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NUC-7738 in Patients with Advanced Solid Tumors

Phase 1 results from the NuTide:701 Phase 1 / 2 Study

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DECLARATION OF INTERESTS

Stefan N. Symeonides

Consultancy/Advisory Role:

Vaccitech, Bicycle Therapeutics, Ellipses Pharma, EUSA Pharma, Eisai, MSD, Bristol-Myers Squibb, Pfizer/EMD Serono, MedAnnex, Boxer Capital, Duke Street Bio

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Merck, Sharp & Dohme, Verastem, Boston Pharmaceuticals, Sierra Oncology, NuCana, BioNTech, Nouscom, Sapience Therapeutics, Roche/Genentech, Incyte

Speaker Bureau:

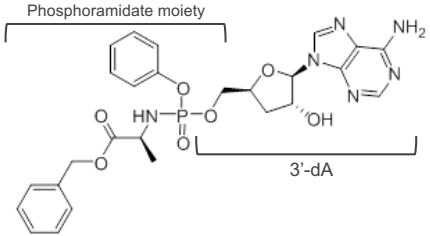
EUSA Pharma, Bristol-Myers Squibb, Ipsen

Travel, Accommodation, Expenses:

Ipsen, Bristol-Myers Squibb, MSD, BioNTech

NUC-7738: RNA Polyadenylation Disruptor

Phosphoramidate transformation of 3'-deoxyadenosine (3'-dA)

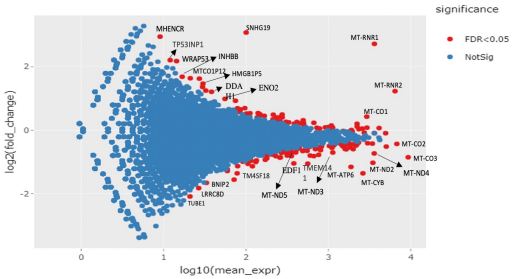


Generates high intracellular levels of active metabolite 3'-dATP in patients' PBMCs & tumors

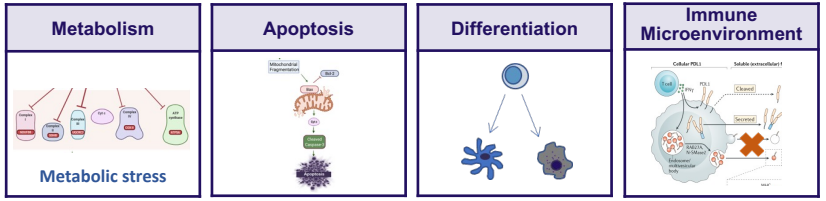
3'-dATP levels generated in patients is comparable to active levels observed *in vitro*

	PBMC *in vitro* (10 μM)	PBMC *in vitro* (50 μM)	PBMCs from patient dosed (2000 mg/m²)
NUC-7738 (pmol/10⁶ cells)	0.23	1.19	1.89
3'-dATP (pmol/10⁶ cells)	6.3	25.5	36.0

