**Design:**
- Randomized non-comparative phase II
  - o = 0.1 one-sided; β = 0.9
  - Arm deemed worthy of further study if lower bound of 90% CI
    - ≥ 0.9

**Background:**
- Cetuximab, an anti-EGFR IgG1 monoclonal antibody, is approved for patients with platinum-resistant, recurrent/metastatic (R/M) HNSCC but only a minority benefit, with overall response rate (ORR) of 10-15%.
- Crossover between EGFR and HGF/Met pathways is a known tumor-intrinsic resistance mechanism.
- HGF is immunosuppressive within tumor microenvironment.

**Objective:**
- Our phase II trial showed safety and preliminary efficacy of cetuximab and ficlatuzumab, a potent humanized IgG1 anti-HGF mAb, in cetuximab-resistant, advanced HNSCC.
- The recommended phase II dose was ficlatuzumab 20 mg/kg and cetuximab 500 mg/m² q 2 weeks.

**Study Design:**
- **Randomized Phase II Trial of Ficlatuzumab with or without Cetuximab in Pan-Head and Neck Squamous Cell Carcinoma (HNSCC)**
- **Stage:**
  - UICC 2010 stage III/IV.
  - HPV+ or -.
- **Inclusion:**
  - Age > 18.
  - ECOG PS 0-2.
  - Histologic confirmation of squamous cell carcinoma.
  - Prior ERT or ERT in R/M setting.
  - HPV+ or -.
- **Exclusion:**
  - Prior anti-PD1 mAb (or ineligible).
  - Platinum Resistant.
- **Prior Treatment:**
  - Previous Anti-EGFR therapy.
  - ≥ 8 weeks since prior ERT.
  - No concurrent ERT.

**Patient Characteristics:**

```
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HPV+</th>
<th>HPV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>32</td>
<td>62</td>
</tr>
<tr>
<td>Male</td>
<td>62%</td>
<td>67%</td>
</tr>
<tr>
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<td>38%</td>
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<tr>
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<td>85%</td>
<td>67%</td>
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<tr>
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<td>9%</td>
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<tr>
<td>AJCC Stage 2</td>
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<tr>
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<tr>
<td>AJCC Stage 4</td>
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<td>40%</td>
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<tr>
<td>HPV+ Status</td>
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<td>92%</td>
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<tr>
<td>HPV- Status</td>
<td>0</td>
<td>8%</td>
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<tr>
<td>HPV+ Status</td>
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<td>92%</td>
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<td>HPV+ Status</td>
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<tr>
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</tr>
<tr>
<td>HPV Status</td>
<td>100%</td>
<td>90%</td>
</tr>
</tbody>
</table>
```

**Overall Survival**
- HPV+ (92%)
- HPV- (90%)

**mPFS**
- HPV+ (27(82%))
- HPV- (20 (67%))

**ORR**
- HPV+ (10/32 (31%))
- HPV- (16/62 (26%))

**Final mPFS by HPV Status**
- HPV+ (27 (82%))
- HPV- (20 (67%))

**Final ORR by HPV Status**
- HPV+ (10/32 (31%))
- HPV- (16/62 (26%))

**Primary Objective:**
- The ficlatuzumab + cetuximab combination met the primary PFS endpoint in pan- HPV+ and HPV- subgroups.

**Secondary Objectives:**
- HPV+ subjects had superior ORR (p=0.02) and mPFS (p=0.08).

**TOXICITY**

- Grade 1–2 pneumonitis (2/32 (6%))
- Grade 1–2 hypothyroidism (1/32 (3%))
- Grade 1–2 proteinuria (2/32 (6%))
- Grade 1–2 weight loss (6/32 (19%))
- Grade 1–2 nausea (6/32 (19%))
- Grade 1–2 vomiting (6/32 (19%))
- Grade 1–2 diarrhea (6/32 (19%))

**TOXICITY by HPV Status**
- HPV+ (7/32 (22%))
- HPV- (13/62 (21%))

**CONCLUSIONS**
- The ficlatuzumab + cetuximab combination met the primary PFS endpoint in pan-refractory, advanced HNSCC.
- All responses, including 2 complete and 4 partial responses, were in HPV+ subjects.
- Notable activity in pan-refractory, HPV+ disease warrants phase III investigation.

**ACKNOWLEDGMENTS**

- Supported by the Investigator Initiated Trial Program of AstraZeneca and the Shared Resources of the University of Arizona Cancer Center (P30 CA023074).

**REFERENCES**

**Funding**
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