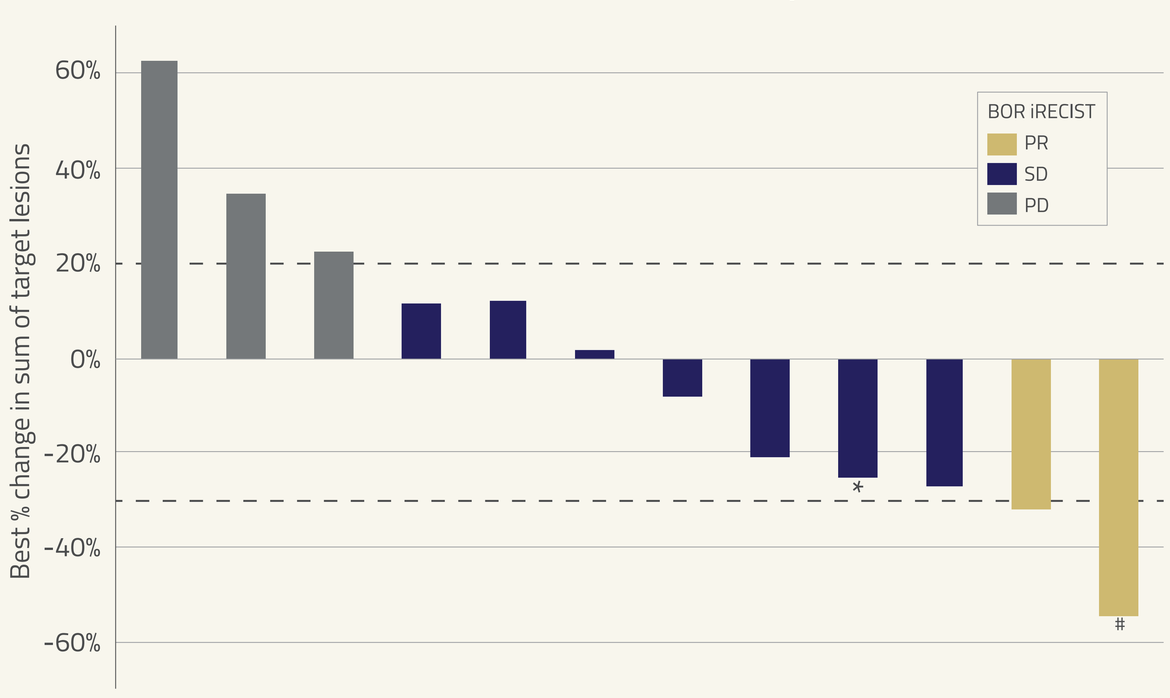

### NUC-7738

- Phosphoramidate modification of 3′-deoxyadenosine (3′-dA, cordycepin)
- Designed to generate high intracellular levels of anti-cancer metabolite 3′-dATP
- Disrupts RNA polyadenylation, altering protein and non-coding RNA levels, profoundly affecting tumor biology[5,6]
- Targets multiple aspects of tumor microenvironment to promote anti-tumor immunity[6-8]
- NUC-7738 synergizes with PD-1 inhibition to drive tumor cell killing[9]

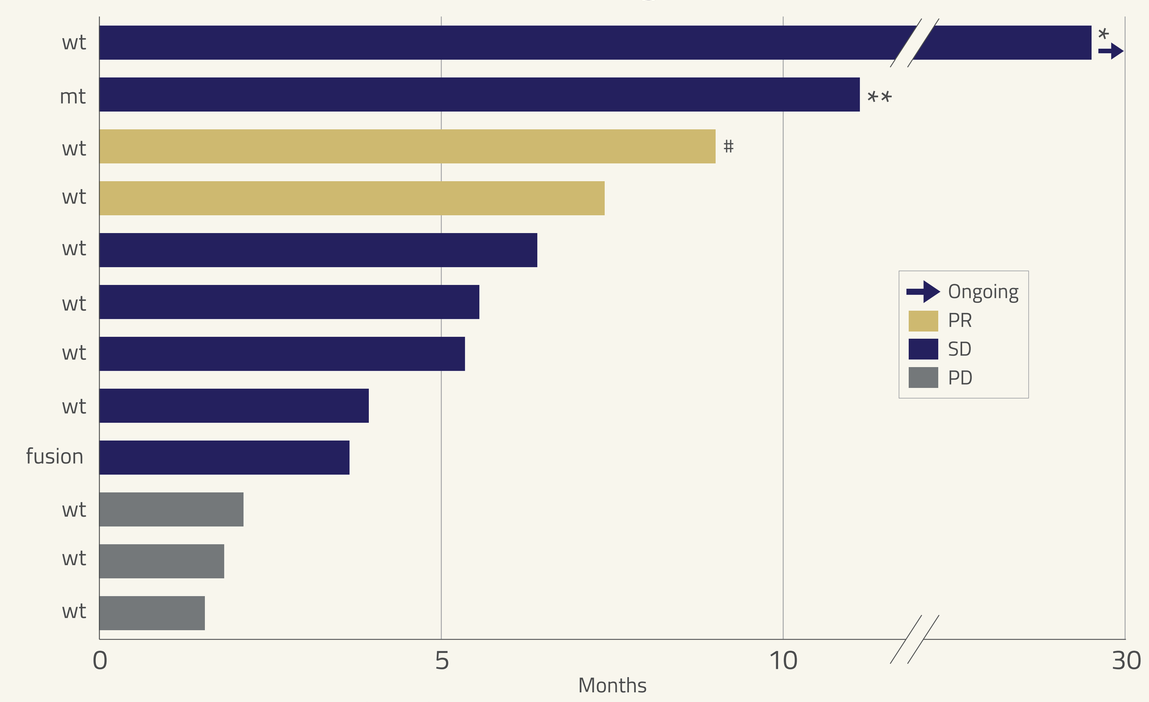
## Promising Efficacy of NUC-7738 + Pembrolizumab