Disrupts polyadenylation and transcription



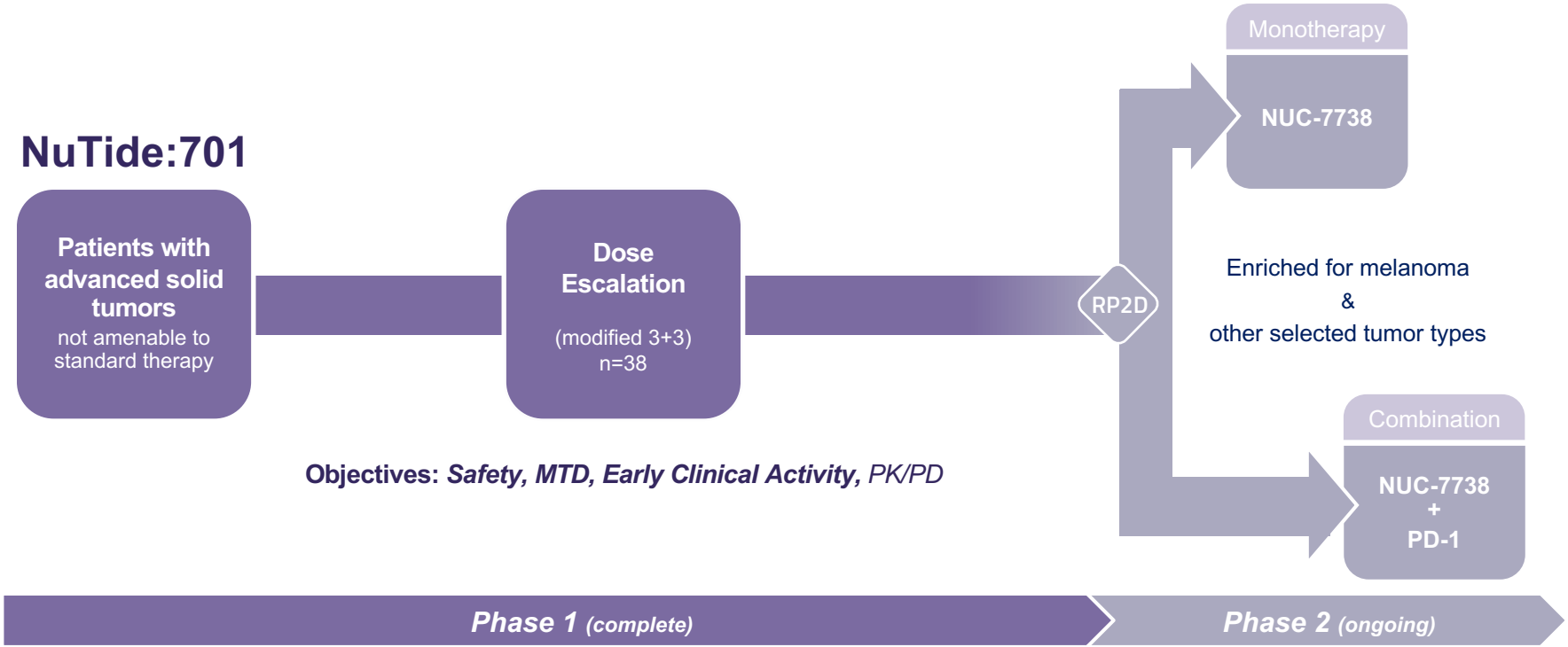
Changes in genes involved in key cellular processes



3'-dA, 3'-deoxyadenosine; 3'-dATP, 3'-deoxyadenosine triphosphate; PBMC, peripheral blood mononuclear cell; RNA, ribonucleic acid

Schwenzer *et al* (2021) *Clin Cancer Res.* 27(23):6500-6513

First in Human Phase 1 Study of NUC-7738 (NCT03428958)



PD, pharmacodynamics; PD-1, programmed cell death protein-1; PK, pharmacokinetics; RP2D, recommended phase 2 dose

Patient Baseline Characteristics and Dose Escalation Cohorts

Baseline Characteristics (n=38)	
Age	
Median (range)	66.5 (39-84)
Sex	
male	16 (42%)
female	22 (57%)
ECOG PS	
0 1	19 (50%) 19 (50%)
Prior Lines of Therapy for Advanced Disease	
Median (range)	2 (0-7)

Solid Tumor Primary Location	n (%) (n=38)
Cutaneous melanoma	6 (16%)
Non-cutaneous melanoma	5 (13%)
Colorectal	3 (8%)
Pleural mesothelioma	3 (8%)
Esophageal/Gastric	3 (8%)
Cervical	3 (8%)
Pancreatic	2 (5%)
Lung adenocarcinoma	2 (5%)
Breast	2 (5%)
Ovarian	2 (5%)
Bile duct	2 (5%)
Other	5 (13%)

