2024 ESMO TAT

Targeted Anticancer Therapies

INTERIM RESULTS OF A PHASE 1/2 TRIAL OF NT219 IN COMBINATION WITH CETUXIMAB IN PATIENTS WITH RECURRENT/METASTATIC (R/M) SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (SCCHN)

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ABSTRACT 27O

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

DECLARATION OF INTERESTS

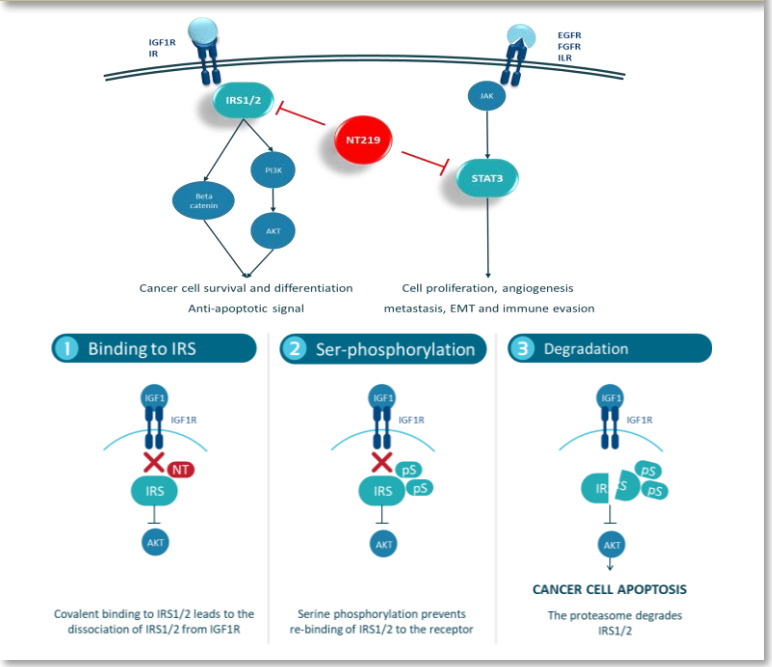
Ari J. Rosenberg, MD

Consulting/advisory: EMD Serono, Astellas, Eisai, Nanobiotix, Novartis, Regeneron, Vaccitech, Galectin, Privo.

NT219 - A FIRST IN CLASS DUAL INHIBITOR OF STAT3 AND IRS1/2

Mechanism of Action

- **A Dual Inhibitor of IRS1/2 and STAT3**
- **Leads to IRS degradation through covalent binding**



- Both STAT3 and IRS1/2 mediate mitogenic, metastatic and anti-apoptotic signals and are highly involved in cancer drug resistance.
- IRS1/2 are scaffold proteins, overexpressed in multiple tumors and regulate major survival pathways such as the PI3K/AKT and WNT/β-catenin.
- STAT3 pathway is required for TGFβ-induced EMT, metastasis, angiogenesis and is a critical player in tumor immune evasion.
- NT219 demonstrated significant efficacy in combination with cetuximab in multiple SCCHN patient-derived xenograft models.
- R/M SCCHN in platinum and anti-PD-(L)1 refractory setting represents unmet need with ORR ~5-19% and median OS of ~6-9 months.[1-4]

1. Cohen et al. Lancet, 393:156-67, 2019; 2. Ferris et al. N Engl J Med, 375:1856-67, 2016; 3. Vermorken et al. J Clin Oncol, 25:2171-7, 2007; 4. . Ferris et al. Annals of Oncology, 34:S554-S555, 2023

PHASE 1/2 STUDY

Dose escalation of NT219 in combination with cetuximab in 2L/3L R/M SCCHN

Objectives and Analysis Population

- **Primary objective**: safety, tolerability, and determination of RP2D of NT219
- **Secondary objectives**: PK, ORR, DoR, PFS and OS
- **Exploratory objectives**: NT219 targets (pIGF1R, pSTAT3, IRS1/2) in tumor biopsies

Enrollment and Interim Analysis

- **Cutoff date**: 25 January, 2024.
- **Enrolled** 17 SCCHN patients
- **Evaluable for efficacy:** 15 patients
- **Withdrawn due to AE**: 2

Dose escalation

Key SCCHN Inclusion Criteria

- Received up to 2 previous regimens for R/M disease
- ECOG PS <2

Treatment plan

- 5 NT219 dose levels (6, 12, 24, 50, 100mg/kg) with cetuximab
- Until PD, toxicity, death or withdrawal for any cause

PATIENT POPULATION

Demographics and Disease Features

Demographics and Disease Features	N= 17
Age median (yrs; range)	58 (28 - 65)
Gender:	
Male	17 (100%)
Race:	
White	16 (95%)
Other	1 (5%)
Prior lines	2 (1-2)
1	5 (29%)
2	12 (71%)
Prior treatments	
ICI	16 (94%)
Platinum	14 (82%)
Cetuximab	5 (29%)
Tumor location	
Oral cavity	76%
Pharynx	18%
Larynx	6%
HPV status:	
Positive/Negative	6 (35%) / 11 (65%)

