#CT205

Safety and Preliminary Activity of Naptumomab Estafenatox (NAP) and Durvalumab in Patients with Advanced or Metastatic Solid Tumors Interim Results from a Phase 1b Trial (NCT03983954)

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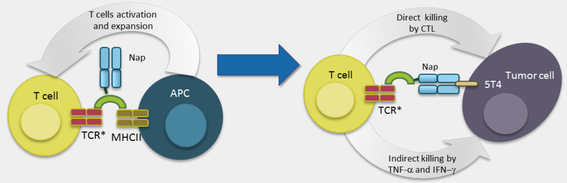
Background

NAP is a chimeric protein composed of a superantigen (SAg) and a Fab targeting the common tumor antigen 5T4. The 5T4 antigen is an oncofetal glycoprotein that is upregulated in many tumors types and also present on stem cells. Its therapeutic effect is unique and associated with activation, expansion and tumor infiltration of SAg-binding specific T cells. The superantigen has been specifically designed to selectively bind **only the subset of T-cells** expressing the vβ6.4 sequence on their T cell receptor, avoiding non-specific T cell over-stimulation (Figure 1).

Facilitating specific T-cell infiltration into the tumor microenvironment is thought to be an effective means of overcoming resistance to PD-L1 blockade (Tang et al 2016).

Durvalumab is a human monoclonal antibody that blocks programmed death ligand 1 (PD-L1).

Preclinical data have shown that NAP induces T cells tumor recognition, turning anti-PD-L1 unresponsive "Cold" tumors into "Hot" responsive tumors and has synergistic antitumor activity in combination with checkpoint inhibitors in animal models (Azulay et al 2018).



Selective T-cell activation and expansion (T-cells with T-cell receptor Vβ6.4) outside of the immunosuppressive TME

Redirection of T-cell trafficking towards the tumor and tumor cell kill

TTS platform is expandable by changing Fab specificity

Figure 1: Nap - A Tumor Targeted Superantigen (TTS) Acting as a Selective T-Cell Redirector

Methods and Trial Design

- Patients: 5T4 expressing advanced/ metastatic solid tumors.
- Design: 3+3 dose escalation followed by an expansion on MTD/RP2D.
- The primary objective was evaluating safety, tolerability, and determining MTD/ RP2D of NAP in combination with durvalumab. Secondary objectives included activity and duration of response based on RECIST 1.1 /iRECIST.
- Pharmacodynamics/ Pharmacokinetics: NAP and durvalumab PK, ADAs HAMA, Cytokines, Vβ6.4+ T-cell counts.
- Key eligibility criteria are presented in Table 1 (Geva at al 2020).
- Next step: cohort expansion in esophageal cancer.

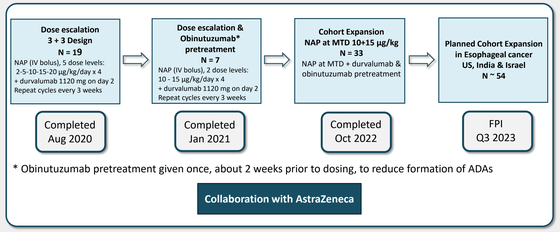


Figure 2: Trial Schema

Table 1: Key Eligibility Criteria

General:	Age > 18, ECOG 0-1, Adequate hematologic and organ function, life expectancy of at least 12 weeks
Tumor types:	Metastatic/ Advanced solid tumors with > 80% probability of being 5T4 positive
Tumor biopsies:	Baseline – may be archived if taken at the stage of metastatic disease Second fresh biopsy – only for patients in the MTD expansion cohort – must have lesion accessible for biopsy
RECIST	Measurable disease – only for patients enrolled in the MTD expansion cohort
Previous cancer therapy:	At least 1 standard systemic therapy and progressed following their most recent regimen • No limit to the number of prior lines of therapy. • Treatment-naive patients will be eligible only if they refused standard treatment. • Patients with prior anti-PD-1, anti PD-L1 or anti CTLA4 therapy are eligible if they have received such therapy for a minimum of 6 months and if they have documented progression of their disease on or off such therapy.

Preliminary Results

Baseline Characteristics:

Patients baseline characteristics are presented in table 2:
59 patients were enrolled, median age was 62 yrs (34-88), 56% female, ECOG 0 in 47% and 1 in 53%. 69% had pancreatic, ovarian or TN breast cancers. Pts received a median of 3 prior lines (0-6) and 7 pts (12%) received prior CPIs.