### PD-1 inhibitor-resistant cutaneous melanoma[8] (n=12)

#### Anti-Tumor Activity




#### Time to Progression




* Patient achieved complete metabolic response on PET (no FDG uptake), while CT-based iRECIST assessment remained stable disease (-25%)
** Treatment discontinued per patient decision
# Discontinued by patient choice; follow-up imaging showed progression of non-target lesion, target lesions remained stable (–55%)

**Favorable Safety Profile**

- Most frequent all-grade TRAEs: nausea (9 pts), ALT increased, diarrhea, vomiting (6 pts each), anemia, fatigue (5 pts each), AST increased (4 pts)
- 5 patients had Grade 3 TRAEs: adrenal insufficiency, ALT/AST increased, diarrhea, fatigue, GGT increased, hyperglycaemia, hypertension, hypotension, immune-mediated hepatitis, vomiting (1 pt each)
- 1 patient had Grade 4 TRAEs: ALT/AST increased; no Grade 5 TRAEs

## Study Design

### NuTide:701 Study

**NUC-7738 in Combination with Pembrolizumab in Patients with PD-1 Inhibitor-Resistant Cutaneous Melanoma**

**Primary Endpoints**
PFS, BOR, ORR, DoR, DCR, DoSD (iRECIST, RECIST)

**Secondary Endpoints**
Safety & Tolerability

**Recruited** (12 patients)
PD-1 inhibitor-resistant cutaneous melanoma[8]

→ **Study Expansion**

**Expansion Cohort** (+28 patients)
***Currently Recruiting***
PD-1 inhibitor-resistant cutaneous melanoma

### Key Inclusion Criteria

- Histologically confirmed metastatic cutaneous melanoma
- Aged ≥18 years
- Measurable disease (RECIST v1.1)
- ECOG PS 0-1
- Disease progression on PD-1 inhibitor (monotherapy or combination)
- May have received BRAF-directed therapy

### Key Exclusion Criteria

- Active CNS or leptomeningeal disease
- >2 prior lines of therapy for advanced/metastatic disease
- Systemic steroid therapy or immunosuppressive therapy (>10 mg/day prednisone or equivalent)
- Prior unresolved toxicity related to anti PD-1 therapy
- Prior treatment with cell therapies

### Dosing Schedule

- 1125 mg/m$^2$ NUC-7738 IV, Q1W + 200 mg pembrolizumab IV, Q3W

### Currently Enrolling (NCT03829254)

- Cambridge — Addenbrooke's Hospital
- Edinburgh — Western General Hospital
- Glasgow — Beatson West of Scotland Cancer Centre
- London — The Royal Marsden Hospital, Chelsea
- London — The Royal Marsden Hospital, Sutton
- London — University College Hospital
- Manchester — The Christie Hospital
- Newcastle — Freeman Hospital
- Oxford — Churchill Hospital
- Preston — Royal Preston Hospital

### Initial Data from Expansion Cohort (9 patients)

- **Treatment well-tolerated and consistent with known safety profile**
  - **Most frequent all-grade TRAEs:** nausea (5 pts), diarrhea (4 pts), vomiting (4 pts), fatigue (3 pts)
  - **3 patients had Grade 3 TRAEs:** ALT/AST increased, generalized tonic–clonic seizure, vomiting (1 pt each)
  - **No Grade 4 or 5 TRAEs**
- **Encouraging signs of efficacy**
  - 1 partial response (unconfirmed), 2 stable disease; all ongoing

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**ABBREVIATIONS:** 3′-dA: 3′-deoxyadenosine 3′-dATP: 3′-deoxyadenosine triphosphate AE: Adverse event ALT: Alanine aminotransferase AST: Aspartate Aminotransferase BOR: Best Overall Response BRAF: B-Raf proto-oncogene, serine/threonine kinase CNS: Central nervous system CT: Computed tomography DCR: Disease Control Rate DoR: Duration of Response DoSD: Duration of Stable Disease ECOG PS: Eastern Cooperative Oncology Group Performance Status FDG: Flurodeoxyglucose GGT: Gamma-glutamyltransferase iRECIST: immune Response Evaluation Criteria in Solid Tumors IV: intravenously MT: Mutant NK cell: Natural Killer cell PD-1: Programmed cell death protein 1 PET: Position Emission Tomography PFS: Progression free survival Pt: Patient ORR: Objective Response Rate Q1W: Once weekly Q3W: Once every 3 weeks RECIST: Response Evaluation Criteria in Solid Tumors RNA: Ribonucleic acid TME: Tumor microenvironment TRAEs: Treatment related AEs WT: Wildtype

Conflicts of Interest for MJP - Financial Interests: BMS, Loreal, Regeneron, Sun Pharma, Genesis & Oxford University Press. Non-Financial Interests: Pierre Fabre & Melanoma Focus


Data cleaning ongoing: data cut off as 30 October 2025. Study sponsored by NuCana.