Abstract #TPS2611

Phase I Study of the Pan-HER Inhibitor Neratinib Given in Combination with Everolimus, Palbociclib or Trametinib in Advanced Cancer Subjects with *EGFR* Mutation/Amplification, *HER2* Mutation/Amplification or *HER3/4* Mutation

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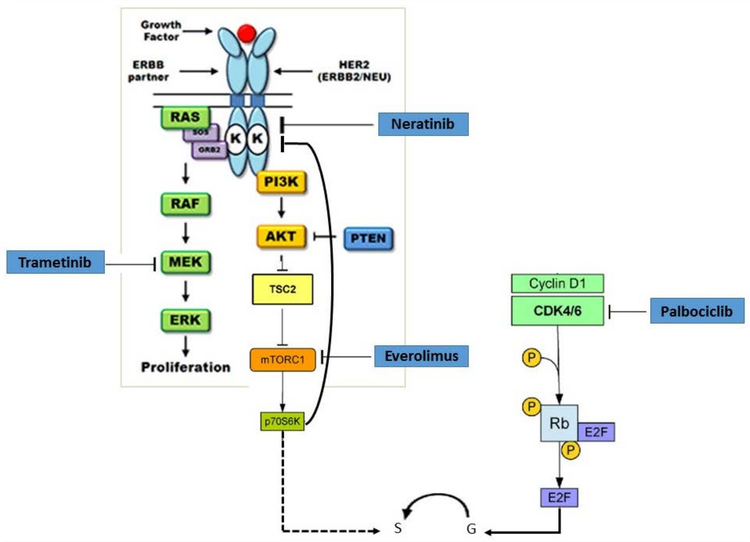
Background

Over expression and aberrant function of ErbB receptor tyrosine kinases (EGFR, HER2, HER3 and HER4) contributes to tumorigenesis. Multiple drugs targeting EGFR or HER2 are already approved for various cancers. In spite of clinical successes with EGFR or HER2 inhibitors, single-agents are prone to drug resistance due to aberrant or compensatory activation of additional downstream signaling pathways. We sought to determine whether neratinib, a potent irreversible pan-HER tyrosine kinase inhibitor, would be safe and efficacious in combination with approved inhibitors of mTOR (everolimus), CDK4/6 (palbociclib), or MEK (trametinib).

Mechanism of Action



Methods

- This is an investigator-initiated, single-center, non-randomized, multi-arm phase I trial of subjects >18 years old with measurable advanced solid tumors with no curative therapeutic options
- Prior HER-2 or EGFR directed therapy allowed
- The study has 3-arms:
  - Arm 1: neratinib and everolimus
  - Arm 2: neratinib and palbociclib
  - Arm 3: neratinib and trametinib
- Patients are selected for each arm at the investigator's discretion based on tumor type and molecular aberrations present
- A standard 3+3 design will be utilized and patients will be recruited into five dose levels for each arm of the study
- Additional subjects will be treated in dose-expansion cohort(s) once the MTD has been established
- A treatment cycle is 28 days
- Primary endpoint is determination of the maximum tolerated dose and dose limiting toxicities for each treatment arm
- Secondary endpoints include pharmacokinetic and pharmacodynamics analysis along with preliminary anti-tumor efficacy
- Prophylactic use of antidiarrheal medication is mandatory during first cycle
- Imaging will be performed at 8 week intervals and response will assessed by RECIST v1.1

Inclusion Criteria

- Advanced or metastatic cancer relapsed or refractory to standard therapy
- Patients must have one of the following:
  - somatic mutations in human epidermal growth factor receptor (EGFR, HER2, HER3, and HER4)
  - EGFR gene amplification (patients with 3+ results on immunohistochemistry testing for EGFR may be allowed to enroll if gene amplification results are unavailable)
  - HER2 gene amplification (patients with 3+ results on immunohistochemistry testing for Her-2 may be allowed to enroll if gene amplification results are unavailable)
- Patients must be ≥18 years of age
- Patients must have measurable disease by RECIST 1.1
- ECOG performance status (PS) 0-1
- Adequate organ function
- Completion of other anticancer therapy within 4 weeks
- WOCBP must have negative serum/urine HCG test (unless prior hysterectomy or menopause)
- Signed informed consent form prior to initiation of the study
- Biopsiable disease to enroll on expansion cohort of 10 patients at the MTD for each arm
- **Only for subjects enrolled in Arm 1 – Neratinib and Everolimus**
  - Fasting lipid profile: Cholesterol less than or equal to 350 mg/dL and triglycerides less than or equal to 400 mg/dL.
  - Subjects who are taking medications with moderate or potent inhibitors or inducers of CYP450 3A4 should be off for 5 half-lives prior to starting everolimus.
- **Only for subjects enrolled in Arm 2 – Neratinib and Palbociclib**
  - Any prior neuropathy should be back to baseline or grade 1
  - Subjects who are taking medications with moderate or potent inhibitors or inducers of CYP450 3A4 should be off for 5 half-lives prior to starting Palbociclib.
- **Only for subjects enrolled in Arm 3 – Neratinib and Trametinib**
  - All skin rash (dermatitis acneiform, erythema, xeroderma, eczema) should be at grade 1 when starting trametinib treatment.
  - History of retinal disorder, dry eye syndrome, or blurry vision need to be evaluated by ophthalmology prior to starting treatment.

