#3096

Interim safety and efficacy results from a Phase 1 Study of NT219 in Adults with Advanced Solid Tumors

Alberto Bessudo[1], Rodolfo Gutierrez[2], Ezra E.W. Cohen[3], Daniel Johnson[4], Benjamin A. Weinberg[5], Ari J. Rosenberg[6], Susanna V. Ulahannan[7], Hadas Reuveni [8,9], Michael Schickler[8,9], Bertrand Liang[9]

1. California Cancer Associates for Research & Excellence (cCARE), Encinitas, CA, USA, 2. The Angeles Clinic & Research Institute, Los Angeles, CA, USA, 3. UCSD Moores Cancer Center, San Diego, CA, USA, 4. Precision Cancer Therapies Program at Ochsner Health, , New Orleans, LA, USA, 5. Georgetown University Medical Center, Washington DC, USA, 6. The University of Chicago Medical Center, Chicago, IL, USA, 7. Stephenson Cancer Center, OU, Oklahoma City, OK /SCRI Nashville, TN, USA, 8. TyrNovo Ltd, Rehovot, Israel, 9. Purple Biotech, Rehovot, Israel

BACKGROUND

- NT219 is a first-in-class small molecule, a direct inhibitor of Insulin Receptor Substrates 1/2 (IRS) and STAT3, promoting IRS degradation and suppressing STAT3 phosphorylation.
- IRS1/2 and STAT3 are major signaling junctions regulated by various oncogenes, mediating mitogenic, anti-angiogenic and metastatic processes.
- IRS1/2 and STAT3 play an important role in the modulation of both the tumor and the tumor microenvironment, affecting drug resistance and duration of response.
- NT219 monotherapy demonstrated significant and durable response in a PDX model of mutated-KRAS colon cancer, supporting clinical exploration. In addition, combination of NT219 with other agents in preclinical studies rationalizes future clinical studies of NT219 with other treatment modalities.
- Targeted degradation IRS2 by NT219 suppressed the increased b-catenin activity in colorectal cancer (CRC) preclinical models, overcame chemo-resistance and immune evasion, and suppressed metastases.
- Efficacy of NT219 was demonstrated in in-vitro cellular based studies, ex-vivo patient-derived biopsies and in-vivo patient derived xenograft preclinical models.

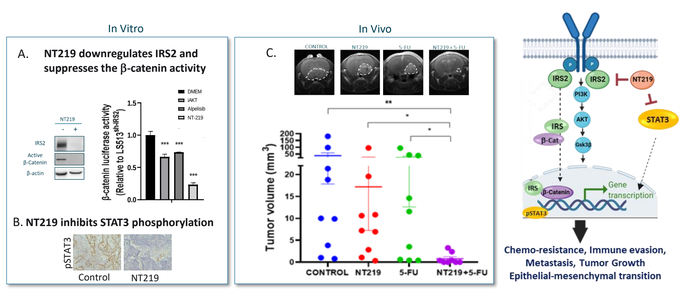

Figure 1: (A) NT219 Suppresses the IRS2 to β-Catenin pathway in CRC cells. (B) IHC of CRC patient derived explants (PDE) treated with NT219 showed significant inhibition of STAT3 phosphorylation. (C) NT219 Significantly enhances the response to 5FU and decreases tumor growth rate of CRC brain metastases when added to 5FU in mouse intracranial model.

- NT219 demonstrated significant and durable response in a PDX model of mutated-KRAS colon cancer as a monotherapy.
- NT219 in combination with α-PD1 re-sensitizes α-PD1 refractory tumors in a humanized PDX model of Gastroesophageal cancer (GEJ).

