Pembrolizumab-based therapy in previously treated extrapulmonary poorly-differentiated neuroendocrine carcinoma (EP-PDNEC)

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Background (Click here for more)

- Typically EP-PDNECs are treated like small cell lung cancer (SCLC).[1-3]
- Optimal therapy for refractory EP-PDNECs has not been defined.
- Immune checkpoint inhibitors (CPI) modulate the body's immune regulatory mechanisms to augment the antitumor response.[4]
- Preliminary studies suggest CPI have safety and activity in SCLC.
- This phase 2 study aims to **evaluate the efficacy and safety of pembrolizumab (PEM)-based therapy** in biomarker unselected EP-PDNECs.

Objectives

Primary:

- Assess overall radiographic response rate by RECIST1.1.

Secondary:

- Assess safety
- Assess progression free survival, duration of response, overall survival

Exploratory:

- irRECIST vs. RECIST1.1
- Baseline PBMC and tumor immune cell profiles
- T cell receptor (TCR) repertoire change from baseline to post-treatment tumor mutation profile
- Ki67 index, PD-L1 expression

Click here to view patient eligibility

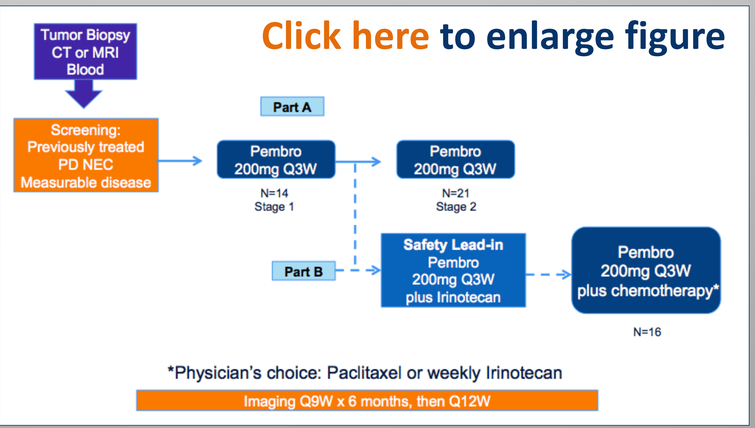
Trial Design

- Open label, adaptive Simon's 2-stage study of PEM alone (Part A) and PEM plus chemotherapy (weekly irinotecan (IRI) or paclitaxel (P); physician' choice) (Part B).

Treatment

- **Part A**: PEM 200 mg IV Q21days for up to 35 treatments
- **Part B**: PEM 200 mg IV Q21days for up to 35 treatments
  +
  IRINOTECAN * 125 m/m2 d 1, 8 of 21 day cycle
  OR
  PACLITAXEL * 80 mg/m2 d 1,8, 15 of 21 day cycle
  * Chemotherapy breaks allowed per institutional practice (up to 3 weeks)

Click here to enlarge figure



Sample Size and Power Calculation

- If >2 out of 14 patients respond by week 18 (Stage 1 Part A), then 21 additional patients will enroll in stage 2 (Part A), corresponding to H_0 10% vs. H_1 26% RR at type I error 0.05 with power 80%.
- If insufficient activity, proceed to Part B, with a safety lead-in of 6-12 pts for IRI/PEM (up to two dose levels, 1 and -1), then 16 more pts accrued for total of 22 pts treated with PEM plus chemotherapy based on one-side binomial test of H_0 10% vs. H_1 31% RR at type I error of 0.05 with power 80%.
- Total N will be 35 (Part A) or 36-42 (Part A then B).

Current Status

- This study is currently open and enrolling patients at UCSF, Memorial Sloan Kettering, and Dana Farber Cancer Institute
- 14 of planned 14 patients in stage I of Part A have been enrolled (6/2017-present)

Click here for references

UCSF School of Medicine
DANA-FARBER CANCER INSTITUTE
Memorial Sloan Kettering Cancer Center

