

# **Circulating evs in progressive nen g3 patients: potential predictors of resistance to combined immune checkpoint inhibitor/tyrosine kinase inhibitor therapy?**

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## **Abstract**

### **Background:**

Extracellular vesicles (EVs) have emerged as crucial mediators of intercellular communication and immune regulation in cancer. By carrying immune checkpoint molecules such as PD-1 and PD-L1, EVs can modulate T-cell responses and facilitate immune escape. In high-grade neuroendocrine neoplasms (NEN G3), where therapeutic options are limited and outcomes remain poor, EV-based biomarkers may provide vital insights into tumor progression, drug resistance, and overall survival.

### **Objective:**

This interim analysis from the ongoing phase II CABOAVENEC study evaluated the circulating EV profiles of 14 progressive NEN G3 patients treated with the anti-PD-L1 antibody AVE (800 mg IV every 2 weeks) in combination with the tyrosine kinase inhibitor cabozantinib (40 mg daily, PO). The primary aim was to correlate EV subpopulations with treatment response, thereby identifying patients who may be resistant to the combined TKI/ICI therapy.

### **Methods:**

Plasma samples were collected from 14 patients prior to treatment initiation and after 16 weeks of therapy. EVs were isolated using established size exclusion chromatography (SEC). A bead-based FACS analysis was employed to quantify EV subpopulations, with particular attention to those expressing PD-1 and PD-L1. Statistical comparisons were performed between responders and non-responders to assess the association of these EV profiles with clinical outcomes.

### **Results:**

At baseline, the overall EV profile did not differ significantly between responders (n=7) and non-responders (n=7). However, non-responders exhibited significantly higher levels of PD-1-positive EVs derived from CD44-positive cells and an increased presence of HLA-DR-positive EVs. After 16 weeks of combined therapy, non-responders (n=5) demonstrated a marked shift in their EV profile, with significant increases in CD42-positive EVs and CD29-positive EVs. Additionally, there was a significant rise in PD-L1-positive EVs derived from CD2- and CD11-positive cells, suggesting an enhanced immunosuppressive signaling within the tumor microenvironment.

### **Conclusion:**

These interim findings suggest that specific EV subpopulations, particularly those expressing PD-1 and PD-L1 along with markers such as CD44, CD42, and CD29, may serve as early biomarkers for resistance to combined TKI/ICI therapy in progressive NEN G3 patients. The observed alterations in EV profiles provide valuable insights into the mechanisms of therapy resistance and may facilitate the development of personalized treatment strategies in this challenging clinical setting.

## **Do you have any conflicts of interest?**

No, I do not have a conflict of interest.