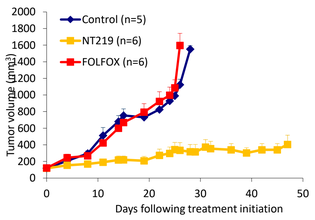

Figure 2: Monotherapy treatment with NT219 showed a significant anti-cancer effect (TGI = 86%, p= 0.001) in a PDX model of mutated KRAS colon cancer

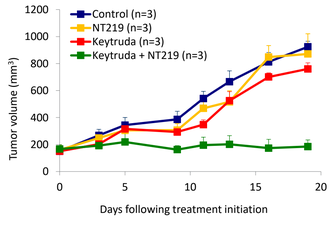

Figure 3: A combined treatment of NT219 with α-PD1 inhibited the growth of α-PD1 refractory tumors (TGI = 98%, p= 0.001) in a humanized PDX model of Gastroesophageal Cancer (GEJ)

METHODS

- A Phase 1/2 study (NCT04474470) includes a dose escalation of NT219 administered weekly for the treatment of relapsed and/or refractory cancer patients.
- In the dose escalation part of the study involving a conventional 3+3 design, patients with recurrent and/or metastatic solid tumors were administered intravenously with NT219 at 3, 6, 12, and 24mg/kg. Safety was assessed according to CTCAE v5 and anti-tumor activity was assessed by the investigators according to RECISTv1.1 using CT/MRI. The primary objectives of this part of the study are to evaluate safety, tolerability, PK and to determine the recommended Phase 2 dose (RP2D).

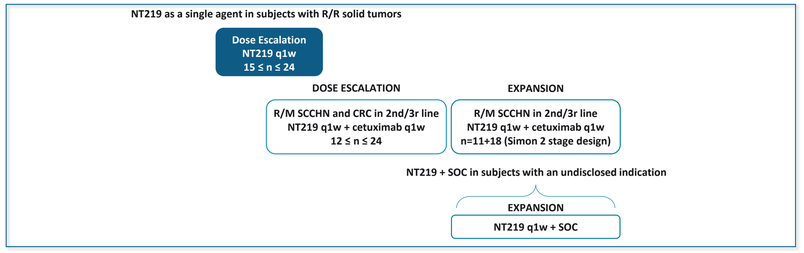

Figure 4: NT219 as a single agent in solid tumors and in combination with cetuximab in patients with R/M SCCHN (squamous cell carcinoma of the head & neck) and CRC (colorectal adenocarcinoma)

RESULTS

Patients: As of data cutoff date of May 12th , 2022, a total of 14 patients were enrolled to 4 NT219 dose levels (3 - 24mg/kg) in the dose escalation phase of the study, of which 12 were evaluable for dose limiting toxicity (DLT) determination, including 4 with colorectal cancer (CRC), 3 with pancreatic cancer, 2 with breast cancer, and one of each of the following cancers: gastroesophageal junction (GEJ), esophageal and appendiceal cancer. Median number of prior treatment regimens for metastatic disease was 4 (2-11).

Demographics of patients treated with NT219 (3, 6, 12, 24mg/kg)			
Median age, years (range)	67 (39-79)	Diagnosis , n (%)	
Sex, n (%)		Pancreatic	3(25%)
Male	4(33%)	GE Junction	1(8%)
Female	8 (67%)	Breast	2(17%)
Ethnicity, n (%)		Colorectal	4(33%)
Not Hispanic or Latino	11 (92%)	Appendiceal	1(8%)
Hispanic or Latino	1 (8%)	SCC of the esophagus	1(8%)
Race, n (%)		Prior Lines of Therapy, n (%)	
White	10 (83%)	2	2 (17%)
Black or African American	2 (17%)	3	3 (25%)
ECOG, n (%)		4	2(17%)
0	5 (42%)	5	2(17%)
1	7 (58%)	6	1(8%)
Median Time from Initial Diagnosis months (range)	36(10-153)	8	1(8%)
		11	1(8%)

Table 1: Demographics of patients

Safety: Eight Grade 3 adverse events (AEs) were observed, including alkaline phosphatase increase, aspartate aminotransferase increase, toxic encephalopathy, worsening back pain, abdominopelvic ascites, closed displaced fracture of right femoral neck, intractable hip pain, and malignant hypercalcemia, with the first 2 considered as possibly related to NT219. No Grade 4 AEs or treatment related deaths were reported.