Starting Dose (mg/m²)	n (n=38)
14	2
28	2
42	1
70	1
112	1
182	1
273	2
400	3
600	6
750	4
900	6
1350	7 (1 DLT fatigue)
2000	2 (2 DLTs fatigue)

Other: jejunal adenocarcinoma, Sertoli cell, leiomyosarcoma, endometrial & chordoma

ECOG, Eastern Cooperative Oncology Group; PS, performance status

Data cleaning ongoing; data cut off 7 Jul 2022

NUC-7738 Well-Tolerated Across All Dose Cohorts

Patients with Treatment-Related Adverse Events (TRAEs)

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 TRAEs (≥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 TRAEs (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%)

- 31 out of 38 (82%) patients experienced a TRAE; **No Grade 4 or 5 TRAEs**
- Other SAEs related to study drug: 1 patient at 600 mg/m²; dyspnoea (Grade 2), pneumonitis (Grade 2) & radiological changes consistent with ILD
- **MTD: 1350 mg/m²** Dose Limiting Toxicities in 3 patients: Grade 3 fatigue (1 at 1350 mg/m², 2 at 2000 mg/m²)

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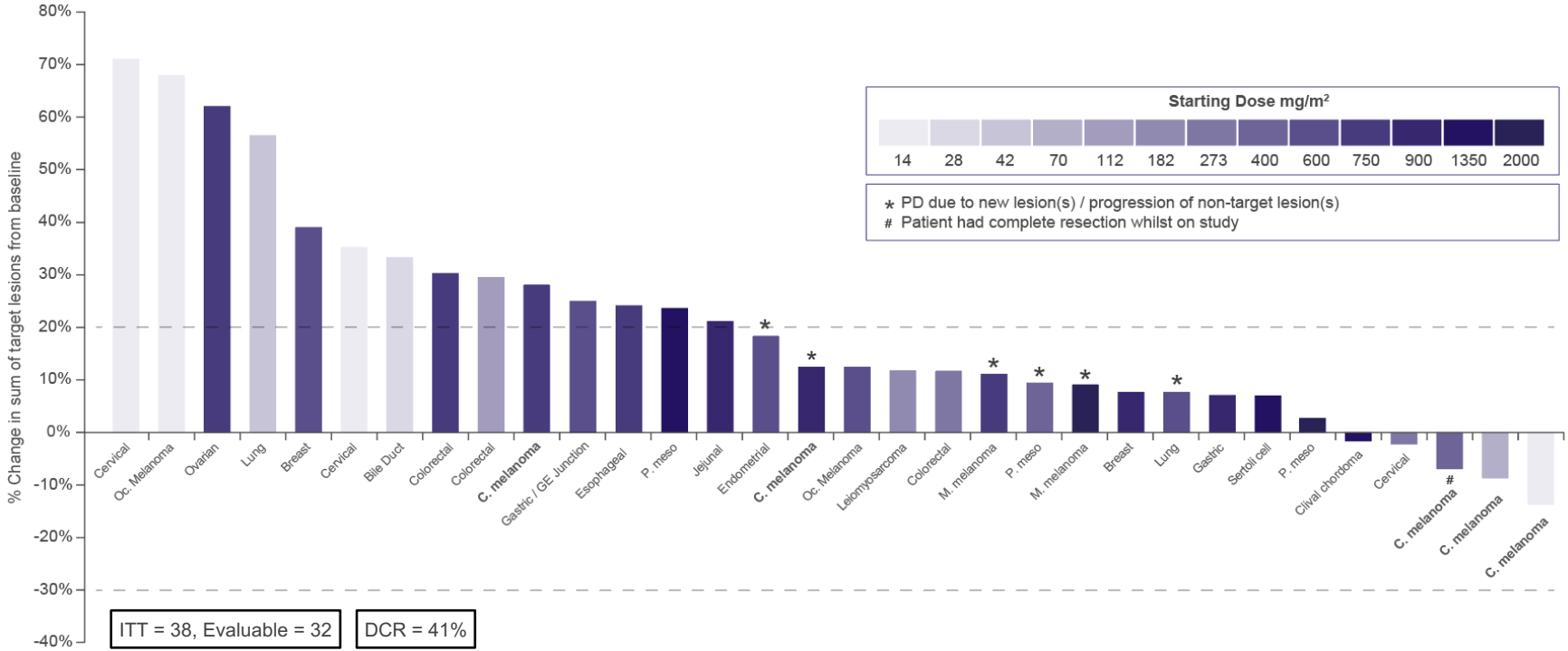
ILD, interstitial lung disease; MTD, maximum tolerated dose; SAE, serious adverse event; TRAE, treatment-related adverse event

