NP-101 in Combination with Nivolumab and Ipilimumab in Metastatic Extra-pulmonary Neuroendocrine Carcinomas (EP-NECs): A Pilot Study

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Poster # C1

Background

- Extrapulmonary Neuroendocrine Carcinomas (EP-NECs) are a heterogeneous group of rare tumors with poor clinical outcome. (1)
- These patients have limited treatment options after progression on first-line platinum-based chemotherapy.
- Although dual immune checkpoint inhibitors (ICPIs) with anti–CTLA–4 and anti–PD–1 blockade have significantly improved outcomes for several solid tumors, they demonstrated modest activity for EP-NECs with 9-26% response rates and low survival rates. (2-4)
- Preliminary data demonstrated that NP-101 (Thymoquinone) enhances T-cell infiltration and is synergistic with dual ICPIs in NEN's cellular models.
- This pilot study evaluated the safety and feasibility of a novel drug (NP-101) plus nivolumab and ipilimumab in patients with metastatic EP-NECs refractory to first-line platinum-based chemotherapy.

Methods

- This is a single-arm pilot study (NCTNCT05262556) in which patients with metastatic EP-NECs received NP-101 (oral capsules), 3000 mg daily, plus ICPIs (intravenous nivolumab 3 mg/kg and Ipilimumab 1 mg/kg) every 3 weeks for 4 cycles.
- Responders resumed NP-101 with the same daily dose (3000 mg daily), plus maintenance biweekly nivolumab (240 mg), and completed 24 weeks of treatment.
- Treatment-related adverse events (TR-AEs) were characterized according to CTCAE v4.03.
- The response rate was estimated according to Immune-based Response Evaluation Criteria in Solid Tumors (iRECIST) and reported along with its Clopper-Pearson Confidence Interval.

Results

- Twelve patients received ≥1 dose of NP-101 and nivolumab plus ipilimumab.
- There were no dose limiting toxicities (DLTs).
- Grade 1/2 TR-AEs occurred in 100% (12/12) of patients.
- The most common G1/2 TR-AEs were fatigue (75%), nausea (41.7%), pruritus (41.7%), vomiting (25%), and abdominal pain (25%).
- 66.6% (8/12) of patients experienced grade 3/4 TR-AEs including rash (25%), nausea (16.7%), vomiting (16.7%), and transaminitis (16.7%).
- No treatment-related Grade 5 toxicities or deaths were recorded.
- The objective response rate (ORR) was 41.7% (2/12 CR + 3/12 PR; 95% CI:15.2-72.3%) for all patients and 50% (2/8 CR + 2/8 PR, 95% CI: 0.16- 0.84) for patients with NEC of gastrointestinal origin.
- The median duration of response is 7.5 months (range: 1.4-19.6 months).
- Preliminary median progression free survival (PFS) is 1.94 months (95% CI: 1.22-8.77) and median overall survival is 6.6 months (range: 1.6-20.9).
- Final median PFS and OS were not estimable with the current follow-up data and is still in progress.

Table.1:Demographics and Clinical Characteristics for Overall EP-NEC patients

Variable	Treatment group (NP-101 plus Nivolumab and ipilimumab)
Median Age (range)-yr	66.6 yrs (43-84)
Gender	
Male–no. (%)	8 (66.7%)
Female –no. (%)	4 (33.3%)
Primary tumor	
▪ Colon	5 (41.6%)
▪ Pancreas	2 (16.6%)
▪ Esophageal	1 (8.3%)
▪ Gynecological	2 (16.6%)
▪ Head and neck	1 (8.3%)
▪ Unknown primary	1 (8.3%)
Ki67 %- Average (range)	83% (64-98)
TMB (1=High, 2=Low)	
▪ High	3 (25%)
▪ Low	9 (75%)
MMR (1=MSI-H, 2=MSS)	
▪ MSI-H	1 (8.3%)
▪ MSS	11 (91.7%)
TP53 (1=Wild, 2=Mutant)	
▪ Wild	5 (41.6%)
▪ Mutant	7 (58.4%)
Rb1 (1=Intact, 2=Loss)	
▪ Intact	7 (58.4%)
▪ Loss	5 (41.6%)

- *ORR: Objective Response Rate
- *PFS: Progression free survival
- *SR: Survival Rate
- *G: Grade

Table.2: Genetic profiling for responders

Patient #	Primary tumor	ORR	TMB (H: High, L: Low)	MMR	TP53	Rb1	Other mutations
1	Colon	CR	H	MSI-H	Mutant	Intact	BRCA-1 CHEK-1
2	Colon	CR	L	MSS	Wild	Intact	
3	Pancreas	PR	L	MSS	Wild	Intact	BRAF KRAS TET
4	Ovarian	PR	L	MSS	Mutant	Loss	
5	Esophageal	PR	H	MSS	Mutant	Intact	

- *ORR: Objective Response Rate, CR: Complete response, PR: Partial response
- *TMB: Tumor Mutational Burden, low TMB as ≤5, high TMB≥10 mutations/MB
- *MMR: Mismatch Repair Status

Figures

Figure 1. Progression Free Survival for the entire cohort and GI cohort.

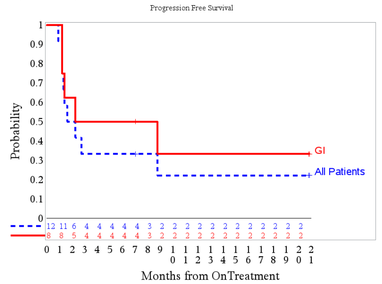


Figure 2. Overall Survival for the entire cohort and GI cohort.

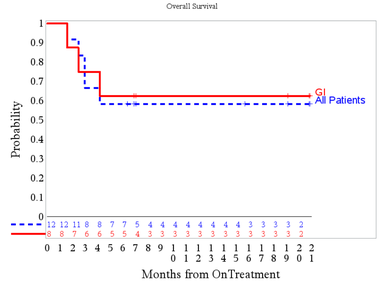
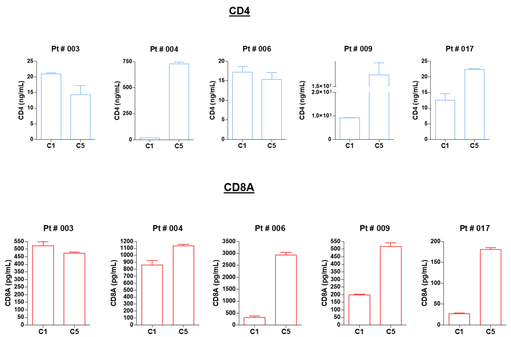


Figure 3. Percentage of CD4 and CD8- T helper lymphocytes in responders at baseline and C5 of NP-101 plus nivolumab and ipilimumab



Conclusion

- The combination of NP-101 plus dual ICPIs (nivolumab and ipilimumab) was safe and well-tolerable regimen with preliminary evidence of anti-neoplastic activity.
- A randomized phase II clinical trial studying the combination is now under development.

References

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