
42% sqclc
27% VAL
VAL

Table 1: VAL demonstrated activity in prior clinical trials sponsored by the US National Cancer Institutes. VAL is approved for the treatment of lung cancer in China; however, clinical adoption is limited by lack of modern data related to mechanism of action (MoA) and utility in the context of standard of care in NSCLC. We have previously demonstrated that VAL 083 circumvents cisplatin-resistance in ovarian cancer cells, in vitro. VAL 083 also exhibits superior activity to cisplatin in both in vitro and in vivo NSCLC models, including TKI-resistant NSCLC.

Here we further differentiate VAL 083 from current standard-of-care in NSCLC by investigating i) the distinct MoA of VAL 083, ii) VAL 083 cytotoxicity in a panel of NSCLC cell lines with varying p53 status and T790M and KRAS mutations, and iii) the combination of VAL 083 with cisplatin or oxaliplatin.

NSCLC: Lung cancer. Including NSCLC, is treated with surgery and chemotherapy with tyrosine kinase inhibitors (TKIs) or platinum-based regimens. EGFR mutated tumors account for 10-15% and of NSCLC in Western and Asian populations, respectively. In EGFR mutated NSCLC, TKI treatment produces dramatic initial improvements, but tumors ultimately recur with new mutations, including T790M. Third generation TKI AZD9291 is effective against recurrent NSCLC with the T790M EGFR mutations, but acquired resistance appears to emerge through RAS signaling, including HRAS mutations. Cisplatin resistance also represents an unmet clinical need, and long-term prognosis in NSCLC remains poor.

Table 2: Historical clinical results with VAL 083 in lung cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Population</th>
<th>Report Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heas et al. (1976)</td>
<td>Advanced lung cancer</td>
<td>42% resp.</td>
</tr>
<tr>
<td>Eagan et al. (1977)</td>
<td>VAL 083 single agent</td>
<td>15% EGFR -</td>
</tr>
<tr>
<td>Eagan et al. (1980)</td>
<td>Advanced SCLC</td>
<td>9% response</td>
</tr>
<tr>
<td>Heas et al. (1981)</td>
<td>Advanced lung cancer</td>
<td>13% response</td>
</tr>
<tr>
<td>Eagan et al. (1981)</td>
<td>VAL 083 single agent</td>
<td>14% response</td>
</tr>
</tbody>
</table>

VAL 083 displays synergy with etoposide, camptothecin, cisplatin and oxaliplatin

The distinct mechanism-of-action of VAL 083 makes it a valuable partner for combination therapies with agents already used in the treatment of GBM and other CNS tumors.

As VAL 083 induce cell cycle arrest in S/G2 phase, we predicted synergy with agents that require cancer cells to be in S/G2 phase for maximum effect, including topoisomerase inhibitors. As expected, VAL 083 demonstrated synergy with etoposide (topoisomerase II inhibitor) and camptothecin (topoisomerase I inhibitor) (Table 2).

VAL 083 also demonstrated synergy with cisplatin and oxaliplatin in NSCLC cell lines, suggesting distinct mechanism-of-action from the platinum-based agents (Figure 2).

**ABSTRACT # 4639:**

**VAL 083 is a bi-functional alkylating agent with proven activity against NSCLC**

**VAL 083 is approved for the treatment of lung cancer in China; however, clinical adoption is limited by lack of modern data related to mechanism of action (MoA) and utility in the context of standard of care in NSCLC. We have previously demonstrated that VAL 083 circumvents cisplatin-resistance in ovarian cancer cells, in vitro. VAL 083 also exhibits superior activity to cisplatin in both in vitro and in vivo NSCLC models, including TKI-resistant NSCLC. Here we further differentiate VAL 083 from current standard-of-care in NSCLC by investigating i) the distinct MoA of VAL 083, ii) VAL 083 cytotoxicity in a panel of NSCLC cell lines with varying p53 status and T790M and KRAS mutations, and iii) the combination of VAL 083 with cisplatin or oxaliplatin. NSCLC: Lung cancer. Including NSCLC, is treated with surgery and chemotherapy with tyrosine kinase inhibitors (TKIs) or platinum-based regimens. EGFR mutated tumors account for 10-15% and of NSCLC in Western and Asian populations, respectively. In EGFR mutated NSCLC, TKI treatment produces dramatic initial improvements, but tumors ultimately recur with new mutations, including T790M. Third generation TKI AZD9291 is effective against recurrent NSCLC with the T790M EGFR mutations, but acquired resistance appears to emerge through RAS signaling, including HRAS mutations. Cisplatin resistance also represents an unmet clinical need, and long-term prognosis in NSCLC remains poor.

**CONCLUSIONS & FUTURE DIRECTIONS:**

- Historical clinical activity combined with a new understanding of the MoA supports the potential of VAL 083 as a possible treatment of chemo-refractory NSCLC

- VAL 083 has a distinct MoA from other chemotherapeutics used in the treatment of NSCLC

- VAL 083 overcomes TKI-resistance in NSCLC cell lines, including cells with the EGFR mutation T790M and KRAS mutations

- VAL 083 displays super-additivity and synergy with both cisplatin and oxaliplatin in NSCLC cell lines, including TKI-resistant cells with T790M or KRAS mutations

- VAL 083 activity is independent of p53 status in a panel of NSCLC cell lines

- VAL 083 displays synergy with topoisomerase inhibitors etoposide and camptothecin, suggesting VAL 083 as part of novel combination therapies

- An open-label post-market clinical trial in China will investigate the activity of VAL 083 in relapsed/refractory NSCLC. Results will provide guidance to physicians under the context of VAL 083 current approval in China, and serve as proof-of-concept for expanded clinical development worldwide.