Table 2: Baseline Characteristics

	Total patients N=59
Age: median (range)	62 (34 – 88)
Gender M/F	26/ 33
ECOG (0/1)	28/ 31
Prior Checkpoint Inhibitors	7
Previous lines of systemic therapy for metastatic disease	3 (0-6)
Pancreas	22
Ovarian	13
TN Breast	6
Cervix	3
Colorectal	3
Endometrium	2
HCC	2
RCC	2
Mesothelioma	2
Prostate	2
Lung	1
Esophagus	1

Safety Profile:

- AEs reported in 57 pts (97%) and included grade 1-2 infusion related reactions (IRRs) in 85%. 95% of IRRs occurred in cycles 1-2 and were rapidly reversible.
- Grade 3 IRRs occurred in 10% of patients.
- Transient and reversible grade 1-2 elevations in liver enzymes occurred in 25% of pts.
- Treatment was discontinued due to toxicities in 4 pts (7%), all at doses above RP2D (NAP 10 µg/kg + durvalumab 1120 mg)
- 23 patients were treated at the RP2D (10mcg/kg). IRRs were reported in 21/23 pts (91%) and grade 3 IRRs occurred in 4 pts, all limited to cycle 1.
- No pts discontinued treatment due to toxicities at the RP2D.

Clinical Activity:

- 4 prolonged responses were seen in 42 patients who were evaluable* for response (Table 3)
  - -Two patients had a complete response (CR): patient with cervical cancer that progressed on prior checkpoint inhibitor (CPI) and a patient with BRCA+ pancreatic cancer
  - -Two patients had partial responses (PR): a patient with hepatocellular carcinoma (HCC) who progressed on prior CPI and a patient with peritoneal mesothelioma.
- 4 patients (10%) had SD, with a median duration of 15 months (5-24+).

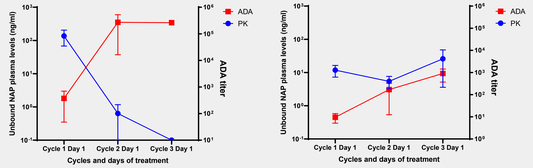
* Evaluable: Exclude patients with single course of NAP, those who discontinued for toxicity before or on cycle 2.

Table 3: Responses (iRECIST)

Pt	Indication	Prior CPI Y / N	Best response	Duration of response
02-002	Pancreatic cancer	N	CR	24 + months
02-009	Cervix	Y (9M, CR)	CR	17 months
02-008	Peritoneal mesothelioma	N	PR	12 months
01-007	Hepatocellular carcinoma	Y (8M, SD)	PR	24 + months

ADA Prevention with Obinutuzumab Pretreatment:

As a result of obinutuzumab pretreatment given once, two weeks prior to NAP/ durvalumab dosing, preliminary results suggest that ADA titers decreased while plasma levels of unbound NAP were maintained throughout treatment cycles (Figure 3, non-QC'd data).



PK (non-QC'd data): Mean ± SEM of unbound NAP plasma levels at 1h following IV administration of NAP at 10 µg/kg. n=1-3 without Obi; n= 8-11 with Obi.
ADA (non-QC'd data): Mean ± SEM of plasma ADA titer prior to IV administration of NAP at 10 µg/kg. n=1-3 without Obi; n= 10-14 with Obi.

Figure 3: Obinutuzumab Decreases ADAs While Plasma Levels of Unbound NAP are Maintained

Conclusions

- NAP is a tumor targeted superantigen, recognizing the tumor-associated oncofetal antigen 5T4.
- NAP is a first in class Selective T-cell Redirection compound.
- NAP RP2D was reached at 10 mcg/kg.
- NAP in combination with the anti PD-L1 checkpoint inhibitor durvalumab, is generally well tolerated, with limited toxicity, mainly G1-2 IRRs, and no treatment discontinuation due to toxicity at the RP2D.
- Safety profile of the combination was consistent with the known profiles for NAP and durvalumab, and no new safety signal was identified for durvalumab.
- Pretreatment with obinutuzumab may reduce the formation of ADAs and preserve NAP plasma levels.
- Responses were seen, lasting for 1 year or longer including CRs, in patients where response to single agent CPI was not expected.
- Further evaluation of this combination is warranted including in patients with prior CPI therapy.
- Cohort expansions are planned including patients with esophageal cancer.

Participating Institutions:

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TEL AVIV SOURASKY MEDICAL CENTER ICHILOV
RAMBAM Health Care Campus
RABIN MEDICAL CENTER BEILINSON • HASHARON

References:

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