SAFETY PROFILE

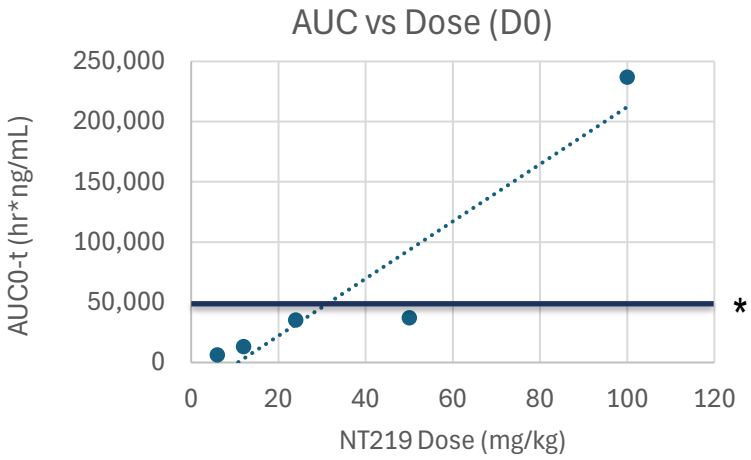
NT219 in combination with cetuximab in 2L/3L R/M SCCHN

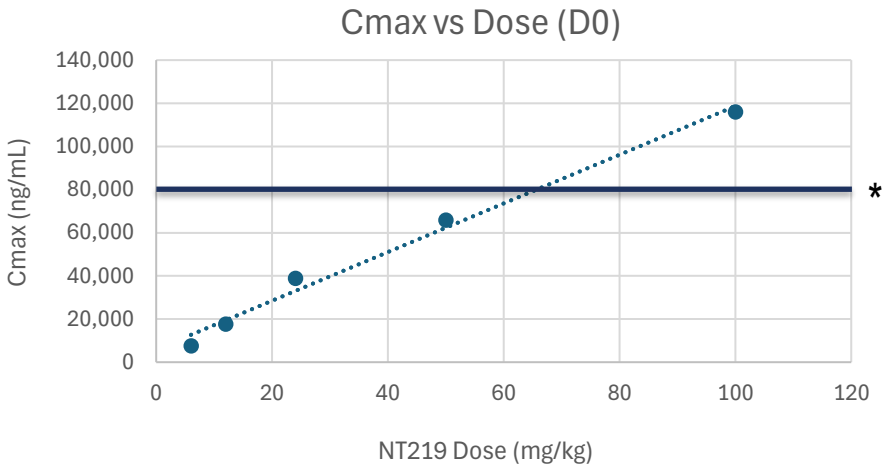
- Well tolerated and manageable safety profile up to 100mg/kg
- Most frequent treatment emergent AEs were Infusion related reactions and nausea
- No treatment-related Grade 4/5 AEs

	Grade 1		Grade 2		Grade 3		Grade 4/5		All	
	Freq.	**%**	**Freq.**	**%**	**Freq.**	**%**	**Freq.**	**%**	**Freq.**	**%**
Infusion related reaction	3	17.6	8	47.1	2	11.8	0	0	13	76.4
Nausea	4	23.5	1	5.9	1	5.9	0	0	6	35.3
Fatigue	4	23.5	1	5.9	0	0	0	0	5	29.4
Headache	2	11.8	1	5.9	1	5.9	0	0	4	23.5
Rash	1	5.9	3	17.6	0	0	0	0	4	23.5
Vomiting	2	11.8	1	5.9	0	0	0	0	3	17.6
Hypertension	0	0	0	0	2	11.8	0	0	2	11.8
Administration	0	0	2	11.8	0	0	0	0	2	11.8
Generalised	1	5.9	1	5.9	0	0	0	0	2	11.8
Hypomagnesemia	1	5.9	1	5.9	0	0	0	0	2	11.8

PHARMACOKINETIC ANALYSES

Dose proportional increase in AUC and Cmax





(*) Exposure & Cmax obtained at the effective dose in mice was observed at the ≥50mg/kg dose in human