Exclusion Criteria

- Patients who are pregnant or breastfeeding
- Prior treatment with a PARP inhibitor
- Known Hepatitis B, Hepatitis C or HIV infection
- Inability or unwillingness to swallow pills or medical condition known to impair oral absorption
- Active infection requiring IV antibiotics or other illness requiring hospitalization
- History of CVA, MI or unstable angina within 6 months
- Known additional malignancy that is progressing or requires active treatment (exceptions: BCC and SCC of skin or in situ cervical cancer)
- Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial
- Known active CNS metastases and/or carcinomatous meningitis; patients with stable, treated brain metastases are allowed and must be off of steroids
- **Only for subjects enrolled in Arm 1 – Neratinib and Everolimus**
  - History of hypersensitivity to everolimus
  - Subjects requiring therapy with immunosuppressive agents such as anti-tumor necrosis factor alpha (TNFα) agents (Etanercept, Adalimumab), azathioprine, methotrexate, cyclosporine, etc. for active autoimmune disorder.
  - Major surgery ≤28 days prior to treatment with everolimus.
- **Only for subjects enrolled in Arm 3 – Neratinib and Trametinib**
  - Albumin less than 3 Gm/dL

Arm 1 – Neratinib and Everolimus

Dose Level	Neratinib (mg) PO daily	Everolimus (mg) PO daily
-1	160	5 QOD*
1	160	5
2	200	5
3	200	7.5
4	240	7.5
5	240	10

Each treatment cycle will be 28 days. There is no break between cycles.
*Everolimus at -1 Dose Level will be once every other day (QOD)

Arm 2 – Neratinib and Palbociclib

Dose Level	Neratinib (mg) PO daily	Palbociclib (mg) PO Daily*
-1	160	75 QOD**
1	160	75
2	200	75
3	200	100
4	240	100
5	240	125

Each treatment cycle will be 28 days. There is no break between cycles.
*Palbociclib is given daily on a 3 week on/1 week off schedule
**Palbociclib at -1 Dose Level will be once every other day (QOD)

Arm 3 – Neratinib and Trametinib

Dose Level	Neratinib (mg) PO daily	Trametinib (mg) PO daily
-2	160	1 (4/3)*
-1	160	1 (5/2)*
1	160	1
2	200	1
3	200	1.5
4	240	1.5
5	240	2

Each treatment cycle will be 28 days. There is no break between cycles.
*Trametinib at -1 Dose Level will be 5 days on and 2 days off. Dose Level -2 will be 4 days on and 3 days off.

Pharmacodynamic Studies (PD)

Correlative Studies

Peripheral Blood:
- Molecular analysis of cfDNA for mechanisms of primary and acquired resistance to therapy
- Functional proteomics with RPPA
- Circulating tumor Markers (optional)

Pre- and Post-treatment Tumor Biopsy:
- Targeted exome sequencing for *ERBB 1-4* mutations and other somatic and germline alterations
- RNAseq
- *BRCA* pathway copy number changes
- Functional proteomics with RPPA
- IHC for HER-2, EGFR, PTEN, INPP4B, pAKT, pMEK, pERK, p-Rb, Ki-67 and others

Current Status

- Site Activation: 10/31/2017
- Enrollment: Ongoing. To date, 8 patients have been enrolled.
  - **Arm 1 – Neratinib and Everolimus: 2**
  - **Arm 2 – Neratinib and Palbociclib: 3**
  - **Arm 3 – Neratinib and Trametinib: 3**

Acknowledgements

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