Figure 2. Common toxicities and on-target resistance mutation limit pan-FGFRi dosing and efficacy. Hyperphosphatemia, diarrhea, skin, and ocular toxicity are common AE associated with pan-FGFRi treatment. Hyperphosphatemia and diarrhea likely represent off-isoform FGFR1/FGFR4-related toxicity (\(P<0.01\), one-way ANOVA). In contrast, all pan-FGFR inhibitors cause hyperphosphatemia (32%-47% increase in serum phosphate levels) and diarrhea (47%) compared to placebo. FGFR2-amplification or FGFR2-mutation is associated with elevated hyperphosphatemia across all FGFRi classes. FGFR2-mutation and FGFR2-amplification were observed in 23 patients who developed FGFR2 kinase domain mutations at progression on pan-FGFRi. FGFR2-mutation and FGFR2-amplification were significantly associated with elevated hyperphosphatemia (FGFR2-mutation: \(P<0.01\), FGFR2-amplification: \(P<0.01\)), diarrhea (FGFR2-mutation: \(P<0.01\), FGFR2-amplification: \(P<0.01\)) and skin toxicity (FGFR2-amplification: \(P<0.01\)). FGFR2-mutation was associated with an increased risk of on-target resistance (FGFR2-mutation: \(P<0.01\)).

**Table 1. Efficacy and safety endpoints for FGFR2-fusion+ ICC**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>FGFR2-fusion+ ICC (n=15)</th>
<th>Pemigatinib (n=33)</th>
<th>ORR</th>
<th>DOR (months)</th>
<th>ORR</th>
<th>DOR (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>23%</td>
<td>36%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mDOR</td>
<td>5.4</td>
<td>2.2</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Key Eligibility Criteria**

- **Age**: \(\geq 18\) years
- **Histology**: Histologically or cytologically confirmed diagnosis of unresectable ICC or other advanced solid tumors
- **Performance Status**: \(\geq 0\)
- **Unresectable**: Histologically or cytologically confirmed diagnosis of unresectable ICC or other advanced solid tumors
- **FGFR2**: FGFR2-mutation or FGFR2-amplification
- **Prior Therapy**: Prior treatment with \(\geq 1\) line of systemic chemotherapy
- **Life expectancy**: \(\geq 12\) weeks
- **Intrahepatic Cholangiocarcinoma**: No prior chemotherapy
- **Pan-readiness**: No prior chemotherapy
- **Other**: No concomitant anticoagulants

**Study Enrollment and Current Status**

The study enrollment for RLY-4008-101 is ongoing. Recruitment of patients to the first dose level will cease as of June 2020 (n=15). Recruitment is ongoing at 11 open centers in the US.

**References**