NSCLC, metastatic

A PHASE IB OPEN LABEL CLINICAL TRIAL OF CONTINUOUS ONCE DAILY ORAL AFATINIB (A) PLUS SIROLIMUS (S) IN PATIENTS (PTS) WITH EGFR MUTATION POSITIVE (EGFR M+) NSCLC AND/OR DISEASE PROGRESSION FOLLOWING PRIOR ERLOTINIB (E) OR GEFITINIB (G)

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Aim: Preclinical data show that A, an irreversible ErbB family blocker, combined with an mTOR inhibitor such as S, may restore sensitivity in EGFR M+ NSCLC pts who progress after E/G. This trial was conducted to identify the maximum tolerated dose (MTD) of A + S.

Methods: Pts with stage IIIB/IV NSCLC who failed ≥1 prior treatment, and whose tumour was EGFR M+, or negative/unknown, but had progressive disease after response or stable disease (SD) for ≥6 months on prior E/G were eligible. Pts received run-in treatment with sirolimus for 8 days before starting the combination therapy. Definition of MTD was initially based on dose-limiting toxicities (DLTs) in cycle (C) 1 (28 days) but with an amendment this was extended to C1 and 2. EGFR mutation was assessed (from blood and archival tumour) and PK sampling was performed. Tumour assessment was performed at week 4, 8, 12, then every 8 weeks.

Results: 39 pts were treated: median age 61y (range: 32-81); male: 15; ECOG 0/1/2: 16/21/2; adeno/squamous/large cell carcinoma: 33/3/3. All had prior E/G; 32 had ≥1 prior chemotherapy. Median treatment duration: 103 days (range: 10-367). Pts were treated at 6 dose levels (A, mg/S, mg): 30/1 (n = 12), 40/1 (n = 3), 30/3 (n = 9), 30/5 (n = 9), 30/10 (n = 3), 40/5 (n = 3), with 30/1 defined as MTD. DLTs (C1 and 2) were seen in 12 pts (Table). The most frequent (≥20%, all grades) drug-related adverse events were: diarrhoea, mucositis, rash, asthenia, decreased appetite and nausea. The best response was partial response (PR) in 4 pts (2 at 30/5, 2 at 40/5); 23 had stable disease (SD) (median duration [days]: 105, range: 51-337). PK, tumour and blood mutation results will be presented.

Table: 1248P DLTs (grade [n]) by dose level

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Diarrhoea</th>
<th>Mucositis</th>
<th>Raised CPK</th>
</tr>
</thead>
<tbody>
<tr>
<td>30/1</td>
<td>G3 (1)</td>
<td>G3 (1)</td>
<td></td>
</tr>
<tr>
<td>40/1</td>
<td>G3 (1)</td>
<td>G3 (1)</td>
<td></td>
</tr>
<tr>
<td>30/3</td>
<td>G3 (2)*</td>
<td>G3 (1)</td>
<td></td>
</tr>
<tr>
<td>30/5</td>
<td>G3 (1)</td>
<td>G3 (1)</td>
<td></td>
</tr>
<tr>
<td>30/10</td>
<td>G3 (1)</td>
<td>G3 (1)</td>
<td></td>
</tr>
<tr>
<td>40/5</td>
<td>G3 (2)</td>
<td>G3 (1)</td>
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</tbody>
</table>

*1 pt had G3 diarrhoea, asthenia, anorexia and iliac fossa pain.

Conclusions: A + S combination had limited tolerability in pts with EGFR M+ NSCLC progressing on E/G mainly due to overlapping DLTs of diarrhoea and mucositis. A 30 mg + 5 mg was defined as MTD. PRs were observed at doses exceeding MTD; SD was observed at all doses.

Disclosure: M. Majem: Membership on an advisory board for Roche, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb and Pfizer; N. Reguart: Membership on an advisory board for Roche, Lilly, Boehringer Ingelheim and Pfizer; C.P. Lee: Employee of Boehringer Ingelheim; S. Kraemer: Employee of Boehringer Ingelheim; D. Schnell: Employee of Boehringer Ingelheim. All other authors have declared no conflicts of interest.