pKDR/KDR ratio as a possible predictor of response in a Phase I/II study of erlotinib and bevacizumab for recurrent or metastatic Head and Neck Cancer

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Abstract (updated)

Background: EGFR activation up-regulates VEGF, which has been correlated with resistance to anti-EGFR agents. We previously reported early results (Vokes, ASCO 2005) of a phase I-II study of the EGFR inhibitor erlotinib (E) with the VEGF antibody bevacizumab (B) in recurrent or metastatic HNC. We now present results from the pharmacodynamic analysis as well as updated outcome data.

Methods: Phase I/II trial of fixed dose erlotinib (E) 150 mg orally daily with escalation of bevacizumab (B) to a maximum of 15 mg/kg q 3 weeks and continued at 15mg/kg in the phase II portion. Pts were randomized to receive the initial bevacizumab dose on either day 1 or 15. Paired biopsies were taken at baseline and after 2 weeks of treatment (after E alone or E+B) and analyzed by immunofluorescence and laser scanning analysis for target inhibition and apoptosis markers (KDR/VEGFR2, EGFR, CD31, and respective activated forms (pKDR, pEGFR)).

Results: 25 biopsies were obtained (6 paired, 12 unpaired, 2 inadequate). At baseline pKDR/KDR (ratio) correlated with complete response (CR > PD/SD/PR p=0.017) and there was correlation (Spearman) between change in tumor size and pKDR/KDR ratio (p=0.04). Paired tissue samples showed that E or E +B treatment increased apoptosis in tumor cells (pre: 0.9%, post: 8%: p=0.028) and endothelial cells (pre: 0%, post: 14.4%: p=0.092). Further, E+B treatment reduced expression of endothelial KDR, EGFR and VEGF levels compared to E alone. The updated overall response rate was 14.6% (48 evaluable patients in the phase II cohort). Updated median follow-up was 7.3 months (2.1 years for patients still alive). The updated median overall/ progression free survival was 7.3 months/ 3.9 months with 30.6% / 8.2% of patients alive at 1 / 2 years.

Conclusions: The clinical efficacy of E+B warrants further investigation in a follow-up study. The pKDR/KDR ratio is a possible predictor of response to E+B, but validation in a larger cohort is necessary. Compared to E alone the combination of E + B showed increased inhibition of endothelial survival factors. *(Supported by NIH N01 CM-57018-16).*

Background

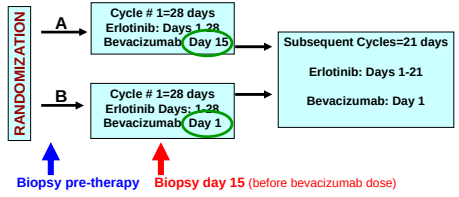
- With a worldwide annual incidence of more than 640,000 cases and an estimated 45,660 cases in the US in 2007 head and neck cancer is the 6th most common cancer worldwide. Approximately 20 - 30% of patients present with metastatic disease at diagnosis.
- Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN) carries a poor prognosis with a median survival of only 6-8 months.
- Treatment is palliative and apart from the recent approval of cetuximab, little progress has been made in the past 3 decades.
- Active agents include taxanes, platinating agents, folate antagonists, 5-FU, and EGFR inhibitors.
- Close to 100% of SCCHN overexpress EGFR
  → Nevertheless EGFR inhibitors only have a response rate of 7.6%-12.6% (gefitinib/ cetuximab), with a stable disease rate of 40-50%.
- Preclinical studies suggest synergism between EGFR inhibition and antiangiogenic therapies → antiangiogenic agents may reverse EGFR resistance.

Study Design

I. Phase I
- Determine DLT, MTD of combination - Fixed standard dose of erlotinib
- Escalating dose of bevacizumab to 15 mg/kg

II. Phase II
- 2-stage design → *22 patients 1st stage, 24 patients 2nd stage*
- RR, TTP, survival - Null hypothesis: RR < 5%, PD at 2 months > 30%
- Correlative laboratory studies

Study Design (continued)



Eligibility

- SCCHN, metastatic and/or recurrent, incurable

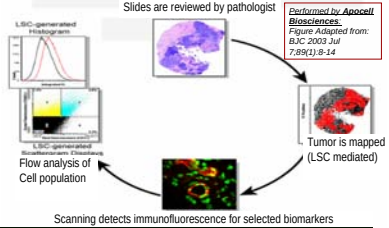
Therapeutic history:
- No more than one prior regimen for recurrent disease
- No prior EGFR- or VEGFR-based therapy for recurrent disease
- Prior irradiation or chemotherapy completed at least 4 weeks prior to enrollment
- Age>18 years, Karnofsky > 60%, Life expectancy > 12 weeks
- Normal organ and bone marrow function