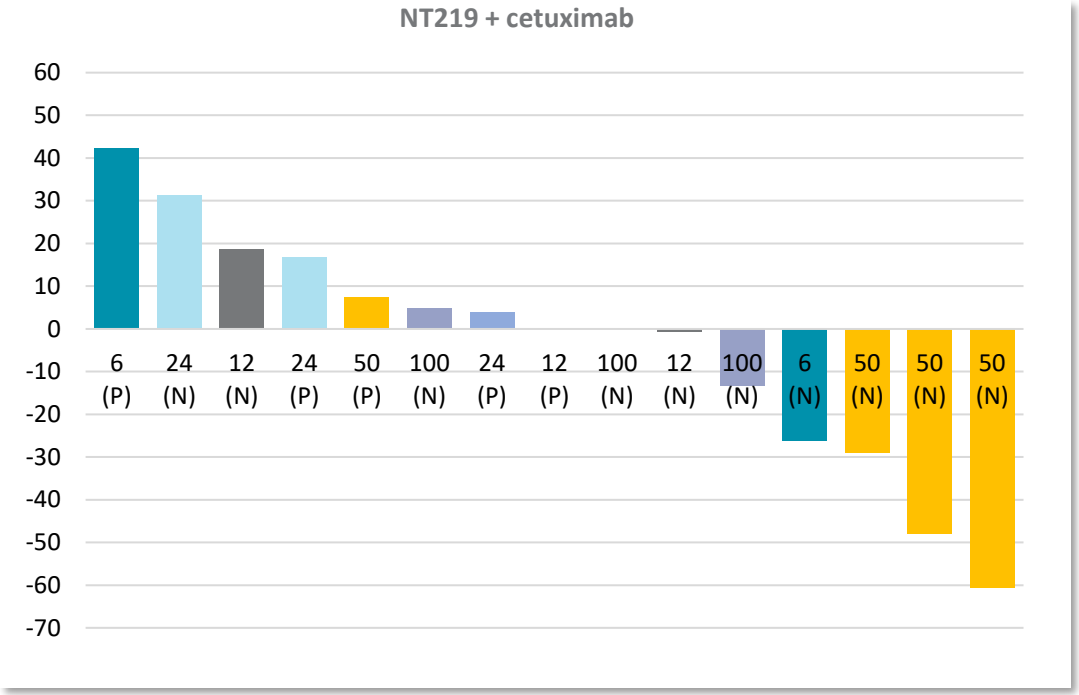
ANTITUMOR ACTIVITY IN 2L/3L R/M HNSCC

Best overall response

15 evaluable patients (all doses)

In the 7 patients at the highest dose levels (50 & 100mg/kg):

- 2 confirmed PR
- 3 SD
- ORR: 28.6%
- DCR: 71.4%

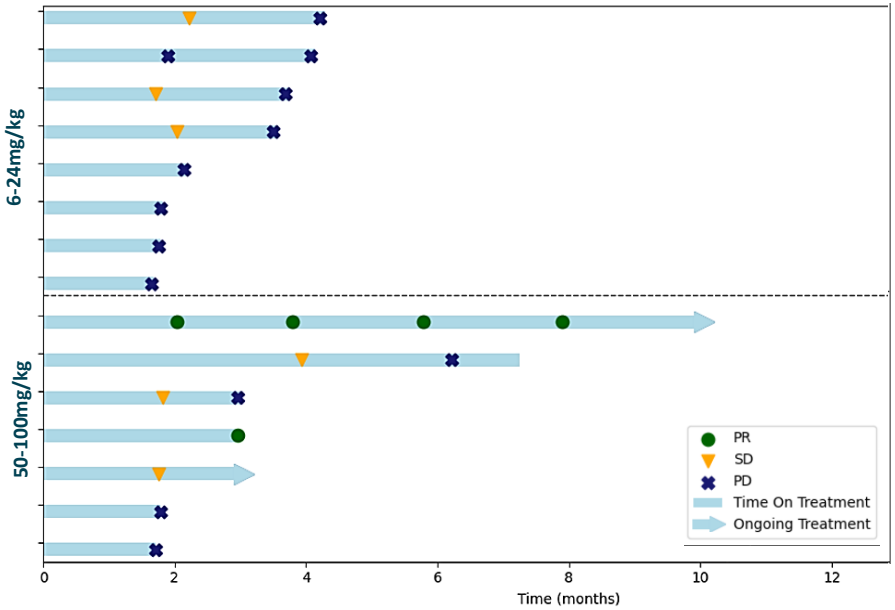


Numbers under horizontal line designate NT219 dose in mg/kg; P designates HPV positive; N designates HPV negative

