Pembrolizumab (P) monotherapy in patients with previously treated metastatic high grade neuroendocrine neoplasms (HG-NENs)

Namrata Vijayvergia[1], Arvind Dasari[2], Eric A. Ross[3], Karen Ruth[3], Samuel Litwin[3], Efrat Dotan[1], Daniel M. Halperin[2], Igor A. Astsaturov[1], Michael J. Hall[1], Nicole M. Ross[1], Daniel McClean[1], Crystal S. Denlinger[1], Steven J. Cohen[4], Paul F. Engstrom[1]
1. Department of Hematology/Oncology, Fox Chase Cancer Center, Philadelphia, PA; 2. Department of GI Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; 3. Department of Biostatistics, Fox Chase Cancer Center, Philadelphia, PA; 4. Jefferson Health System/ Abington Memorial Hospital, Abington
Study supported by Merck Investigator Studies Program Grant

CLICK TO GO BACK TO KIOSK MENU

Background and Rationale

- Increasing incidence of neuroendocrine neoplasms including HG-NENs[1]
- No current standard of care after failure of first line platinum/etoposide doublet
- Various chemotherapy agents used with poor response to therapy despite increased risk of toxicity
- Promising activity of checkpoint inhibitors in small cell lung cancer and Merkel cell carcinoma[2,3]
- Previously published literature suggesting a higher rate of mutations in HG-NENs compared to low grade NENs[4]
- Provided rationale for conducting a phase II study of Pembrolizumab in HG-NENs with the primary objective to assess response (NCT02939651)

Study design and statistical methods

Screening period (within 28 days) → Treatment assignment → On treatment period → Follow-up period

Metastatic HG-NEN
Eligibility:
- Histologically confirmed HGNET with Ki67>20%
- Prior exposure to platinum based chemotherapy
- PS : ECOG 0-1
- Informed consent
- Measurable disease
- Exclude any high grade NETs of large or small cell type of lung/thymus origin, merkel cell carcinoma.

→ Single arm study pembrolizumab 200 mg IV over 30 min given every 3 weeks → Treat until progression defined by RECIST 1.1 (every 9 weeks for 1 year, then every 12 weeks) or unacceptable toxicity* or for a total of 35 cycles → Follow up visit for toxicity (at 1 month) and survival follow up (every 12 weeks)

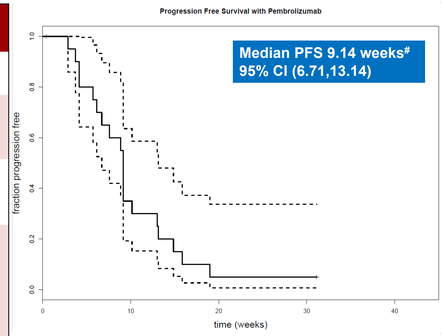
* Pts may be treated beyond first progression under protocol defined circumstances

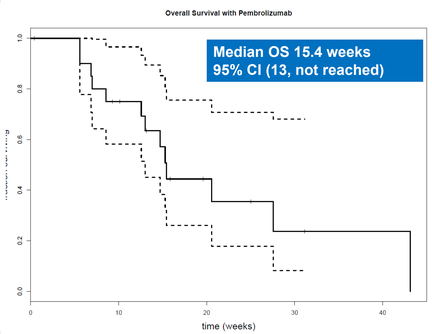
Primary endpoint: Overall Response Rate (ORR)
Secondary endpoints
- **Progression free survival (PFS)**
- **Overall survival (OS)**

- Patients enrolled at 2 major academic cancer centers
- N = 21
- Null hypothesis: p <= 0.05 against the alternative hypothesis: p >= 0.20
- 8.5% level of significance and with 82.1% power.
- ORR less than 5.0% will be of no interest
- After 21 patients are evaluated if 3 or more patients with favorable response are observed then the null hypothesis is rejected.