Correlatives

- Pre-therapy and on-therapy samples
- Tumor tissue and blood
- Serum VEGF, TGFα *(previously presented)*
- Tumor endothelial cell apoptosis
- % apoptosis of endothelial cells = #apoptotic cells/#total cells x 100
- **VEGF, KDR/ p-KDR, ERK/ p-ERK, EGFR/ P-EGFR, TUNEL in Tumor cells & Vessels**

Correlative Methods

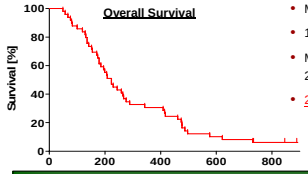
Laser Scanning Cytometry
- Automated quantitative analysis on a continuous scale
- Capable of analyzing entire tissue sections
- Quantification of of thousands of cells
- High Sensitivity of lasers
- Simultaneous detection of multiple biomarkers (multiplex)



Results: Response (updated)

- Phase II portion (N=48 patients)
- **CR: 2 (4%), PR: 5 (10%)**, SD: 26 (54%), PD: 15 (31%)
- **ORR 14.6% (95%CI: 6.1–27.8)**
- 19 patients achieved SD or better for 6 cycles or more

Results: Survival (updated)



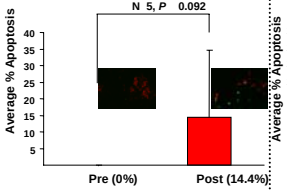
- Median OS 7.3 / PFS 3.9 months
- 1 / 2 -year survival 30 / 8%
- Median Follow-up (all/alive) 223 days/ 2.1 years
- 2 Patients with lasting CR (>2 years)

Results: Samples Acquisition

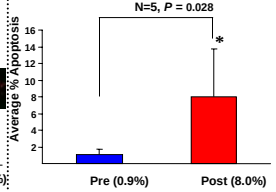
- 25 tumor biopsies obtained
  - 6 paired pre/on-therapy samples*
  - 12 unpaired pre-therapy samples
- 3 arm A (erlotinib single agent *2 wks, then add Bev)
- 3 arm B (erlotinib plus bevacizumab from start)
- 2 samples (8%) inadequate for analysis

Results: pre/post change in Apoptosis

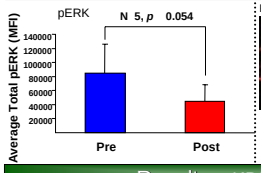
Endothelial Cells (CD31 & TUNEL)

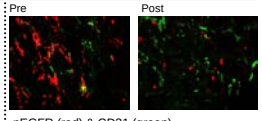


Tumor Cell Apoptosis (TUNEL)



Results: pre/post change in pERK/ pEGFR

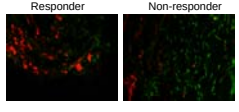




pEGFR (red) & CD31 (green)

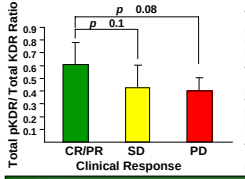
Changes in pEGFR and pERK similar

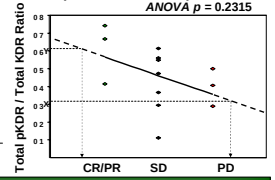
Results: pKDR/KDR Ratio



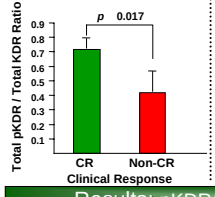
Phospho-KDR (red) / total KDR (green) Ratio *(fractional level)*

Results: pKDR/KDR Ratio predicts Response

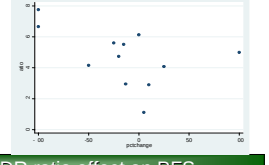




Results: pKDR/ KDR predicts CR/ change tumor size

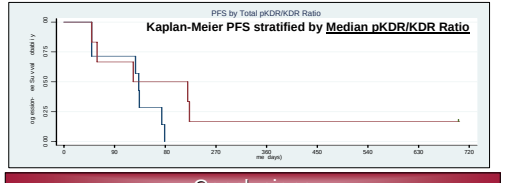


Change in tumor size correlates with pKDR/KDR ratio Ratio (Spearman's correlation – **p=0.04)**



Results: pKDR/ KDR ratio effect on PFS

Higher pKDR/KDR ratio associated with better PFS (**HR = 0.678** per one SD incr. in Ratio Association does not reach statistical significance (*p* = 0.176) by Cox regression



Conclusions

- The combination of bevacizumab and erlotinib has activity in Head and Neck Cancer – with occasional complete responses, maintained >2 years.
  → *further study of this combination is indicated*
- The ratio of total pKDR/KDR is a possible predictive marker of complete response.
- A confirmatory study with a larger N is needed to validate pKDR/KDR ratio further.
- Erlotinib or erlotinib/bevacizumab increase tumor cell and endothelial cell (EC) apoptosis.