Sitravatinib + tislelizumab in patients with anti-PD-(L)1 refractory/resistant metastatic non-small cell lung cancer

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Introduction

Programmed death protein (Pdgp) inhibitors are effective first-line treatments for advanced non-squamous cell lung cancer (NSCLC).

Tislelizumab is currently being investigated in several solid tumor types.Sitravatinib is an oral spectrum-selective tyrosine kinase inhibitor targeting TAM (TYRO3, AXL, MER) receptors.Tislelizumab is an anti-PD-1 antibody designed to minimize binding to PD-1.

Methods

An open-label, multicenter, non-randomized, multi-cohort, Phase 1b trial was conducted (NCT03666143). Study design and endpoints are summarized in Figure 1.

Cohorts reported herein included patients with non-squamous (cohort A) or squamous (cohort F) metastatic NSCLC that is R/R to anti-PD-(L)1 therapy.

Resistant disease was defined as partial response, complete response, or stable disease for ≥2 weeks per RECIST v1.1, followed by radiographic disease progression.

Radiotherapy was defined as radiographic disease progression ≥12 weeks after initiation of treatment.

Table 1. Baseline demographic and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=47)</th>
<th>Squamous (n=23)</th>
<th>Non-squamous (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Median (range)</td>
<td>60.0 (25–79)</td>
<td>60.0 (25–79)</td>
</tr>
<tr>
<td>Sex, (%)</td>
<td>Male 20 (42.6)</td>
<td>11 (47.8)</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>Race, (%)</td>
<td>White 20 (42.6)</td>
<td>11 (47.8)</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>0 21 (44.7)</td>
<td>11 (47.8)</td>
<td>10 (41.7)</td>
</tr>
<tr>
<td>NSCLC histology at diagnosis, n (%)</td>
<td>Squamous 23 (48.9)</td>
<td>23 (48.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Non-squamous 24 (51.1)</td>
<td>0 (0.0)</td>
<td>24 (51.1)</td>
</tr>
<tr>
<td>Histology</td>
<td>Age, years</td>
<td>Median (range)</td>
<td>60.0 (25–79)</td>
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<tr>
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<td>Median (range)</td>
<td>60.0 (25–79)</td>
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</tr>
</tbody>
</table>

Conclusions

• Treatment with sitravatinib + tislelizumab had a manageable safety and tolerability profile in patients with metastatic NSCLC that is R/R to anti-PD-(L)1 therapy.

• The combination demonstrated promising antitumor activity: patients achieved an ORR of 13.6%, DCR of 86.4%, and a median PFS of 5.2 months.

• These findings support sitravatinib in combination with tislelizumab as a potential treatment option for patients with metastatic NSCLC that is R/R to anti-PD-(L)1 therapy, and further investigation is warranted.

Safety

The median duration of exposure was 17.9 weeks (range: 1.3 to 53.9) for sitravatinib and 19.8 weeks (range: 3.0 to 51.1) for tislelizumab.

Mean relative dose intensity was 77.8% (SD: 21.7) for sitravatinib and 34.1% (SD: 10.4) for tislelizumab.

All patients had ≥1 treatment-emergent adverse event (TEAE) (Table 2). Tislelizumab was observed in 68.1% of patients (Table 2) (Figure 1). The combination was the most reported with sitravatinib: TEAE (≥ Grade 3) in 9 patients (19.1%), Table 2, which was well managed with anti-hypertensives. One patient had hypertension that led to sitravatinib dose reduction, four patients had hypertension (prognosed terms) that led to sitravatinib dose adjustment, and one patient had hypertension that led to tislelizumab dose modification.

All patients had ≥1 treatment-related adverse event (TRAE) and ≥1 Grade 3 TRAE (Table 2). TRAEs leading to death were reported in 1 patient in each of 3 subgroups treated (1 case of ischemic stroke unassociated with sitravatinib, and 1 case of unspecified death related to sitravatinib + tislelizumab).

Efficacy: Tumor response

Treatment with sitravatinib + tislelizumab demonstrated antitumor activity, with an objective response rate of 13.6% (Table 3).

The median duration of response was 6.9 months (Table 3).

Median time to response was 2.7 months (1.4 to 5.5 months).

Confirmed partial response was reported in 6 patients (13.6%) (Table 3 and Figure 2).

Disease control was achieved in the majority of patients (86.4%) (Table 3).

Efficacy: Survival

The combination also demonstrated improved survival: patients achieved a median OS of 13.6 months and a 12-month OS rate of 52.7% (95% CI: 41.5, 62.9) (Table 3 and Figure 3).

In summary, sitravatinib in combination with tislelizumab had a manageable safety and tolerability profile in patients with metastatic NSCLC that is R/R to anti-PD-(L)1 therapy, and further investigation is warranted.

References


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Efficacy: Tumor response

Defined cut-offs for PD-L1 tumor cell or immune cell expression were used to investigate whether there was an association between PD-L1 expression and tumor response.

Based on current results, no association was observed (Figure 4) and further exploration is required in a larger population.

Efficacy: PD-L1 expression and tumor response

The combination of sitravatinib and tislelizumab led to an improved expression of PD-L1 and tumor cell and immune cell expression.

In summary, sitravatinib in combination with tislelizumab had a manageable safety and tolerability profile in patients with metastatic NSCLC that is R/R to anti-PD-(L)1 therapy, and further investigation is warranted.