Adaptive cellular immunotherapy with APN401, autologous cbl-b silenced peripheral blood mononuclear cells: Data from a phase I study in patients with solid tumors

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BACKGROUND
- Castilas-B-lineage lymphoma protein-b (cbl-b), an E3 ubiquitin ligase acts as intracellular master immune checkpoint limiting activation of all immune cell types relevant for antitumor immunity
- Targeting cbl-b offers the opportunity to override numerous relevant "checkpoints" including sensitivity to Treg, suppression by TGF-β, and immune regulation by CTLA-4 and PD-L1/PD-1 pathways
- Cbl-b knock out mice have been shown to reject various tumors efficiently

Silencing of cbl-b enhances human T cell and NK cell activity
- APN401 is an advanced therapeutic medical product (ATMP) consisting of PBMC of individual patients obtained by leukapheresis that are silenced ex-vivo for the cbl-b gene with an appropriate si-RNA by electroporation and re-infused within one day. All relevant immune cell types for antitumor immunity such as CD8+ T, DN, NK, NKT, B, APC are transiently activated (Figure 1).
- A marked decrease of cbl-b expression can be achieved for approx. 14 days

PATIENTS AND METHODS
- Patients with advanced and metastatic solid tumors not eligible for standard therapies were included into a single dose, dose-ranging, open-label phase I trial (NCT02166255) at Wake Forest Baptist Medical Center. Autologous PBMC were obtained by leukapheresis, transfected with cbl-b siRNA ex vivo by electroporation; 5, 10 or 50 x 10^7 silenced PBMC/kg (Cohorts I – III) were infused within 30 min within 24 hours.
- Primary study objectives: Safety, tolerability and to establish the maximum tolerated dose (MTD).

SELECTED REFERENCES

RESULTS
- 16 advanced cancer patients (median age 63 years; 7 males / 9 females) were treated once with APN401 in 3 dose cohorts with up to 50 x 10^7 PBMC/kg (Table 2)
- APN401 infusions were well tolerated; DLT was not reached (Table 1)
- There was no immediate hypersensitivity or evidence for autoimmune adverse effects
- Cbl-b silencing led in all PBMC preparations to enhanced secretion of cytokines IL-2 and IFN-γ upon TCR stimulation in-vitro (Figure 2)
- PBMC responses to common tumor antigens were enhanced during the follow-up period, seen up to 6 months after treatment (secreton of IFN-γ; Figure 3)
- Four previously progressive patients (2 pancreatic, 1 colon, 1 RCC) had stable disease as best tumor response during the study (Table 2)
- The strongest response to common tumor antigens was observed in a patient with the best objective clinical response (metastatic colon cancer; disease stabilization for approx. 1 year; Figure 3)

OUTLOOK
- Presently, a Phase Ib study is ongoing with three infusions of 50 x 10^7 PBMC/kg every 4 weeks in 10 patients with advanced solid tumors. Interim results show a similar safety profile as observed in Phase I
- A controlled Phase II multi-dose study in a maintenance setting of pancreatic cancer is in advanced preparation

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