AE Term	Total	Grade 1	Grade 2	Grade 3	Grade 4/5
Fatigue	6	6			
Constipation	4	4			
ALP increased	3	2		1	
ALT increased	3	1	2		
Anemia	3	1	2		
AST increased	3	1	1	1	
Diarrhea	3	2	1		
Headache	3	3			
Nausea	3	2	1		
Abdominal pain	2	1	1		
Belching	2	2			
Cough	2	2			
Dizziness	2	2			
Dyspnea	2	2			
Edema limbs	2	2			
Fever	2	2			
Hot flashes	2	2			
Hyperhidrosis	2	2			
Urinary tract infection	2		2		
Abdominopelvic Ascites	1			1	
Closed displaced fracture of right femoral neck	1			1	
Intractable right hip pain	1			1	
Malignant hypercalcemia	1			1	
Toxic Encephalopathy	1			1	
Worsening back pain	1			1	
Abdominopelvic Ascites	1			1	

Table 2: Most frequent and severe adverse events (AEs)

Efficacy: (A) For the 12 evaluable patients, best overall response included one confirmed PR (GEJ patient, > 5.5 months duration of response following end of treatment), and 3 SD (3 of 4 CRC patients; ALL mutated KRAS) with one patient awaiting follow up MRI/CT scans. As of the cutoff date, 10/12 patients that completed the DLT period are either on treatment or in follow up (range 1.1 to 18 months).

(B) CT imaging of the GEJ tumor at baseline screening and after 5 months of treatment with NT219 . GEJ cancer case (mutated KRAS, TP53). CT scan (left) showed a tumor in the gastroesophageal junction (GEJ). Treatment with NT219 resulted in complete resolution of this lesion (right). Complete resolution of all non-target lesions (two lymph nodes) has also been demonstrated.

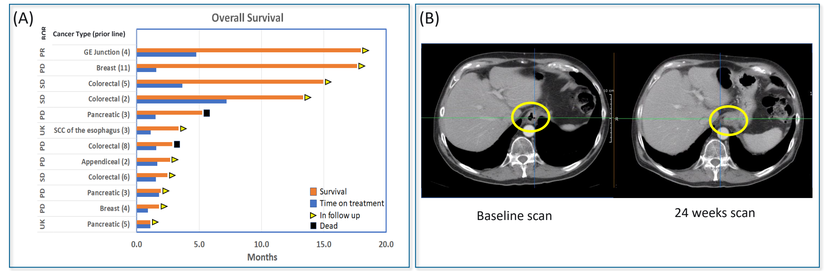

Figure 5: Efficacy analysis in advanced cancer patients (as of May 12th, 2022). Cancer type and number of previous lines of treatment are indicated.

CONCLUSIONS

- NT219 at doses up and including 24 mg/kg was well tolerated without DLTs in advanced cancer patients.
- Encouraging initial efficacy signal: durable PR in a GEJ patient and SDs in 3/4 CRC patients (ALL with mutated KRAS).
- These initial clinical observations are consistent with the pre clinical findings in a PDX model of mutated-KRAS colon cancer using NT219 monotherapy. Furthermore, combination of NT219 with other agents in preclinical studies supports future clinical trials of NT219 with other treatment modalities.
- Combination treatment of cetuximab with escalating NT219 doses in patients with recurrent/metastatic CRC and squamous cell carcinoma of the head and neck (SCCHN) has begun.
- An expansion cohort in patients with recurrent/metastatic SCCHN will be initiated at the conclusion of this combination dose escalation part.

The study is sponsored by Purple Biotech Ltd; no conflicts of interest to declare