Background and References

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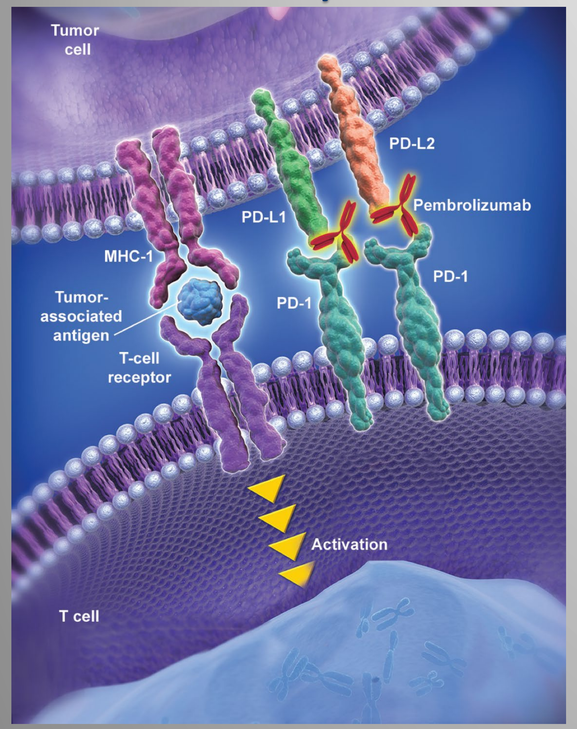
Figure 1. Role of PD-1 Pathway in Tumor Immunity



MHC-1 = major histocompatibility complex 1; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2.

Background

- Optimal therapy for refractory EP-PDNECs has not been defined (typically treated like small cell lung cancer, (SCLC))[1,2,3]
- Immune checkpoint inhibitors (CPI) modulate the body's immune regulatory mechanisms (including PD1 pathway, Figure 1) in order to augment the antitumor response[4]
- Preliminary studies suggest CPI have activity in SCLC
  - PDL1(+) platinum-refractory SCLC treated with pembrolizumab (PEM, an anti-PD-1 antibody, Figure 1), N=24[5]
    - 32% of 145 tumors PDL1(+)
    - 33% RR (1 CR, 7 PR); 54% with PD as best response
  - Unselected platinum-treated SCLC[6]
    - 10% RR in 98 pt-nivolumab 3mg/kg (NIV, anti-PD-1 antibody);
    - 23% RR in 61 pt-NIV 1mg/kg plus ipilimumab 3 mg/kg (IPI, anti-CTLA4 antibody);
    - 19% RR in 54 pt-NIV 3 mg/kg plus IPI 1 mg/kg; Responses regardless of PDL1 status (17%>1%)
- PDL1 expression correlates with grade in EP-PDNEC[7,8]
  - 7/17 (41%) G3 gastroenteropancreatic-NEC PDL1(+) [8]
- The efficacy of CPI in EP-PDNEC has not been defined
  - Exception: avelumab (anti-PD-L1 antibody) approved for Merkel cell carcinoma [9,10]
- PEM approved for melanoma, head and neck squamous cell carcinoma, Hodgkin Lymphoma, MSI-H cancer, non-small cell lung cancer, and urothelial cancer
- This phase 2 study aims to evaluate the efficacy and safety of PEM-based therapy in biomarker unselected EP-PDNECs.
- Clinical trial registry number: NCT03136055

Acknowledgements

- Trial participants and their caregivers
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References

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Trial Design

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Table 1. Patient Eligibility

KEY INCLUSION CRITERIA	KEY EXCLUSION CRITERIA
Histologically confirmed locally advanced or metastatic PDNEC (small or large cell)	Merkel cell carcinoma Well differentiated G3 NET
Mixed tumors (e.g. MINEN, MANEC) allowed if the high grade (small or large cell) NEC component comprises >50% of the original sample or subsequent biopsy	Known active CNS metastases and/or carcinomatous meningitis.
Biomarker “unselected”	History of immunodeficiency
Progressive disease after at least 1 prior systemic chemotherapy regimen • No limit to # prior regimens • Early progression on/after adjuvant chemotherapy counts as first-line therapy	Receiving systemic steroid therapy or immunosuppressive therapy within 7 days prior to 1st dose of trial treatment (physiologic doses of steroids ok)
≥ 1 measurable lesion	Gilbert’s disease (safety run-in, Part B only)
ECOG PS 0 or 1	Active autoimmune disease requiring systemic treatment in the past 2 years
Subjects must consent to baseline tumor biopsy (if risk is acceptable)	History of (non-infectious) pneumonitis (interstitial lung disease) requiring steroids or current pneumonitis
Adequate end-organ function	

Figure 2. Trial Design