n*, number of patients receiving each dose level at any time during the study
**, total number of patients who experienced TRAE

Best Tumor Response in Evaluable Patients



Notes: The percent change from baseline is the maximum percent decrease (or minimum increase if no decrease) in tumor size at a given visit relative to baseline. Tumor size is the sum of diameters of the target lesions.

c.melanoma, cutaneous melanoma; DCR, disease control rate; GE, gastro/esophageal; ITT, intention-to-treat; m. melanoma, mucosal melanoma; o.melanoma, ocular melanoma; p. meso, pleural mesothelioma; PD, progressive disease

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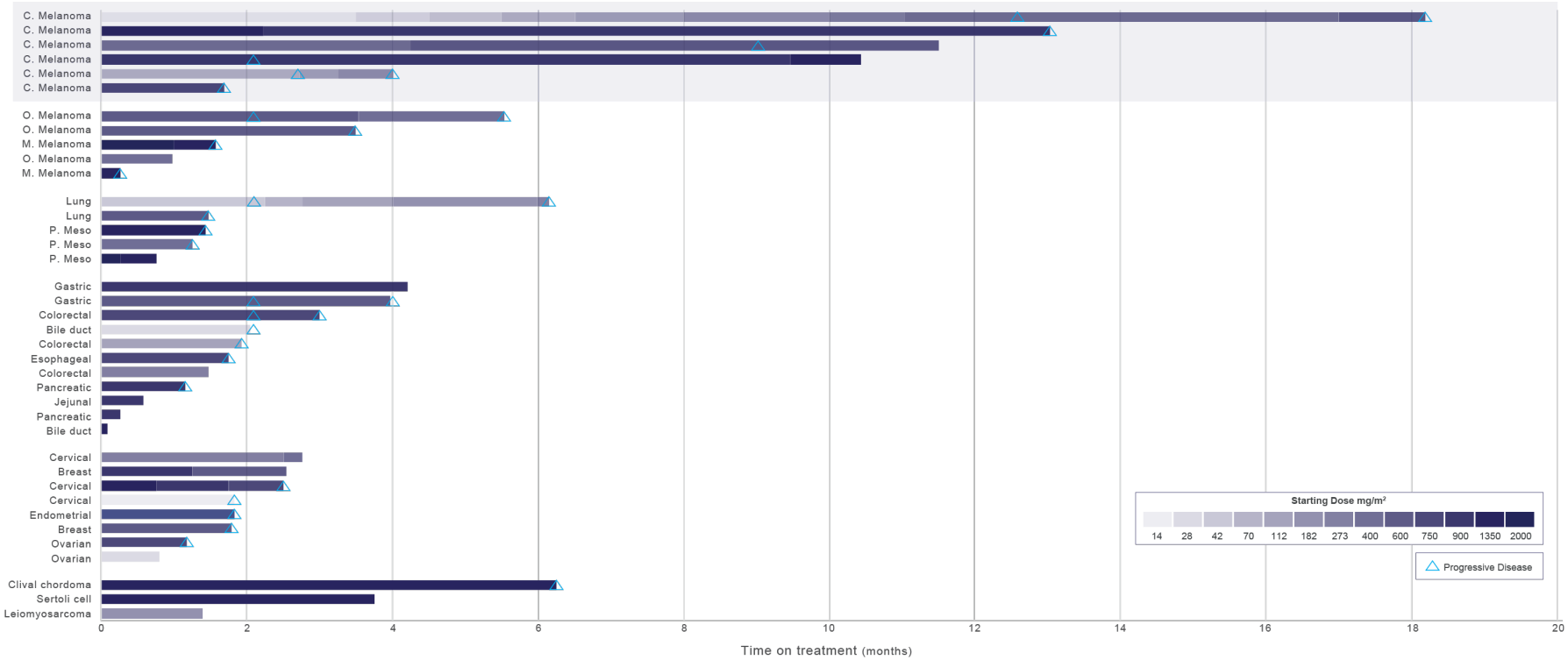
Duration of Treatment



