Abstract

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 II trial of fixed dose erlotinib (E) (150 mg orally daily) with escalation of bevacizumab (B) to a maximum of 15 mg/kg 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 (8 paired, 12 unpaired, 2 inadequate). At baseline, pKDR/KDR ratio correlated with complete response (CR) or partial response (PR) 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: 9.8%) and endothelial cells (pre: 6%, post: 14.4%, p=0.062). Further, E+B treatment reduced expression of endothelial KDR, EGFR and VEGF levels compared to E alone. The updated overall response rate was 14.4% (8 evaluable patients in the phase II cohort). Updated median overall survival was 7.3 months (2.1 years for patients still alive). The updated median progression free survival was 7.3 months 3.9 months with 30.6% 3.2% 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)

Results: Response (updated)

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<tr>
<th>Clinical Response</th>
<th>ORR 14.6% (95%CI: 6.1–27.8)</th>
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<tr>
<td>CR: 2 (4%)</td>
<td>PR: 5 (10%)</td>
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<td>19 patients achieved SD or better for 6 cycles or more</td>
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Results: Samples Acquisition

- 25 tumor biopsies obtained
- 6 paired, 12 unpaired, 2 inadequate for analysis

Results: pKDR/KDR predicts CR/change tumor size

Higher pKDR/KDR ratio associated with better PFS (HR = 0.575 per one SD incr in Ratio) Association does not reach statistical significance (p = 0.176) by Cox regression

Results: pKDR/KDR ratio predicts Response

Kaplan-Meier curve stratified by pKDR/KDR Ratio

- 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 bevacizumab/erlotinib increase tumor cell and endothelial cell (EC) apoptosis.