Results

Baseline characteristics	
Age in years Median (range)	54 (27-73)
Gender	
Male N (%)	11 (52%)
Female N (%)	10 (48%)
Performance Status	
0 N (%)	9 (43%)
1 N (%)	12 (57%)
Primary site	
Pancreas N (%)	6 (30%)
Gastro-esophageal N (%)	3 (14%) 5 (23%)
Colon/rectum N (%)	6 (23%)
Unknown N (%)	1 (10%)
Kidney N (%)	
Ki 67 score	
<55 % N (%)	11 (52%)
>/= 55% N (%)	10 (48%)





Best Overall Response	N (%)
Partial Response	**1 (4.7%)**
Stable Disease	3 (14.2%)
Progressive Disease	12 (57.1%)
Disease Control Rate (CR+PR+SD)	4 (19%)

CORRELATIVE TESTING

- 15 patients with available archival tissue
- 7 samples (47%) had PD-L1 staining >1%
- 8 samples (53%) had evidence of TILs >2+ (>10 TILs/HPF)
- Staining pattern in responder
  - negative for PD-L1
  - >20 TILs/HPF

Overall Safety

Treatment Emergent Adverse Events*		All	Grade 1	Grade 2	Grade 3
		N	N	N	N
Toxicity Category	Adverse Event				
Gastrointestinal disorders	Abdominal pain	4	2	2	.
	Diarrhea	4	3	1	.
	Nausea	5	5	.	.
	Vomiting	2	2	.	.
General disorders and administration site conditions	Fatigue	6	2	3	1
	Other	3	2	1	.
Laboratory	Alkaline phosphatase increased	3	1	.	2
	AST increased	2	.	.	2
Metabolism and nutrition disorders	Anorexia	3	1	2	.
	Hypercalcemia	1	.	.	1
	Hyperkalemia	1	.	.	1
Musculoskeletal	Back pain	3	1	2	.
Renal and urinary disorders	Acute kidney injury	1	.	.	1
	Dyspnea	3	2	.	1
Skin and subcutaneous tissue	Pruritus/Rash	3	3	.	.

* Only Grade 1-2 toxicities occurring in >10% patients are depicted
^ Possibly or probably related to study drug

Drug Related Adverse Events^		Grade All	Grade 3
		N	N
Toxicity Category	Adverse Event		
Gastrointestinal disorders	Bloating	1	.
	Diarrhea	2	.
	Dry mouth	1	.
	Gastrointestinal disorders - Other	1	.
	Nausea	2	.
	Vomiting	1	.
General disorders and administration site conditions	Edema limbs	2	.
	Fatigue	6	.
	General disorders-Other	1	.
Investigations	Alkaline phosphatase increased	2	2
	Aspartate aminotransferase increased	2	2
Metabolism and nutrition disorders	Anorexia	3	.
	Hypercalcemia	1	1
	Hyperkalemia	1	1
Skin and subcutaneous tissue	Pruritus/Rash	3	.
≥ grade 3 study drug-related treatment-emergent adverse event		6 (28%)	
Treatment-emergent adverse event leading to study drug discontinuation		0	
Adverse events leading to death		0	

Conclusions

- Pembrolizumab, though generally well tolerated, showed limited activity as a single agent in HG-NENs in this study
- Study highlights that high grade GI NENs differ from small cell lung cancer, also reflected by their varying molecular profile[4]
- Correlative testing suggestive of high PD-L1 staining and presence of TILs.
- Future studies using combination immunotherapies and/or combination with cytotoxic drugs may be of interest in this aggressive tumor type as many patients progressed before the 12 week mark.

References

1. Dasari, Arvind, et al. "Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States." *JAMA oncology* 3.10 (2017): 1335-1342.
2. Antonia, Scott Joseph, et al. "Phase I/II study of nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC): CA209-032." (2015): 7503-7503.
3. Nghiem, Paul T., et al. "PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma." *New England Journal of Medicine* 374.26 (2016): 2542-2552.
4. Vijayvergia, Namrata, et al. "Molecular profiling of neuroendocrine malignancies to identify prognostic and therapeutic markers: a Fox Chase Cancer Center Pilot Study." *British journal of cancer* 115.5 (2016): 564.

Acknowledgement: Shafat Quadri, PhD (Merck MSL), Siddhartha Rawat (protocol developer)