c.melanoma, cutaneous melanoma; GE, gastro/esophageal; m. melanoma, mucosal melanoma; o.melanoma, ocular melanoma; p. meso, pleural mesothelioma

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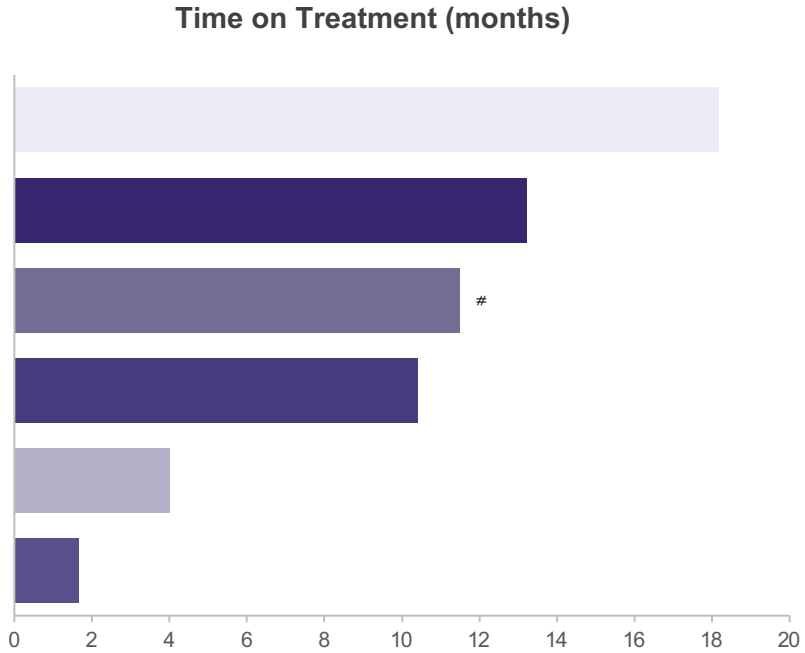
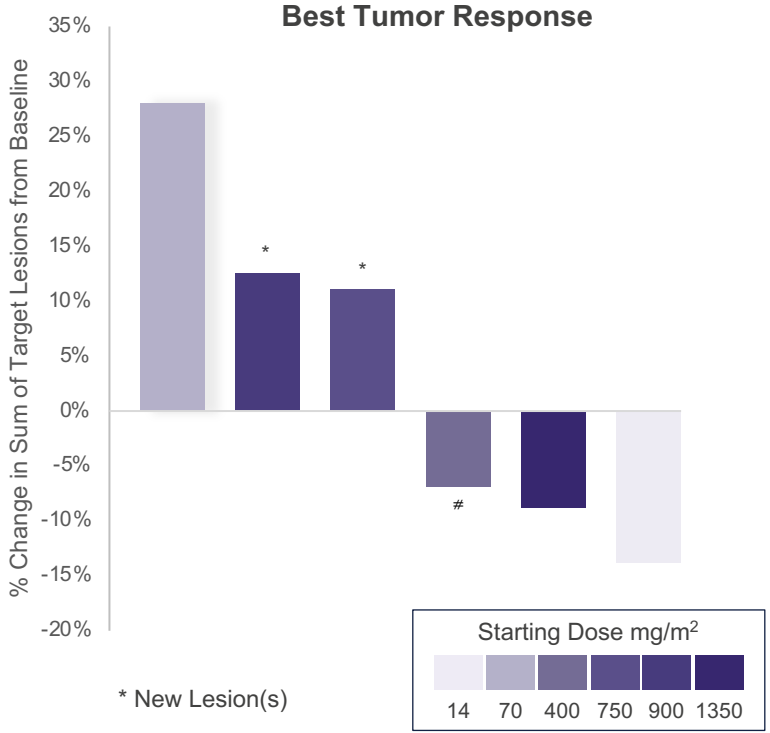
Evidence of Clinical Activity in Cutaneous Melanoma