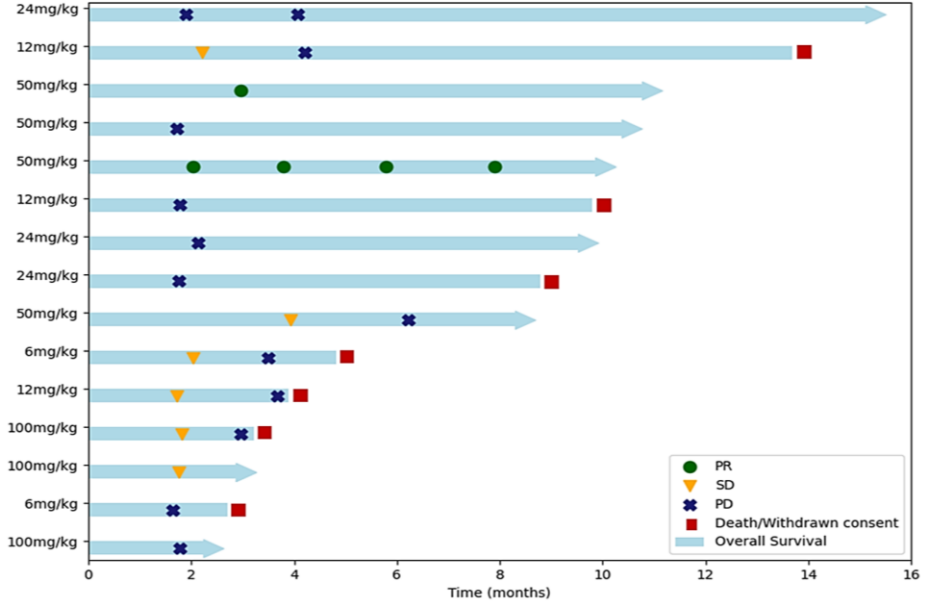
NT219 & CETUXIMAB IN 2L/3L R/M HNSCC

Treatment duration and survival

Time on Treatment



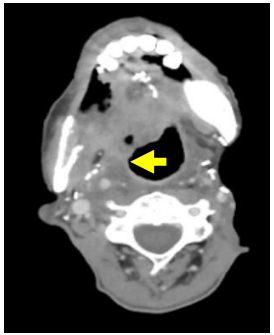
Survival



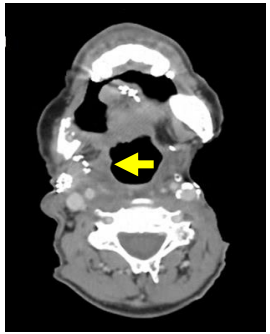
Median follow-up of 9.4 months (95% CI: 3.4-10.0)

CLINICAL RESPONSE TO NT219 & CETUXIMAB

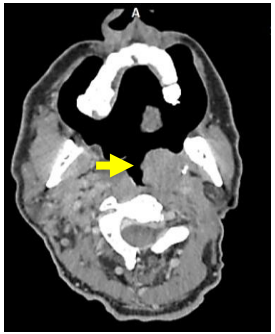
Neck lesions



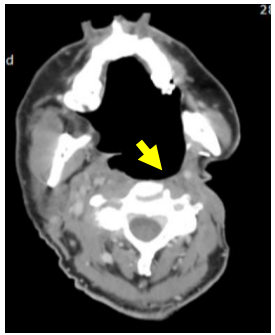
March 2023



July 2023

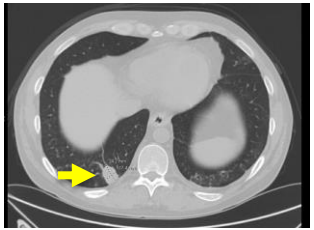


April 2023

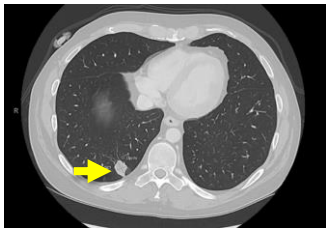


November 2023

Lung lesion



June 2023



September 2023

Patient 1	
HPV	Negative
Prior Therapy	1L: cetuximab/Rt; 2L: pembro/MCLA-158
NT219+cetuximab	6 weeks (withdrew due to IR)
RECICT 1.1	**Partial Response (-60%)**

Patient 2	
HPV	Negative
Prior Therapy	1L: pembro
NT219+cetuximab	40 weeks on treatment (ongoing)
RECICT 1.1	**Partial Response (-48%)**

Patient 3	
HPV	Negative
Prior Therapy	1L: nivo; 2L: pembro/carbo/5FU
NT219+cetuximab	27 weeks on treatment
RECICT 1.1	**Stable disease (-29%)**

CONCLUSIONS

NT219 in combination with cetuximab in 2L/3L R/M SCCHN

- Novel dual inhibition of STAT3 and IRS1/2
- **NT219 in combination with cetuximab is well tolerated with a manageable safety profile**
- Exposure at 50mg/kg and 100mg/kg is equivalent to effective dose levels in animal models
- **Anti-tumor activity seen in previously treated *HPV negative* 2L/3L R/M SCCHN patients**
  - ✓ **ORR @ 50 & 100mg/kg: 28.6%**
  - ✓ **DCR @ 50 & 100mg/kg: 71.4%**
- NT219 RP2D determined as 100mg/kg
- **In preparation of a phase 2 study of NT219 in combination with cetuximab w/wo chemotherapy in 2L R/M SCCHN**

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THANK YOU

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