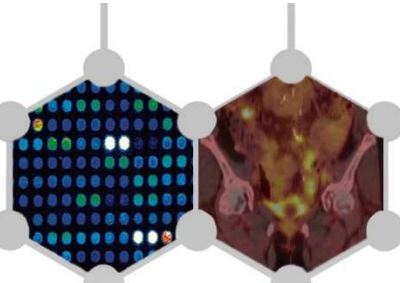

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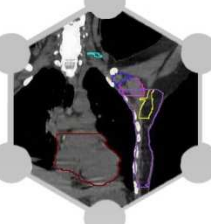

HN1436

"Post-Operative Concurrent EGFR Inhibition with Afatinib and Radiation Versus Post-Operative Radiotherapy Alone in High Risk Cutaneous Squamous Cell Carcinoma of the Head and Neck"

Mohan Suntha & Christine Chung

Background

- Most non-melanoma skin cancers are cured with local therapy alone (85-100%).
- Cure rates are worse for those with advanced disease, with survival of ~ 50%.
- 40-45% achieve 5-year locoregional control (LRC) for advanced disease following surgery alone.
- Radiation therapy (RT) improves LRC by 15-20%.
- Adjuvant chemo-radiation improves outcome over RT alone in high risk mucosal SCCHN.
- TROG is testing the benefit of adjuvant carboplatin wit concomitant RT following surgery.

Rationale for Combining EGFR inhibitor with RT

- Overexpression of EGFR in SCCHN
- EGFR presence in cutaneous SCC (cSCC)
- Studies have shown activity for EGFR inhibition with either Gefitinib or erlotinib in the preop setting
- A mutli center Phase II trial showed that Cetuximab monotherapy resulted in a 11% response rate & 69% disease control rate in unresectable, recurrent or metastatic cSCC
- The combination of EGFR inhibition is being studied in the adjuvant setting within NRG Oncology (RTOG 0920).

Weber et al CCR, Maubec E et al, JCO 2011

Rationale for Using Afabtinib

- Is an irreversible ErbB family blocker
- Approved in NSCLC with EGFR activating mutation
- Has demonstrated antiproliferative activity in preclinical models
- Has comparable clinical efficacy with cetuximab in a phase IIR trial in recurrent or metastatic mucosal HNSCC
- Is being tested as an adjuvant treatment after CRT in LA HNSCC in a phase III study (LUX-Head & Neck 2)

Burtness B et al, Trials 2014

Proposed Trial Design

- **Phase I Run-In**
  - Post-Operative daily Afatinib (40 mg) and RT (60 Gy) for 6 weeks
  - Dose -1: Afatinib, 30mg PO daily, + RT
- **Phase II**
  - Arm 1: Post-operative RT alone, 60-66 Gy in 2 Gy fractions, 5 days/week + concurrent placebo
  - Arm 2: Post-operative RT, 60-66 Gy in 2 Gy fractions + concurrent Afatinib (dose based on phase I run in)

Proposed Trial Design
Concurrent Phase 1 Studies Followed by a Randomized Phase 2

Two Distinct Patient Populations for Phase 1 Studies

Group 1 : Immune Competent

Group 2 : Immune Compromised

Group 2: Organ transplant recipients, CLL, h/o lymphoma

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Decision Regarding Phase 2 Trial

- Afatinib dose determined for both populations from concurrent phase 1 trials
- If Dose is the same for both groups then both groups eligible for enrollment on Phase 2 at determined dose
- If different MTD for each population, then use lower dose in Phase 2 study
- If one group unable to tolerate lowest dose of Afatinib (most likely immune compromise) , then limit accrual on Phase 2 study
- If neither group tolerates Afatinib at lowest dose, then study closes before Phase 2 study

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Endpoints to be Evaluated

- Primary Endpoint for Phase I: Grade 4 mucositis, grade 3 in-field skin reaction, grade 4 febrile neutropenia, or any grade 5 event
- Primary Endpoint for Phase II: Loco-regional control (LRC)
  - Secondary Endpoints:
    - Disease-free survival;
    - Overall Survival
    - Acute and late toxicities

Eligibility

Gross total resection of primary or recurrent cSCC with the following pathologic features:

- Advanced primary disease (p T3-4 with cartilage invasion, skeletal muscle, bone involvement);
- High-risk nodal disease (intraparotid nodal disease or cervical nodes with $\geq$ 2 nodes or LN $\geq$ 3 cm or extra-capsular extension [ECE]);
- Other high risk pathologic feature (perineural invasion or lymphovascular invasion, intransit metastasis or close/positive margin)
- Immune compromised patients allowed, at least for the run-in phase I

Exclusion Criteria

- Gross residual disease following surgery;
- Unresectable disease;
- Prior RT to the region of study that would result in overlap of RT fields.
- Prior EGFR therapy

Statistical Design

- Each phase I group will enroll 11 patients, to ensure 9 evaluable patients.
- If less than 4 patients experience DLT adverse events, then the phase I component closes, and the trial moves to phase II.
- If greater than or equal to 4 patients experience unacceptable toxicity, then the afatinib dose is reduced to 30 mg/d & an additional 11 patients are enrolled to evaluate the toxicity profile.

Statistical Design

Phase II:

- Assume a 15 % error rate, 85% power, and HR of 0.46;
- We expect to see a 15% improvement in LRC with a baseline of 70% in control arm;
- Accrual: 144 patients in phase II (up to 22 in each phase I).

Laboratory Correlative Study

- Targeted sequencing for gene mutations within the RAS/PI3K/PTEN/mTOR pathway from archived pre-treatment tumors.
- This is an exploratory study to assess the potential association between activation of the pathway due to mutations and increased local failure.
- We expect to find mutations in approximately 40% of the tumors, extrapolating from HPV-negative HNSCC.