NUC-7738 treatment enabled complete resection (R0)

All melanoma patients had prior immunotherapy



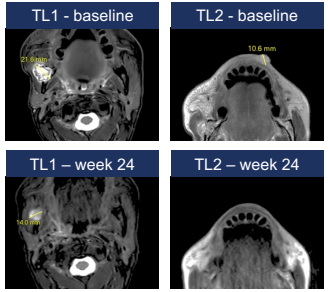
* New Lesion(s)

Data cleaning ongoing; data cut off 7 Jul 2022

Evidence of NUC-7738 Clinical Activity

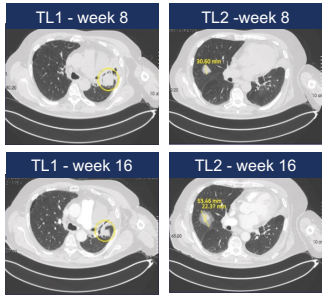
Metastatic Clival Chordoma - 72 years female

- **1 prior line** imatinib: progressed at 19 months
- NUC-7738 dose 1350 mg/m^2
- **Stable disease 6 months**
- Bleeding from nasal lesion resolved
- **45% reduction in mandibular lesion**
- **Complete disappearance of lip lesion**



Metastatic Lung Adenocarcinoma - 65 years male

- **2 prior lines** i) carboplatin + pemetrexed: progressed at 6 months ii) docetaxel: progressed at 4 months
- NUC-7738 starting dose 42 mg/m^2 (4 dose escalations)
- **Treatment duration 6 months**
- **46% reduction in lung lesion 1**
- **Change in character in lung lesion 2**
  small dense core surrounded by a larger diffuse "ground-glass" periphery



Metastatic Melanoma - 62 years female

- **2 prior lines** i) nivolumab + ipilimumab: discontinued within 1 month; ii) CK7 inhibitor: progressed within 1 month
- NUC-7738 starting dose 14 mg/m^2 (8 dose escalations)
- **Stable disease 12 months** treatment duration 18 months due to clinical benefit
- **14% reduction in tumor volume**

Metastatic Melanoma - 65 years female

- **1 prior line** nivolumab + ipilimumab: discontinued within 1 month
- NUC-7738 starting dose 400 mg/m^2 (1 dose escalation)
- **Stable disease 9 months,** treatment duration 11 months due to clinical benefit
- **7% reduction in tumor volume**
- **NUC-7738 treatment enabled complete resection** patient had diffuse disease that was inoperable prior to NUC-7738

CK7, cytokeratin 7

Data cleaning ongoing; data cut off 7 Jul 2022

Conclusions

- NUC-7738 is a new anti-cancer agent with novel mechanism of action
- Favorable safety profile
- MTD is 1350 mg/m^2
- Evidence of anti-tumor activity demonstrated across broad range of tumors and doses
- Phase 2 study (NuTide:701) ongoing
  - Monotherapy in melanoma & other selected tumors
  - Combination with PD-1 inhibitor in melanoma

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MTD, maximum tolerated dose; PD-1, programmed cell death protein-1

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